ILCA conference

ILCA Annual Conference 2026

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3-5 September 2026

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Index of Authors
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General Session 1: Surveillance and Diagnosis

O-01 DIAGNOSTIC PERFORMANCE OF THE GAAD SCORE FOR DETECTING SMALL HCC IN PEOPLE WITH CIRRHOSIS: A UK MULTICENTRE STUDY

Irdina Nadziruddin [1], Klaudia Kowska [2], Joao Leite [3], Tim James [3], James Robineau [4], Emily Ashwin [2], Benjamin Schuster-Böckler [1], Shalin Abraham [1], Reeba Babu [2], Tamsin Cargill [5], Waleed Fateen [5], Emma Culver [5], Azim Ansari [2], Phillipa Matthews [2], Jane McKeating [6], Chun Xiao Song [1], James McCullagh [7], Michael Pavlides [8], Andrew Blake [4], The DeLIVER Consortium, Eleanor Barnes [5,6], and Hamish Innes [10]

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Introduction: Hepatocellular carcinoma (HCC) accounts for around 17 deaths/day in the UK [1], with over 70% diagnosed late, limiting treatment options [1]. Early detection improves outcomes, with 5-year survival increasing to about 70% through curative interventions like resections [2]. Guidelines recommend biannual ultrasound surveillance with or without α-fetoprotein (AFP) for patients with cirrhosis; however, its effectiveness is limited by operator dependence, reduced sensitivity, and poor image quality [3]. Blood-based tests may offer an accessible alternative. The GAAD score, combining gender, age, AFP, and PIVKA-II, is a blood test for HCC detection, but its performance to detect small HCC in a pan-aetiology cirrhotic cohort remains unclear. Our primary aim was to validate the diagnostic performance of GAAD for detecting small HCC in a pan-aetiology cirrhotic cohort. A secondary aim was to evaluate the association between GAAD and incident HCC. Our findings are preliminary as patient follow-ups are ongoing.

Methods:The DeLIVER programme recruited patients across 48 UK sites. In a case-control analysis, patients with cirrhosis without HCC (Pearl cohort) were compared with patients with cirrhosis and HCC (SELiNa cohort), both recruited across overlapping sites. SELiNa comprised patients with cirrhosis and small HCC (BCLC 0/A; 1-3 nodules <3 cm, preserved liver function, performance status 0-1). GAAD scores were obtained using Elecsys® AFP and Elecsys PIVKA-II assays on the Cobas® e411 analyser (Roche-supported). Baseline GAAD distributions were assessed, along with the sensitivity (Sn) and specificity (Sp) for small HCC detection at Roche's predefined threshold of 2.57.

For incidence analysis, non-HCC controls were followed to assess HCC incidence. Person-time was calculated from baseline to the earliest of HCC, death, or censoring date. We compared how incidence rate of HCC varied according to GAAD score to assess if baseline GAAD predicted future HCC risk.

Results: A total of 1367 patients with cirrhosis without HCC (controls) and 202 patients with cirrhosis and HCC (cases) were included in the case-control analysis. Controls were mostly alcohol-related liver disease (n=674), metabolic dysfunction-associated steatotic liver disease (MASLD) (n=499), and viral hepatitis (n=159), while cases were mostly MAFLD (n=76) and alcohol-related liver disease (n=69). Median and interquartile ranges for baseline GAAD scores were significantly lower in controls compared to cases at 1.5 (0.69-3.35) and 5.8 (3.34-7.97) respectively (p <0.01). At a predefined threshold of 2.57, GAAD demonstrated a Sn of 81% (95% CI: 75-86) and Sp of 68% (95% CI: 65-70) for small HCC detection.

For incidence analysis, 1219 non-HCC controls were included in the final analysis after suitable exclusions. Mean follow-up was 2.21 years. A total of 27 incident cases of HCC were observed. The incidence rate was 2.32 (95% CI: 1.28-3.37) per 100 person-years in the high GAAD group. This was over five times higher than the incidence in the low GAAD group at 0.43 (95% CI: 0.13-0.72) HCCs per 100 person-years.

Conclusion: GAAD showed excellent Sn for detecting small HCC and could distinguish cirrhosis with and without small HCC; however, its lower Sp may limit its utility as a standalone surveillance tool, needing further evaluation. GAAD successfully identified patients at increased risk of developing HCC in the future, suggesting its potential use in risk stratification.

Ref

1.British Liver Trust
2.American Cancer Society
3.Polpichai,N. et al. Gastroenterology Report 13(2025)

Disclosure of Interest: N/A

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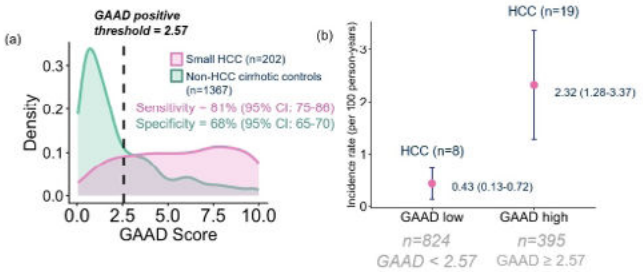

Fig1 (a) Shows the GAAD distribution between the cases and controls. (b) Shows the incidence rates of hepatocellular carcinoma (HCC) by GAAD group. Points represent incidence rates (per 100 person-years), and error bars indicate 95% confidence intervals.

O-02 MULTIMODAL DEEP LEARNING FOR FOCAL LIVER LESION DETECTION USING ULTRASOUND AND CLINICAL DATA IN HCC SURVEILLANCE

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Introduction: Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality, with incidence rising in the context of cirrhosis and metabolic dysfunction-associated steatotic liver disease. Guidelines recommend biannual ultrasound (US) with alpha-fetoprotein for surveillance, but sensitivity for early detection remains suboptimal, particularly in patients with obesity, cirrhosis, or overlapping focal liver lesions (FLLs). Few studies have evaluated whole-image multimodal models that combine US with routinely available clinical variables. This study developed and evaluated a multimodal deep-learning pipeline that integrates B-mode US and clinical variables to identify FLLs relevant to HCC surveillance.

Methods:In a retrospective, multi-vendor, multi-scanner study, 14,755 B-mode liver US images from 1,243 patients (2016–2022) were annotated by two board-certified radiologists for cyst, nodule/mass (including HCC/ICC/hemangioma/metastasis), focal fatty infiltration, focal fatty sparing, and any lesion. Patients were split into training/validation (n=993) and held-out test (n=250) sets. An end-to-end pipeline [(1)] filtered liver-containing frames, [(2)] detected and cropped the field-of-view, [(3)] estimated LI-RADS visualization score, and [(4)] performed lesion classification using a multimodal fusion model combining a Swin Transformer (image encoder) and an FT-Transformer (clinical encoder: age, sex, BMI, diabetes, hypertension, cirrhosis, fatty liver). Five one-vs-all classifiers were trained. Operating points targeted 95% sensitivity for any lesion and nodule/mass, and 95% specificity for other findings. Performance was assessed at image and patient levels with AUROC, sensitivity, specificity, PPV, NPV, and bootstrap 95% confidence intervals (CI). Permutation importance and saliency maps supported interpretability.

Results: Inter-rater agreement was high (Cohen's κ 0.93–0.95 for most findings; 0.68 for focal fatty infiltration). At the patient level, AUROCs were 0.953 (any lesion), 0.946 (cyst), 0.949 (nodule/mass), 0.880 (focal fatty infiltration), and 0.942 (focal fatty sparing). For cysts, sensitivity was 79.25% (95%CI 69.01–88.89) and specificity 94.57% (90.91–97.78). For nodules/masses, sensitivity was 94.60% (90.47–98.25) and specificity 81.56% (74.28–88.00). For focal fatty sparing, sensitivity was 70.60% (56.86–84.21) and specificity 94.62% (91.24–97.55). For focal fatty infiltration, sensitivity was 56.82% (30.75–81.25) and specificity 94.86% (91.91–97.46). Multimodal fusion yielded consistent AUROC and larger AUPRC gains over image-only and tabular-only baselines. Permutation analysis showed image features dominated predictions, with age and BMI as leading clinical contributors; saliency maps concentrated within lesion regions.

Conclusion:A multimodal pipeline integrating B-mode liver US with routinely collected clinical variables accurately identifies focal liver lesions relevant to HCC surveillance and outperforms unimodal approaches. This guideline-concordant, interpretable tool may support real-world HCC surveillance, reduce expert workload, and improve the diagnostic accuracy of non-expert operators.

Disclosure of Interest: N/A

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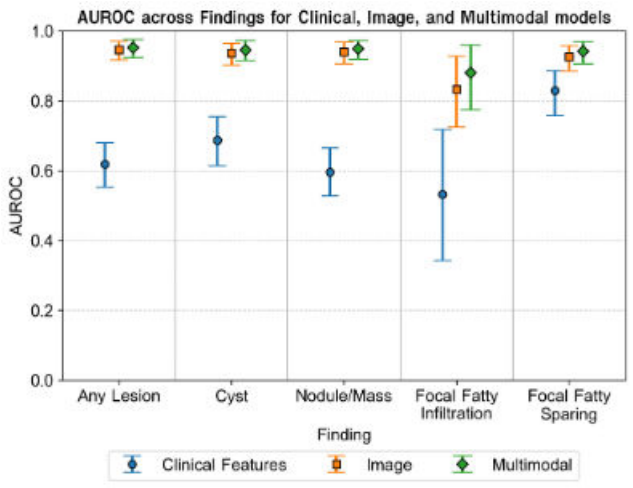

O-03 PIVKA-II SERUM LEVELS ENHANCE PROGNOSTIC STRATIFICATION BEYOND BCLC STAGING IN NEWLY DIAGNOSED HEPATOCELLULAR CARCINOMA: A MULTICENTRE COHORT STUDY

Damone Francesco [1], Caviglia GianPaolo [2], Faita Francesco [3], Colombatto Piero [1], Oliveri Filippo [1], Guariglia Marta [3], Ricco Gabriele [1], Gaia Silvia [4], Romagnoli Veronica [1], Cavallone Daniela [1], Rolle Emanuela [4], Carucci Patrizia [4], Bonino Ferruccio[3] and Brunetto Maurizia Rossa [1,3,5]

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Background: Current prognostic tools for Hepatocellular Carcinoma (HCC), including the Barcelona Clinic Liver Cancer (BCLC) staging system, rely on liver function, tumour burden and performance status, yet fail to capture tumour biological heterogeneity and aggressiveness. This multicentre cohort study investigated whether baseline serum Protein induced by Vitamin K Absence-II (PIVKA-II) levels could complement BCLC staging to enhance prognostic accuracy.

Methods: A cohort of 605 consecutive patients with newly diagnosed HCC, enrolled between 2010 and 2024 at two Italian tertiary referral centres, was analysed. PIVKA-II was incorporated as a continuous variable. The primary endpoint was Overall Survival (OS). Prognostic performance was evaluated by comparing two Cox proportional hazards models: one based on BCLC stage alone and the other additionally incorporating baseline PIVKA-II. Discrimination and calibration were assessed using time-dependent AUC, Brier score, and C-index at 24, 36, and 60 months. Internal validation was performed through a 70/30 train–test split approach.

Results: BCLC stage distribution was as follows: 83 patients BCLC-0, 284 BCLC-A, 151 BCLC-B, and 87 BCLC-C. Median OS for the overall cohort was 29.0 months, with stage-specific medians ranging from 47.9 months (BCLC-0) to 10.7 months (BCLC-C) ($p<0.001$). Adding PIVKA-II to the BCLC model substantially improved prognostic discrimination at mid- and long-term timepoints: time-dependent AUC at 36 months was 80.8% versus 75.7% ($p=0.006$), rising to 79.3% versus 73.1% at 60 months ($p=0.002$). Calibration also marginally improved with PIVKA-II integration, as evidenced by lower Brier scores at 36 months (18.9% vs 19.2%) and 60 months (19.8% vs 20.1%). Overall discriminative ability favoured the integrated model (C-index: 0.71 vs 0.68).

Conclusions: Baseline PIVKA-II serum levels offer meaningful prognostic value beyond BCLC staging in patients with newly diagnosed HCC, significantly enhancing mid- and long-term survival prediction. These results support the design of prospective studies aimed at incorporating tumour biomarkers into established staging frameworks, in line with a precision medicine approach to HCC management.

Disclosure of Interest: N/A

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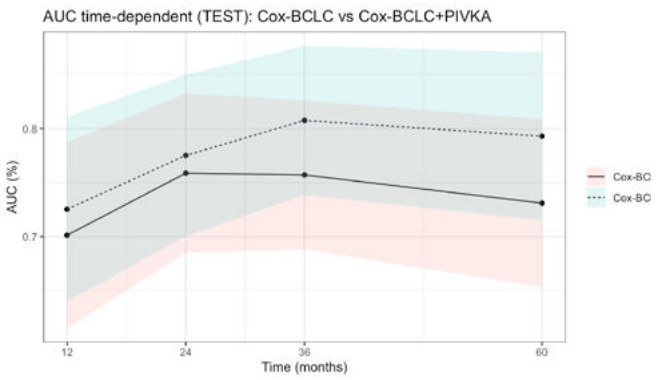

O-04 ABBREVIATED GADOXETIC ACID–ENHANCED MAGNETIC RESONANCE IMAGING VERSUS ULTRASONOGRAPHY FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE IN HIGH-RISK PATIENTS WITH CIRRHOSIS: A RANDOMIZED CONTROLLED TRIAL (AMRIUS)

Hyo Jung Park[1], Jonggi Choi[2], So Yeon Kim[1](correspondence), Dong Wook Kim[1], Sang Hyun Choi[1], Won-Mook Choi[2], Sung Won Chung[2], Danbi Lee[2], Ju Hyun Shim[2], Han Chu Lee[2], Young-Suk Lim[2], Amit G. Singal[3], Seong Ho Park[1]

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Introduction: This study aimed to compare the effectiveness of biannual Gadoxetic acid–enhanced abbreviated magnetic resonance imaging (HBP-AMRI) versus ultrasonography (US) for hepatocellular carcinoma (HCC) surveillance in high-risk patients with cirrhosis.

Methods: In this prospective, open-label, single-center randomized controlled trial, patients with high-risk liver cirrhosis (annual HCC risk > 5%) were enrolled. Participants were randomized 1:1 to HBP-AMRI group or US group for two biannual surveillance rounds. The primary endpoint was the detection rate of Barcelona Clinic Liver Cancer (BCLC) 0 or A HCC. Secondary endpoints included false referral rate, stage distribution at diagnosis, and the rate of curative treatment.

Results: Between August 2022 and October 2024, 806 participants were randomized to the HBP-AMRI ($n = 403$) or US ($n = 403$) group. HCC were detected in 44 participants (32 in HBP-AMRI and 12 in US), with a median size of the largest HCC of 1.5 cm (IQR, 1.2–2.1 cm). BCLC stages at diagnosis were stage 0 in 59.1% (26/44), A in 31.8% (14/44), B in 4.5% (2/44) and C in 4.5% (2/44). The detection rate of BCLC 0 or A HCC was significantly higher in the HBP-AMRI group (7.2% [29/403]) than in the US group (2.7% [11/403], $p = 0.004$). HBP-AMRI also showed higher detection rates than US for BCLC 0 HCC (5.7% [23/403] vs. 0.7% [3/403], $p < 0.001$) and all-stage HCC (7.9% [32/403] vs. 3.0% [12/403], $p = 0.002$). The false referral rate was significantly higher in the US group (4.4% [32/733]) than in the HBP-AMRI group (2.1% [15/705], $p = 0.018$). The HBP-AMRI group demonstrated an earlier BCLC stage distribution compared with the US group ($p = 0.009$).

Conclusions: HBP-AMRI using gadoxetic acid demonstrated superior performance to US for HCC surveillance in cirrhotic patients at high risk for developing HCC, with higher detection rate of early-stage HCC and fewer false referrals (ClinicalTrials.gov, NCT06312826).

Disclosure of Interest: N/A

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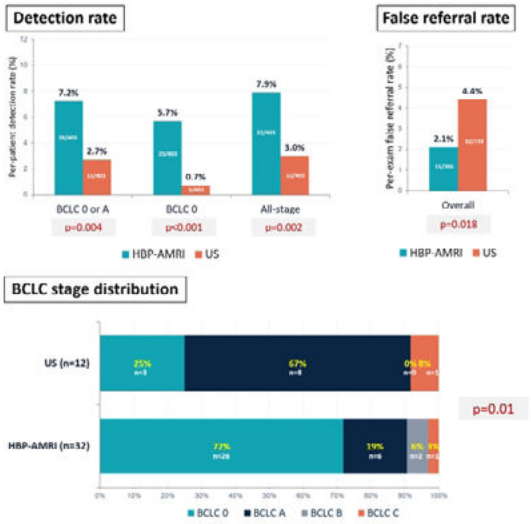
Images:

Table. Detection and False referral rates of HBP-AMRI and US groups

	AMRI group	US group	p-value
Detection rate			
Intention-to-treat			
BCLC 0 or A	7.2% (29/403)	2.7% (11/403)	0.004
BCLC 0	5.7% (23/403)	0.7% (3/403)	<0.001
All	7.9% (32/403)	3.0% (12/403)	0.002
Per-protocol			
BCLC 0 or A	7.7% (29/377)	2.9% (11/382)	0.003
BCLC 0	6.1% (23/377)	0.8% (3/382)	<0.001
All	8.5% (32/377)	3.1% (12/382)	0.002
False referral rate	2.1% (15/705)	4.4% (32/733)	0.018

Detection rate was calculated per patient. False referral rate was calculated per completed examination (HBP-AMRI, 705 examinations; US, 732 examinations) and is not separately stratified by intention-to-treat or per-protocol.

BCLC, Barcelona Clinic Liver Cancer; HBP-AMRI, hepatobiliary phase-abbreviated magnetic resonance imaging; US, ultrasonography.



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General Session 2 - Molecular Pathogenesis, Cell Biology and Translational Research

O-05 A GRAPH CONVOLUTIONAL NEURAL NETWORK INTEGRATING SPATIAL MULTI-OMICS IDENTIFIES MICROENVIRONMENTAL DRIVERS OF POST-IMMUNOTHERAPY RECURRENCE IN HCC

Junbing Chen [1,2], Yunfan Sun [1], Jian Zhou [1].

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Introduction: The CARES-009 phase III clinical trial demonstrated the efficacy of the perioperative camrelizumab plus rivoceranib "sandwich" regimen for resectable hepatocellular carcinoma (HCC), significantly improving postoperative prognosis including event-free survival. However, a considerable proportion of patients still experience tumor recurrence and poor prognosis after this therapy. Predicting recurrence risk and elucidating its molecular mechanisms are critical unmet scientific needs. Deciphering the spatial heterogeneity of the tumor microenvironment is key to understanding immune evasion and drug resistance linked to recurrence.

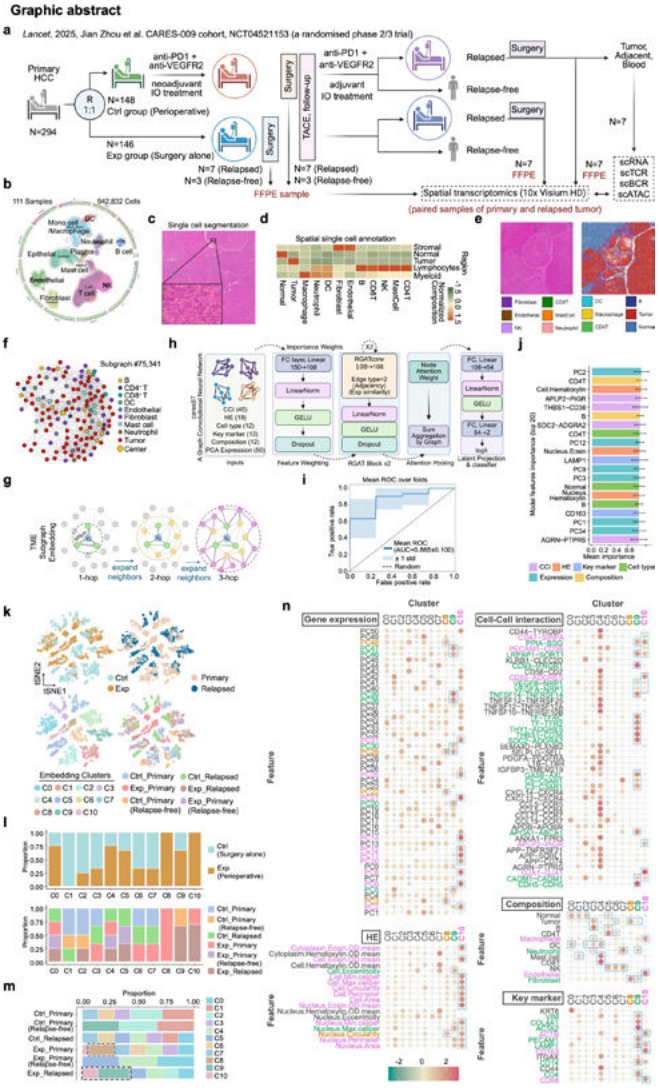
Methods: We performed 10x Visium HD spatial transcriptomics (ST) on 35 surgical specimens from 20 CARES-009 patients, including paired primary and relapsed tumors. Paired single-cell multi-omics (transcriptome, immune repertoire, ATAC) from the tumor, adjacent tissue, and peripheral blood of 7 relapsed patients were utilized for single-cell resolution deconvolution and soft-label transfer. Based on high-resolution ST, we constructed Delaunay triangulation-based microenvironment subgraphs, where cells serve as nodes containing multimodal data (gene expression, cell-cell interactions, H&E features, and cell annotations). We developed "caresST," a Graph Convolutional Neural Network (GNN) model integrating these multimodal inputs to predict clinical relapse. Subgraph embeddings were clustered and reduced via t-SNE to map spatial heterogeneity across treatment modalities and clinical outcomes.

Results: ST analysis identified 12 major cell types mapped as soft labels. The caresST model successfully predicted tumor relapse with an AUC of 0.865. Subgraph embedding yielded 11 distinct spatial clusters. Cluster 8 (C8), predominantly comprising fibroblasts and tumor cells, was significantly enriched in the primary tumors of treatment-group patients who subsequently relapsed. Conversely, C9 and C10 were enriched in the relapsed tumors of the treatment group. C9 consisted mainly of tumor cells, neutrophils, and fibroblasts, exhibiting upregulated CD93-IFNGR1 and SDC2-ADGRA2 signaling. Neutrophil-secreted CD93 blocked IFN-γ signaling and T-cell activation, while fibroblast-secreted SDC2 induced vascular abnormalities. In C10, M2 macrophage-secreted CD55 acted on endothelial ADGRE5 to inhibit T-cell adhesion and promote abnormal vascularization. These spatial findings were validated through immunohistochemistry in the whole CARES-009 cohort. Both in vitro and in vivo experiments confirmed that blocking these pathways sensitized HCC to the camrelizumab plus rivoceranib regimen.

Conclusion: The novel caresST model effectively integrates spatial multimodal omics, identifying unique spatial cellular order and signaling communication in the primary and relapsed tumors of the treatment group. Fibroblast aggregation in primary tumors strongly correlates with postoperative relapse. Upon relapse following targeted immunotherapy, tumors orchestrate immune evasion and therapy resistance via neutrophil-derived CD93 which inhibits T-cell activation, and fibroblast-derived SDC2 or M2 macrophage-derived CD55 which induce vascular abnormalities. Co-targeting these specific microenvironmental interactions presents a promising clinical strategy to overcome immunotherapy resistance during HCC recurrence.

Disclosure of Interest: N/A

Images:



O-06 SPATIALLY RESOLVED MULTIOMICS OF THE METASTATIC ECOSYSTEM GUIDES THERAPEUTIC STRATEGIES IN HEPATOCELLULAR CARCINOMA

Junbing Chen [1,2], Yunfan Sun [1], Jia Fan [1], Jian Zhou [1]

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Introduction: Hepatocellular carcinoma (HCC) is hallmarked by high rates of multi-organ recurrence and distant metastasis, which are the primary causes of treatment failure and poor prognosis. The immune microenvironment of metastatic lesions exhibits striking organ-specific spatiotemporal heterogeneity, yet its regulatory mechanisms and tailored therapeutic strategies remain largely undefined. Here, we aimed to establish a robust immune microenvironment classification for HCC metastases, decode organ-specific immune escape mechanisms, and develop precision intervention approaches.

Methods: We constructed a large-scale HCC primary-recurrence-metastasis cohort (189 patients, 626 samples) with integrated multi-omics data, including single-cell multi-omics, spatial multi-omics, bulk omics, and digital pathology. A spatial graph convolutional neural network model (spoGNN) was developed to define microenvironment subtypes. We performed multi-omics profiling, cell trajectory analysis, cell–cell communication inference, and in vivo or ex vivo preclinical experiments to dissect mechanisms and validate therapeutic strategies for lymph node, peritoneal, and distant organ metastases.

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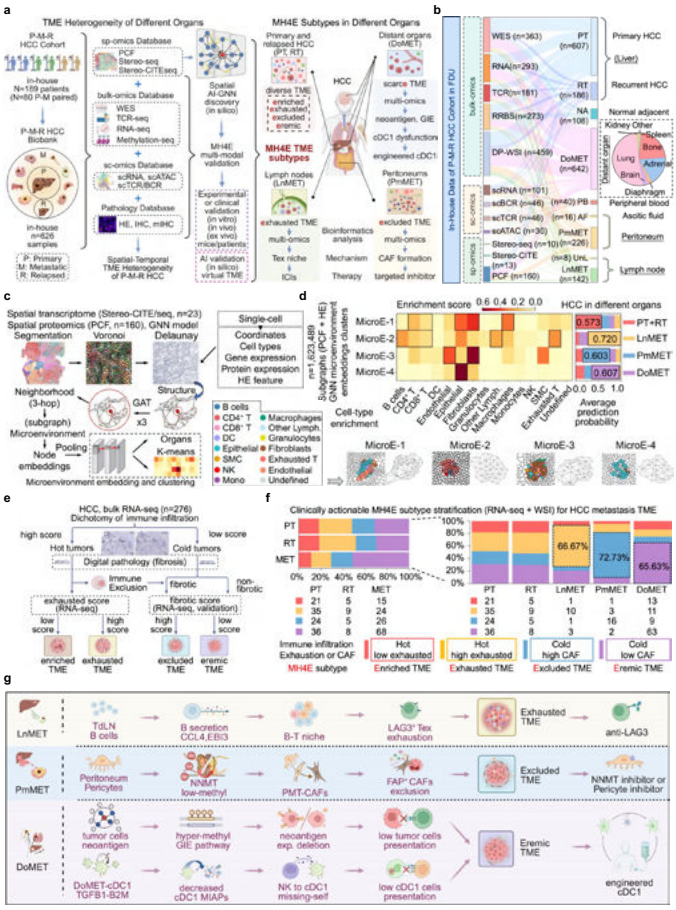
Results: We first established the MH4E immune microenvironment classification (enriched, exhausted, excluded, eremic) and revealed strict organ-specific distribution: lymph node metastases were dominated by the exhausted subtype (66.67%), peritoneal metastases by the excluded subtype (72.23%), and distant organ metastases (lung, bone, adrenal) by the eremic subtype (65.63%). Mechanistically, In lymph node metastases, B cells recruit T cells via the CCL4–CCR5 axis and activate STAT3 to upregulate LAG3, forming an exhausted B–T cell niche. In peritoneal metastases, NNMT drives pericyte-to-cancer-associated fibroblast trans-differentiation via metabolic–epigenetic remodeling, creating a physical stromal barrier that excludes immune cells. In distant metastases, tumor cell immunogenomic alterations and cDC1 B2M dysfunction synergistically disrupt antigen presentation, leading to an immune-desert phenotype. Preclinically, anti-LAG3 therapy sensitized lymph node metastases to anti-PD-1; NNMT inhibition overcame peritoneal immune exclusion; and B2M-engineered cDC1 cell therapy reversed immune desert in distant metastases.

Conclusion: The MH4E classification systematically defines the spatiotemporal heterogeneity of HCC organ-specific metastases. Organ-specific mechanisms underpin distinct immune escape programs, enabling precision therapy tailored to metastatic sites. These findings shift HCC treatment toward an organ-metastasis-based precision medicine paradigm.

Disclosure of Interest: N/A

Image:



O-07 A SINGLE-CELL HCC ATLAS REVEALS CAF-DRIVEN RESISTANCE TO ATEZOLIZUMAB PLUS BEVACIZUMAB

Guillem Cano-Segarra[1], Ana H de Sande[1], Albert Gris-Oliver[1], Ezequiel Mauro[1], Marta Piqué-Gili[1], Judit Peix[1], Júlia Huguet-Pradell[1,2], David Camell-Raventos[1,2], Anna Vila-Escoda[1,2], Carla Montironi[1,3], Agavni Mesropian[1], Ugne Balaseviciute[1], Tiago de Castro[2], Marcus Zeitlhoefler[2], Sarah Cappuyns[4], Jeroen Dekervel[5], Daniela Sia[2], Roser Pinyol[1] and Josep M. Llovet[1,2,6].

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Introduction: Cancer-associated fibroblasts (CAFs) promote tumor survival through modulating the tumor microenvironment, yet their relevance in hepatocellular carcinoma (HCC) progression and role in response to immunotherapies remain poorly defined. Here, we characterized CAFs in HCC and assessed their implication into atezolizumab+bevacizumab (atezo+bev) treatment response.

Methods: Seven single-cell RNA sequencing (scRNA-seq) datasets encompassing 197 HCCs (422,561 cells) were integrated to resolve CAF transcriptional states. Single-cell subtype-specific gene signatures were generated and used to deconvolute CAF composition in 837 HCC cases (532 early and 305 advanced). Associations with molecular and immune HCC subclasses were evaluated. Differential gene expression analysis and LASSO regression were applied to bulk RNA-seq data (n=247) to derive a CAF-based atezo+bev non-response signature (CAF-NR), and its prognosis and predictive capacity was evaluated in both the IMbrave150 trial (n=177) and phase Ib GO30140 (n=128).

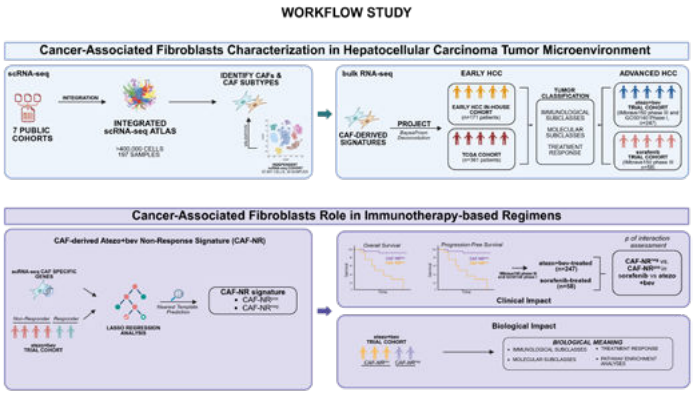
Results: Integrative scRNA-seq analysis revealed that CAFs account for 2–10% of HCC tumor cells and defined 5 transcriptionally distinct subtypes, including a novel previously unrecognized endothelial-like CAF population. Through single-cell CAF-specific signatures, the iMyo/POSTN CAF subtype, characterized by extracellular matrix remodeling, was shown to be the most prevalent subtype in both early (38%) and advanced (82%) HCC. The 16-gene CAF-NR signature demonstrated specificity in atezo+bev compared with sorafenib (interaction p=0.0015).

Furthermore, CAF-NR retained independent predictive value relative to previously reported atezo+bev-response signatures (OR 4.26, 95% CI 2.45-7.58; p<0.001). CAF-NR tumors (60%) were associated with immune exclusion and metabolic dysfunction and IGF2 overexpression.

Conclusion: By creating a scRNA-seq HCC atlas we identified 5 distinct CAF subtypes. CAFs contributed to atezo+bev refractoriness by establishing an immune excluded, metabolically dysfunctional niche and IGF2 overexpression.

Disclosure of Interest: N/A

Image:



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O-08 TITLE: CIRCULATING EXTRACELLULAR VESICLES CAPTURE LIVER DISEASE PROGRESSION AND PREDICT IMMUNOTHERAPY RESPONSE IN HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) is associated with poor prognosis due to late diagnosis and heterogeneous response to systemic therapies, including immunotherapy. Identifying biomarkers enabling both patient stratification and prediction of immunotherapy response remains a major unmet need. Circulating extracellular vesicles (EVs), key components of the tumor circulome, represent a promising source of liquid biopsy biomarkers. This study aimed to assess whether circulating EVs reflect liver disease progression and predict immunotherapy response.

Methods: In a prospective cohort of approximately 130 patients with cirrhosis, HCC, and healthy controls, EVs were isolated from plasma by size-exclusion chromatography, yielding EV preparations depleted of soluble proteins and lipoproteins. EVs were characterized by nanoparticle tracking analysis, Western blot, ELISA, and multiplex flow cytometry. Associations between EV-associated protein expression, disease stage, and immunotherapy response were evaluated.

Results: Nanoparticle tracking analysis showed that neither EV concentration nor size distribution differed between groups, indicating alterations in EV composition rather than quantity. Analysis of EV surface markers revealed a progressive remodeling of EV surface protein composition across liver disease stages. Tumor- and angiogenesis-associated proteins (CD142, SSEA-4, CD146, EpCAM) were enriched in HCC, while immune-related markers (CD4, CD8, CD69, CD19) highlighted tumor–immune interactions. Several markers were already elevated in cirrhotic patients, indicating early alterations of the circulating vesicle compartment. PD-L1 and CTLA-4, both therapeutic targets of immune checkpoint inhibitors in HCC, were detectable in plasma; however, only their EV-associated levels discriminated patient groups, underscoring the superior biological relevance of EV-based profiling. Importantly, preliminary analyses suggested that CD24, an emerging immune checkpoint involved in tumor immune evasion, was the only biomarker significantly associated with response to immunotherapy, with lower levels in responders.

Conclusion: These findings reveal that circulating EVs capture early and progressive alterations of the tumor microenvironment and provide clinically relevant biomarkers for both disease stratification and prediction of immunotherapy response in HCC.

Disclosure of Interest: N/A

O-09 ATF4 REGULATES EXTRACELLULAR AMINO ACID COMPOSITION, AND ITS LOSS ENHANCES THE ANTITUMOR RESPONSE IN HEPATOCELLULAR CARCINOMA.

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Introduction: Hepatocellular carcinoma (HCC) is a highly lethal cancer, characterized by a highly immunosuppressive tumor microenvironment (TME) that inherently limits the efficacy of immune checkpoint blockade, with only one third of patients currently responding to treatment. Tumor adaptation to this hostile environment is impacted by the unfolded protein response (UPR) and integrated stress response (ISR). The transcription factor ATF4 it is the mainstream regulator of metabolic and redox homeostasis downstream of UPR and ISR; however, its specific contribution to HCC immunogenicity remains poorly defined. This study investigates the mechanistic role of ATF4 in orchestrating metabolic-driven immune evasion and therapeutic resistance in HCC.

Methods: We integrated transcriptomic data from human primary HCC cohorts (TCGA-LIHC, ICGC-LIRI-JP, OEP000321) to map UPR effector signatures (ATF4, ATF6, XBP1). CRISPR/Cas9-engineered Atf4, Atf6, and Xbp1 knockout (KO) murine HCC models were created and profiled using RNA-seq. ATF4 impact in amino acid metabolism intra and extracellularly was studied with UHPLC. The immunological impact of ATF4 was assessed via in vitro macrophage differentiation/polarization flow cytometry assays and in vivo syngeneic models to evaluate tumor kinetics, TME composition, and response to systemic anti-VEGFA and anti-PD1 therapies.

Results:Clinical multi-cohort analysis revealed that activated ATF4 and XBP1 signatures predict highly proliferative, dedifferentiated tumors, vascular invasion, and poor overall survival. These signatures were consistent across mutational backgrounds and predominantly enriched in tumor cells. In vivo, ATF4 was essential for tumor growth in an immune-dependent manner (effect lost in immunodeficient models). Atf4-KO tumors underwent dramatic TME remodeling, becoming highly inflamed with robust $CD4^+/CD8^+$ T lymphocyte infiltration and significantly reduced immunosuppressive macrophage and myeloid populations. Mechanistically, ATF4 coordinates a vast stress-adaptive rewiring, driving amino acid transport, selective translation, and mitochondrial maintenance. In Myc/ß-catenin models, Atf4 deletion profoundly altered the extracellular amino acid composition, notably depleting proline and serine. Crucially, ATF4-KO conditioned media failed to support M2 macrophage polarization—a defect functionally rescued by exogenous proline and VEGFA supplementation. Therapeutically, Atf4 ablation potently sensitized previously refractory tumors to anti-VEGFA and anti-PD1 blockade, markedly improving tumor control and survival.

Conclusion: ATF4 acts as a central regulator of metabolic adaptation and immune evasion in HCC, promoting an immunosuppressive tumor microenvironment by modulating amino acid metabolism and macrophage function. Its role in metabolic reprogramming, selective translation, and nutrient availability positions it as a critical node in the tumor-immunity interaction. Inhibition of ATF4 not only limits tumor growth but also sensitizes the tumor to immunotherapy. Taken together, these findings identify ATF4 and the UPR as promising therapeutic vulnerabilities in HCC.

Disclosure of Interest: N/A

O-10 TGFß INHIBITOR (ANTI-GARP) RESTORES ANTI-TUMOR IMMUNITY AND PROLONGS SURVIVAL IN EXPERIMENTAL MASH-HCC RESISTANT TO ANTI-PDL1+ANTI-VEGFA THERAPY

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Background and Aims: Atezolizumab (anti-PDL1) plus bevacizumab (anti-VEGFA) (atezo+bev) is one first-line standard-of-care (SOC) treatment for advanced hepatocellular carcinoma (aHCC) with ~30% objective responses. Clinical benefit is hindered in non-viral HCC, including metabolic dysfunction-associated steatohepatitis (MASH)-related cases. MASH-HCC tumors are enriched in TGFß signaling, which has been associated with resistance to atezo+bev in tumors with an immune dessert tumor microenvironment. The TGFß–anchoring receptor GARP controls the bioavailability and the immunosuppressive effect of the TGFß1. Hence, we hypothesized that GARP blockade might revert immune suppression and overcome resistance to anti-PDL1+anti-VEGFA (SOC) in MASH-HCC.

Method: GARP expression was evaluated in one single-cell RNAseq dataset (n=38) and three bulk RNAseq datasets of early HCC (n=399) and atezo+bev-treated aHCC (n=253) patients. For in vivo experiments, we used an immunogenetic MASH-HCC mouse model of diet-induced steatohepatitis with MYC and CTNNB1 overexpression, shown to drive atezo+bev resistance. After tumor onset, mice were treated with SOC+anti-GARP, SOC alone, anti-GARP alone or placebo. Spectral cytometry and immunohistochemical analysis of αSMA in tumor samples, along with measurement of serum TGF-ß levels by enzyme-linked immunosorbent assay, were performed on day 14 (n=5 per arm). Remaining animals were followed for overall survival (OS) analysis (n=7/arm).

Results: GARP overexpression (fold-change >1.5) was a marked trait of resistance to atezo+bev ($p=0.04$), with 100% of GARPhigh patients being non-responders, and representing 11% (n=13/123) of all non-responders within non-inflamed tumors. GARP expression positively correlated with TGFß signaling across three independent cohorts ($p<0.001$, GARP expression was 2-fold change higher in TGFß positive vs rest). Further, scRNAseq analysis revealed that GARP was predominantly expressed in cancer-associated fibroblasts (CAFs, $p<0.001$). In mice, both anti-GARP alone and SOC+anti-GARP significantly extended OS compared to placebo (median of 35 and 25 vs 18 days since treatment start, $p=0.038$ and $p=0.048$), as opposed to SOC alone ($p=0.2$).

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Mechanistically, treatment with anti-GARP reduced CAF activation (αSMA positivity, anti-GARP containing vs non-anti-GARP arms, p=0.04), together with a systemic decrease in the active-to-total TGFß ratio (anti-GARP containing vs non-anti-GARP arms, p=0.05). Specifically, compared to placebo, SOC+anti-GARP induced a shift from central memory (CD62L+CD127+) to tumor-resident (CD62L-CD69+) CD8+ T cells (p=0.03) accompanied by a total T cell increase (from 7% to 16%, p<0.05), including both CD8+ (p=0.003) and CD4+ (p=0.02) T cells, suggesting a partial rescue of the tumor immunosurveillance. Accordingly, tumors from SOC+anti-GARP-treated mice presented increased infiltration of both effector (CD44+PD1+TIM3-) (p=0.04) and exhausted (PD1+TIM3+) CD8+ T cells (p=0.007). Among CD4+ T cells, SOC+anti-GARP also increased antigen-experienced CD44+ (p=0.04) cells. None of these immune modulations were observed with SOC alone and anti-GARP monotherapy.

Conclusions: TGFß signaling and GARP expression is associated with primary resistance to atezo+bev. In an immunotherapy resistant murine model of MASH-HCC, GARP inhibition enhances antitumoral immunity, extends OS and appears as a promising therapeutic target in atezo+bev refractoriness.

Disclosure of Interest: N/A

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General Session 3 - Therapy & Miscellaneous

O-11 INTERLEUKIN 15–ARMORED GPC3 CAR T CELLS FOR PATIENTS WITH SOLID CANCERS

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Background: Chimeric antigen receptor (CAR) T cell therapy has shown high efficacy in hematologic malignancies but limited success in solid tumors, partly due to inhibitory tumor microenvironments and insufficient cytokine support. Glypican 3 (GPC3) is selectively expressed in multiple solid tumors, including hepatocellular carcinoma, and represents a rational immunotherapy target. Interleukin 15 (IL 15) enhances T cell persistence and metabolic fitness. This study evaluated whether IL 15 co expression improves the expansion, intratumoral survival, and antitumor activity of GPC3 CAR T cells (15.CAR) in humans.

Methods: In four phase I trials (GAP, GLYCAR, AGAR, CATCH), 24 patients with relapsed/refractory GPC3 positive solid tumors, including hepatoblastoma and hepatocellular carcinoma, received lymphodepletion with cyclophosphamide and fludarabine followed by GPC3 CAR T cells with or without IL 15 co expression at two dose levels. Safety was monitored through Day 28. Tumor response was assessed by RECIST v1.1 and serum α fetoprotein (AFP). CAR T cell expansion was quantified by qPCR and flow cytometry. Functional and transcriptional characteristics of infusion products and post infusion CAR T cells were analyzed via single cell RNA seq, multiparameter flow cytometry, cytotoxicity assays, and single cell cytokine profiling. An inducible caspase 9 (iC9) safety switch was available for toxicity management.

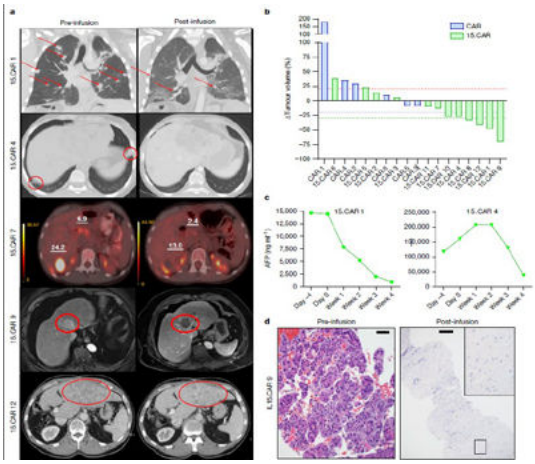
Results: GPC3 CAR alone produced no objective responses (0/6 at DL2) with stable disease in three patients. In contrast, 15.CAR treatment achieved a disease control rate of 66.7% (8/12) and an objective response rate of 33.3% (4/12), including marked radiographic tumor reductions and biopsy confirmed extensive tumor necrosis. Two responders with AFP secreting tumors exhibited substantial AFP declines. Peripheral expansion was significantly higher with 15.CAR, especially in responders. Cytokine release syndrome (CRS) was more frequent with 15.CAR but manageable with IL 1/IL 6 blockade; iC9 activation rapidly reversed severe CRS in three patients. Tumor infiltrating 15.CAR T cells from responders demonstrated upregulation of AP 1 (FOS/JUN) and type I interferon signaling and repression of SWI/SNF chromatin remodeling components, correlating with improved intratumoral function and persistence.

Conclusions: IL 15 armored GPC3 CAR T cells are safe, demonstrate enhanced expansion, and produce meaningful antitumor responses in patients with GPC3 positive solid tumors. Distinct transcriptional programs—including AP 1 activation and SWI/SNF repression—in responder tumor infiltrating T cells identify potential biomarkers and therapeutic targets to further optimize CAR T cell efficacy in solid cancers.

Abbreviations (Required by AACR): AFP, α fetoprotein; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DL, dose level; GPC3, glypican 3; iC9, inducible caspase 9; IL 15, interleukin 15; RECIST, Response Evaluation Criteria in Solid Tumors;

Disclosure of Interest: N/A

Image:



a–d, Antitumor responses were determined by comparison of pre- and post-infusion three-dimensional imaging. a, Coronal computed tomography (CT) images of chest (15.CAR 1), axial CT chest (no. 15.CAR 4), PET–CT (15.CAR 7), MRI abdomen (15.CAR 9) and axial CT abdomen (15.CAR 12) showing pre- and post-CAR T cell infusion. Red arrows and circles represent tumors. Numbers represent standardized uptake values of tumors in the liver shown by PET. b, Waterfall plot representing changes in tumor volumes of patients treated with 3 × 10[7] m−2 CAR

O-12 TACROLIMUS-RESISTANT, TCR-DEFICIENT, GPC3-SPECIFIC CAR T CELLS FOR SAFE AND EFFECTIVE TREATMENT OF HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION

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Background: Liver transplantation is a curative treatment for early-stage hepatocellular carcinoma (HCC), while immunotherapy remains the first-line therapy for advanced disease. However, managing recurrent HCC after liver transplantation poses a significant therapeutic challenge, as immune checkpoint inhibitors are contraindicated due to the high risk of allograft rejection. Tumor-specific chimeric antigen receptor (CAR) T cells targeting glypican-3 (GPC3) offer a promising alternative strategy. Here, we describe a CAR T cell platform designed for post-transplant application, featuring CRISPR/Cas9-mediated knockout of the FK506-binding protein 12 (FKBP12) locus to confer tacrolimus-resistance and maintain CAR T cell function under continuous immunosuppression. Concurrent disruption of the TRAC locus eliminates T cell receptor (TCR) expression, reducing the risk of allograft rejection mediated by the endogenous TCR of these tacrolimus resistant CAR T cells.

Methods: Resting human T cells were electroporated with a ribonucleoprotein (RNP) complex composed of a 1:1 mixture of single-guide RNAs targeting FKBP12 and TRAC, pre-incubated with recombinant high-fidelity Cas9 protein. Following electroporation, cells were expanded in culture with CD3/CD28 beads and supplemented with IL-2, IL-7, and IL-15 and transduced with a second-generation anti-GPC3-CAR. Engineered T cells were validated and analyzed by genomic sequencing, flow cytometry, cytotoxicity assays using HCC cell lines, and antigen-specific stimulation assays.

Results: Knockout efficiencies for TRAC and FKBP12 following electroporation ranged from 70-90%, as determined by flow cytometry and genomic sequencing, respectively. TCR-negative CAR T cells were enriched to high purity (> 99%) using conventional Magnetic-Activated Cell Sorting for CD3-negative cells. Upon GPC3-specific antigen stimulation, tacrolimus significantly inhibited interferon-gamma (IFN-γ) production in wildtype (WT) CAR T cells, but not in FKBP12 knockout (KO) cells (169.6 pg/ml vs. 9903 pg/ml, $p = 0.0035$). The cytotoxic activity of WT CAR T cells co-cultured with Hep3B (1.49% vs. 54.03%, $p < 0.0001$) and HepG2 (23.35% vs. 92.30%, $p < 0.0001$) tumor cells was markedly reduced in the presence of tacrolimus, whereas KO CAR T cells maintained a robust killing capacity under the same conditions.

Conclusion: This dual-edited CAR T cell platform offers a safe and effective approach for the development of cellular immunotherapy for recurrent HCC in the post-transplant setting while continuing tacrolimus-based immunosuppression.

Disclosure of Interest: N/A

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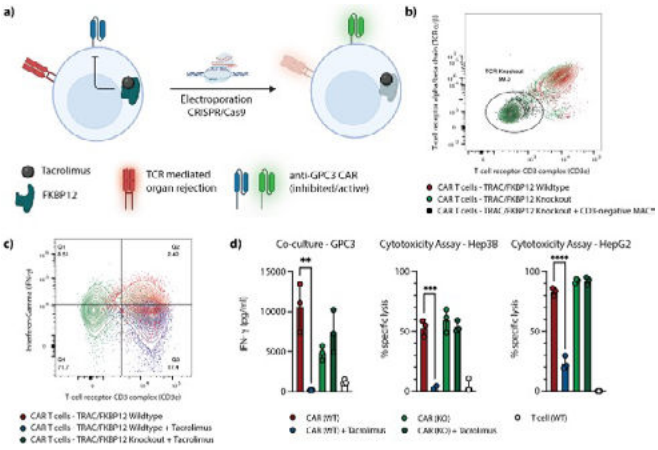

O-13 A PHASE II TRIAL OF SINTILIMAB PLUS ANLOTINIB IN ADVANCED ICC: EFFICACY, SAFETY, AND SINGLE-CELL INSIGHTS INTO TUMOR ECOSYSTEM REMODELING

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Background: Chemotherapy-free PD-1/TKI strategies in unresectable intrahepatic cholangiocarcinoma (ICC) remain investigational, and the biological determinants of response are poorly understood. We conducted a prospective phase II study of sintilimab plus anlotinib and integrated clinical outcomes with baseline single-cell RNA sequencing (scRNA-seq).

Methods: In this single-center, open-label, single-arm phase II study (ChiCTR2000035901), patients with pathologically confirmed unresectable ICC received sintilimab 200 mg on day 1 plus anlotinib 12 mg on days 1-14 every 21 days. Thirty patients with pathologically confirmed unresectable ICC received sintilimab (200 mg, intravenously, day 1) plus anlotinib (12 mg, orally, days 1-14) every 21 days. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), conversion-to-surgery rate, duration of response (DoR), and treatment-related adverse events (TRAEs). Baseline tumor biopsies were analyzed by scRNA-seq.

Results: At a median follow-up of 23.8 months (95% CI, 16.5-38.0), the ORR was 40.0% (12/30; 95% CI, 22.7-59.4), with a DCR of 80.0% (24/30; 95% CI, 61.4-92.3). Seven patients (23.3%) underwent conversion surgery, all achieving R0 resection; two achieved pathological complete response and two major pathological responses. Median OS and PFS were 18.3 months and 8.2 months, respectively, and were markedly prolonged in responders. Median DoR was 10.9 months. TRAEs occurred in 80.0% of patients, with grade 3 events in 20.0% and no grade 4-5 toxicity. scRNA-seq revealed distinct ecosystem features associated with clinical outcomes: responders harbored proliferative and immunogenic tumor cells with activation of anlotinib-targeted cell-cycle pathways, alongside enriched cytotoxic and proliferative CD8+ Tex_MKI67 cells. In contrast, non-responders showed enrichment of CXCL12+ and GALECTIN9+ endothelial cells that constrained CD8+ T-cell activity.

Conclusion: Sintilimab plus anlotinib demonstrated promising efficacy and a favourable safety profile as a first-line, chemotherapy-free treatment for unresectable ICC. Baseline tumor ecosystems characterized by proliferative and immunogenic tumor cells, cytotoxic CD8+ T cells, and endothelial-mediated immunosuppression were associated with clinical benefit and may help identify response-associated tumor ecosystem states.

Disclosure of Interest: N/A

O-14 HEPATOBILIARY MULTIDISCIPLINARY TUMOR BOARD CHANGES DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH FOCAL LIVER LESIONS

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Introduction: Hepatobiliary cancers are a leading cause of cancer-related mortality in the United States (1). In 2020, liver cancer was ranked among the top three causes of cancer death across 46 countries, suggestive of a significant global disease burden (2). These tumors range widely in their clinical presentation, radiologic diagnosis and surgical management, making them challenging to manage independently. Accordingly, a multidisciplinary approach involving hepatologists, surgeons, oncologists, and radiologists can be useful in ensuring patients receive appropriate care. At the University of Chicago, this approach has been formalized through a hepatobiliary multidisciplinary tumor board (MDTB) that occurs weekly to discuss complex malignant and benign cases. The purpose of this study was to investigate demographics, recommendations, and outcomes from MDTB to determine their utility in impacting care of patients with hepatobiliary lesions.

Methods: This was a retrospective, descriptive analysis of data from 2017-2020. Data included demographics, diagnoses, recommendations, and outcomes of subjects discussed during MDTB. Data were entered into a REDCap database and analyzed via Microsoft Excel (v16.76) and R software (v2025.05.0+496).

Results : In total, 940 subjects were included in this analysis. Hepatocellular carcinoma (HCC) was the most common liver lesion for which subjects were referred to MDTB (46%), most often due to chronic viral hepatitis (61%). After case discussion at MDTB, 31% of subjects had their diagnosis changed; 18% had their diagnosis changed from malignant to non-malignant, 7% had their diagnosis changed from non-malignant to malignant, and 6% had non-malignant mass management changed due to further characterization. Of those subjects whose diagnoses were changed from non-malignant to malignant, 66% were found to have new HCC. As a result of MDTB, 22% of subjects overall were recommended to undergo further procedures including surgical resection, radioembolization, and liver transplantation. Among those recommended for procedures, TARE was most commonly suggested (64%). In total, 12% of subjects avoided unnecessary next steps following discussion in MDTB, including unnecessary procedures (4%), biopsies (3%), treatment (3%), and imaging (2%). Those subjects whose diagnoses were changed from malignant to non-malignant were most likely to avoid unnecessary next steps (17%, p= 0.002). MDTB recommendations largely were in accordance with AASLD guidelines (89%), most regularly at level 2 AASLD level of evidence (87%).

Conclusion: Our longitudinal findings suggest the importance of MDTB not only in identifying malignancies that otherwise were misdiagnosed as benign, but also in reassuring patients of benign disease to prevent further unnecessary surveillance imaging or procedures. MDTB decreased unnecessary next steps including procedures, biopsies, treatment, and imaging. MDTB also identified patients who needed further management of malignant lesions previously deemed benign. This approach led to increased appropriate diagnoses and reduced patient burden of unnecessary testing including decreased additional costs, travel, and emotional distress from an incorrect malignancy diagnosis. MDTB is a valuable tool that positively impacts diagnosis and management of patients with hepatobiliary tumors.

1. SEER Cancer Statistics Factsheets:Common Cancer Sites. National Cancer Institute. Bethesda, MD
2. Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. J Hepatol. 2022;77(6):1598-1606

Disclosure of Interest: N/A

Images:

Table 1: Demographics and underlying tumors of patients evaluated at hepatobiliary multidisciplinary tumor board.

Sex	
Female	437
Male	500
Unknown	3
Race	
American Indian or Native Alaskan	2
Asian, Mideast Indian	73
Black, African American	218
More than once race	25
Native Hawaiian/Other Pacific Islander	4
Patient declined	9
Unknown	56
White	553
Ethnicity	
Hispanic or Latino	96
Not Hispanic or Latino	805
Patient Declined	7
Unknown	32
Characterization of tumor	
Benign bile duct/gallbladder lesions	22
Benign liver lesions	127
Bile duct/gallbladder cancers	121
Colorectal cancer liver metastases	17
Hepatocellular carcinoma	429
Neuroendocrine liver metastases	1
Other pathology	215
Other primary liver malignancy	8

Oral Communications

Saturday, 5 September 2026

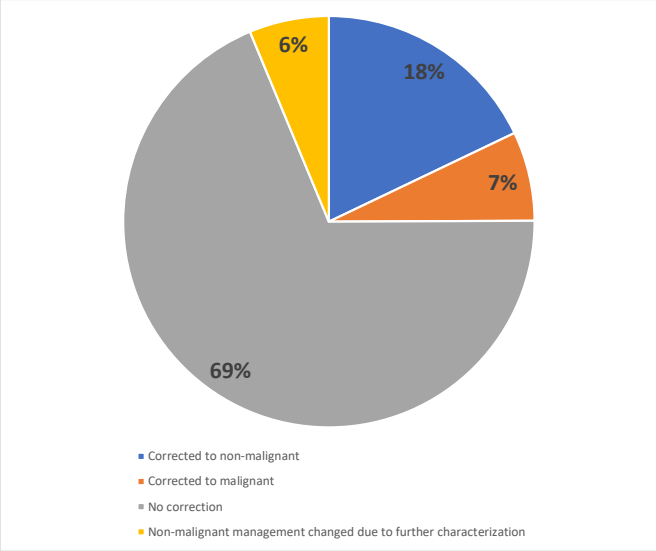

Figure 1: Changes in tumor diagnosis following hepatobiliary multidisciplinary tumor board discussion.

O-15 TUMOR-AGNOSTIC CTDNA METHYLATION PROFILING ENABLES PREOPERATIVE RISK STRATIFICATION AND PATHOLOGICAL RESPONSE ASSESSMENT IN HEPATOCELLULAR CARCINOMA

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Introduction: Clinical management of hepatocellular carcinoma (HCC) is becoming increasingly complex, encompassing curative resection for early-stage disease and multimodal treatment strategies across disease stages. However, preoperative risk stratification and timely evaluation of treatment response remain challenging due to the lack of reliable blood-based tools. Tumor-agnostic circulating tumor DNA (ctDNA) methylation profiling may help address these unmet clinical needs by enabling real-time, noninvasive assessment of tumor biology and therapeutic efficacy.

Methods: We prospectively enrolled 211 HCC patients undergoing curative hepatectomy and collected plasma samples within 24 hours prior to surgery (Ts). In parallel, an independent neoadjuvant therapy cohort of 27 HCC patients treated with immune checkpoint inhibitor-based systemic therapy was included, in which plasma samples were obtained at baseline before treatment initiation (Tb) and prior to surgery (Ts). All plasma samples were analyzed using the GutSeer. A tumor-agnostic machine learning model was developed based on 342 HCC patients and 1,415 healthy individuals to generate a methylation-based cancer score (MCS) for prognostic stratification and pathological response assessment.

Results: The hepatectomy cohort was followed for a median of 25.6 months with 58 recurrences. Preoperative Ts MCS was significantly associated with advanced tumor stage, larger tumor size, and vascular invasion, indicating its ability to reflect tumor burden and underlying biological aggressiveness. Based on Ts MCS, patients were stratified into low-risk (n = 52) and high-risk (n = 159) groups, yielding a hazard ratio (HR) of 11.36 (95%CI: 2.77–46.56; $p < 0.001$) and a negative predictive value of 96.2%. Multivariate analysis confirmed Ts MCS as an independent predictor of recurrence (HR = 6.86, 95%CI: 1.63-28.96; $p = 0.009$).

In the neoadjuvant therapy cohort, MCS decreased significantly from Tb to Ts ($p < 0.001$). The change of MCS (Tb-Ts) was strongly negatively correlated with the proportion of residual viable tumor ($R = -0.70$, $p < 0.001$), indicating MCS changes closely mirror pathological response. Consistently, MCS change accurately discriminated major pathological response (MPR, ≤50% viable tumor cells) from non-MPR (AUC = 0.859), outperforming changes of alpha-fetoprotein (AUC = 0.724) and des-gamma-carboxy prothrombin (AUC = 0.682).

Conclusion: This study demonstrates that tumor-agnostic ctDNA methylation profiling enables effective preoperative risk stratification in resectable HCC. Furthermore, dynamic changes in MCS provide a precise, noninvasive biomarker for assessing pathological response to systemic therapy. These findings highlight the broad clinical utility of methylation-based liquid biopsy approaches across surgical and systemic treatment settings in HCC.

Disclosure of Interest: N/A

Top-Scored Poster Basic-Translational

Friday 4 September from 10:30 to 11:00 am

P-001 AN IMMUNE-RELATED PATHOLOGIC RESPONSE SCORE PREDICTS SURVIVAL AFTER IMMUNE CHECKPOINT INHIBITOR–BASED CONVERSION THERAPY IN HEPATOCELLULAR CARCINOMA

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Introduction: Immune checkpoint inhibitor (ICI) based conversion therapy (NAT) is increasingly utilized in the management of initially unresectable hepatocellular carcinoma (HCC). However, the clinical significance of immune-related pathologic response (irPR) features remain poorly understood in HCC.

Methods: A total of 217 HCC patients who received ICI-based conversion therapy (ICT) followed by curative-intent resection were enrolled and randomly assigned to a discovery cohort and a validation cohort at 2:1 ratio. 13 irPR features, including tumor infiltrating lymphocyte (TILs), tertiary lymphoid structures, lymphoid aggregates, plasma cell infiltration, granulomas, neutrophils, foamy macrophages, cholesterol clefts, hemosiderin-laden macrophages, giant cells, neovascularization, and mature fibrosis, were comprehensively evaluated on routinely processed hematoxylin-eosin stained tumor bed sections from post-ICT surgical specimens. Kaplan-Meier and Cox regression analyses were further performed. To explore differences in the tumor microenvironment, bulk mRNA sequencing was performed on FFPE samples from patients in the discovery cohort. Bioinformatics and statistical analyses were conducted using R version 4.4.1, with the Wilcox test applied for group comparisons.

Results: In discovery cohort, four irPR features (TILs, lymphoid aggregates, neutrophils, and foamy macrophages) demonstrating significant associations with overall survival (OS) in univariable Cox regression analysis ($p<0.05$) were subsequently selected for construction of the immunotherapeutic response score (ITRS). Patients were stratified according to ITRS into ITRSlow (scores 0-1) and ITRShigh (scores 2-4). ITRSlow patients had significantly improved OS (HR=4.17; 95%CI: 1.64-10.60; P=0.003) and relapse-free survival (RFS) (HR=2.07; 95%CI: 1.32-3.23; P=0.001), with median RFS of 32.33 vs.8.53 months compared with ITRShigh patients. On multivariable analysis, ITRS remained independently associated with OS (HR=2.81; 95%CI: 1.06-7.43; P=0.038) and RFS (HR=2.10; 95%CI: 1.32-3.33; P=0.002). These findings were further confirmed in the validation cohort.

Transcriptomic profiling of FFPE tumors (n=41) revealed a markedly immune-inflamed phenotype in ITRSlow tumors, with enrichment of immune-related GO/KEGG pathways. Immune deconvolution analyses demonstrated globally increased immune and stromal infiltration in ITRSlow tumors supported by higher ESTIMATE immune and stromal scores and lower tumor purity (all $P<0.001$). Hierarchical clustering classified tumors into "hot" and "cold"immune states, with a substantially higher proportion of "hot" tumors in the ITRSlow group (65.4% vs. 13.3%, Fisher's exact P=0.003). CD8+ T-cell infiltration was consistently elevated in ITRSlow tumors across MCPcounter, CIBERSORT, and TIMER (all $P<0.05$). Functionally, ITRSlow tumors exhibited enhanced antigen presentation (increased MHC-II and related gene-sets, $P<0.05$), along with heightened CD8+ T-cell activation, cytotoxicity, and exhaustion signatures (all $P<0.05$), indicating a biologically coherent, immune-active microenvironment underlying favorable clinical outcomes.

Conclusion: An irPR feature–based ITRS robustly predicts both OS and RFS in HCC patients following ICT. The ITRS is readily applicable in routine diagnostic pathology practice and provides novel insights into the biological mechanisms underlying immunotherapy resistance.

Disclosure of Interest: N/A

P-002 MOLECULAR PROFILING OF HEPATOCELLULAR NODULES IN VASCULAR LIVER DISEASES REFINES NOSOLOGICAL CLASSIFICATION AND REVEALS A DISTINCT GENOMIC LANDSCAPE

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Introduction: The molecular spectrum of hepatocellular nodules arising in vascular liver diseases (VLD) remains poorly understood. We aimed to characterize their mutational and transcriptomic landscape.

Methods: Hepatocellular nodules were analyzed by using whole genome sequencing and/or whole exome sequencing and RNA sequencing. Pathological diagnoses were classified as certain or uncertain based on original reports (n=63) and a subset of these tumors have been independent reviewed by 3 expert pathologists (n=48/63). A molecular diagnosis was assigned to each lesion based on driver mutations, copy number variation (CNV) and transcriptomic profiles. Control groups included 473 hepatocellular adenomas (HCA) and 385 hepatocellular carcinomas (HCC) arising outside VLD with available molecular datasets.

Results: We included 63 hepatocellular nodules from 47 patients with VLD (median age 38 years; 46.8% of female). Fourteen patients had Budd–Chiari syndrome, 13 had a portosystemic shunt, 13 had porto-sinusoidal vascular disorder, five had chronic portal vein thrombosis in a non-cirrhotic liver, and two had chronic cardiac hepatopathy.

Diagnostic uncertainty affected 30% of nodules on initial pathological report and remained high after expert review (46%), but was reduced to 8% following molecular profiling. Molecular analysis enabled classification into 27 HCC, 30 HCA, 5 regenerative macronodules and 1 hepatic angiosarcoma. Four among the 5 lesions initially diagnosed as FNH-like were reclassified as regenerative macronodules based on the absence of somatic mutations and CNV, and because they clustered with non-tumoral liver tissue without forming a distinct transcriptomic entity. The last lesion diagnosed as FNH-like was reclassified bex3HCA due to a somatic mutation in the exon 3 of CTNNB1.

Compared to HCC arising outside VLD, VLD-associated HCC occurred more frequently in women ($P<0.001$) and at a younger age (P=0.045) and exhibited enrichment of CTNNB1 exon 3 mutations (48% in VLD versus 24% in control, P=0.01), and a lower prevalence of TP53 mutations (4% in VLD versus 33% in control, P=0.003).

Patients with VLD-associated HCA were less frequently female compared with HCA not developed on VLD (39.1% in VLD versus 86.4% in control, $P<0.001$). Among women, those with VLD-associated HCA were less likely to have a history of estrogen-based contraception use (50% in VLD versus 89.4% in control, $P<0.001$). VLD-associated HCA showed overrepresentation of the bex3HCA subtype (34.3% in VLD versus 8.4% in control, $P<0.001$) and fewer inflammatory HCA (11.4% in VLD versus 34.9% in control, P=0.008).

HCA on VLD harbored a high rate of TERT promoter mutations (14.3%) and a high prevalence of borderline lesion between HCA and HCC (31.4%) and evidence of malignant transformation in HCC in 11.4%. Finally, HNF1A-inactivated HCA in VLD (45.7% of all HCA) presented an atypical non-steatotic phenotype driven by suppression of lipogenic pathways in both tumor and adjacent non-tumoral liver at the transcriptomic level.

Top-Scored Poster Basic-Translational

Friday 4 September from 10:30 to 11:00 am

Conclusion: Comprehensive molecular profiling substantially improves classification of hepatocellular nodules in VLD, reduces diagnostic uncertainty, and uncovers a distinct genomic landscape, including CTNNB1 enrichment across tumors types, high malignant transformation rate of HCA, reduced TP53 mutations in HCC and inflammatory subtypes in HCA, and with suppression of lipogenic pathway in HNF1A-inactivated adenomas. These findings support the routine integration of molecular profiling into the diagnostic workup of VLD-associated nodules.

Disclosure of Interest: Honoraria

P-003 ST-SINGLE CELL COMPOSITION OF TERTIARY LYMPHOID STRUCTURES AND PREDICTION OF RESPONSE TO IMMUNOTHERAPY IN HCC

Dylan James Crawshaw [(1)], Guillem Cano-Segarra [(1)], Anna Vila-Escoda [(1,2)], Albert Gris-Oliver [(1)], Carla Montironi [(1,3)], Eduardo Mullen [(4)], Laia González Pérez [(1)], Roser Pinyol [(1)], Ezequiel Mauro [(1)], Josep M Llovet [(1,2,5)]

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Background: Despite advances in immunotherapy for advanced HCC (aHCC), many patients do not benefit, highlighting the need of biomarkers. Tertiary lymphoid structures (TLS) are organized ectopic lymphoid aggregates of immune, stromal, and vascular elements, yet no objective assessment of their average composition and clinical implications has been reported in this setting. We aimed to quantitatively define the cellular composition of intratumoral TLS, develop a spatial transcriptomics-informed TLS gene signature from pre-immunotherapy biopsies, and assess its association with the molecular and immune subclasses of HCC, as well as clinical outcomes and response to immunotherapy.

Methods: Single-cell spatial transcriptomics (ST) was performed on 27 aHCC samples using the Xenium Prime 5,000-gene panel (10x Genomics), customized with 100 additional genes. TLS regions on H&E slides were identified through corroborated pathological reviews. Only TLS regions with high consensus between the two pathologists (n=10) were retained to establish the ground truth TLS set. TLS composition was estimated in the intratumoral TLS (iTLS) from the ST cohort. Differential expression analysis from relevant immune and vascular cell subsets in these TLS was performed to derive a 36-gene TLS signature. Nearest Template Prediction classified aHCC samples as TLS+ or TLS-, categories which were then used to assess associations with molecular and immune subclasses of HCC, and clinical outcomes in patients from the phase Ib & III RCT (GO30140 and IMbrave150 cohorts, n=247 total).

Results: The expert-curated iTLS (n=7) exhibit a total of 17195 cells. These structures consist of 12% B cells (including plasma cells), 22% CD4+ T cells, 6% CD8+ T cells, 4% dendritic cells, and 3% endothelial cells, representing an immune-enriched tissue niche. Our 36-gene TLS signature, with 30 upregulated and 6 downregulated genes, classified 30% of RCTs patients as TLS+ (n=73), 80% (n=58) of which were associated with proliferation/Wnt-TGFb/S1-class tumors and inflamed immune class (p<0.001). Absence of TLS was associated to immune-excluded tumors (p<0.001). TLS+ samples showed significant MET, Notch, and TGFβ-Wnt signaling enrichment compared to TLS- samples (p<0.001). Overall ORR was 33%, but in TLS+ was 50% (OR 2.67, 95%CI 1.46-4.91; p=0.001), with notable enrichment of CD4+ Treg, CD8+ Temra, CD8+ Tex, and cDC1 in this subset (p<0.05). TLS+ patients presented longer PFS compared to TLS- patients (median PFS, 9.5 months vs. 5.9 months; HR 0.66, 95%CI 0.45-0.97; p=0.033), while no significant differences in OS were observed.

Conclusions: By integrating spatial transcriptomics with bulk RNA-seq, we developed a framework to define TLS in aHCC and provide the first quantitative description of their cellular composition. A 36-gene signature identified TLS+ cases, enriched for inflamed tumor classes, and associated with higher ORR and longer PFS under atezo–bev. These findings support TLS as a promising biomarker of immunotherapy benefit in aHCC and provide a foundation for further validation and clinical translation.

Disclosure of Interest: N/A

Image:

	B cells (B cells and plasma cells)	CD4+ T cells	CD8+ T cells	Dendritic cells	Endothelial cells
Percentage (%) of TLS	12.6	22.6	6.6	4.4	3.3
Genes	*MS4A1*, *CD79A*, *IKZF3*, *CXCR4*, *IL10RA*, *RAC2*, *CORO1A*, *CD52*	*TRAC*, *TRBC1*, *TRBC2*, *CD3E*, *CD8A*, *GZMK*, *IL7R*, *SELPLG*, *FOSB*, *KLF2*, *CCL5*, *SP110*		*SOCS3*, *CCL2*, *CCL19*, *IL16*, *LGALS9*, *SIGLEC1*, *PTK2B*	*POSTN*, *THY1*, *CXCL12*, *VTN*, *FGG*, *FGA*, *FGB*, *AMBP*, *SERPINA1*

Table 1: Representative genes of the 36-gene TLS signature of each immune and stromal component of TLS, and iTLS composition. Gene names in red are upregulated, while the ones in blue are downregulated. % expresses the average percentage of these relevant cell fractions across the 7 iTLS analyzed in the ST cohort.

P-004 SPATIALLY RESOLVED DEVELOPMENTAL HIERARCHY AND SUBCLONAL EVOLUTION OF HEPATOBLASTOMA AFTER CHEMOTHERAPY

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Introduction: Hepatoblastoma (HB), the most common pediatric liver cancer, displays marked intra-tumor heterogeneity and cellular plasticity that contribute to chemotherapy resistance and relapse. Single-cell studies have identified a continuum of HB cell states ranging from hepatocytic to liver progenitor phenotypes, but their spatial organization and evolutionary relationships remain poorly understood. We aimed to define the spatial architecture, developmental hierarchy, and drivers of HB cell-state evolution after chemotherapy.

Methods: We performed a retrospective multi-scale analysis of HB samples from French collections. Spatial transcriptomics (Visium) was conducted on 11 post-chemotherapy primary tumors. High-plex sequential immunofluorescence (36-plex SeqIF) was performed on 37 tumor sections from 30 patients (Fig.A). These data were integrated with centralized histopathological review, genomic profiling, and spot-level copy-number inference.

Results: Spatial transcriptomics identified a continuous distribution of tumor cell states between hepatocytic and liver progenitor programs, correlated to fetal and embryonal histology, respectively. Two spatial modes of phenotypic evolution were observed: discrete progenitor-rich nodules delimited by fibrotic stroma, and spatially connected hepatocytic-to-progenitor transitions through intermediate cell states. Copy-number alterations, spatially resolved, revealed a highly branched evolution in post-chemotherapy HB, with subclonal boundaries overlapping nodular architectures and phenotypic domains. Recurrent chromosomal gains were enriched in progenitor-like regions and involved chromosome arms harboring key regulators of liver progenitor transcriptional programs, supporting a direct role for copy-number alterations in stabilizing specific cell identities (Fig.B).

SeqIF resolved 9 HB tumor cell states organized hierarchically in a developmental-like tree, recapitulating the developmental trajectories stemming from the hepatic stem cell along 3 differentiation lineages: hepatocytic, biliary, and epithelio-mesenchymal lineages. These trajectories were not only observed across tumors but also traversed within individual tumors, where neighboring malignant cells occupied successive positions along the same lineage, consistent with ongoing differentiation and de-differentiation dynamics in situ (Fig.C). Proliferative activity was concentrated in stem-like and progenitor states and declined with differentiation, indicating that tumor growth is preferentially sustained by less differentiated compartments. In addition, tumor cell phenotypes showed consistent associations with the composition and organization of the surrounding stromal microenvironment, suggesting that local non-tumoral cues contribute to shaping malignant cell identity. Together, these findings support a model in which HB evolution results from the interaction between plastic developmental trajectories, genetically constrained subclonal expansion, and local stromal architecture.

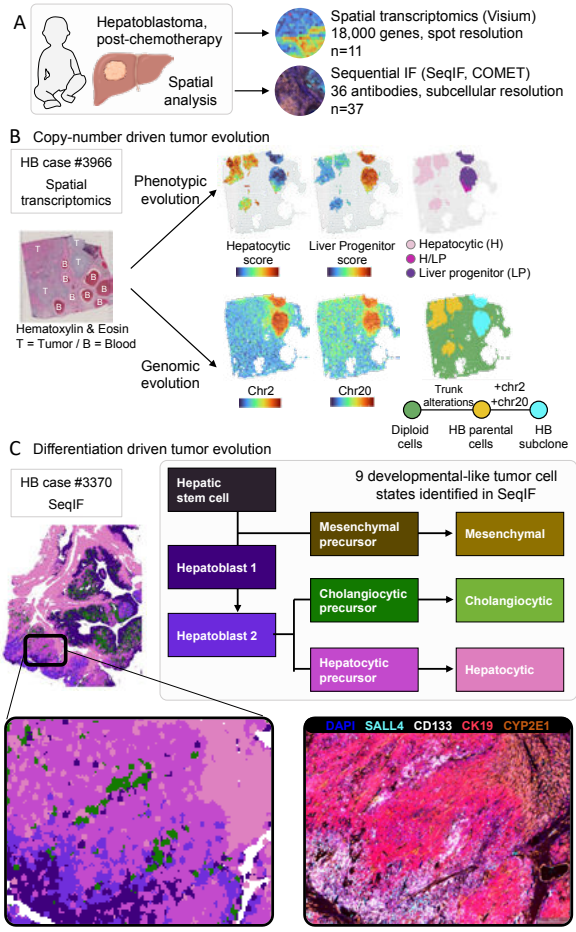
Conclusion: HB intra-tumor heterogeneity is shaped by a developmental-like hierarchy of tumor cell states influenced by genomic alterations, spatial organization, and stromal interactions. Our findings support a model in which spatially constrained cell-state transitions, modulated by the local microenvironment, and genetically defined subclonal expansion jointly drive HB evolution after chemotherapy. This framework may help guide strategies to target chemoresistant cell populations by disrupting lineage transitions or spatially organized supportive niches.

Disclosure of Interest: N/A

Top-Scored Poster Basic-Translational

Friday 4 September from 10:30 to 11:00 am

Images:



P-005 NSUN2-MEDIATED RNA M5C METABOLIC REPROGRAMMING DRIVES NK-CELL IMMUNE EVASION IN HEPATOCELLULAR CARCINOMA

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Introduction: Resistance to immune checkpoint blockade remains a major challenge in hepatocellular carcinoma (HCC). Natural killer (NK) cells are essential mediators of antitumor immunity but frequently exhibit impaired infiltration and cytotoxicity in HCC. Although tumor metabolic reprogramming contributes to immune suppression, the epitranscriptomic mechanisms connecting cancer metabolism with NK-cell dysfunction remain poorly understood. We investigated whether the 5-methylcytosine (m5C) RNA methyltransferase NSUN2 promotes HCC progression by coupling glycolytic reprogramming to NK-cell immune evasion.

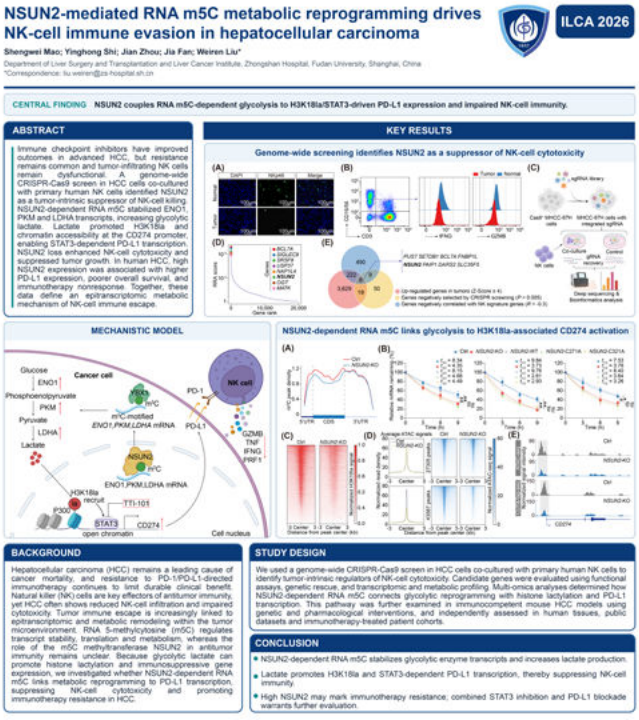
Methods: A genome-wide CRISPR/Cas9 loss-of-function screen was performed in HCC cells co-cultured with primary human NK cells to identify tumor-intrinsic regulators of NK-cell-mediated cytotoxicity. Integrated m5C epitranscriptomic sequencing, RNA sequencing, CUT&Tag, ATAC-seq, ChIP-seq, RNA stability assays and metabolic profiling were used to define the molecular mechanism. NK-cell cytotoxicity, cytokine production and tumor-cell killing were evaluated in vitro. Functional and therapeutic effects were validated using syngeneic subcutaneous and orthotopic HCC models, a spontaneous murine HCC model and an in vivo human NK-cell cytotoxicity model. Clinical relevance was assessed using paired human HCC tissues, TCGA-LIHC, a tissue microarray of 355 patients and an independent cohort of 30 patients receiving anti-PD-1 therapy.

Results: The CRISPR screen identified NSUN2 as a tumor-intrinsic suppressor of NK-cell-mediated cytotoxicity. NSUN2-mediated m5C modification, recognized by YBX1, increased the stability and expression of ENO1, PKM and LDHA transcripts. This enhanced glycolytic flux and lactate production without being attributable solely to changes in tumor-cell proliferation. Lactate accumulation increased histone H3 lysine 18 lactylation (H3K18la), enhanced chromatin accessibility at the CD274 promoter and facilitated STAT3 recruitment, thereby activating PD-L1 transcription. Genetic depletion of NSUN2 or pharmacological inhibition of glycolysis reduced H3K18la and PD-L1 expression, restored NK-cell effector activity and increased tumor-cell killing; exogenous lactate rescued the immunosuppressive phenotype. In immunocompetent mouse models, NSUN2 knockout increased intratumoral NK-cell infiltration and expression of cytotoxic effector molecules while suppressing tumor growth. NK-cell depletion, but not CD8+ T-cell depletion, substantially reversed this antitumor effect, demonstrating a predominant dependence on NK cells. Clinically, NSUN2 was upregulated in HCC and positively correlated with PD-L1 expression in the 355-patient tissue microarray (R=0.39, P<0.001). High NSUN2 expression was associated with reduced NK-cell infiltration, unfavorable survival and non-response to anti-PD-1 therapy. Finally, combining the STAT3 inhibitor TTI-101 with anti-PD-L1 treatment enhanced NK-cell infiltration and cytotoxicity, reduced tumor burden and prolonged survival in orthotopic and spontaneous HCC models.

Conclusion: NSUN2 promotes HCC immune evasion through an m5C–glycolysis–lactate–H3K18la–STAT3–PD-L1 regulatory axis that restricts NK-cell-mediated antitumor immunity. These findings identify NSUN2-dependent metabolic and epigenetic reprogramming as a mechanism of immunotherapy resistance and provide a rationale for combining STAT3 pathway inhibition with immune checkpoint blockade in HCC.

Disclosure of Interest: N/A

Image:



P-006 MIRNAS AS BIOMARKERS OF PLATINUM RESISTANCE IN PATIENTS WITH ADVANCED BILIARY TRACT CANCER UNDERGOING SECOND-LINE FOLFOX: A TRANSLATIONAL ANALYSIS OF THE ABC-06 TRIAL.

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Introduction: The ABC-06 randomized phase 3 trial showed a modest benefit in overall survival (OS) with second-line FOLFOX compared to active symptom control (ASC) in patients with advanced biliary tract cancer (BTC) [6.2 vs 5.3 months, adjusted hazard ratio 0.69 (95% CI, 0.50-0.97); p=0.031].(1) Previous data indicate that microRNAs can mediate chemoresistance. miR-1249 is a BTC-specific biomarker, which induces resistance to cisplatin and gemcitabine through the expansion of CD133+ cells. (2) miR-1307 was studied in pancreatic adenocarcinoma (PDAC) and mediates resistance to FOLFIRINOX by modulating cell response to DNA damage. (3) We aimed to evaluate the role of both miR-1249 and miR-1307 in a larger cohort of patients with BTC undergoing platinum.

Methods: We conducted a non-prespecified exploratory analysis of samples from the ABC-06 trial. miR-1249 and miR-1307 baseline serum concentrations were assessed blinded to clinical data using digital droplet PCR. Concentration cutoffs were identified using Maximally Selected Interaction Statistics (MSIS). Kaplan-Meier method and Cox regression were used for survival analyses. A two-tailed p-value <0.05 was accepted as statistically significant.

Results: Of 162 patients, 106 (65%, ASC=52, ASC + FOLFOX=54) were included in the miRNA cohort; due to serum availability, miR-1249 concentration was unavailable for 2 patients (1 in each arm). Median age was 67 (IQR, 61-73) and patients had intrahepatic cholangiocarcinoma (iCCA, 42.5%), extrahepatic CCA (28.3%), gallbladder cancer (19.8%), while a minority had ampulla of Vater cancer (9.4%). Clinical outcomes of the miRNA cohort mimicked those of the trial cohort, with FOLFOX yielding a median OS of 6.9 vs 5.5 months (HR 0.74, 95% CI 0.49-1.12, p=0.15), but failing to meet statistical significance possibly due to the smaller population size. The radiological median progression-free survival (PFS) in FOLFOX-treated patients was 3.55 months, with a 6-month PFS rate of 33%. Sensitivity to first-line platinum-based chemotherapy did not affect miRNA concentration at baseline. For miR-1249, a concentration of 8325 copies/mL resulted significantly correlated with response to therapy (p=0.01). Patients with low miR-1249 (N=11) had clinical benefit from FOLFOX (8.47 vs 2.3 months, HR 0.08, 95% CI 0.01-0.73, p=0.005). By contrast, patients with high miR-1249 (N=93) did not have any benefit from chemotherapy (6.8 vs 5.33 months, HR 0.85, 95% CI 0.55-1.32, p=0.5). At MSIS analysis, no statistically significant cutoff was identified for miR-1307 (lowest interaction p-value=0.103 for 43425 copies/mL). miR-1307 was studied in PDAC (3) and its concentration was unevenly distributed across BTC subtypes, with lower values in patients with iCCA (p=0.02). This suggests that different resistance mechanisms might be at play based on primary tumor site.

Conclusion: These data further support the role of miR-1249 as a biomarker of resistance to platinum-based chemotherapy in BTC, which can identify a small subgroup of patients (10% of the miRNA cohort) who benefit from FOLFOX. miR-1307 failed to clearly discriminate patients who benefit from chemotherapy. The role of both miRNAs may be worth investigating in larger cohorts, with miR-1307 being assessed exclusively in patients with extrahepatic BTC, considering its non-homogenous distribution across BTC subtypes.

References: 1. Lamarca A. et al. Lancet Oncol. 2021, 2. Carotenuto P. et al. Hepatology. 2020, 3. Carotenuto P et al. Nat Commun. 2021.

Disclosure of Interest: Honoraria

P-007 CIRRHOTIC MASLD-HCC IS ASSOCIATED WITH A DISTINCT IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT AND POORER OUTCOMES IN ATEZOLIZUMAB PLUS BEVACIZUMAB TREATMENT AS OPPOSED TO NON-CIRRHOTIC COUNTERPARTS

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Introduction: The impact of metabolic dysfunction-associated liver disease (MASLD) on immunotherapy response in advanced hepatocellular carcinoma (aHCC) remains unclear. As a major risk factor and prognostic determinant, cirrhosis critically shapes the tumor microenvironment (TME). Our aim was to assess the impact of MASLD-HCC with or without cirrhosis, and their associated TME composition, on the efficacy of immunotherapy in aHCC.

Methods: A multicenter retrospective cohort (2019-2023) of 239 patients treated with first line atezolizumab and bevacizumab (atezo+bev) was queried. Transcriptomic profiles were used for molecular and functional characterization and deconvoluted with BayesPrism to define tumor immune infiltration. Spatial transciptomics was reported in a subset of MASLD-HCC specimens (n=8 cirrhotic and 5 non-cirrhotic) to define cellular interactions and spatial ecosystems associated with patients' outcome.

Results: The cohort had a median age of 69 years old, was predominantly male (80%), and 67% had cirrhosis. BCLC stages B and C accounted for 29% and 68% of the patients, respectively. The main etiology was viral (28%), followed by MASLD (21%). After median follow-up of 12 months (IQR 6-17), the median overall survival (OS) was shorter in MASLD patients (12.2 vs 18.6 months, HR 1.56 [95% CI: 1.02-2.37], p=0.039). Among the 49 MASLD-HCC patients, concomitant presence of cirrhosis (53%) was associated with shorter OS (9.89 vs 16.72 months, HR 2.82 [95% CI 1.27-6.25], p=0.011), and independently associated with mortality (HR 3.24 [95% CI 1.25-8.35], p=0.015) as well as ECOG-PS >1 (HR 8.42 [95% CI 1.81-39.24], p=0.007), after adjustment for AFP ≥400ng/ml, and macrovascular invasion. When comparing gene expression profiles, cirrhotic tumors harbored significantly higher proportion of naïve CD8 T cells (p=0.047), gamma-delta T cells (p=0.044), two macrophage subtypes associated with resistance to atezo+bev [TREM2+ (p=0.014) and SPP1+ (p=0.010)], and CXCL10+ macrophages (p=0.017). Furthermore, neighborhood analysis within a radius of 100µm around any of these three subtypes of macrophages showed an enrichment in glycolysis signatures (p=0.062, 0.068, 0.048, respectively), which have been previously associated with Warburg effect, immune evasion and CD8 T cell exhaustion, and a decrease in antigen presentation signatures (p=0.045, 0.127, 0.093, respectively) in cirrhotic vs non-cirrhotic MASLD-HCC. Finally, transcriptomic profile of cirrhotic MASLD-HCC cases was enriched in decitabine (p=0.031) and 5-azatidine (p=0.051) target gene sets, and DNMT1 expression (p=0.042) compared to non-cirrhotic counterparts, suggesting a potential susceptibility to combination strategies with DNA methyl transferase inhibitors in this subset of patients.

Conclusion: Cirrhotic MASLD-HCC patients present a unique and distinct TME compared with non-cirrhotic MASLD-HCC, characterized by immunosuppressive macrophages and immune evasion, which might explain the decreased response to immunotherapies.

Disclosure of Interest: N/A

P-008 TRANSCRIPTOME-WIDE IDENTIFICATION OF IMMUNOGENIC TUMORAL ANTIGENS IN ADVANCED HEPATOCELLULAR CARCINOMA REVEALS NON-CANONICAL TARGETS FOR NOVEL IMMUNOTHERAPY STRATEGIES

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Introduction: The antigenic landscape underlying the antitumor immune response remains poorly characterized. Current antigen identification platforms are limited by low predictive accuracy, a primary focus on exonic mutations and a lack of functional validation of immunogenicity. Systematic and unbiased identification of tumoral antigens is critical for the development of novel immunotherapy strategies in advanced HCC (aHCC). We aimed to comprehensively map the antigenic repertoire in aHCC using a novel, transcriptome-wide approach which includes functional validation of each antigen.

Method: Two patients with aHCC were selected for antigen discovery. For the first patient, who achieved a complete pathological response to durvalumab plus tremelimumab, paired pre-treatment and on-treatment tumor biopsies were available. For the second patient with a hepatitis B related aHCC and who exhibited a partial response to the same treatment regimen, pre-treatment tumor tissue and matched peripheral blood mononuclear cells (PBMC) were obtained. Single-cell RNA sequencing combined with T-cell receptor (TCR) sequencing was performed to characterize the T-cell repertoire, enabling identification of the 12 most prevalent CD8$^+$T-cell clonotypes within each sample.

After excluding duplicate clonotypes between timepoints, 19 and 18 unique, patient-specific, potentially tumor-antigen directed TCRs were selected. Each TCR was cloned in a reporter T cell

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line and co-cultured with an HLA matched antigen-presenting cell (APC) line expressing the patient-specific tumor transcriptome library. T-cell activation was detected via GFP reporter expression, allowing identification and isolation of activated APC–T cell clusters. APCs were subsequently expanded and the integrated antigen-encoding sequence was retrieved by Sanger sequencing.

Expression of identified antigenic sequences was validated in our in-house scRNA-seq dataset and in public cohorts, including TCGA and GTEx. Peptide pulsing experiments were performed with candidate antigenic peptides to define the epitope and the TCR affinity for these antigens.

Results: We identified a tumoral antigenic sequence for 13 out of 37 TCRs analyzed. Notably, only 2 antigens were derived from somatic mutations, whereas the majority originated from non-canonical sources, including cancer-testis antigens, overexpressed genes, alternative open reading frames, and hepatitis B surface antigen. Expression of several of the detected antigens identified in these patients was also detected in tumors from other HCC patients and across other tumor types within the TCGA dataset, indicating the presence of shared tumor antigens between cancer patients. Remarkably, 4 different TCRs were found to recognize the same antigen, which represented a cancer-testis antigen, reactivated in the hepatocyte cluster of this patient and expressed in approximately 30% of all HCC patients in TCGA. Peptide pulsing experiments confirmed minimal epitopes and HLA-restricted TCR recognition, with functional avidity spanning a broad range (EC50: 0.001–20 µM).

Conclusion: Using a transcriptome-wide antigen identification platform with functional validation, we demonstrate that immunogenic tumor antigens in aHCC predominantly arise from non-canonical sources beyond somatic mutations. Many of these antigens fall outside the scope of conventional antigen prediction pipelines. The identification of shared antigens and convergent T-cell responses highlights their potential as targets for both personalized and off-the-shelf immunotherapy strategies.

Disclosure of Interest: N/A

P-009 DUAL ROLE OF ATR IN METABOLIC HOMEOSTASIS AND MALIGNANT TRANSFORMATION IN MASLD

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Background and aims: The incidence of Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form Metabolic dysfunction-associated steatohepatitis (MASH) have become the most prevalent chronic liver disease and a terrifyingly health problem (1). Key molecular mechanisms behind this sequence have to be still clarified. We previously demonstrated that Replication Stress and DNA damage response play a pivotal role in DNA lesions accumulation in MASLD (2). In this study, we investigated how Ataxia telangiectasia and Rad3-related protein (ATR), a central regulator of the replicative stress (RS) response, influences the progression from MASLD to hepatocellular carcinoma (HCC).

Methods: A MASLD-HCC murine model was established first by injecting 5-week-old male C57BL/6J mice with AAV-Tbg-SaCas9-mediated CRISPR-Cas9 to achieve hepatocyte-specific depletion of ATR (ATRΔHep) and ROSA26 (ROSA26ΔHep, control). At 6 weeks, mice were fed either a Western Diet enriched in fructose (WDF) and a choline-deficient high-fat diet (CDAHFD) to induce MASLD-driven HCC. Mice were euthanized at 5, 7 and 9 months after diets. Tumor incidence was followed by ultrasound imaging. Histopathology (HE, Sirius Red, KI67, γ-H2AX), RNA-seq, lipidomic, and metabolomic approaches were performed.

Result: First, we observed in our MASLD preclinical models that ATR deficiency did not significantly alter the clinical severity of MASLD (e.g. steatosis, fibrosis). Interestingly, lipidomic analyses revealed an up regulation of de novo lipogenesis with a specific accumulation of neutral lipids, specifically 51 TAG and 16 DG species. Integrated multi-omic analysis (RNA-seq and metabolomics) further uncovered a metabolic reprogramming of the TCA cycle and purine nucleotide biosynthesis. This shift was accompanied by a mitochondrial bioenergetic signature suggestive of uncoupled oxidative phosphorylation; specifically, despite a compensatory upregulation of proximal respiratory chain components (mt-ND1, SDHB, mt-COX1), the terminal complex (mt-ATP6) was significantly downregulated, indicating impaired ATP synthesis. Transcriptomic and biochemical analyses further revealed that ATR deficiency triggers an apoptotic response via activation of the caspase-8/PARP cascade. Histological analysis reveal also that ATR deficiency triggered both a marked increase in hepatocyte proliferation (Ki67 positive cells) and DNA damage response (γ-H2AX positive cells) in MASLD parenchymal tissues. Paradoxically, despite this increase in parenchymal damage and compensatory proliferation, long-term challenge with a MASLD-HCC inducing diet revealed that ATRΔHep mice displayed a significantly lower incidence of HCC compared to ROSA26ΔHep mice.

Conclusion: Our findings suggest that while ATR is essential for metabolic and mitochondrial homeostasis during MASLD, its deficiency may protect against hepatocarcinogenesis, potentially by pushing damaged hepatocytes toward apoptosis rather than malignant transformation.

Disclosure of Interest: N/A

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P-011 PROGNOSTIC IMPLICATIONS AND RISK STRATIFICATION OF BLEEDING EVENTS IN ADVANCED HEPATOCELLULAR CARCINOMA TREATED WITH ATEZOLIZUMAB/BEVACIZUMAB

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On behalf of the Real-life Practice Experts for HCC (RELPEC) Study Group and hepatocellular carcinoma experts from 48 clinics in Japan (HCC 48) Group.

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Introduction: While atezolizumab combined with bevacizumab (Atez/Bev) significantly improves outcomes in unresectable hepatocellular carcinoma (uHCC), the incidence and prognostic weight of bleeding complications of Atez/Bev in real-world practice remains unclear. This study investigates the primary determinants of hemorrhagic adverse events (BL-AEs) and comprehensively evaluates their time-dependent effect on patient survival to establish better clinical risk stratification.

Methods: We conducted a retrospective cohort analysis of 981 uHCC patients receiving Atez/Bev across multiple institutions. The cohort was stratified by the occurrence of any-grade BL-AEs. To determine risk factors for BL-AEs, we utilized multivariable logistic regression. To evaluate the true prognostic impact of bleeding while mitigating immortal time bias, we applied inverse probability weighting (IPW), time-dependent Cox proportional hazards models, and landmark survival analyses at 3 and 6 months.

Results: Among the cohort, 10.4% (n=102) experienced BL-AEs, with a median onset of 106 days. Notably, baseline antithrombotic therapy did not elevate the bleeding risk. Instead, multivariable analysis identified advanced portal vein tumor thrombosis (Vp ≥3: OR 1.85, p=0.030) and extrahepatic metastasis (OR 1.60, p=0.043) as primary predictors. Radiologic response rates and progression-free survival were comparable between groups. However, overall survival (OS) was markedly reduced in patients with BL-AEs (median 16.7 vs. 24.8 months, p=0.03). This survival detriment persisted after IPW adjustment (17.3 vs. 24.5 months, p<0.001) and was confirmed via time-dependent Cox modeling (HR 1.47, p=0.007) and 3-month landmark analysis (p=0.004). Furthermore, patients experiencing BL-AEs showed significant deterioration in post-bleeding ALBI scores (p<0.001). These results suggesting that bleeding may reflect underlying aggressive disease rather than being a direct cause of mortality.

Conclusion: Hemorrhagic events during Atez/Bev therapy are strongly dictated by aggressive tumor biology—such as advanced portal vein tumor thrombosis and extrahepatic metastasis—rather than concurrent antithrombotic use. While bleeding serves as a critical harbinger of poor OS and subsequent hepatic decompensation, the administration of Atez/Bev should not be withheld solely based on baseline antithrombotic regimens.

Disclosure of Interest: N/A

P-012 LENVATINIB PLUS HEPATIC-ARTERIAL INFUSION CHEMOTHERAPY WITH CISPLATIN FOR PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA REFRACTORY TO OR UNSUITABLE FOR IMMUNE-CHECKPOINT INHIBITORS: A MULTICENTER, RANDOMIZED, PHASE II TRIAL IN JAPAN

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Introduction: In the current treatment landscape for advanced hepatocellular carcinoma (HCC), combination immunotherapies are the standard first-line options. However, effective subsequent-line strategies for patients who are refractory to or unsuitable for immune-checkpoint inhibitors (ICIs) remain an urgent clinical need. While lenvatinib plus hepatic-arterial infusion chemotherapy (HAIC) with cisplatin (Lenva+CDDP) has shown high anti-tumor response for treatment-naïve HCC, its efficacy in the post-ICI setting has not been established. This study compared the efficacy and safety of the Lenva+CDDP combination to those of lenvatinib in Japan.

Methods: Patients with advanced HCC (Child-Pugh A) who had either failed prior ICI therapy or were unsuitable for ICIs were enrolled in this multicenter, open-label, randomized, phase II trial in Japan (jRCT104120163). Patients were randomized (1:2) to receive either lenvatinib monotherapy (Group A: 8 or 12 mg daily) or lenvatinib plus HAIC with cisplatin (Group B: 65 mg/m² administered via the hepatic artery every 4–6 weeks). The primary endpoint was the objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.

Results: A total of 57 patients were enrolled (Group A: 19, Group B: 38); while the median age was significantly higher in Group B (73.0 years) than in Group A (70.0 years; P=0.009), other baseline characteristics were well-balanced. Regarding efficacy and survival, Group B demonstrated a significantly higher ORR (36.8% [95% CI: 21.8–54.0]) compared to Group A (5.3% [95% CI: 0.1–26.0]; P=0.011), and a significantly longer median PFS (9.0 months [95% CI: 5.8–10.1] vs. 4.3 months [95% CI: 1.8–7.6]; HR 0.46 [95% CI: 0.25–0.85]; P=0.009). Meanwhile, safety analyses revealed that HAIC-related adverse events, including renal dysfunction and biliary disorders, occurred in three patients each (7.9%) in Group B, and the mean increase in Child-Pugh score from baseline to the end of treatment was significantly greater in Group B (1.26 ± 0.22) than in Group A (0.22 ± 0.35; P=0.029).

Conclusion: Lenvatinib plus HAIC with cisplatin significantly improved ORR and PFS compared to lenvatinib monotherapy in Japanese patients with advanced HCC who were refractory to or unsuitable for ICIs. These findings suggest that the Lenva+CDDP combination is a highly effective treatment option following immunotherapy, provided that liver function is carefully monitored.

Disclosure of Interest: N/A

P-013 RISK-BASED HEPATOCELLULAR CARCINOMA SURVEILLANCE USING INCIDENCE THRESHOLDS IN ANTIVIRAL-TREATED ASIAN PATIENTS WITH CHRONIC HEPATITIS B

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Friday 4 September from 10:30 to 11:00 am

Heart Hospital, Dongtan, Republic of Korea, [5]Division of Gastroenterology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, Background & aim: Although the risk of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) has been decreased by the use of antiviral agents, HCC surveillance is still performed based on the strategy in the era of pre-antiviral treatment. This study aimed to investigate the annual incidence rate of HCC corresponding survival thresholds and risk stratification of HCC by prediction risk score in Asian patients receiving antiviral treatment for CHB.

Methods: A nationwide population-based cohort study comprised 199,413 CHB patients receiving antiviral treatment from the Korean National Health Insurance Service between 2012 and 2023. The difference in annual incidence rates of HCC was compared in the low-risk (n=125,935), intermediate-risk (n=57,961), and high-risk (n=15,517) groups by HCC-RESCUE score. Also, we calculated HCC-RESCUE scores corresponding to surveillance thresholds.

Results: The mean age was 47.2 years. The proportion of male sex was 61.8%. During a median follow-up of 7.3 years (interquartile range, 3.9-10.3 years), 15,233 patients developed HCC. The annual incidence rates were 0.31%, 1.09%, and 1.856% in the low-risk, intermediate-risk, and high-risk groups, respectively. After multivariable adjustment, the risk of HCC was higher in the intermediate- (hazard ratio [HR] 3.48, 95% confidence interval [CI] 3.35-3.61), and high-risk groups (HR 5.90, 95% CI 5.62-6.19) compared with the low-risk group (p<0.001). The HCC-RESCUE scores corresponding 0.2%, 1.5%, and 3.0% of the annual incidence rates were 47, 66, and 90.

Conclusion: HCC surveillance in patients with CHB is performed based on survival thresholds and the annual incidence of HCC with detailed risk stratification. The prediction score-based approach considering the annual incidence rate of HCC corresponding survival thresholds is helpful to optimize surveillance strategies in Asian patients with CHB.

Disclosure of Interest: N/A

P-016 INFLAMMATION-DRIVEN HEPATIC INJURY DRIVES EARLY POSTOPERATIVE RECURRENCE IN HEPATOCELLULAR CARCINOMA WITHOUT TUMOR-RELATED RISK FACTORS

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Introduction: Early postoperative recurrence remains a major factor compromising the therapeutic benefit of surgery and the long-term prognosis of patients with hepatocellular carcinoma (HCC). We aimed to identify patients without tumor-related risk factors who still experienced early recurrence, and to explore the underlying mechanisms and therapeutic strategies.

Methods: We retrospectively analyzed 2,382 patients with HCC. ERMLH prediction model was developed based on 1,589 HCC patients without tumor-related risk factors, which was internally validated in 370 patients and externally validated in 98 patients. An additional cohort of 325 patients was employed to assess its performance in a broader population. Specimens from patients without tumor-related risk factors underwent RNA sequencing, western blot and IHC. The therapeutic effect of the anti- inflammation was evaluated in two mouse models.

Results: ERMLH model stratified HCC patients without tumor-related risk factors into low-, middle-, and high-risk groups, with 2-year recurrence rates of 8.3%, 19.1%, 31.7% in the training cohort, 7.3%, 14.2%, 36.1% in the internal validation cohort and 7.5%, 14.3%, 37.5% in the external validation cohort, respectively (both P < 0.0001). A cohort with tumor-related risk factors, grouped by ERMLH model, also exhibited significantly different early recurrence rates. Transcriptomic analysis and animal experiments indicate that hepatocyte inflammatory injury and activation of the NF-κB pathway are key factors promoting early recurrence of HCC. Aspirin attenuated liver inflammation and tumor growth in vivo, supporting inflammation-targeted intervention for preventing recurrence.

Conclusion: The ERMLH model effectively predicted early recurrence in HCC patients without tumor-related risk factors. Peritumoral inflammation-triggered hepatocellular injury played a pivotal role in early recurrence, and anti-inflammatory therapy represented a promising intervention to reduce recurrence in this population.

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Disclosure of Interest: N/A

P-017 INTEGRATION OF POSTOPERATIVE CTDNA METHYLATION AND MICROVASCULAR INVASION FOR MINIMAL RESIDUAL DISEASE DETECTION AND EARLY RECURRENCE PREDICTION IN HEPATOCELLULAR CARCINOMA

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Introduction: Minimal residual disease (MRD) is a major determinant of early recurrence after curative resection for hepatocellular carcinoma (HCC). This study evaluated the prognostic value of perioperative circulating tumor DNA (ctDNA) methylation and investigated whether its integration with microvascular invasion (MVI), a pathological manifestation of MRD, could improve early recurrence prediction.

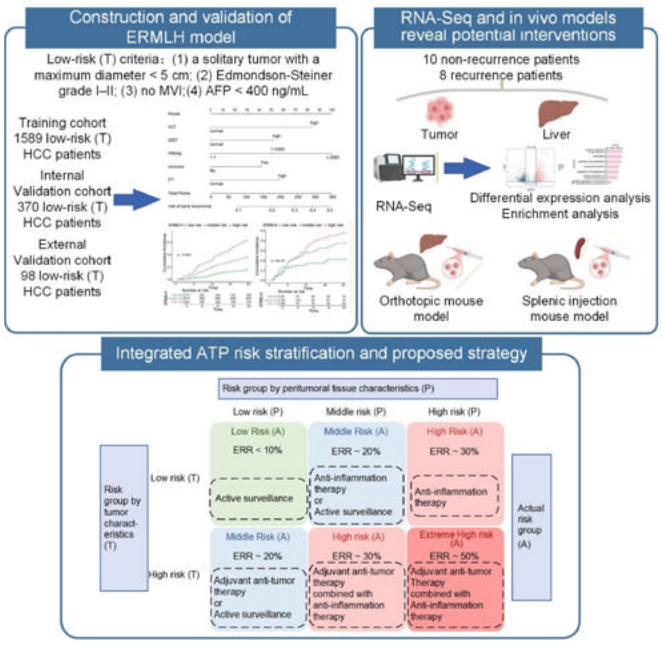
Methods: Patients with HCC undergoing radical resection were enrolled, with peripheral blood collected before surgery and on postoperative day 7. Plasma ctDNA methylation was assessed using multiplex PCR-based bisulfite amplicon sequencing and a previously established HCC methylation model. Early recurrence was defined as recurrence within 24 months after surgery. Associations among ctDNA status, MVI, early recurrence, and recurrence-free survival (RFS) were analyzed using chi-square tests, Kaplan-Meier analysis, and Cox regression models.

Results: Among 111 enrolled patients, 84 HCC patients with available postoperative ctDNA (post_ctDNA) data were included. Preoperative ctDNA score (79.8 vs 72.2, p>0.05) and positivity (36.0% vs 26.7%, p>0.05) were not significantly associated with early recurrence. In contrast, post_ctDNA positivity was associated with a higher incidence of early recurrence (58.3% vs 26.7%, p=0.006) and shorter RFS (median, 20.15 months vs not reached, p<0.001). MVI, another form of MRD, was also associated with increased early recurrence (47.6% vs 23.8%, p=0.023) and shorter RFS (median, 23.50 months vs not reached, p=0.016). Notably, post_ctDNA score (37.05 vs 35.50, p=0.995) and positivity (31.0% vs 26.2%, p=0.629) did not differ significantly according to MVI status, suggesting complementary MRD information. In multivariable analysis, post_ctDNA status (p=0.018, sHR=2.384, 95% CI 1.162-4.891) and MVI (p=0.028, sHR=2.354, 95% CI 1.099-5.042) independently predicted early recurrence. Patients negative for both markers were defined as MRD-negative, whereas those positive for either marker were defined as MRD-positive. MRD-positive patients had a higher incidence of early recurrence (47.2% vs 16.1%, p=0.004) and shorter RFS (median, 23.50 months vs not reached, p=0.005). Integrated MRD assessment improved the negative predictive value for early recurrence to 83.9%, compared with MVI alone and postoperative ctDNA alone (76.2% and 73.3%, respectively), and independently predicted early recurrence (p=0.009, sHR=3.629, 95% CI 1.388-9.492).

Conclusion: Postoperative ctDNA methylation was associated with early recurrence after HCC resection. Integration of post_ctDNA status with MVI provides complementary MRD assessment and improves early recurrence risk stratification.

Disclosure of Interest: N/A

Image:



Posters

Molecular Pathogenesis, Cell Biology and Translational Research

P-018 SPATIAL MULTI-OMICS REVEALS AN IMMUNOTHERAPY-INDUCED DRUG-TOLERANT PERSISTER STATE IN HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality. Although targeted therapy combined with immunotherapy has improved clinical outcomes, many patients still follow a trajectory of initial response followed by persistent tolerance and disease relapse, suggesting that residual tumor cells may survive through adaptive mechanisms. Recent studies have proposed that therapeutic pressure can induce drug-tolerant persister (DTP) cells, a reversible tumor cell state that enables survival under treatment. However, whether immunotherapy induces a DTP state in HCC and how such cells are maintained within the spatial tumor microenvironment remain unclear.

Methods: We established an integrated multi-omics HCC cohort combining spatial transcriptomics, bulk transcriptomics, and clinical follow-up. The discovery cohort included 10x Visium HD spatial transcriptomic profiling of tumors from 13 HCC patients treated with preoperative targeted therapy combined with immunotherapy (6 responders and 7 non-responders) and 4 untreated HCCs. Independent validation was performed using bulk RNA-seq datasets (n = 45). Spatial deconvolution, malignant cell re-clustering, pseudotime trajectory inference, and spatial neighborhood analysis were applied to characterize therapy-associated tumor states and their ecological niches.

Results: Residual viable tumor percentage (RVT%) was an independent predictor of recurrence-free survival. Notably, patients achieving pathological complete response still exhibited only ~50% 4-year recurrence-free survival, suggesting occult residual resistant disease. Spatial profiling revealed that resistant tumors displayed increased monocyte/macrophage infiltration and reduced B-cell abundance within tumor cores. Re-clustering of malignant cells identified a distinct subpopulation (Cluster_7) selectively enriched in post-treatment resistant tumors. This population exhibited a low-proliferative, stress-adapted, EMT-like transcriptional program with enrichment of oxidative stress and inflammatory response pathways, consistent with a DTP-like phenotype. Pseudotime analysis supported a therapy-induced state transition rather than expansion of a pre-existing resistant clone. Across independent cohorts, enrichment of this DTP-like program was associated with early recurrence and inferior overall survival. Spatially, these cells preferentially localized to the invasive tumor front. Neighborhood analysis further demonstrated that the DTP niche was characterized by enrichment of tumor-associated macrophages and endothelial cells, accompanied by depletion of B cells and effector/memory CD8+ T cells, forming a low-inflammatory, endocytosis-enhanced microenvironment.

Conclusion: Our study identifies a therapy-induced DTP-like tumor cell state and a macrophage–vascular suppressive niche as a key spatial ecological unit underlying persistent resistance after immunotherapy in HCC. These findings support a shift from a tumor-intrinsic resistance model toward a tumor–microenvironment co-tolerance framework and highlight DTP-associated spatial ecosystems as potential therapeutic targets to prevent relapse.

Disclosure of Interest: N/A

P-019 CIRCULATING NEOANTIGEN-SPECIFIC T CELLS PREDICT IMMUNOTHERAPY RESPONSE, MONITOR RESISTANCE, AND REVEAL A STRESS-ASSOCIATED TARGETABLE STATE

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Introduction: Targeted-immunotherapy combinations, specifically PD-1 inhibitors paired with lenvatinib, have revolutionized hepatocellular carcinoma (HCC). Yet, clinically useful, noninvasive biomarkers for predicting response and dynamically monitoring efficacy remain limited. Most current blood-based biomarkers reflect tumor burden rather than tracking systemic antitumor immunity. Circulating neoantigen-specific peripheral blood lymphocytes (NeoPBLs) represent a crucial pool of tumor-reactive cells with potential for longitudinal monitoring. However, their transcriptomic identity, clinical significance, and role in therapeutic resistance remain poorly defined.

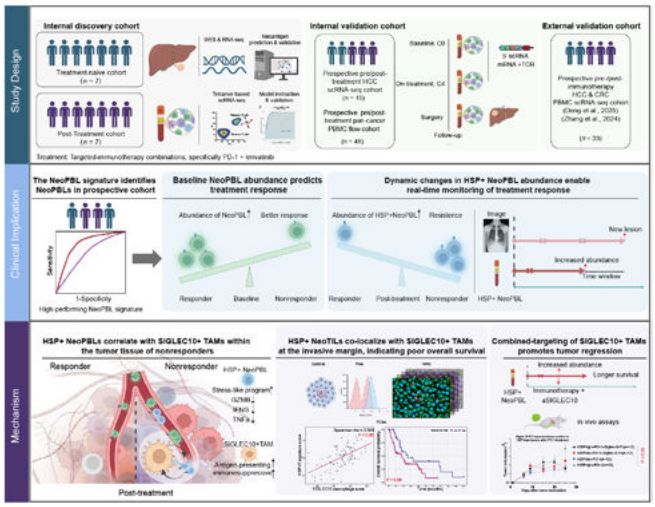
Methods: We established four distinct cohorts to characterize NeoPBLs. An internal discovery cohort, comprising treatment-naive and post-treatment (PD-1 + lenvatinib) peripheral blood with avaliable matched tumor samples from 14 HCC patients, was utilized for neoantigen-reactive signature discovery via tetramer-based sorting and single-cell RNA sequencing (scRNA-seq). From this, we developed an AI-based NeoPBL gene signature model. This model was subsequently validated across three independent cohorts: internal validation cohort 1 (prospective pre/post-treatment scRNA-seq, n=15), internal validation cohort 2 (prospective pre/post-treatment flow cytometry, n=48), and external validation cohorts encompassing public datasets (GSE236581, GSE235863) covering both HCC and colorectal cancer. Mechanisms were explored via pseudotime trajectory inference, multiplex immunohistochemistry (mIHC), TCGA-LIHC data analysis, and in vivo assays.

Results: Our AI-derived NeoPBL signature identified tumor-reactive CD8+ T cells in peripheral blood more accurately than existing tumor-infiltrating lymphocyte (TIL) markers. Across validation cohorts, higher baseline NeoPBL abundance consistently predicted a favorable clinical response to combination immunotherapy. Notably, we identified a specific HSP+ NeoPBL subset, characterized by stress-related transcriptional programs, which was enriched in non-responders post-treatment. TCR-sharing and pseudotime analyses revealed that these HSP+ NeoPBLs maintain a clonal lineage with NeoTILs, tracing a trajectory from systemic circulation to the tumor microenvironment. This HSP+ state correlated with an enrichment of SIGLEC10+ tumor-associated macrophages (TAMs), displaying a dual antigen-presenting and immunosuppressive phenotype within the tumor tissue of nonresponders. Spatial profiling via mIHC confirmed the co-localization of SIGLEC10+ TAMs and HSP+ NeoTILs at the invasive margin. Furthermore, TCGA-LIHC analysis correlated SIGLEC10+ TAM features with poor prognosis and increased intratumoral HSP+ T-cell abundance. Crucially, in vivo functional assays demonstrated that targeting Siglec-g+ TAMs attenuated the HSP-associated T-cell resistance state and restored antitumor efficacy.

Conclusion: NeoPBLs serve as a noninvasive "liquid biopsy" for predicting therapeutic response and dynamically tracking targeted-immunotherapy outcomes across diverse cancer types. The treatment-induced accumulation of HSP+ NeoPBLs acts as a cellular indicator of therapeutic resistance, governed by an immunosuppressive niche driven by SIGLEC10+ TAMs. These findings provide a rationale for NeoPBL-guided clinical monitoring and support the clinical development of SIGLEC10+ TAM-targeted combination strategies to overcome immunotherapy resistance.

Disclosure of Interest: N/A

IMAGE:



P-020 GUT MICROBIAL COMPOSITION CONTRIBUTES TO THE RISK OF EARLY RECURRENCE AFTER NEOADJUVANT IMMUNOTHERAPY IN RESECTABLE HEPATOCELLULAR CARCINOMA

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Introduction: While neoadjuvant immune checkpoint inhibitors (nICI) prior to liver resection (LR) lead to anti-tumour response, it is unclear if they may improve risk of post-operative recurrence. The gut microbiome is a key modulator of the tumour microenvironment and influences response to therapy. We aimed to explore how the gut microbiome evolves under therapeutic pressure of nICI and examine its potential as a non-invasive biomarker of recurrence following nICI.

Methods: PRIME-HCC is a phase Ib, single-arm trial evaluating nICI prior to liver resection (LR) in early HCC. We performed full-length 16S rRNA gene sequencing on serial stool samples taken before and after nICI. After quality control and 10% prevalence filtering, several microbiome metrics were correlated with recurrence and recurrence free survival (RFS). Microbial composition was examined based on relative abundance of individual phyla and genera. Within-sample diversity was calculated based on richness and evenness metrics. Between sample diversity was calculated using the Bray-Curtis Index. Differential abundance analysis was performed using EdgeR, DESeq2 and Aldex2 to identify specific taxa associated with HCC recurrence. Only those taxa identified as significant by more than one package were retained.

Results: Of 24 patients (pts) with HCC, most BCLC A (71%), 63% had cirrhosis due to viral (38%) or non-viral (50%) etiologies. At data cut-off and median follow-up of 43 months (95% CI 36-46 months), 13 pts (54%) had HCC recurrence. Paired stool samples, taken before and after nICI, were subjected to 16S rRNA gene sequencing. After quality control and filtering, 38 samples were included for downstream analysis. The gut microbiome of HCC pts was dominated by Bacillota and Bacteroidota phyla, and the top 3 genera were Bacteroides (21%), Prevotella 9 (7.37%) and Akkermansia (5.59%). There were no significant differences in gut microbiome composition before and after nICI.

Categorizing patients according to recurrence (Rec vs NoRec), we found no significant differences in alpha or beta diversity, and there was a similar degree of dysbiosis in both groups at both timepoints. Using differential abundance analysis, we found baseline samples of Rec pts to be enriched with Prevotella 9 genus (adjusted p-value 0.018). In the presence of Prevotella 9, 83% had HCC recurrence, 80% of which occurred within 24 months of LR. In contrast, in Prevotella 9 negative pts, recurrence rate was only 38%. The presence of Prevotella 9 was associated with shorter RFS (median 19.8 months vs NR).

Conclusion. PRIME-HCC demonstrates for the first time the relevance of gut microbiome in shaping recurrence risk following nICI. Stool enrichment in Prevotella 9 identifies pts with higher risk of early recurrence after LR.

Disclosure of Interest: N/A

P-021 SENESCENCE DEFINES METABOLIC-IMMUNE STATES ACROSS LIVER AND TUMOUR ECOSYSTEMS IN HEPATOCELLULAR CARCINOMA

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Introduction: Aging is associated with progressive changes in the liver and increased risk of chronic liver diseases, including hepatocellular carcinoma (HCC). As the global population ages, the burden of HCC is expected to increase. Senescence-associated dysregulation is increasingly recognised in liver disease. However, its role in metabolic and immune remodeling in the liver and HCC remains poorly understood.

Methods: Multiple senescence gene sets (SenMayo, GOBP: Cellular Senescence, SenNet, and SHGS) were integrated to derive a 28-gene liver senescence gene signature (LiverSen). LiverSen was applied to bulk RNA-seq data from adjacent non-tumour liver tissues (n=37 patients) to stratify samples into high- and low-senescence groups for pathway enrichment analysis. Age-related immune changes in the mouse liver (5, 12, 24 months) were assessed using CyTOF.

In HCC tumour tissues, Spearman correlation of the LiverSen signature across HCC tumour sectors (n=137 tumour sectors from 37 patients) was used to derive a 22-gene HCC-specific senescence signature (HCCSen), capturing intra-tumour heterogeneity. Tumour sectors were stratified into high- and low-HCCSen groups for bulk RNA-seq pathway enrichment analysis and CyTOF immune profiling. HCCSen was further evaluated at the patient level in the TCGA-LIHC cohort.

Results: In non-tumour liver tissues, senescence scores were not significantly associated with chronological age, and instead stratified them into distinct metabolic and immune states. High-LiverSen samples were enriched for metabolic and mitochondrial pathways, whereas the low-LiverSen samples were enriched for immune processes. CyTOF analysis of aging mouse liver showed decreased immune density with age, with younger livers enriched for cNK, DCs, and naïve B cells, whereas aged livers were enriched for senescent (KLRG1+) and exhausted (PD1+/CTLA4+) T and B cells. Together, these findings indicate that senescence defines metabolic and immune remodeling states in the liver.

In tumour sectors, bulk RNA-seq and CyTOF analyses revealed a similar metabolic-immune pattern. High-HCCSen tumours showed enrichment of metabolic pathways and a predominantly immunosuppressive tumour microenvironment, characterised by Treg, exhausted T cells, and immunosuppressive myeloid populations. In contrast, low HCCSen tumours exhibited enrichment of extracellular matrix and immune pathways alongside a more immune-active tumour microenvironment, with increased activated CD8 T cells, NKT, and DC. These patterns were recapitulated in the TCGA-LIHC Cohort. Collectively, metabolic and immune patterns identified in non-tumour liver tissues were preserved in tumour tissues, indicating that the tumours reflect underlying senescence-associated biology already present in the liver.

Conclusion: LiverSen and HCCSen capture conserved yet distinct biological states across non-tumour and HCC, defined by metabolic and immune reprograming, independent of chronological age. In HCC, these states are associated with distinct tumour immune microenvironments, with high-senescence tumours exhibiting a metabolically enriched and immunosuppressive profile, and low-senescence tumours demonstrating an immune-active profile. These findings position senescence as a key biological determinant of tumour-immune context in HCC, with potential implications for patient stratification and immunotherapy response.

Disclosure of Interest: N/A

P-022 INTEGRATED MOLECULAR AND HISTOLOGICAL PROFILING OF LIVER YOLK SAC TUMOR AND ITS PATIENT-DERIVED CELL LINE REVEALS C-MYC–FOXM1 ONCOGENIC DEPENDENCIES

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Introduction: Primary yolk sac tumor of the liver (HYST) is uncommon disease with less than 20 cases reported worldwide and is often misdiagnosed as HCC. It is a type of germ cell tumor that arises from embryonic tissue left over from fetal development. Survival can vary widely depending on the stage of the tumor and the effectiveness of therapy. Therefore, in-depth molecular and histological characterization of HYST and the development of representative models are essential to better understand and diagnose this disease and to develop patient-specific therapeutic options.

Methods: Samples of adjacent liver and tumor tissue were collected and processed from a 66-year-old female patient. Long-term culture of patient-derived cell line (PCL) was established. Histological characteristics of the tissues, xenograft tumors and PCL were analyzed by immunohistochemistry (IHC) and immunofluorescence (IF). Transcriptomic profiling was performed by RNA sequencing followed by time-course, GSEA, IPA and CIBERSORTx analyses. Potentially actionable mutations were identified by targeted DNA sequencing and SNP arrays and validated by western blot. Dose–response and synergy experiments were conducted to investigate targeted inhibition of the identified oncogenic pathways and their impact on cell migration using xCELLigence.

Results: Tumor tissue showed a solid trabecular growth pattern with areas of necrosis but without Schiller-Duval bodies. The newly derived PCL fully recapitulated the morphological characteristics of the primary cancer both in vitro and in vivo. IF and IHC analyses demonstrated expression of typical HYST markers (AFP, CK19), which were effectively maintained in xenografts, PCL, and spheroids. Transcriptomic profiling confirmed activation of embryonic markers, enrichment of T cells, reduction of macrophages, and FOXM1 activation, which persisted in PCL. GISTIC analysis identified amplifications on chromosomes 8q24.3 (MYC-related), 9q34.11, and 22q12.2, regions previously associated with poor survival in pancreatic neuroendocrine tumors—suggesting a potentially aggressive disease. MYC upregulation as well as FOXM1 activation, validated by western blot, indicated an oncogenic regulatory link between these two pathways. NGS further revealed oncogenic TP53 and actionable KDR mutations, both highly conserved in PCL. Targeted inhibition of the FOXM1–MYC network confirmed sustained therapeutic sensitivity and significantly reduced cell migration. Further, selective vulnerability associated with the KDR mutation could be observed.

Conclusion: Here, for the first time, we were able to dissect the liver HYST at an unprecedented molecular level and at the same time establish a primary cell line. We identified molecular alterations that could be used to effectively predict patient response to targeted therapy and serve as an effective model for this extremely rare disease.

Disclosure of Interest: Stocks

Posters

P-023 ASH1L DRIVES HEPATOCELLULAR CARCINOMA PROGRESSION THROUGH TRANSCRIPTIONAL REGULATION OF EXTRACELLULAR MATRIX GENES

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Introduction: Recent studies have suggested that ASH1L promotes tumor progression and contributes to an immunosuppressive microenvironment in hepatocellular carcinoma (HCC). However, the molecular mechanisms by which ASH1L regulates HCC development remain unclear. This study aimed to investigate the oncogenic role of ASH1L in HCC and to elucidate its function in tumor progression.

Methods: To investigate the oncogenic role of ASH1L in HCC, protein expression was examined by western blot to identify cell lines with different endogenous levels. ASH1L expression was silenced in Hep3B and SNU-739 cells using lentivirus-mediated shRNA, followed by puromycin selection for three days to obtain stable knockdown cell lines. The efficiency of ASH1L knockdown was verified using qPCR and western blot. The functional consequences of ASH1L suppression were assessed using viability, colony formation, invasion, and migration assays. In addition, RNA sequencing of ASH1L-silenced cells was conducted to identify ASH1L-regulated genes, followed by validation using qPCR. All experiments were conducted in triplicate, and statistical significance was analyzed using a two-tailed Student's t-test.

Results: ASH1L expression was relatively high in Hep3B and SNU-739 cells, compared to other HCC cell lines. ASH1L knockdown significantly reduced cell viability and colony formation in both HCC cell lines for 3 days post-transfection. In addition, the invasive and migratory capacity was markedly reduced in Hep3B and SNU-739 cells. RNA sequencing using the SNU-739 cell line confirmed that suppression of ASH1L expression led to decreased expression of genes associated with extracellular matrix organization. Consistently, qPCR validation confirmed the downregulation of these ASH1L-regulated genes, supporting the role of ASH1L in promoting extracellular matrix remodeling and tumor progression.

Conclusion: ASH1L promotes HCC progression by regulating cell proliferation, invasion, and migration, likely through transcriptional regulation of extracellular matrix–related genes. These suggest that ASH1L functions as an oncogenic factor in HCC and may be a potential therapeutic target.

Disclosure of Interest: N/A

P-024 HYPEROXIC STRESS IN THE CIRCULATION REPROGRAMS CIRCULATING TUMOR CELLS TOWARD DORMANCY AND METASTATIC FITNESS IN HEPATOCELLULAR CARCINOMA

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Introduction: Metastasis and postoperative recurrence remain the dominant barriers to long-term survival in hepatocellular carcinoma (HCC). Circulating tumor cells (CTCs), the key mediators of hematogenous spread, are central to metastatic progression through their capacity to survive and adapt functionally within the bloodstream. Unlikely the primary tumor microenvironment, the circulation is exposed to higher oxygen tension and thus represents a unique hyperoxic stress niche. Yet how this blood-flow associated hyperoxic microenvironment reprograms CTC states and influences their metastatic potential remains unknown. Here, we focus on the hyperoxic conditions of the circulation and investigate their role in regulating CTC dormancy and metastasis-related programs.

Methods: We combined single-cell RNA sequencing, in vitro hyperoxic culture models, and in vivo functional assays to define CTC functional states and their regulatory mechanisms in HCC. CTCs from distinct vascular compartments were subjected to ingle-cell transcriptomics profiling and pathway enrichment analysis. Hyperoxic (60% O_2) versus normoxic (21% O_2) conditions were used to assess effects on proliferation and metastatic phenotypes, while a tail vein injection model was applied to evaluate CTC survival and metastatic colonization in vivo. Statistical analyses were performed using Student's t-test, nonparametric tests, and Kaplan–Meier survival analysis.

Results: Single-cell analysis revealed that CTCs segregated into proliferative (activated) and low-proliferative (dormant) states (Fig. 1A,B), with dormant CTCs significantly enriched in the peripheral arterial circulation. Transcriptomic profiling showed that this subpopulation was characterized by upregulation of oxidative stress–related genes, including SOD1, SOD2, GPX1, and NFE2L2, together with enrichment of reactive oxygen species (ROS)–associated pathways (Fig. 1C,D). Pseudotime analysis further suggested a dynamic transition from activated to dormant states (Fig. 1E). Clinically, a higher proportion of dormant CTCs was significantly associated with increased postoperative recurrence and shorter recurrence-free survival (Fig. 1G).

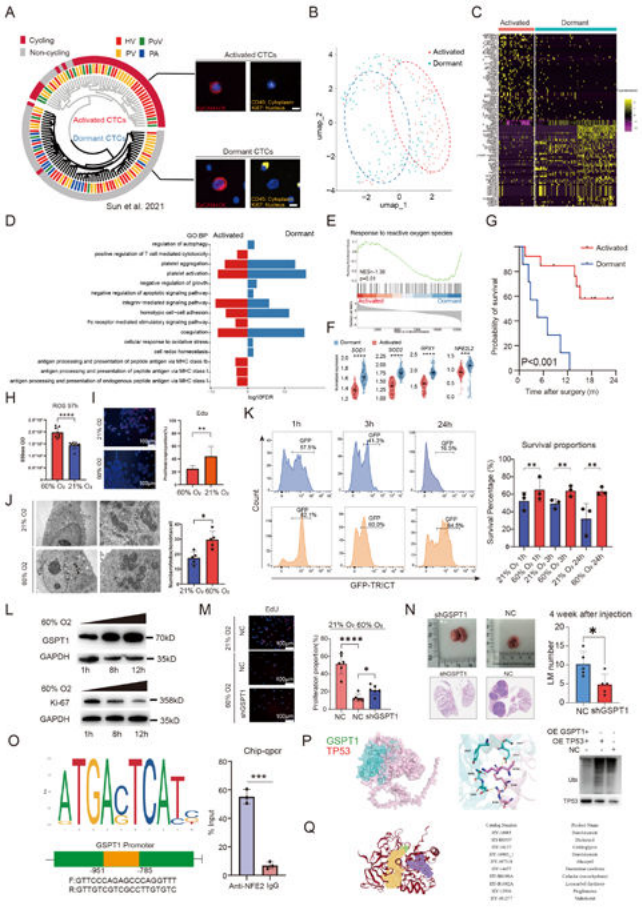
Consistent with vascular anatomy and pathway enrichment results, in vitro experiments showed that a hyperoxic microenvironment markedly increased intracellular ROS levels, reduced proliferation and induced G1-phase arrest, thereby promoting a reversible dormant state (Fig. 1H-J). Hyperoxic preconditioning further enhanced tumor cell survival under circulatory stress in vivo (Fig. 1K).

Mechanistic analyses identified GSPT1 as a key regulator that was upregulated under hyperoxia and consistently enriched in dormant CTCs (Fig. 1L-N). Further inverstigation showed that hyperoxia-induced oxidative stress promoted nuclear translocation of NFE2 (Fig. 1O), thereby enhancing GSPT1 transcription. In parallel, GSPT1 formed a complex with TP53 and was associated with reduced TP53 ubiquitination (Fig. 1P). Finally, drug screening analyses identified Vadadustat as a potential inhibitor targeting GSPT1 (Fig. 1Q).

Conclusion: These findings showed that the blood flow–associated hyperoxic microenvironment drives CTC dormancy through ROS-mediated oxidative stress, thereby promoting CTC survival and metastatic fitness in the circulation. This process is accompanied by GSPT1 upregulation and altered TP53 protein stability. Clinically, an increased proportion of dormant CTCs was significantly associated with postoperative recurrence, supporting its potential as a prognostic biomarker and a therapeutic target in HCC.

Disclosure of Interest: N/A

Image:



Posters

P-025 NOVEL 68GA-PSMA PET IMAGING FOR DISEASE ASSESSMENT IN ADVANCED HEPATOCELLULAR CARCINOMA PATIENTS

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Prostate-specific membrane antigen (PSMA) is highly expressed in tumor-associated neovasculature in hepatocellular carcinoma (HCC), highlighting its promise as a theranostic target. Approximately 6% of patients with solid tumors experience pseudoprogression. Here we utilized novel 68Ga-PSMA PET imaging and immune profiling to characterize two pseudoresponders. Methods: HCC patients receiving first line immune checkpoint inhibitors (ICI) were enrolled in prospective study (NCT05176223) to evaluate the efficacy of 68Ga-PSMA PET as a theranostic paired with peripheral blood CyTOF analysis to assess treatment response and identify potential biomarkers. RECIST 1.1 utilizes solid tumor diameter and volumetric measurements to determine disease state (PD, SD, PR, CR) whereas PET (positron emission transmission) detects gallium-68, a radioactive isotope, which is preferentially internalized by PSMA+ cells. 68Ga-PSMA PET PERCIST is therefore specific to PSMA+ cells leading to increased resolution of the tumor burden and neovasculature which may help discern pseudo-response, due to TILs (tumor infiltrating lymphocytes) which lack PSMA expression, compared to progressive disease. Results: Twenty-five evaluable patients were enrolled between Oct 2022 and Nov 2024. Median follow up was 22.1 months (Q1, Q3: 14.5-23.7). Baseline characteristics: median age 68 yr, 72% males, 88% White, 68% CP A, 32% CP B, 32% BCLC B, 68% BCLC C, 36% with MVI and 56% received a/b and 40% received d/t treatments. PSMA was positive in 96% of patients at baseline with median SUVmax at baseline 14.3 (range 5.1-40.5) and background median liver SUVmax 3.9 (range 2.1-6.8). Median (95%CI) PFS were 5.6 (4.6-12.5) and 5.6 (4.6-12.5) months by RECIST and mRECIST. Median OS was 18.6 (7.2-NE) months. Two pseudo-progressors, show PERCIST response compared to RECIST disease progression. CyTOF immune profiling shows a unique abundance of CCR7+ cells in the CD8 compartment not shared amongst other groups. Additionally, T1 abundances in the CD4 compartment align with CR/PR RECIST response assessment. Further validation is needed with a larger cohort, but 68Ga-PSMA looks to be a promising theranostic for early detection of pseudoprogression. Conclusion: PERCIST assessment at T1 for two pseudoprogressors indicated treatment response was discordant with RECIST criteria that indicated disease progression. Combining the PERCIST assessment with the CyTOF analysis, here we identify a unique population at baseline and T1 specific to pseudoprogression.

Disclosure of Interest: N/A

P-026 FATE DETERMINATION OF PROGENITOR EXHAUSTED-LIKE CD8+ T CELLS IN THE TUMOR/DRAINING LYMPH NODE IMMUNE AXIS AND ITS ROLE IN IMMUNOTHERAPY RESISTANCE OF LIVER CANCER

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Introduction: Liver cancer remains a leading cause of cancer-related death worldwide, and more than 60% of patients lose the opportunity for curative surgery when diagnosed. Immune checkpoint inhibitors (ICIs) have markedly reshaped the therapeutic landscape of liver cancer. However, resistance remains a major obstacle to further improving treatment efficacy. Progenitor exhausted CD8+ T cells (Tpex) are considered a key cellular population responding to ICIs therapy. Nevertheless, the role of Tpex fate transition in immunotherapy remains unclear. It is unknown whether Tpex continuously shapes local antitumor immune responses through the tumor/tumor-draining lymph node (TDLN) immune axis. Its impact on immunotherapy outcomes also remains to be defined.

Methods: This study included 17 patients with liver cancer, including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). A total of 71 samples were collected, including tumor, para-tumor tissue, peripheral blood, and TDLNs. Among these patients, 7 were treatment-naive, and 10 underwent surgery after immunotherapy; of the latter, 5 achieved major pathological response (MPR, defined as viable tumor cells <50%) and 5 did not. All samples were subjected to single-cell RNA sequencing and single-cell T-cell receptor (TCR) sequencing (Fig. 1A).

Results: ICIs therapy enhanced the effector function of CD8+ T cells in TDLNs, while intratumoral CD8+ T cells displayed a state characterized by concurrent effector activation and terminal exhaustion (Fig. 1B). Immunotherapy markedly activated the HLA-DR+ Tpex subset in TDLNs (Fig. 1C). This subset retained the potential to differentiate into effector cells (Fig. 1D) and may serve as a key cellular basis for sustaining antitumor immune responses during treatment. TCR clonal tracing further showed that HLA-DR+ Tpex cells originating from TDLNs could migrate into tumor tissues, where they underwent functional reprogramming within the tumor microenvironment and differentiated into effector subsets with antitumor activity (Fig. 1E). These findings suggest that the migration of key CD8+ T-cell subsets from lymph nodes to tumors, together with their fate transition, represents an important step in antitumor immune responses. Further analysis showed that metastatic lymph nodes exhibited a markedly immunosuppressive microenvironment, with a significantly increased proportion of terminally exhausted CD8+ T cells, weakens the overall efficacy of immunotherapy (Fig. 1F). In addition, we found that SPP1+ macrophages were significantly enriched in metastatic lymph nodes (Fig 1G). CellPhoneDB analysis suggested that SPP1+ macrophages may influence the differentiation state of Tpex through the TNF/TNFR1 axis, driving the Tpex subset toward terminal exhaustion, thereby weakening antitumor immunity and contributing to resistance (Fig. 1H).

Conclusion: ICIs activate the HLA-DR+ Tpex subset in TDLNs, which subsequently migrates into tumors and differentiates into effector cells to exert antitumor immune functions. It is suggested that Tpex serves as a key cellular basis linking immune responses between tumors and TDLNs. Lymph node metastasis may disrupt this tumor/TDLN immune axis through SPP1+ macrophage-mediated immunosuppressive remodeling, driving terminal exhaustion of Tpex and thereby contributing to ICI resistance.

Disclosure of Interest: N/A

Image:

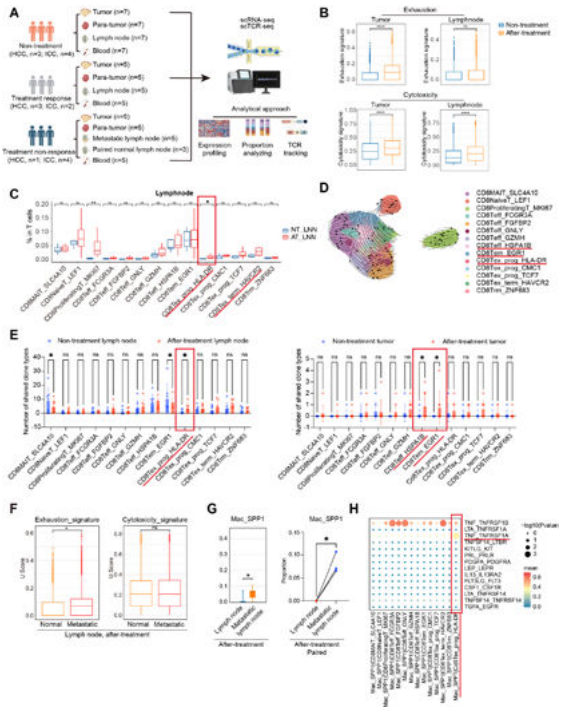

Figure 1. (A) Schematic overview of the enrolled sample types and the sequencing analysis workflow. (B) UCell analysis of exhaustion and effector function scores of CD8+ T cells in tumors and lymph nodes from the treatment-naive and treated groups. (C) Proportions of CD8+ T-cell subsets in TDLNs in the treatment-naive (NT) and after-treatment (AT) groups. (D) RNA velocity analysis of CD8+ T cells. (E) Distribution of shared TCR clones between lymph nodes and tumors across CD8+ T-cell subsets in lymph nodes from the treatment-naive and treated groups, and distribution of TCR clones derived from lymph node HLA-DR+ Tpex across CD8+ T-cell subsets in tumors from the treatment-naive and treated groups. (F) UCell scores of exhaustion and effector function of CD8+ T cells in normal lymph nodes and metastatic lymph nodes under the treatment setting. (G) Differences in the proportion of SPP1+ macrophages between normal lymph nodes and metastatic lymph nodes, as well as paired comparisons of SPP1+ macrophage proportions between normal and metastatic lymph nodes from the same patients. (H) CellPhoneDB analysis between SPP1+ macrophages and different CD8+ T-cell subsets.

Posters

P-027 FROM BULK TO SINGLE-CELL RNA SEQUENCING: A PROGNOSTIC RISK SCORE REVEALS TUMOR MICROENVIRONMENT HETEROGENEITY IN HBV-RELATED HEPATOCELLULAR CARCINOMA

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Introduction: Hepatitis B virus (HBV)-related hepatocellular carcinoma (HBV+HCC) exhibits extreme heterogeneity, driving variable clinical outcomes and resistance to immune checkpoint inhibitors (ICIs). This study aimed to develop a robust Prognostic Risk Score (PRS) and decode PRS-associated tumor microenvironment (TME) heterogeneity at single-cell resolution to uncover mechanisms of ICI resistance and novel therapeutic targets.

Methods: We integrated bulk RNA-seq data from 359 HBV+HCC patients across TCGA-LIHC, LIRI-JP, and CHCC-HBV cohorts to construct the PRS via LASSO Cox regression, which was then validated in an independent GEO cohort (GSE14520, N=218). Additionally, scRNA-seq data (GSE151530, N=12) were analyzed to dissect intratumoral heterogeneity. CellChat and Monocle2 were utilized to elucidate intercellular communication and pseudo-time differentiation trajectories.

Results: The PRS independently and accurately stratified patients into high- and low-risk groups with distinct overall survival. High PRS strongly predicted ICI resistance, correlating with advanced tumor stages, hyperactive proliferation, and suppressed hepatocyte function . scRNA-seq revealed profound malignant cell heterogeneity: the low-PRS subset (Malignant cells_APOC3) retained metabolic functions, whereas high-PRS subsets (HIST1H4C, PGA5, PTTG1) exhibited aggressive, proliferative phenotypes. Following ICI treatment, the HBV+HCC TME displayed effector T cell depletion alongside the expansion of resistant malignant subclones and the contraction of sensitive subclones. CellChat analysis indicated that ICI treatment adaptively altered signaling networks, particularly upregulating MIF and SPP1 pathways from sensitive subclones. Trajectory analysis identified RAN and RAC1 as critical regulators of tumorigenic plasticity and myeloid specialization. Notably, parallel in vitro analyses utilizing targeted knockouts further confirm the essential roles of RAN and RAC1 in driving the migration and invasion capacities of malignant cells.

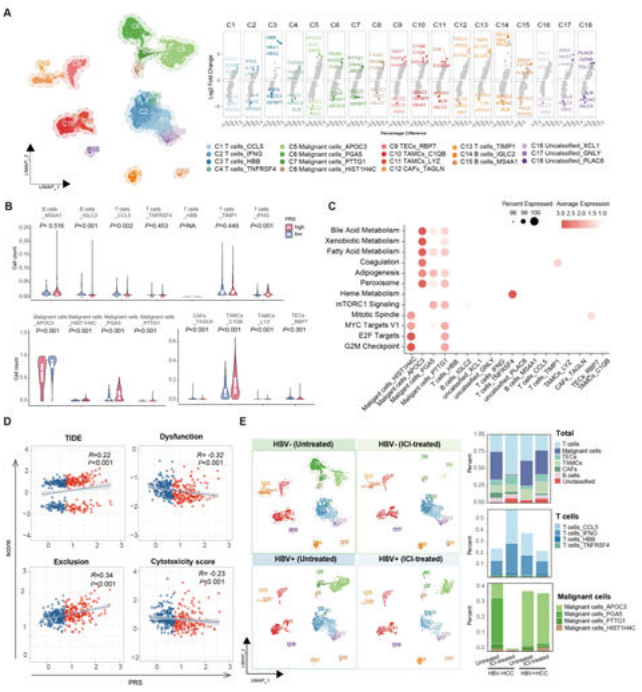
Conclusion: We established a highly predictive PRS for HBV+HCC prognosis and comprehensively mapped its associated TME heterogeneity. By deciphering the single-cell dynamics of ICI resistance, we highlight RAN and RAC1 as critical drivers of tumor progression and highly promising therapeutic targets to overcome the immunosuppressive TME.

Disclosure of Interest: N/A

Images:

Table S2: Clinical characteristics of traning cohort and validation cohort.

Clinical Characteristics of traning cohort						Clinical Characteristics of validation cohort	
CHCC-HBV cohort (HBV+HCC, N = 159)		LIRI-JP cohort (HBV+HCC, N = 229)		TCGA-LIHC cohort (HBV+HCC, n = 352)		GEO cohort (HBV+HCC, N = 218)	
Characteristics	No (%)	Characteristics	No (%)	Characteristics	No (%)	Characteristics	No (%)
Age		Age		Age		Age	
< = 60	88 （55.70%）	< = 60	27 (43.55%)	< = 60	50 （36.23%）	< = 60	176 (80.73%)
> 60	70 （44.30%）	> 60	35 (56.45%)	> 60	88 （63.77%）	>60	39 (17.89%)
Gender		Gender		Gender		Gender	
Female	31 （19.62%）	Female	10 (16.13%)	Female	45 （32.61%）	Female	29 (13.30%)
Male	127 （80.38%）	Male	52 (83.87%)	Male	93 （67.39%）	Male	189 (86.70%)
Tumor number		Virus genomic integrations		Histologic grade		BCLC stage	
1	117 （74.05%）	No	42 (67.74%)	G1	25 （18.12%）	0	20 (9.17%)
>1	41 （25.95%）	Yes	20 (32.26%)	G2	69 （50.00%）	A	147 (67.43%)
Tumor size		TNM stage		G3	42 （30.43%）	B	24 (11.01%)
<=5cm	75 （47.47%）	I	13 (20.97%)	G4	1 （0.72%）	C	27 (12.39%)
> 5cm	83 （52.53%）	II	24 (38.71%)	AFP level		TNM stage	
Liver cirrhosis		III	21 (33.87%)	Low (<=300ng/ml)	88 （63.77%）	I	92 (42.20%)
No	46 （29.11%）	IV	4 (6.45%)	High (>300ng/ml)	50 （36.23%）	II	77 (35.32%)
Yes	112 （70.89%）	HBVDNA		Inflammation		III	49 (22.48%)
Tumor thrombus		N	18 (29.51%)	None	45 （51.14%）		
No	121 （76.58%）	Y	43 (70.49%)	Mild	36 （40.91%）	Cirrhosis	
Yes	37 （23.42%）			Sever	7 （7.95%）	N	17 (7.80%)
AFP				RACE		Y	201 (92.20%)
Low (<=300ng/ml)	59 （37.34%）			Asian	76 （56.72%）	AFP (>/<=300ng/ml)	
High (>300ng/ml)	99 （62.66%）			Non-Asian	58 （43.28%）	NA	4 (1.83%)
BCLC stage				ECOG		high	96 (44.04%)
A	67 （42.41%）			<2	78 （71.56%）	low	118 (54.13%)
B	52 （32.91%）			≥2	31 （28.44%）		
C	39 （24.68%）			TNM stage			
TNM stage				I	42 （30.43%）		
I	91 （57.59%）			II	38 （27.54%）		
II	13 （8.23%）			III	52 （37.68%）		
III	52 （32.91%）			IV	2 （1.45%）		
IV	2 （1.27%）			HBV Surface Antibody			
HBcAb				N	80 （57.97%）		
N	9 （5.70%）			Y	58 （42.03%）		
Y	149 （94.30%）			HBV Core Antibody			
				N	81 （58.70%）		
				Y	57 （41.30%）		
				HBV DNA			
				N	127 （92.03%）		
				Y	11 （7.97%）		
				Child_pugh			
				A	63 （82.89%）		
				B	12 （15.79%）		
				C	1 （1.32%）		
				vascular_tumor_cell_type			
				None	57 （55.34%）		
				Mrico	41 （39.81%）		
				Macro	5 （4.85%）		



P-028 STUDY ON THE ROLE AND MECHANISM OF SEPHS1 IN PROMOTING THE MALIGNANT PROGRESSION OF HEPATOCELLULAR CARCINOMA

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Introduction: High metastatic potential is a highlighted hallmark of hepatocellular carcinoma (HCC), yet the mechanisms remain unclear. This study aimed to identify key genes driving HCC metastasis and to investigate the role and mechanisms of the top-ranked candidate, selenophosphate synthetase 1 (SEPHS1).

Methods: A multi-tiered bioinformatics screening strategy was applied to integrate multiple GEO datasets encompassing distinct metastasis-associated phenotypes, including high-metastatic-potential cell models, vascular invasion, lung metastasis and advanced clinical progression. Intersecting DEGs across datasets and two HCC clinical cohorts yielded prioritized candidates. SEPHS1 was functionally validated via migration/invasion, flow-based cell-endothelial adhesion, transendothelial migration and proliferation assays in vitro. A tail-vein pulmonary metastasis model, a tumor cell extravasation model, and an orthotopic intrahepatic xenograft model were established in vivo. Further, RNA-seq and APEX2-MS were employed to elucidate underlying mechanisms. SEPHS1 associations with immune infiltration, checkpoint expression, and immune phenotype scores were evaluated using public HCC transcriptomic datasets.

Results: Multi-dataset intersection identified 33 candidates consistently upregulated in metastasis-related datasets, with SEPHS1 most significantly elevated. Clinically, SEPHS1 was upregulated in HCC and associated with poor prognosis and diminished immunotherapy response. SEPHS1 promoted the migration, invasion, proliferation, endothelial adhesion, and transendothelial migration in vitro, and facilitated extravasation and distant colonization in vivo. Mechanistically, RNA-seq and APEX2-MS implicated an adhesion–cytoskeleton axis. SEPHS1 knockdown impaired cytoskeletal remodeling, evidenced by reduced F-actin intensity and lamellipodia formation, accompanied by decreased phosphorylation of FAK, PAK1, cofilin and SMAD3, indicating SEPHS1 sustains malignant progression via the FAK/PAK1/cofilin axis. Besides, high SEPHS1 correlated with macrophage, Treg, and MDSC enrichment, checkpoint upregulation, and elevated immune exclusion scores, suggesting an immune-excluded TME unfavorable to immunotherapy response.

Conclusions: Our study suggests that SEPHS1 promotes HCC malignant progression, by activating FAK/PAK1/cofilin pathway to drive cytoskeletal remodeling, identifying SEPHS1 as a potential therapeutic target for HCC.

Disclosure of Interest: N/A

Posters

P-029 CFDNA-DERIVED TUMOUR FRACTION PREDICTS CLINICAL OUTCOMES IN PATIENTS WITH HCC RECEIVING RADIOTHERAPY FOR INTRAHEPATIC OLIGOPROGRESSION ON IMMUNOTHERAPY

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Introduction: Stereotactic body radiotherapy (SBRT) is increasingly utilized in hepatocellular carcinoma (HCC).1 However, response assessment following radiotherapy treatment is challenging because radiotherapy exerts its therapeutic anti-cancer effects through delayed necrosis, resulting in the persistence of arterial phase hyperenhancement up to one year.2 Our team has previously developed and validated the chromosome arm-level z-score analysis (CAZA) to analyse circulating cell-free DNA to inform tumour fraction without the need of tumour biopsy.3 In this study, we present the pilot data on the utility of CAZA-derived tumour fraction (TF) in predicting response and survival.

Methods: Patients with intrahepatic oligoprogression on atezolizumab plus bevacizumab, who are determined by multidisciplinary team (MDT) to be suitable for SBRT were recruited since 2025 at the Prince of Wales Hospital, Hong Kong. Enrolled Patients received 27.5 to 50Gy in 5 fractions, over 2 weeks, as per RTOG-1112 trial. Peripheral blood samples were collected before the first fraction of SBRT (pre-RT) and 2 weeks after SBRT (post-RT). cfDNA extraction, processing and extraction were performed as previously described.3,4 CAZA was applied to estimate TF in pre-RT and post-RT specimens. Patients were follow-up every 3 weeks to continue systemic treatment, with imaging arranged every 8 weeks, until disease progression, intolerable toxicity, lost to follow-up, or death. The primary endpoint is objective response rates (ORR) assessed by RECIST 1.1. Secondary endpoint is progression-free survival.

Results: Six patients with intrahepatic oligoprogression on atezolizumab plus bevacizumab were recruited (Table 1). Median age was 69.5 (range: 52-79). 5 of them were male and BCLC B stage respectively. Total 9 tumours were treated with a median size of 3.0cm (range: 1.8-10.3cm). Median TF pre-RT was 5.9% (range: 3.7-10.2%) and post-RT was 4.1% (range: 0-9.8%). Four patients had decreased TF post-RT, whereas 2 patients had increased TF post-RT (Figure 1). In those four patients who had TF drop, one patient died due to liver failure without disease progression. The ORR in this group was 50% and the median PFS was 8.1 months. In the two patients with increased TF, one patient developed disease progression. The ORR in this group was 0% and the median PFS was 6.8 months.

Conclusion: The pilot data suggest that CAZA-derived TF could potentially predict response and survival in patients with HCC receiving SBRT for intrahepatic oligoprogression on immunotherapy.

Disclosure of Interest: Research/Education grant

Images:

Table 1. Patients' baseline characteristic, tumour fraction change, and survival following receipt of radiotherapy at oligoprogression on immunotherapy in the pilot cohort

ID	Sex	Age	BCLC stage	Number of lesions treated	Size of lesions prior RT (cm)	Size of lesions after RT (cm)	Total size change (%)	Tumour fraction change	Progress or death	PFS (mos)
TMC	M	77	C	1	7.1	7.1	0	Decrease (10.2% →9.8%)	1	6.7
YKS	M	64	B	3	3.0, 3.0, 2.6	2.4, 1.6, 1.6	-35	Decrease (6.9%→ 0%)	0	12.0
KCS	M	67	B	1	4.3	2.5	-42	Decrease (3.7%→ 3.5%)	0	8.0
YKH	M	72	B	1	10.3	9.8	-4	Increase (4.1%→ 4.7%)	1	7.5
CMS	F	52	B	1	1.8	1.8	0	Increase (4.8%→ 5.4%)	0	6.0
FKT	M	79	B	2	7.2, 4.0	5.2, 2.9	-28	Decrease (7.9%→ 0%)	0	5.6

BCLC: Barcelona Clinic Liver Cancer; mos: months; PFS: progression-free survival; RT: radiotherapy

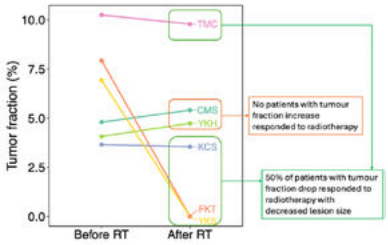

Figure 1. CAZA-derived tumour fraction changes (%) in plasma in pre-RT and 2 weeks post-RT. Two out of 4 patients with decreased tumour fraction achieved radiological response, in comparison to none of the patients with increased tumour fraction achieved radiological response.

P-030 FATE TRANSITION OF PROGENITOR EXHAUSTED-LIKE CD8+ T CELLS IN THE TUMOR/DRAINING LYMPH NODE IMMUNE AXIS AND ITS ROLE IN IMMUNOTHERAPY RESISTANCE OF LIVER CANCER

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Introduction: Liver cancer remains a leading cause of cancer-related death worldwide, and many patients lose the opportunity for curative surgery at diagnosis. Immune checkpoint inhibitors (ICIs) have markedly reshaped the treatment landscape of liver cancer, including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). However, therapeutic resistance remains a major barrier to durable clinical benefit. Progenitor exhausted CD8+ T cells (Tpex) are increasingly recognized as a key cellular population underlying ICI-induced antitumor immunity. However, whether TDLNs harbor a functionally distinct Tpex reservoir, and whether Tpex fate transition influences antitumor immunity and immunotherapy outcomes through the tumor–TDLN immune axis, remains unclear.

Methods: This study included 17 patients with liver cancer, comprising HCC and ICC. A total of 71 specimens were collected, including tumor tissue, para-tumor tissue, peripheral blood, and TDLNs. Ten patients underwent surgery after immunotherapy-based systemic therapy, whereas 7 treatment-naive patients served as controls. Among treated patients, 5 achieved major pathological response (MPR, defined as <50% viable tumor cells) and 5 did not. All specimens were profiled by single-cell RNA sequencing and single-cell T-cell receptor (TCR) sequencing. HLA-DR+ Tpex cells in TDLNs were further assessed by flow cytometry. Patients were also stratified according to HLA-DR+ Tpex abundance in lymph nodes for survival analysis. To investigate the effect of macrophages on Tpex fate, SPP1+ or SPP1- tumor-associated macrophages (TAMs) sorted from HCC samples were co-cultured with HLA-DR+ Tpex cells.

Results: ICI therapy enhanced the effector function of CD8+ T cells in TDLNs, whereas intratumoral CD8+ T cells displayed concurrent effector activation and terminal exhaustion. Immunotherapy markedly increased the HLA-DR+ Tpex subset in TDLNs, which was further validated by flow cytometry. In an HCC immunotherapy cohort from our center, a higher proportion of HLA-DR+ Tpex cells in lymph nodes was associated with better survival outcomes. RNA velocity analysis indicated that this subset retained the potential to differentiate into effector T cells. TCR clonal tracing further showed that HLA-DR+ Tpex cells originating from TDLNs could migrate into tumors, where they underwent functional reprogramming and differentiated into effector CD8+ T-cell subsets with antitumor activity. In contrast, metastatic lymph nodes exhibited a markedly immunosuppressive microenvironment, with an increased proportion of terminally exhausted CD8+ T cells. SPP1+ macrophages were significantly enriched in metastatic lymph nodes and further confirmed by flow cytometry. CellPhoneDB analysis suggested that SPP1+ macrophages may drive Tpex toward terminal exhaustion through the TNF/TNFR1 axis, thereby weakening antitumor immunity and contributing to therapeutic resistance.

Conclusion: ICIs activate and expand HLA-DR+ Tpex cells in TDLNs, which subsequently traffic into tumors and differentiate into effector cells to mediate antitumor immunity. These findings identify TDLNs as an important Tpex reservoir and support a key role for Tpex in the tumor–TDLN immune axis. Lymph node metastasis may disrupt this axis through SPP1+ macrophage-mediated immunosuppressive remodeling, promoting premature terminal exhaustion of Tpex and contributing to resistance to ICI therapy.

Disclosure of Interest: N/A

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Images:

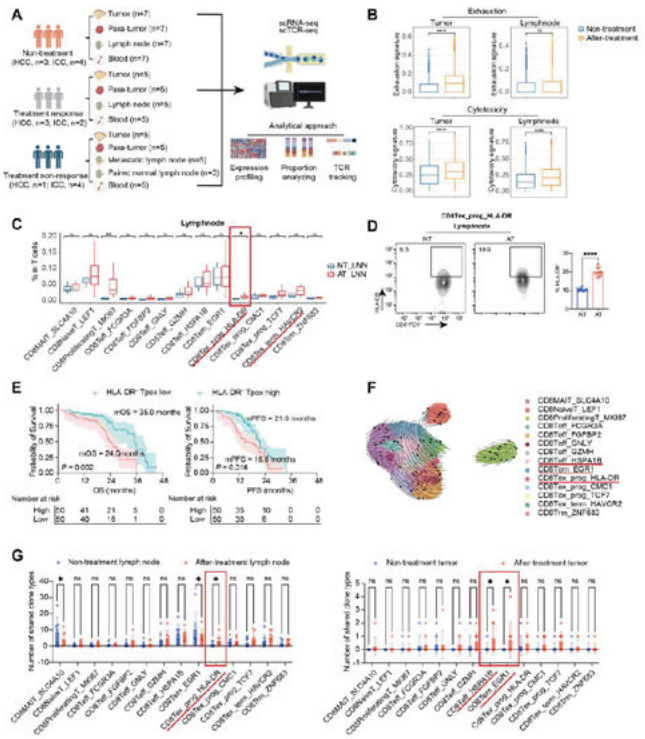

Figure 1. (A) Schematic overview of the enrolled sample types and the sequencing analysis workflow. **(B)** UCell analysis of exhaustion and effector function scores of CD8⁺ T cells in tumors and lymph nodes from the treatment-naive and treated groups. **(C)** Proportions of CD8⁺ T-cell subsets in TDLNs in the treatment-naive (NT) and after-treatment (AT) groupsbased on single-cell RNA sequencing. **(D)** Detection of the HLA-DR+ Tpex subset in TDLNs by flow cytometry from patients after immunotherapy. **(E)** Overall survival (OS) and progression-free survival (PFS) of patients stratified into HLA-DR⁺ Tpex-high and HLA-DR⁺ Tpex-low groups according to the cutoff value defined by HLA-DR⁺ Tpex mIHC staining of TDLNs. **(F)** RNA velocity analysis of CD8⁺ T cells. **(G)** Distribution of shared TCR clones between lymph nodes and tumors across CD8⁺ T-cell subsets in lymph nodes from the treatment-naive and treated groups, and distribution of TCR clones derived from lymph node HLA-DR⁺ Tpex across CD8⁺ T-cell subsets in tumors from the treatment-naive and treated groups.

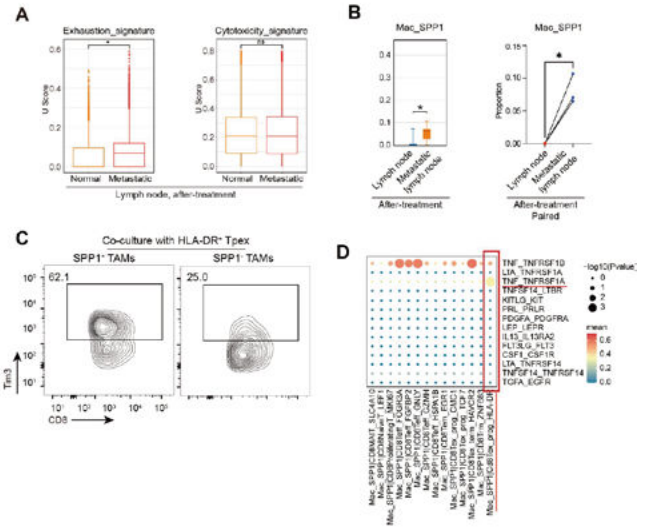

Figure 2. (A) UCell scores of exhaustion and effector function of CD8⁺ T cells in normal lymph nodes and metastatic lymph nodes under the treatment setting. **(B)** Differences in the proportion of SPP1⁺ macrophages between normal lymph nodes and metastatic lymph nodes, as well as paired comparisons of SPP1⁺ macrophage proportions between normal and metastatic lymph nodes from the same patients. **(C)** The Tim3 level of HLA-DR⁺ Tpex cells after co-culture with sorted SPP1⁺ or SPP1⁻ TAMs from patients with HCC detected by flow cytometry. **(D)** CellPhoneDB analysis between SPP1⁺ macrophages and different CD8⁺ T-cell subsets.

P-031 HEPATIC DECOMPENSATION IS DRIVEN BY UNDERLYING LIVER DISEASE RATHER THAN IMMUNOTHERAPY CHOICE IN INRESECTABLE HEPATOCELLULAR CARCINOMA

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Background and Aims: Immunotherapy combinations have transformed the treatment of HCC, but their effects on hepatic decompensation remain unclear. This project compares the incidence of ascites, hepatic encephalopathy (HE), and variceal bleeding (AVB) under atezolizumab bevacizumab (Atezobev) versus durvalumab–tremelimumab (DurvaTreme).

Methods: This multicenter retrospective study included patients treated with first-line AtezoBev or DurvaTreme. Patients were matched 1:1 using propensity score methods. Hepatic decompensation (defined as the occurrence of ascites, HE, and/or AVB) occurring after treatment initiation and prior to progression (per RECIST 1.1) was compared between the two groups.

Results: Among 1,053 patients, 908 received AtezoBev and 145 DurvaTreme. Patients treated with DurvaTreme more frequently had a history of AVB (23% vs. 12%, p=0.001) and ascites (23%

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vs. 15%, p=0.008). After matching, 280 patients were analyzed; in both groups, about 60% were BCLC-C, 35% had vascular invasion, 20% had prior AVB, 24% had prior ascites, 50% had varices, 8% had ascites, 40% received non-selective beta-blockers, 60% were Child-Pugh A, and 24% were ALBI grade 1.

After a median follow-up of 20.1 months, OS was similar between patients treated with AtezoBev and DurvaTreme (median OS 20.8 months vs. not reached, p=0.25). Hepatic decompensation occurred in 27.9% patients treated with AtezoBev and 23.6% patients treated with DurvaTreme (p=0.49), with a median time to decompensation of 3.47 and 1.97 months (p=0.02), respectively. AVB was more frequent in the AtezoBev group (13.8% vs. 5.7%, p=0.03), whereas the incidence of HE and ascites did not differ between groups. Early hepatic decompensation within the first 3 months of treatment, was more frequent in the AtezoBeva group (18.5% vs. 6.4%, p<0.001). Hepatic decompensation-related death occurred in 13.5% patients in the AtezoBev group and 23.1% patients in the DurvaTreme group (p=0.31). Only history of ascites (OR 3.37, p=0.001) was independently associated with hepatic decompensation, but not the type of treatment received.

Conclusion: AtezoBev and DurvaTreme were associated with similar OS, but differed in the pattern of hepatic decompensation, with higher rates of AVB and observed in the AtezoBev group. These differences were largely driven by baseline liver disease severity, particularly a history of ascites, which emerged as the main determinant of decompensation risk, rather than treatment choice itself.

Disclosure of Interest: Consulting

P-032 STROMAL TGF-β3 DRIVES EMT AND PRO-METASTATIC REPROGRAMMING IN INTRAHEPATIC CHOLANGIOCARCINOMA AND ASSOCIATES WITH TREATMENT RESPONSE

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Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer, characterized by limited treatment options and poor prognosis. Epithelial-mesenchymal transition (EMT) is a hallmark of tumor progression, promoting cell migration, invasion, and therapy resistance. Among the TGF-ß isoforms, TGF-ß1 and TGF-ß2 have been extensively studied in iCCA, whereas the role of TGF-ß3 remains poorly understood. Emerging data suggest increased TGF-ß3 expression in iCCA, but its cellular origin, molecular function, and clinical significance are largely unknown.

Expression of TGF-ß3 and its cellular sources were analyzed using single-cell and bulk RNA sequencing from public datasets and internal patient cohorts. Transcriptomic analyses, including GSEA, IPA, Metascape, and CIBERSORTx, were used to identify molecular pathways associated with TGF-ß3 expression. Functional studies in two patient-derived iCCA cell lines assessed the effects of TGF-ß3 on migration, invasion, and colony and sphere formation. EMT induction was validated via RNA sequencing and immunofluorescent staining. Serum TGF-ß3 levels were measured in iCCA patients, including those receiving chemo-/immunotherapy, and correlated with treatment response.

Gene expression analyses revealed elevated TGF-ß3 levels in iCCA tissues, with high expression detected in approximately 25% of cases. Single-cell RNA-seq profiling identified cancer-associated fibroblasts (CAFs) as the main TGF-ß3 source within the tumor microenvironment. Transcriptomic profiling indicated enrichment of TGF-ß3, NOTCH, and WNT signaling pathways, as well as gene sets related to EMT and apical junction alterations. Functional assays confirmed that TGF-ß3 significantly enhances migration, invasion, colony and sphere formation in iCCA cells. EMT induction was evidenced by the downregulation of E-cadherin and EpCAM and upregulation of vimentin. GSEA and IPA analyses revealed concomitant enrichment of fibrogenesis and EMT-related genes, including IL-11, PDGFB, MMP9, and COL5A1, suggesting a positive feedback loop between CAFs and tumor cells mediated by TGF-ß3. In serum samples, TGF-ß3 levels were elevated in a subset of patients and decreased following chemo- or immunotherapy.

These findings identify stromal TGF-ß3 as a novel and clinically relevant driver of EMT and pro-metastatic reprogramming in iCCA. A distinct patient subgroup characterized by high TGF-ß3 expression exhibits increased invasiveness but shows potential responsiveness to systemic therapy, highlighting TGF-ß3 as a candidate biomarker as well as a therapeutic target.

Disclosure of Interest: N/A

P-033 TARGETING DICKKOPF-1 UNLOCKS SYNERGISTIC ANTITUMOR IMMUNITY WITH PD-L1 BLOCKADE IN HEPATOCELLULAR CARCINOMA

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Background and Aims: Dickkopf-1 (DKK1), a secreted Wnt antagonist, is frequently overexpressed in hepatocellular carcinoma (HCC) and has been implicated in tumor progression. However, its role in immune regulation and therapeutic response remains unclear. We investigated the immunomodulatory function of DKK1, its association with programmed death-ligand 1 (PD-L1), and the potential benefit of DKK1 inhibition combined with anti–PD-L1 therapy.

Methods: We employed patient samples, human HCC cell lines with DKK1 knock-out (KO) or overexpression, and a syngeneic murine HCC model. PD-L1 expression was assessed by immunohistochemistry, western blotting, and qRT-PCR. T-cell activity was evaluated through Jurkat co-culture assays and cytokine secretion. The pharmacologic DKK1 inhibitor WAY-262611 was tested alone or in combination with anti–PD-L1 in vitro and in vivo.

Results: High DKK1 expression correlated with increased PD-L1 levels in human HCC tissues and cell lines, while DKK1 KO reduced PD-L1 expression. Co-culture experiments revealed that DKK1 suppressed Jurkat T-cell viability and IFN-γ production. Treatment with WAY-262611 downregulated PD-L1 expression and reduced tumor cell migration. In vivo, Hepa1-6 DKK1 tumors displayed enhanced growth suppression when treated with combined DKK1 inhibition and anti–PD-L1, compared with either agent alone (P<0.05). Dual blockade significantly increased $CD8^+$ T-cell infiltration and reduced immune evasion.

Conclusions: DKK1 promotes immune escape in HCC by upregulating PD-L1 and impairing T-cell function. Pharmacologic inhibition of DKK1 augments the antitumor efficacy of PD-L1 blockade, suggesting that DKK1 is a promising therapeutic target and biomarker for immunotherapy combinations in HCC.

Disclosure of Interest: N/A

P-034 MONOCLONAL ANTIBODIES TARGETING EXTRACELLULAR REGION OF CELL SURFACE LANCL1 SUPPRESSES TUMORIGENESIS IN HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) remains a common and lethal form of cancer worldwide. Within HCC, liver tumour-initiating cells (LTICs) are a self-renewing subset that play a crucial role in tumor development and resistance to therapy. Previously, we identified LANCL1 as a functional cell surface marker that facilitates HCC tumor initiation via the FAM49B/Rac1 pathway, leading to decreased cellular reactive oxygen species (ROS). In this study, we investigate the potential of targeting LANCL1 on the cell surface using antibody-based strategies for future therapeutic translation.

Methods: We produced murine monoclonal antibodies (mAbs) and assessed their effectiveness through various in vitro assays, including sphere formation, cytotoxicity, migration, and invasion assays on HCC cell lines; and evaluated their impact in vivo using an orthotopic HCC mouse model.

Results: The human LANCL1 protein shares significant sequence similarity with LANCL2 in its central region. To generate antibodies specific to LANCL1's extracellular N-terminal domain, we used a peptide corresponding to amino acids 1-42 of human LANCL1 as the immunogen. Screening of supernatants from hybridoma clones was performed via ELISA using the immunogen, Western blot analysis on denatured and native forms of the 1-42aa peptide expressed in E. coli B21 lysates, and on full-length LANCL1 expressed in PLC/PRF/5 cells. Clonal mAbs demonstrating specific binding to LANCL1 were identified through flow cytometry on LANCL1-overexpressing HCC cells. These antibodies effectively inhibited sphere formation, induced notable cytotoxic effects, and reduced migration and invasion in vitro. In vivo, the mAbs significantly suppressed tumor growth and lung metastasis of PLC/PRF/5 cells in an immunodeficient orthotopic HCC mouse model.

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Conclusion: Targeting the surface-expressed LANCL1 on HCC cells with monoclonal antibodies effectively diminished aggressive tumor behaviors and tumor-initiating capacity. These findings lay a promising groundwork for developing anti-LANCL1 antibody therapies for clinical application.

Disclosure of Interest: N/A

P-035 LR-VID: A LONG-READ SEQUENCING-BASED DETECTOR FOR COMPREHENSIVE AND HIGH-RESOLUTION CHARACTERIZATION OF HEPATITIS B VIRUS INTEGRATIONS IN HEPATOCELLULAR CARCINOMA

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Introduction:Hepatitis B virus (HBV) can promote the development of hepatocellular carcinoma (HCC) through multiple mechanisms, including viral integration. Viral integrations are HBV-induced structural alterations that disrupt gene function through insertional mutagenesis, with several hotspots such as TERT, CCNE1, and MLL4 have been reported. They can also promote HCC through the induction of chromosomal instability and the continuous exogenous expression of HBV genes. Previous studies utilizing short-read sequencing, typically ranging from 50 to 300 bases, had limited resolution and primarily limited to the detection of virus-host junctions. This impedes a comprehensive understanding of their role in the hepatocarcinogenesis. We built the LR-VID algorithm that leverages long-read sequencing, ranging from approximately 1 to 100 kilobases, to enable a comprehensive and high-resolution characterization of viral integrations in HCC, and to advance insights into their roles in HCC development.

Methods: We analyzed Oxford Nanopore whole-genome sequencing reads in 3 simulated datasets of different HBV genotypes and real data of 29 HBV-associated HCC patients, which include 20 from our in-house cohort and 9 from the Pan-Cancer Analysis of Whole Genomes (PCAWG). The simulated datasets were prepared with vector-integration-simulation-pipeline 0.0.2 and NanoSim 3.0.2. For our in-house cohort, ligation protocol libraries were prepared and sequenced on the PromethION R10.4.1 flow cells, controlled by MinKNOW 24.06.15. The mean coverage was 31× for the simulated datasets, 40× for our in-house cohort, and 9× for the PCAWG cohort. Reads for each sample were pre-processed using Chopper 0.8.0 to remove low-quality and adapter bases, and any reads shorter than 100 bases were also discarded. Our detector then identified viral integrations and their adjacent hosts by mapping reads to the pan-genotypic HBV (A-J), and human (hs1) reference genomes, using minimap2 2.30 augmented by BLAST 2.16.0.

Results: We validated LR-VID using 3 simulated datasets with 20 known viral integration events each. All 60 events were successfully detected, with 96.2% of the host and viral breakpoints determine to be located within 5 bases of the ground truth. In all cases, detected breakpoints deviated by no more than 12 bases. The validated algorithm was then applied to the 29 HBV-associated HCC patient samples. Overall, a total of 829 events were identified across all patients. Of these, 68 events were classified as high-confidence QC-passed events, supported by at least four reads that completely or partially spanned the event. Notably, 7 out of 9 PCAWG patients had no QC-passed events, likely due to the substantially lower coverage (ranging from 4× to 13×). The remaining 2 PCAWG and 20 in-house cohort patients had between 1 and 9 QC-passed events, with a mean event size of 1,856 bases.

Conclusion: Our algorithm, LR-VID, utilizes long-reads to extend resolution beyond the virus-host junctions, which were previously the only possible focus using short-read data. We achieved a comprehensive, ultra high-resolution characterization of viral integration events in HCC, laying the groundwork for further insights into their role in the development of the disease.

Disclosure of Interest: N/A

P-036 TARGETING CRIP1 CONDENSATION SUPRESSES THE DEVELOPMENT AND THE IMMUNE ESCAPE OF HEPATOCELLULAR CARCINOMA

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Introduction: Emerging evidence indicates that epigenetic remodeling of intrinsic tumor genes, driven by immune pressure, serves as a critical mechanism that further exacerbates immune evasion and ICB therapy resistence1. However, the role of epigenetic regulators in enhancing HCC immunotherapy remains to be explored2. CRISPR/Cas9 screening provides a powerful technical tool for systematically and unbiased identification of tumor cell susceptibility3,4. Therefore, we used an in vivo mouse model of orthotopic liver tumors to conduct two rounds of rigorous in vivo screening to systematically identify key epigenetic regulators that regulate the immune tumor microenvironment and thus affect the efficacy of ICB therapy.

Methods: To elucidate the mechanisms of ICB resistance and enhance therapeutic efficacy for HCC, we conducted mouse model of orthotopic liver tumors to conduct two rounds of rigorous in vivo CRISPR/Cas9 epigenetic sublibrary screening to systematically identify Cysteine rich protein 1(CRIP1) as a key epigenetic mediator of immune evasion and ICB resistance in HCC. The therapeutic potential of combining CRIP1 inhibition with anti-PD-1 ICB blockade was rigorously validated across multiple preclinical platforms, including immunocompetent mouse models, patient-derived organoids(PDO) ,and patient-derived tumor fragments(PDTF).

Results: CRISPR screening identified CRIP1 as a critical epigenetic regulator of immune evasion, demonstrating that its presence significantly suppresses anti-tumor immune responses. Tumor cell-intrinsic CRIP1 is markedly overexpressed in HCC, especially in ICB-resistant HCC, and directly interacts with E4F1. Consequently, silencing E4F1 disrupts CRIP1-mediated liquid–liquid phase separation and prevents the formation of CRIP1 condensates. Enhanced nuclear translocation of CRIP1 facilitates its binding to the C-C motif chemokine ligand 15 (CCL15) promoter, thereby driving CCL15 transcription and secretion. CRIP1-mediated transcriptional activation of CCL15 recruits M2-like macrophages, thereby forming immunosuppressive microenvironment and weakening anti-tumor immunity in HCC. Furthermore, compounds AE-848 identified through virtual screening can enhance the efficacy of anti-PD-1 therapy in mouse models, PDO, and PDTF.

Conclusion: CRIP1-driven LLPS activates the CCL15/M2-like macrophage axis, establishing an TIME that excludes CD8+ T cells in HCC. Targeting CRIP1 enhances the sensitivity of HCC tumors to anti-PD-1 therapy, providing a synergistic therapeutic approach.

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Disclosure of Interest: N/A

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Images:

Targeting CRIP1 condensation supresses the development and the immune escape of hepatocellular carcinoma

Lizhuang Shu, MD,PhD[1]; Muzi Cao, MD, PhD[1]; Hui Liu, MD, PhD[1]; Mufan Ji, MD, PhD[1]; Jia Fan, MD, PhD[1]; Yunfan Sun, MD, PhD[1,*]; Jian Zhou, MD, PhD[1,*]

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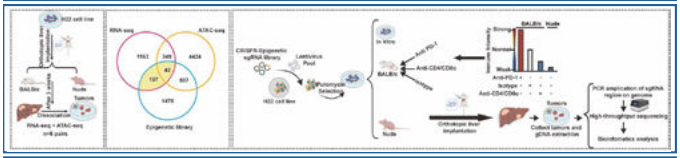
Introduction

Emerging evidence indicates that epigenetic remodeling of intrinsic tumor genes, driven by immune pressure, serves as a critical mechanism that further exacerbates immune evasion and ICB therapy resistence[1]. However, the role of epigenetic regulators in enhancing HCC immunotherapy remains to be explored[2]. CRISPR/Cas9 screening provides a powerful technical tool for systematically and unbiased identification of tumor cell susceptibility[3,4]. Therefore, we used an in vivo mouse model of orthotopic liver tumors to conduct two rounds of rigorous in vivo screening to systematically identify key epigenetic regulators that regulate the immune tumor microenvironment and thus affect the efficacy of ICB therapy.

Materials and Methods



Results

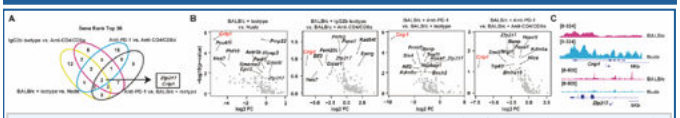


Figure 1. ***In vivo*** **CRISPR screen identifies epigenetic regulators of tumor immunity. A.** Intersection of the gene rank top 30 CRISPR negative screening genes under different immune stresses. **B.** Landscape of differential genetic dependencies identified by custom epigenetic CRISPR screening. **C.** Schematic diagram of chromatin accessibility for Crip1 and Zfp217

Results

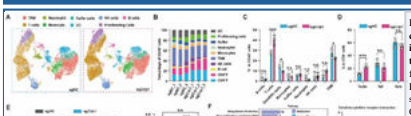


Figure 2. Loss of CRIP1 in tumor cells triggers CD8⁺ T cell-mediated anti-tumor immunity by promoting their infiltration and activation, thereby sensitizing tumors to anti-PD-1 therapy. A. scRNA-seq of CD45+ cells from orthotopic liver tumors in mice after Crip knockout. **B-C.** Changes in the proportion of different immune cell subsets in different samples. **D.** Comparative analysis of $CD8^+$ T cell sub-population dynamics across experimental groups. **E.** Representative images of orthotopic liver tumors in mice treated with combined anti-mouse-CD8α therapy, along with quantitative images of fluorescence intensity and tumor weight at sacrifice. **F.** Changes in genes enriched in the cytokine pathway after knocking down CRIP1. **G.** Representative RNA-FISH images showing CRIP1 expression (green) and CCL15 (yellow) mRNA distribution. **H.** Feature plot of CCR1 expression in immune cells.

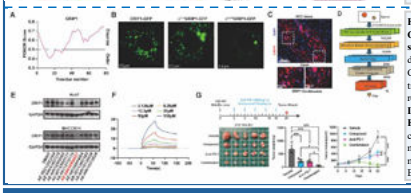


Figure 3. Targeting CRIP1 phase separation with $C_{16}H_{13}NO_2S$ remodels the tumor microenvironment to synergize with anti-PD-1 blockade. A. The intrinsic disorder region of CRIP1 predicted using PONDR. **B.** Confocal representation of condensates of plasmids with truncated CRIP1-IDR. **C.** Immunofluorescence representation of CRIP1 condensation in HCC tumor tissue. **D.** Virtual screening diagram for finding CRIP1 inhibitors. **E.** Immunoblotting against CRIP1 in Huh7 and MHCC97H cells treated with agents from D. **F.** SPR binding affinity measurements between compound and CRIP1. **G.** BALB/c mice bearing H22 tumors were treated with indicated drugs. Excised tumor images and serial tumor volumes.

Conclusion

CRIP1-driven LLPS activates the CCL15/M2-like macrophage axis, establishing a TIME that excludes $CD8^+$ T cells in HCC. Targeting CRIP1 enhances the sensitivity of HCC tumors to anti-PD-1 therapy, providing a synergistic therapeutic approach.

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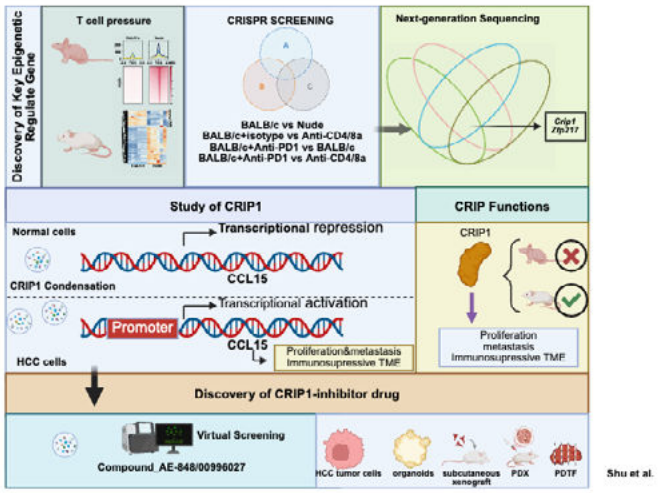

P-037 TARGETING WNT/β-CATENIN WITH LIPOPHILIC STATINS SENSITIZES HEPATOCELLULAR CARCINOMA TO LENVATINIB

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Introduction: Lenvatinib, an oral multikinase inhibitor, is approved for unresectable hepatocellular carcinoma (HCC), but drug resistance limits its efficacy through mechanisms that remain poorly defined. Here, we show that statins — particularly lipophilic statins — enhance the antitumor activity of lenvatinib in lenvatinib-resistant HCC by suppressing β-catenin nuclear translocation.

Methods: Huh7 and Hep3B cells were treated with lenvatinib alone or in combination with ICG-001, a ß-catenin/CBP antagonist. Lenvatinib-resistant cells (LRCs) were established by long-term lenvatinib exposure of Huh7 cells. LRCs and Hep3B cells were then treated with lenvatinib alone or in combination with simvastatin or rosuvastatin, and evaluated by immunoblotting, quantitative PCR, luciferase reporter, and cell viability assays. We also retrospectively analyzed 586 patients with HCC who initiated lenvatinib at a single tertiary center between October 2018 and December 2024. Overall survival (OS) and progression-free survival (PFS) were compared between baseline statin users (n=57) and non-users (n=529) using crude analyses and 1:4 propensity score matching (PSM) based on demographic, tumor, liver function, and laboratory variables. An exploratory subgroup analysis further compared rosuvastatin (a hydrophilic mechanistic comparator; n=28) with lipophilic statins (atorvastatin, simvastatin, pitavastatin; n=29) among statin users.

Results: Hep3B cells were relatively resistant to lenvatinib compared with Huh7 cells, owing to higher intrinsic Wnt/ß-catenin activity. ß-catenin inhibition augmented lenvatinib-induced cell death in Hep3B cells, whereas LRCs and Huh7 cells transfected with mutated ß-catenin exhibited a resistant phenotype. In LRCs and Hep3B cells, lipophilic — but not hydrophilic — statins combined with lenvatinib significantly increased apoptotic cell death compared with lenvatinib alone. Consistently, lipophilic statins inhibited ß-catenin nuclear translocation in a p300-dependent manner. In the clinical cohort, statin users had significantly longer OS (9.4 vs. 6.8 months; HR 0.63, 95% CI 0.46–0.88; p=0.006) and PFS (5.7 vs. 3.5 months; HR 0.72, 95% CI 0.54–0.96; p=0.023) than non-users. After 1:4 PSM (52 vs. 208 patients), the OS benefit was attenuated but remained directionally favorable (9.9 vs. 9.0 months; HR 0.72, 95% CI 0.50–1.02; p=0.068), whereas PFS no longer differed significantly (6.0 vs. 4.5 months; HR 0.84, 95% CI 0.61–1.15; p=0.284). In line with the preclinical findings, lipophilic statins were associated with numerically longer OS than the hydrophilic comparator among statin users (12.9 vs. 7.6 months; HR 0.65, 95% CI 0.34–1.20; p=0.169).

Conclusions: Activation of Wnt/ß-catenin signaling confers intrinsic resistance to lenvatinib, which is abrogated by lipophilic statins. Combining lenvatinib with lipophilic statins may therefore be a promising strategy to enhance lenvatinib sensitivity in HCC.

Disclosure of Interest: N/A

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P-038 Inter-individual variability in immune responses to PD-L1 blockade in hepatocellular carcinoma

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Introduction: Programmed death-ligand 1 (PD-L1/CD274) is a key immune checkpoint that enables tumor immune evasion through interaction with programmed cell death protein 1 (PD-1) on immune cells. Immune checkpoint inhibitors (ICIs) have improved outcomes in hepatocellular carcinoma (HCC), particularly in combination regimens, and are increasingly used beyond advanced disease stages. However, therapeutic responses remain highly heterogeneous and are not fully explained by tumor-intrinsic features alone. Effective immunotherapy relies on the interplay between tumor susceptibility and host immune competence, which varies substantially among individuals. This study, therefore, aims to characterize PD-L1 expression and to assess inter-individual variability in the functional impact of PD-L1 blockade on immune cell–mediated cytotoxicity.

Methods: PD-L1 protein expression was evaluated by Western blot in paired HCC and adjacent non-tumoral (NT) tissues (n=55). Surface PD-L1 expression was assessed by flow cytometry in HCC cell lines representing S1/TGFβ–Wnt (JHH6, HLE, HLF) and S2/progenitor (Huh7, Hep3B) subtypes. PD-L1–targeting ICIs (atezolizumab, durvalumab) were employed. Peripheral blood mononuclear cells (PBMCs) from five healthy donors were activated using CD3/CD28 Dynabeads. These cells were then co-cultured with HCC cells at different effector-to-target (E:T) ratios. Cytotoxicity was measured using real-time impedance (Maestro Z) and Annexin V/PI assays.

Results: PD-L1 was upregulated in 60% of HCC tissues compared to NT (p=0.020), particularly in virus-related cases, and inversely correlated with BMI (R=–0.344; p=0.020). Elevated PD-L1 expression in NT tissue was associated with increased recurrence risk (HR 2.25; p=0.048). Multiple PD-L1 glycoforms were identified, with enrichment of different glycosylated species (~50, ~45, ~39 kDa) in tumors, suggesting altered protein maturation.

Among HCC cell lines, S1 models exhibited higher surface PD-L1 expression (JHH6: 16,200; HLF: 4,000) compared to S2 models (Huh7: 300; Hep3B: 110), consistent with DepMap data. In JHH6 cells, ICIs induced rapid and sustained PD-L1 blockade (>99% reduction in surface staining). Functionally, activated PBMCs showed robust activation (increased CD69 and CD137) and upregulation of PD-1 (~2% to ~13.5%). Co-culture induced early apoptosis (1.8-fold at 4 h; 4.7-fold at 24 h, p<0.001) and time- and dose-dependent cytotoxicity, with <50% tumor cell viability at E:T ratios of 1:1 and 1:2 by 40 h and 70 h, respectively.

Responses to PD-L1 blockade were heterogeneous: 3/5 donors showed enhanced $CD8^+$ T cell–mediated cytotoxicity, while one donor showed no benefit. Donor 01 exhibited ~10% additional killing at 72 h, whereas donor 05 showed sustained cytotoxicity with a marked increase after 60–72 h, particularly following durvalumab treatment (durvalumab: –26% vs. atezolizumab: –15% viability at 96 h).

IFN-γ stimulation increased PD-L1 expression, including membrane-associated forms, and enhanced ICI efficacy, promoting earlier and greater tumor cell killing (24 h: –12% to –19%; peak at 61 h: atezolizumab –35%, durvalumab –46%), supporting an immune-priming effect.

Conclusion: PD-L1 is frequently upregulated in HCC and enriched in S1-like subtypes. PD-L1 blockade enhances immune-mediated cytotoxicity in a donor-dependent manner, underscoring the importance of host immune variability. Integrating PD-L1 biology with tumor subclassification and functional immune profiling may improve patient stratification and optimize immunotherapeutic strategies in HCC.

Disclosure of Interest: N/A

P-039 INTRATUMORAL ESCHERICHIA COLI REPROGRAMS $CD8^+$ T CELLS TO PROMOTE TUMOR RECURRENCE AND IMMUNOTHERAPY RESISTANCE IN HEPATOCELLULAR CARCINOMA

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Introduction: The role of intratumoral microbiota in hepatocellular carcinoma (HCC) remains poorly understood, particularly with respect to postoperative recurrence and antitumor immunity. We aimed to characterize recurrence-associated intratumoral microbiota in HCC, elucidate their immunoregulatory mechanism, and identify potential therapeutic targets.

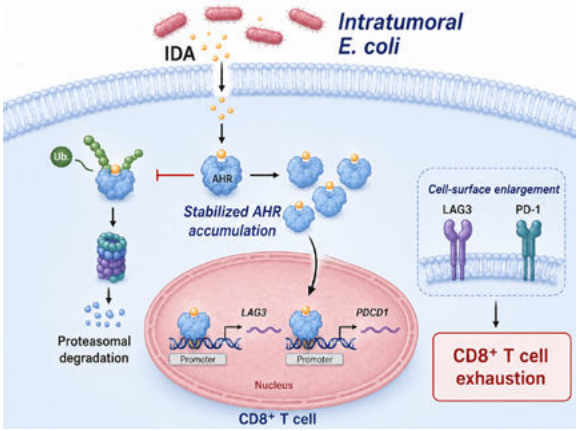
Methods: We performed 16S rRNA gene sequencing of paired tumor and adjacent liver tissues from 149 patients with HCC. Fluorescence in situ hybridization (FISH) and quantitative PCR were used to validate bacterial abundance. Single-cell RNA sequencing, metabolomics profiling, and mechanistic assays were applied to define the underlying immune and molecular pathways. Functional validation was conducted using orthotopic mouse models and patient-derived organotypic tumor spheroid (PDOTS).

Results: The composition of the intratumoral microbiota differed significantly between recurrent and non-recurrent HCCs. Escherichia coli (E. coli) was markedly enriched in tumors from patients who developed recurrence, as validated by FISH and qPCR. In vitro, E. coli did not directly alter the proliferative, invasive, or migratory capacity of HCC cells. However, single-cell transcriptomic analysis revealed a strong association between E. coli enrichment and the accumulation of exhausted LAG3+CD8+ T cells. Metabolomics profiling identified indoleacrylic acid (IDA), an E. coli-derived metabolite, as a key immunomodulatory effector. IDA induced upregulation of LAG3 and PD-1 in CD8+ T cells, promoted T-cell exhaustion and impairing cytotoxic function. Mechanistically, IDA directly bound to aryl hydrocarbon receptor (AHR), inhibited its ubiquitination-mediated AHR degradation, and promoted AHR nuclear translocation. ChIP-qPCR and dual-luciferase reporter assays demonstrated that nuclear AHR directly bound to the promoter regions of LAG3 and PDCD1, thereby enhancing their transcription. In orthotopic mouse models and PDOTS, disruption of the IDA-AHR axis suppressed tumor progression and synergistically enhanced the antitumor efficacy of anti-PD-1 therapy.

Conclusion: Our study identifies an intratumoral microbiota-metabolite-immune checkpoint axis in HCC, whereby intratumoral E. coli promotes CD8+ T-cell exhaustion through IDA-AHR-mediated induction of LAG3 and PD-1. Targeting this pathway may provide a rational strategy to overcome immune dysfunction and improve the efficacy of immunotherapy in HCC.

Disclosure of Interest: N/A

Image:



P-040 THE PRMT1–ROR1–DHCR7 AXIS DICTATES FERROPTOSIS SENSITIVITY IN HEPATOCELLULAR CARCINOMA

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Introduction: Ferroptosis, a unique form of non-apoptotic cell death, represents a therapeutic vulnerability in tumours. However, elucidating the tumour-intrinsic regulatory mechanism by which tumour cells display adaptive response to ferroptosis remains a challenging task.

Methods: The TCGA database was used to analyze the overall survival duration of HCC patients. The effects of receptor tyrosine kinase like orphan receptor 1 (ROR1) and protein arginine methyltransferase 1 (PRMT1) on HCC cell viability was validated through CCK-8 assays. The impact of ROR1 and PRMT1 on HCC cell lipid peroxidation levels were validated through flow cytometry. The therapeutic efficacy of targeting ROR1 or PRMT1 in combination with sorafenib treatment was evaluated through in vivo combination therapy experiments. The correlation between PRMT1 and ROR1 expression levels, the correlation between ROR1 and 7-dehydrocholesterol reductase(DHCR7) expression levels as well as DHCR7 pY468 signal in HCC tissues were examined by immunohistochemistry (IHC).

To further explore the underlying mechanisms by which PRMT1-ROR1-DHCR7 axis contributes to ferroptosis resistance, co-immunoprecipitation (Co-IP) and Mass spectrometry were used to identify potential proteins interacting with ROR1. The expression levels of ROR1 and PRMT1, their interaction, the phosphorylation of the DHCR7 protein were confirmed by Western blotting and Co-IP. Cycloheximide (CHX) chase assays were performed to reveal the impact of post-translational modifications on protein degradation.

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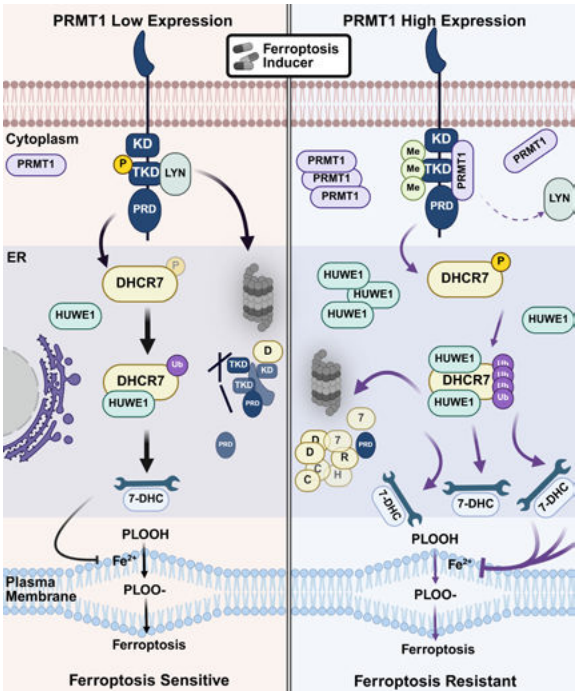
Results: The analysis of the TCGA database revealed that liver cancer patients with higher ROR1 or PRMT1 expression exhibited a poorer prognosis, and ROR1 or PRMT1 expression was increased in hepatocellular carcinoma at advanced stages. Knockdown of ROR1 or PRMT1 in HCC cell lines significantly decreased cell viability and increased lipid peroxidation levels. For in vivo validation, Ror1-KD or Prmt1-KD tumors responded better to sorafenib with reduced tumor progression and elevated 4-HNE abundance. Furthermore, in clinical HCC tissues, the PRMT1 expression was positively corrrelated with ROR1 levels, the ROR1 expression was positively correlated with DHCR7 pY468 signal while negatively with DHCR7 expression.

Mechanistically, through Co-IP and Mass spectrometry, DHCR7 was identified as a candidate protein interacting with ROR1, and further validated by Co-IP experiments. In vitro kinase asssays confirmed ROR1 phosphorylates DHCR7 at Tyr 468 which facilitates the E3 ligase HUWE1 binding to DHCR7 to accelerate its degradation, resulting the accumulation of 7-DHC. Then, 7-DHC can be exploited by cancer cells to shields phospholipids from autoxidation. Furthermore, through proteomics analysis, we identified protein PRMT1 as an interacting partner of ROR1 and PRMT1 stabilized ROR1 through inhibiting LYN-mediated ROR1 degradation. Knockdown of PRMT1 resulted in reduced ROR1 protein expression. Besides, the interaction between PRMT1 and ROR1 enhanced when exposed to ferroptosis inducer. This, in turn, contributes to ferroptosis resistance.

Conclusion: This study demonstrates that ROR1 acts as a key regulator of ferroptosis sensitivity through manipulating DHCR7 which controls the accumulation of 7-DHC in HCC. Besides, PRMT1 interacts with ROR1 and the interaction is enhanced to prevent ROR1 degradation when exposed to RSL3, thereby contributing to counteracting ferroptosis. We propose that targeting the upregulation of the PRMT1-ROR1-DHCR7 pathway provides a potential strategy to overcome ferroptosis resistance for HCC therapy.

Disclosure of Interest: N/A

Image:



P-041 HEPATITIS B VIRUS INTEGRATION IN PRIMARY AND METASTATIC HEPATOCELLULAR CARCINOMA: INSIGHTS INTO CLONAL EVOLUTION AND DISTANT SPREAD

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Introduction: Chronic hepatitis B virus (HBV) infection is a major cause of hepatocellular carcinoma (HCC). Integration of HBV DNA into the host genome is a critical molecular event in hepatocarcinogenesis and has been associated with genomic instability, dysregulated gene expression, and tumor progression. As HCC frequently metastasizes to the lung, characterization of HBV integration in matched primary and metastatic lesions may help clarify tumor clonality, evolutionary trajectories, and the potential role of viral integration in distant spread. However, HBV integration landscape in metastatic HCC remains poorly defined.

Methods: We analyzed 4 paired fresh-frozen primary HCC and lung metastatic tumors, together with adjacent non-tumor liver tissues collected from patients who underwent curative hepatectomy followed by resection of lung metastasis. Tissue specimens with no necrosis or hemorrhage were selected. Genomic DNA was extracted from sliced tissue samples for library construction and whole-genome sequencing. Sequencing data were obtained from the NCBI database (PRJNA203353). HBV integration was assessed in primary liver tumors, adjacent non-tumor liver tissues, and matched lung metastatic tumors. Candidate integration events were identified using chimeric read pairs, in which one read aligned to the human genome (hg38) and the paired read aligned to the HBV genome, as well as soft-clipped reads partially mapping to both human and HBV sequences. Integration events supported by at least 3 reads were retained. Integration sites were annotated with ANNOVAR to identify the nearest affected genes. Comparative analyses between primary and metastatic tumors were performed at multiple levels, including the number of integration events, overlap of integration sites, affected genes, and estimated clonality based on supporting read counts.

Results: HBV integration events were detected in all primary HCCs and matched lung metastasis samples. A total of 22 integration sites were identified in primary HCCs and 17 in lung metastases, with a mean of 5 events per sample. The number of HBV integration events was slightly higher in primary liver tissues than in matched lung metastases. At least 2 HBV integration events were shared between each primary tumor and its matched lung metastasis, supporting a common clonal origin. In this small cohort, cases with larger primary tumors tended to harbor more shared integration events. In addition, lesion-enriched integration events that preferentially occurred at either liver tissue or lung tissue were observed, indicating ongoing clonal diversification after metastatic dissemination. Gene-level comparison showed both shared and site-specific HBV-affected genes, suggesting that metastatic lesions retained ancestral integration patterns while acquiring additional alterations during progression.

Conclusion: Primary HCC and matched lung metastases share HBV integration events that support a common clonal origin, while also displaying distinct integration profiles consistent with continued clonal evolution. These findings suggest that HBV integration profiling may provide insight into metastatic seeding and tumor progression in HBV-associated HCC and may help identify integration-related biomarkers with potential biological and clinical relevance.

Disclosure of Interest: N/A

P-042 SPATIAL ORGANIZATION OF IMMUNE AND VASCULAR NICHES DETERMINES RESPONSE TO ATEZOLIZUMAB PLUS BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

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Background: Atezolizumab plus bevacizumab (atezo+bev) is one of the standard first-line therapies for advanced hepatocellular carcinoma (aHCC), achieving ~30% objective responses. In inflamed tumors, atezo+bev response was linked to CD8$^+$ effector T cells (CD8_Tex and CD8_Temra) and CXCL10$^+$ macrophages (Macro_CXCL10), and resistance, to TREM2$^+$ macrophages (Macro_TREM2) and CD14$^+$ monocytes (Mono_CD14). In non-inflamed tumors, resistance was associated with high expression of NRP1, a broad-spectrum cytokine co-receptor, binding to VEGF and TGFβ, among others. Here, we assessed how the spatial organization of immune cells within the tumor microenvironment (TME) determines response and resistance to atezo+bev.

Methods: Single-cell spatial transcriptomics was performed on 27 aHCC samples using the Xenium Prime 5,000-gene panel (10x Genomics), customized with 100 additional genes. Cell-to-cell distances were computed using the dbscan package [radius (r) = 300 µm]. Immune cell clusters were defined as ≥3 immune cells within an area of r=100 µm using a density-based algorithm. Nearest-neighbor enrichment was assessed comparing "near" (≤50 µm) versus "far" (50<r≤150 µm). Ligand–receptor interactions between T cells and other TME cell populations were inferred.

Results: Spatial transcriptomics of the 27 aHCCs yielded 4.6M cells. In inflamed tumors (n=11), CD8_Tex, CD8_Temra, and Macro_CXCL10 populations were significantly closer to tumor cells in responders (p=0.02, p=0.08, and p=0.14, respectively), indicating intratumoral localization, as opposed to resistant cases (n=7) where these populations were mostly found in the tumor periphery. Responders also exhibited significantly higher levels of immune-recruiting interactions, including PD-L1–PD-1, CXCL9–CXCR3, and CXCL10–CXCR3 (all p<0.05). In contrast, resistant tumors were enriched in immunosuppressive spatial niches composed of pure Macro_TREM2 clusters (10% vs 0%, p=0.009), mixed Macro_TREM2–Mono_CD14 clusters (27% vs 5%, p=0.03), and mixed Macro_TREM2–CD8$^+$ T cell clusters (38% vs 22%, p=0.04). Further, they presented significantly higher levels of the immunosuppressive CXCL12–CXCR4 axis. Non-inflamed tumors (n=16) presented a TME composition comparable to inflamed tumors, except for the lymphoid compartment (8% in inflamed vs 4% in non-inflamed, p=0.02). Of note, endothelial cells (ECs, representing around 2.5% of the total 4.6M cells) exhibited the highest proportion of NRP1-high cells (~20%), significantly exceeding the proportion in the rest of TME populations (~5%; p = 0.0004). In resistant tumors (n=11), only NRP1 high ECs presented significantly increased TGFβ signaling and hypoxia within their immediate neighborhood compared to responders (n=5). This was specific to ECs, as NRP1-high non-EC populations showed no enrichment for TGFβ or hypoxia in their surrounding neighborhood (p=ns). Moreover, these NRP1-high EC niches were significantly enriched in immunosuppressive macrophages (TREM2$^+$ and CX3CR1$^+$ macrophages; p=0.038 and p=0.008, respectively). Additionally, pro-angiogenic SPP1$^+$ macrophages were located significantly closer to NRP1-high ECs in non-responder patients (p=0.03).

Conclusion: In inflamed tumors, effective anti-tumor immunity is associated with close proximity to tumor cells, while resistance is driven by immunosuppressive macrophage niches. Non-inflamed tumors presented significantly less lymphoid cells and increased TGFβ/NRP1 signaling.

Disclosure of Interest: N/A

P-043 FEASIBILITY OF HYPERPOLARIZED [1-13C] PYRUVATE MRI IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: Noninvasive diagnosis of hepatocellular carcinoma (HCC) remains challenging in indeterminate liver lesions (Liver Imaging Reporting and Data System [LI-RADS] 3–4), which often lack the vascular imaging features required for diagnosis, including arterial phase hyperenhancement and washout. Hyperpolarized [1-^{13}C]pyruvate MRI (HP-MRI) enables real-time assessment of in vivo metabolism and detects metabolic alterations that may precede the development of characteristic vascular changes in HCC pathogenesis. By tracking pyruvate conversion to lactate and alanine, HP-MRI provides indirect measures of lactate dehydrogenase (LDH) and alanine aminotransferase (ALT) activity, consistent with altered metabolism in malignancy. We therefore evaluated whether HP-MRI can identify metabolic features associated with malignant progression in indeterminate liver lesions.

Methods: In this prospective single-center feasibility study, 14 participants underwent HP-MRI: 10 patients with focal liver lesions and 4 healthy volunteers. Clinical CT/MRI was used for lesion identification and LI-RADS categorization. Dynamic ^{13}C imaging was used to calculate lactate-to-pyruvate (L/P), alanine-to-pyruvate (A/P), and alanine-to-lactate (A/L) ratios and corresponding tumor-to-background ratios (TBRs). A total of 11 lesions were analyzed, including 5 lesions characterized as established HCC at baseline and 6 indeterminate lesions (LI-RADS 3–4) at baseline. Indeterminate lesions were followed for at least 13 months to determine outcome. Indeterminate lesions were followed for at least 13 months to determine outcome. Among the indeterminate lesions, 1 lesion was inconclusive, and 1 LI-RADS 3 lesion resolved during follow-up. The remaining 4 LI-RADS 4 lesions in the indeterminate group were diagnosed as HCC during follow-up. The primary analysis compared established HCC at baseline (n=5) with indeterminate lesions (LI-RADS 4) that subsequently progressed to HCC during follow-up (n=4). Indeterminate lesions were followed for at least 13 months. Group comparisons were performed using unpaired t-tests, and effect sizes were reported as Hedges' g with 95% confidence intervals.

Results: Compared with established HCC (n=5), indeterminate lesions that later progressed to HCC (n=4) had lower A/P (0.033 vs 0.072, p=0.029) and lower A/L (0.261 vs 0.973, p=0.015). These differences were maintained after normalization to surrounding liver parenchyma, with lower A/P-TBR (0.700 vs 0.979, p=0.012) and A/L-TBR (0.399 vs 0.973, p=0.033). Effect sizes for alanine-indexed metrics were large (Hedges' g 1.58–2.00). In contrast, L/P and L/P-TBR did not differ significantly between groups. One LI-RADS 3 lesion and one LI-RADS 4 lesion without confirmed HCC showed A/L TBR values near 1, indicating metabolic similarity to background liver. Additionally, cirrhosis was associated with reduced alanine-related liver ratios, but alanine-indexed TBR metrics remained discriminatory at lesion level.

Conclusion: HP-MRI was feasible in patients with focal liver lesions and provided complementary metabolic information beyond conventional imaging. Reduced alanine-indexed ratios, particularly A/L and A/L-TBR, were associated with subsequent progression of indeterminate lesions to HCC. These findings suggest that HP-MRI may detect metabolic alterations associated with early tumor development that precede vascular changes required for noninvasive imaging diagnosis, and support its further evaluation as a biomarker for risk stratification of indeterminate liver lesions.

Disclosure of Interest: N/A

Image:

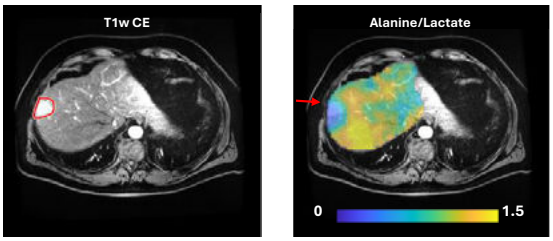

Figure 1. Reduced alanine-to-lactate ratio (A/L) on hyperpolarized [1-^{13}C]pyruvate MRI is associated with progression to hepatocellular carcinoma in indeterminate liver lesions without characteristic washout.

P-044 PREDICTING ATEZOLIZUMAB-BEVACIZUMAB RESPONSE IN HCC: HEAD-TO-HEAD COMPARISON OF ALBI AND CRAFITY SCORING SYSTEMS

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Introduction: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide. The combination of immunotherapy regimen using atezolizumab and bevacizumab has been established as the standard first-line systemic therapy for unresectable HCC following the IMbrave150 trial; however, treatment responses remain highly variable. Since the regimen is costly, response prediction before treatment initiation is important. The Albumin-Bilirubin (ALBI) score and the CRAFIT score have both been proposed as predictive biomarkers for immunotherapy outcomes. Head-to-head comparisons of their relative discriminatory performance for treatment response are not available. This study aimed to directly compare the predictive performance of ALBI and CRAFITY scores for immunotherapy response in a real-world cohort of HCC patients.

Methods: This single-center prospective cohort study included 110 consecutive patients with confirmed HCC who received at least six cycles of atezolizumab (1200 mg) and bevacizumab (15 mg/kg) every three weeks between January 2023 and December 2025. HCC was diagnosed as per AASLD guidelines using typical radiological features and histopathology, wherever indicated. The ALBI score was calculated using the validated formula: ($\log_{10}$ bilirubin × 0.66) + (albumin × −0.085).

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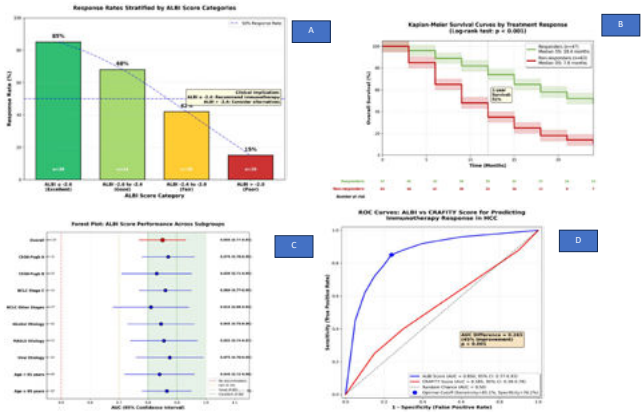
The CRAFITY score was determined by assigning 1 point each for CRP ≥1 mg/dL and AFP ≥100 ng/mL (range 0–2). Treatment response was categorized according to mRECIST criteria as positive (complete or partial response) or progressive disease. Receiver Operating Characteristic (ROC) curves were constructed and Areas Under the Curve (AUC) were calculated using the trapezoidal rule (DeLong method for 95% CIs). Optimal score cutoffs were determined using Youden's index. Subgroup analyses were stratified by Child-Turcotte-Pugh (CTP) class, BCLC stage, and etiology.

Results: Of 110 patients (male-to-female ratio 1.6:1; mean age 63.76 ± 10.9 years), the most common underlying etiologies were alcohol-related liver disease (38%), metabolic dysfunction-associated steatotic liver disease (MASLD, 30%), hepatitis B (17%), and hepatitis C (15%). Seventy-five patients (68%) were CTP class A and 35 (32%) were CTP class B. The majority (66%) presented with BCLC stage C disease. Forty-seven patients (42.7%) demonstrated a positive response to immunotherapy, with 30 (64% of responders) achieving partial response and 16 (34%) achieving complete response; while 63 patients (57.3%) had progressive disease. One-year overall survival was 43%, with non-responders having a median survival of 8.2 months. The ALBI score demonstrated superior predictive ability for positive immunotherapy response (AUC 0.689, 95% CI: 0.51–0.87) compared to the CRAFITY score (AUC 0.585, 95% CI: 0.39–0.78), representing an 18% relative improvement in discrimination. Responders had significantly lower ALBI scores compared to non-responders (mean −2.645 vs. −1.988, p<0.05). An ALBI threshold of −2.5 (Youden's index) provided the optimal sensitivity and specificity. Subgroup analyses across CTP class, BCLC stage, and etiology consistently demonstrated superior predictive performance of ALBI over CRAFITY.

Conclusion: The ALBI score is superior to the CRAFITY score for predicting immunotherapy response in HCC patients receiving atezolizumab and bevacizumab. Lower ALBI scores, reflecting better-preserved hepatic reserve, are significantly associated with improved treatment outcomes.

Disclosure of Interest: N/A

Image:



Response rates stratified by ALBI score categories declined progressively from 85% (ALBI ≤ −2.6) to 15% (ALBI > −2.0); (B) Kaplan-Meier curves demonstrating significantly superior median overall survival in responders versus non-responders (18.4 vs. 7.8 months; log-rank p < 0.001), (C) Forest plot showing consistent ALBI score discriminatory performance (AUC 0.810–0.875) across subgroups including Child-Pugh class, BCLC stage, etiology, and age. (D) ROC curve analysis showing ALBI score (AUC = 0.850, 95% CI: 0.77–0.93) significantly outperformed the CRAFITY score (AUC = 0.585, 95% CI: 0.39–0.78)

ALBI: Albumin-Bilirubin; CRAFITY: C-reactive protein and Alpha-fetoprotein in ImmunoTherapY; AUC: Area Under the Curve; HCC: Hepatocellular Carcinoma; BCLC: Barcelona Clinic Liver Cancer; OS: Overall Survival.

P-045 TRANS-CHALCONE ENHANCES CISPLATIN SENSITIVITY BY INDUCING GPX4-MEDIATED FERROPTOSIS IN HEPATOBLASTOMA.

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Introduction: Hepatoblastoma (HB), the most common liver cancer among children, is frequently associated with metastasis, recurrence, and chemoresistance. Cisplatin (DDP), which offers a survival rate of over 80%, is limited by its resistance and toxicity, and no second-line treatment has been reported for hepatoblastoma. Ferroptosis, a form of cell death distinct from other forms of cell death, is mediated by the accumulation of iron-related lipid ROS. It has emerged as a promising target for therapeutic intervention. trans-chalcone (TC), a flavonoid precursor, is a compound with anticancer activities which might be involved in the regulation of mitochondrial ROS-related ferroptosis. This study aimed to investigate the anticancer activities and mechanisms of TC in combination with DDP.

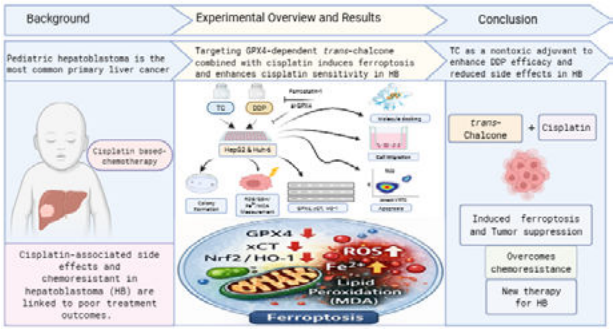
Methods: The HepG2 and HuH-6 cells were treated with TC and/or DDP in a dose- and time-dependent manner. Cell proliferation, migration, invasion, and clonogenic ability were measured using MTT, wound healing, and transwell assays. Cell apoptosis was determined by Annexin V staining. The intracellular ROS was measured by flow cytometry. The mitochondrial membrane potential was determined by TMRE staining. Ferroptotic markers glutathione (GSH), malondialdehyde (MDA), and Fe2+ were measured by biochemical detection. The expression of Nrf2, HO-1, GPX4, and xCT was determined by Western blot. Molecular docking analyzed the binding affinity of TC to GPX4 proteins. HB cells were transfected with GPX4 siRNA to investigate the pathway of TC and DDP-mediated ferroptosis in vitro. Additionally, HB cells were co-treated with Ferroptosis inhibitor (fer-1) to validate the involvement of ferroptosis in trans-chalcone and cisplatin–mediated cytotoxicity. Finally, GPX4 expression was analyzed by Western blot in hepatoblastoma tumors and corresponding normal tissues obtained from patients undergoing surgical resection. All experimental data are presented as mean ± SD, and statistical significance was determined using one-way ANOVA with Tukey's post hoc test in GraphPad Prism, with $p < 0.05$ considered significant.

Results: Co-administration of TC and DDP showed synergistic effects on inhibiting cell proliferation, migration, invasion, and colony formation in HB cells. This was associated with significantly increased levels of ROS, MDA, and Fe^{2+} and decreased antioxidant capacity (GSH). Molecular docking revealed a strong binding affinity between TC and GPX4. This suggested that ferroptosis was induced in hepatoblastoma cells. This was accompanied by downregulation of Nrf2, HO-1, GPX4, and xCT, along with mitochondrial dysfunction, consistent with ferroptosis-related pathways. TC significantly enhanced ferroptotic sensitivity and overcame cisplatin resistance by regulating GPX4. Notably, inhibiting ferroptosis and knocking down GPX4 significantly reduced the effects of TC and DDP through Western blot analysis. Moreover, GPX4 expression was significantly lower in tumor tissues than in adjacent normal tissues in hepatoblastoma patients.

Conclusion: This study demonstrates that trans-chalcone enhances cisplatin sensitivity in hepatoblastoma by inducing GPX4-dependent ferroptosis. Targeting ferroptosis represents a promising strategy to overcome chemoresistance and a potential therapeutic approach for HB management.

Disclosure of Interest: N/A

Image:



P-046 ATEZOLIZUMAB AND BEVACIZUMAB THERAPY COMBINED WITH EXPANDED NK CELLS SIGNIFICANTLY PROLONGS SURVIVAL IN VIVO HEPATOCELLULAR CARCINOMA MODEL.

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Introduction: Atezolizumab plus bevacizumab (Ate+Beva) proved better efficacy compared to sorafenib for advanced hepatocellular carcinoma (HCC) patients in IMbrave150 trial. However objective response rate of Ate+Beva therapy is around 30%, therefore several trials about combination protocol such as dual immune check point inhibitor plus bevacizumab etc. are ongoing to overcome this unmet need. Natural killer (NK) cell therapy is considered as promising tool that can enhance the efficacy of immunotherapy via several mechanism, however there are no studies about this issue. Therefore we performed preclinical study for efficacy of Ate+Beva therapy combined with expanded NK cell in HCC in vivo model.

Methods : SNU-398 cells were subcutaneously injected into the left flank (2.5×10^6) and right thigh (5×10^6) of SCID mice. Four days later, atezolizumab (10 mg/kg) and bevacizumab (5 mg/kg) were administered intraperitoneally, and NK cells (1×10^7) were injected via the tail vein. Tumor size (length × width) was measured twice weekly. Atezolizumab, bevacizumab, and NK cell treatments were repeated three times at 1-week intervals (Figure 1).

Results: Total 16 mice were categorized as four groups (Control, NK monotherapy, Ate+Beva, NK+Ate+Beva). The effect about shrinkage of tumor volume & survival rate were maximized in the NK+Ate+Beva therapy group compared to other three groups with significance statistically (Figure 2, 3). There were no meaningful toxicity in NK+Ate+Beva group compared to other three groups.

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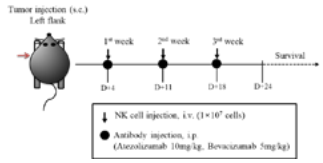
Conclusion: This study demonstrates that combination of NK cell with Ate+Beva can improve the efficacy of Ate+Beva therapy in HCC preclinical model. Further clinical prospective studies are needed for proving synergistic effect of NK cell and Ate+Beva therapy to HCC patients.

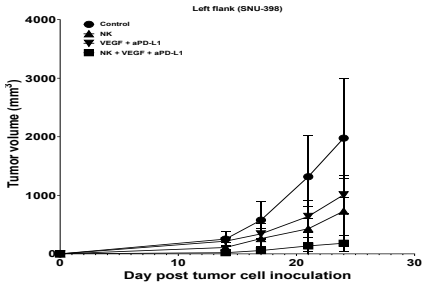
Disclosure of Interest: N/A

Image:

1. Mouse Treatment Scheme

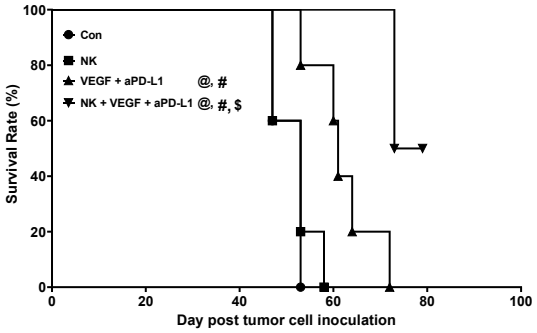


2. Assessment of Tumor Size



1 vs 2	0.0230
1 vs 3	0.0940
1 vs 4	0.0010
2 vs 3	0.8850
2 vs 4	0.5000
3 vs 4	0.0130

3. Asessment of Survival Rate



P-047 EARLY DETECTION AND PREDICTION OF LIVER METASTASES: THE ROLE OF SERUM BIOMARKERS IN CLINICAL DECISION-MAKING

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Background: Early detection of liver metastases remains a major challenge in oncology, as conventional imaging methods often identify metastatic disease at a relatively advanced stage. Serum tumor biomarkers may reflect tumor burden, metastatic spread, and biological aggressiveness earlier than imaging techniques, thereby providing an opportunity for earlier intervention and improved patient stratification.

Aim: To evaluate the sensitivity of selected serum biomarkers (TPS, TK, CEA) and their combinations for early detection of liver metastases and to assess their potential role in predicting disease progression.

Methods: A total of 288 patients with solid tumors were included in this retrospective study. Serum levels of tissue polypeptide-specific antigen (TPS), thymidine kinase (TK), and carcinoembryonic antigen (CEA) were measured using standardized immunoanalytical methods. Sensitivity was assessed at -9, -6, -3, and 0 months prior to imaging-confirmed diagnosis of liver metastases, with specificity set at 95%. Combinations of biomarkers were analyzed to determine their added diagnostic value.

Results: Sensitivity increased progressively with proximity to the time of diagnosis. At -9 months, sensitivity ranged from 8% (CEA) to 29% for combined markers, indicating early but limited detectability. At -6 and -3 months, sensitivity further increased, particularly for combined approaches. At the time of diagnosis, sensitivity reached up to 90% for marker combinations. Combinations such as TPS+CEA and TK+CEA consistently outperformed individual biomarkers. Importantly, elevated biomarker levels frequently preceded imaging-confirmed metastases, suggesting their ability to reflect early tumor progression and aggressive biological behavior.

Conclusion: Serum tumor biomarkers represent not only diagnostic tools but also dynamic indicators of tumor activity. Their longitudinal assessment may support earlier staging, guide timely imaging (CT, PET), and improve multidisciplinary clinical decision-making. Elevated levels should be interpreted as an indication for further diagnostic evaluation rather than definitive evidence of metastatic disease.

Disclosure of Interest: N/A

P-048 FERULA ASSAFOETIDA TRIGGERS PROGRAMMED CELL DEATH AND IMMUNOMODULATES PRO-SURVIVAL SIGNALING IN HUMAN HEPATOCELLULAR CARCINOMA (HEPG2) CELLS

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Introduction: Hepatocellular carcinoma (HCC) remains difficult to manage due to chemoresistance and hepatotoxicity. Although Ferula assafoetida is recognized for its pharmacological versatility, its therapeutic impact in the context of HCC remains significantly under-investigated.

Objective: This study aims to investigate the effects of F. assafoetida on the proliferation of the human liver cancer HepG2 cell line and elucidate its underlying molecular mechanisms of action.

Methods: Various extracts of F. assafoetida were prepared, and their cytotoxic properties against HepG2 cells were examined using the MTT assay. Cell cycle progression and the induction of apoptosis were evaluated using the CytoII™ cell imaging system. Immunomodulatory effects on cytokine profiles were measured via ELISA, and RT-qPCR analysis was conducted to monitor transcriptional changes in target gene expression.

Results: Among the screened preparations, the methanolic extract demonstrated the most potent dose-dependent anti-proliferative efficacy, characterized by a significant induction of programmed cell death. Assessment of the extract's immunomodulatory effects revealed a favorable antitumor cytokine profile, evidenced by significant elevation of TNF-α secretion and inhibition of IL-6 levels. Transcriptional profiling via RT-qPCR confirmed that the extract significantly modulated key signaling cascades, triggering the upregulation of the tumor suppressor PTEN alongside the downregulation of the oncogenic transcription factors SOX2 and NOTCH1.

Conclusion: F. assafoetida methanolic extract demonstrates potent antitumor activity against hepatoma cells by driving cell cycle arrest and apoptosis. Mechanistically, it exerts these effects by modulating inflammatory cytokines and disrupting oncogenic signaling. Specifically, restoring the "PTEN brake" effectively suppresses the PI3K/AKT pathway, thereby inhibiting the oncogenic drivers SOX2 and NOTCH1. These preclinical data highlight the therapeutic promise of F. assafoetida in liver cancer management, either as a standalone treatment or as a pharmacological adjuvant.

Disclosure of Interest: N/A

P-049 EFFECTS OF RESISTANCE TRAINING AS A PREVENTIVE STRATEGY AGAINST HEPATIC CANCER VIA MODULATION OF HEPATIC CELL PROLIFERATION IN A NOTCH1 OVEREXPRESSION ANIMAL MODEL

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Introduction: Notch signaling, particularly mediated by Notch1, plays a crucial role in the regulation of hepatic cell proliferation and differentiation, being associated with both regenerative and pathological processes in the liver, including tumorigenesis. In this context, non-pharmacological strategies such as physical exercise have been investigated for their potential to modulate molecular pathways involved in hepatic homeostasis.

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This study aimed to evaluate the effects of resistance exercise on hepatic proliferative and tumorigenic markers in an animal model overexpressing Notch1.

Methods: Experimental groups included control animals, Notch1-overexpressing sedentary animals, and Notch1-overexpressing animals subjected to resistance training. At the end of the experimental period, liver samples were collected for histological analysis, gene expression analysis and RNA sequencing.

Results: Notch1 overexpression increased inflammatory infiltration, fibrosis, and markers associated with tumorigenesis. In contrast, resistance exercise significantly modulated the expression of proliferative markers, including Mki67 and Top2a, in Notch1-overexpressing animals, suggesting a regulatory effect on hepatic proliferative activity, even in the absence of changes in Notch1 pathway expression. Additionally, transcriptomic analysis revealed that exercise-induced gene modulation was associated with the downregulation of NF-κB–related pathways, concomitant with the upregulation of biological processes involved in the regulation of deoxyribonuclease activity and negative regulation of centrosome duplication

Conclusion: In conclusion, resistance exercise shows potential as a preventive and therapeutic strategy to modulate hepatic proliferation and tumorigenesis, particularly in conditions involving dysregulation of the Notch1 pathway.

Disclosure of Interest: N/A

P-050 SOLUBLE FAP SUSTAINS CANCER-ASSOCIATED FIBROBLAST ACTIVATION VIA A STAT3/IL-6 POSITIVE FEEDBACK LOOP IN HEPATOCELLULAR CARCINOMA

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Introduction: Cancer-associated fibroblasts (CAFs) are key regulators of the tumor microenvironment in hepatocellular carcinoma (HCC), contributing to tumor progression, immune modulation, and therapeutic resistance. Fibroblast activation protein (FAP), a hallmark marker of activated CAFs, is present in both membrane-bound and soluble (sFAP) forms. While FAP-positive CAFs have been implicated in HCC progression, the biological function of sFAP and its role in maintaining CAF activation remain poorly understood. In this study, we characterized FAP-positive CAF subsets and investigated the mechanisms by which sFAP regulates CAF activation, with a particular focus on STAT3/IL-6 signaling.

Method: Single-cell RNA sequencing and spatial transcriptomic analyses were performed to identify FAP-positive CAF subsets and their interactions with macrophages in hepatocellular carcinoma. The effects of soluble FAP on CAF activation and STAT3/IL-6 signaling were evaluated using in vitro functional assays.

Results: Single-cell RNA sequencing revealed that FAP was predominantly expressed in a matrix CAF subset in hepatocellular carcinoma. Soluble FAP levels were significantly elevated in the serum of patients with HCC, and CAFs were identified as a major source of soluble FAP within the tumor microenvironment. FAP-high CAFs exhibited increased STAT3 phosphorylation compared with FAP-low CAFs, which was further confirmed by confocal imaging demonstrating enhanced p-STAT3 signals in FAP-positive CAFs. FAP knockdown reduced the expression of inflammatory cytokines, including IL-6 and CCL2. Spatial transcriptomic analysis revealed close spatial proximity between FAP-positive CAFs and IL-6–expressing macrophages. Furthermore, macrophage-conditioned medium increased FAP expression and STAT3 phosphorylation in CAFs, whereas IL-6 neutralization attenuated these effects. In a Hepa1-6 syngeneic HCC mouse model, pharmacological inhibition of FAP reduced the abundance of FAP-positive cells and suppressed tumor growth.

Conclusion: Soluble FAP sustains CAF activation through a STAT3/IL-6 signaling axis and promotes CAF–macrophage crosstalk in HCC. The antitumor effects of FAP inhibition in a syngeneic HCC model support the therapeutic potential of targeting the FAP–STAT3–IL-6 pathway.

Disclosure of Interest: N/A

P-051 PROTON PUMP INHIBITORS USE, GUT MICROBIOME COMPOSITION AND OUTCOMES OF PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED WITH IMMUNOTHERAPY IN FIRST-LINE SETTING

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Introduction: Proton pump inhibitors (PPIs) are widely used and can significantly alter gastric acidity and gut microbiome composition. Growing evidence indicates that the gut microbiota plays a key role in modulating response to cancer immunotherapy (IT), and that microbiome dysbiosis—potentially induced by concomitant medications such as PPIs—may impair treatment efficacy. In an exploratory analysis of a clinical trial in patients with advanced hepatocellular carcinoma (HCC) treated in the second-line setting, PPI use was associated with decreased overall survival (OS). However, data in HCC, particularly in the first-line (1L) setting, remain limited.

Aims and Methods: We aimed to study the association between PPI use and 1) gut microbiome composition and 2) outcomes of patients with HCC treated with IT in the first-line (1L) setting.

The study included patients from three different cohorts: 1) a prospective and multicenter Spanish cohort of patients treated with IT in 1L (RETO); 2) IMbrave 150 and 3) GO30140 trial (atezolizumab and bevacizumab). Data of cohort 2 and 3 were obtained from the Vivili platform. PPI exposure in the previous 2 months was prospectively registered in the RETO cohort (never, occasionally or always); in cohort 2 and 3 it was retrieved and defined as having at least one PPI prescription lasting ≥30 days within the 30-day window surrounding the inclusion date. In the RETO cohort, longitudinal stool samples were collected at baseline, month 1 and month 3 of treatment with IT. Microbiome analysis was performed by shotgun metagenomics sequencing. Machine-learning approaches and SHAP values were used to determine the relative contribution of microbiome features. OS was the primary endpoint. Cox regression models with inverse probability of treatment weighting (IPTW) were used in cohort 2 and 3 to assess associations between clinical variables, PPI exposure and OS.

Results: In total, 453 patients were included: 391 treated with IT in 1L (143 from IMbrave150; 131 from GO30140; 67 with atezolizumab-bevacizumab and 50 with tremelimumab-durvalumab from the RETO cohort). PPI use was associated with changes in the composition of microbiome in the RETO cohort. Increased alpha diversity was observed at species level (p-value for Chao1 and Shannon indexes were 0.07 and 0.091, respectively). Differential abundance across multiple bacterial families and species was also identified, including specific species of the oral microbiota (ie higher abundance of Streptocuoccus salivaris, Streptococcus parasanguinis, Coprobacter fastidiosus and Bifidobacterium dentium).

PPI use (n=56/274) was associated to a non-statistically significant worse OS in PPIs-exposed (HR: 1.19, 95% CI 0.75 to 1.87) in patients from cohorts 2 and 3 after IPTW.

Conclusions: PPI use is associated with increased alpha diversity and "oralization" of the gut microbiome composition in patients with HCC treated with IT. However, PPI use is not associated with a significantly reduced efficacy of IT in patients with HCC treated in 1L setting.

Disclosure of Interest: N/A

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Image:

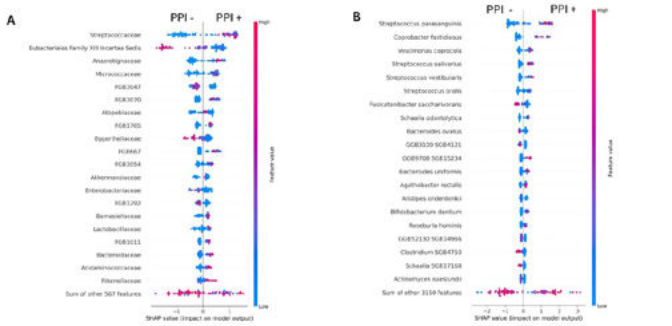

Figure 1. SHAP (SHapley Additive exPlanations) values for microbial taxonomic features associated with use of PPIs (panel A for family and panel B for species). Each bar represents the Shapley value of a respective taxa, quantifying its impact on the model's prediction. Polarizing features, ie. those that partitioned the SHAP values, indicate those taxa that are high (blue) or low (red) in each group (with or without PPI).

P-132 ACAT1-MEDIATED NPM1 ACETYLATION ORCHESTRATES FATTY ACID METABOLISM REPROGRAMING AND PROMOTES IMMUNOTHERAPY RESISTANCE IN HEPATOCELLULAR CARCINOMA

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Introduction: Immunotherapy-based combination regimens have become preferred strategies for advanced HCC. However, therapeutic efficacy remains limited. Tumor metabolic reprogramming, particularly fatty acid metabolism, supports malignant growth and reshapes the tumor immune microenvironment. While the metabolic basis of immunotherapy resistance remains poorly defined. ACAT1 is a mitochondrial enzyme, which can also function as an acetyltransferase to regulate tumor progression and immune responses. The function and mechanism of ACAT1 in metabolism-mediated immunotherapy resistance in HCC require further investigation.

Methods: Pretreatment biopsies from patients with HCC receiving targeted therapy plus immunotherapy underwent transcriptomic and proteomic profiling. Integrated multi-omics analysis and LASSO regression identified candidate drivers of immunotherapy resistance, which were validated in vitro and in vivo. Metabolomic profiling, dietary interventions, and stable isotope tracing were further used to define how oleic acid contributes to immunotherapy resistance.

Results: Immunotherapy resistance was characterized by activation of metabolic pathways, particularly fatty acid metabolism, accompanied by suppression of immune-related pathways. Immune deconvolution revealed increased M2 macrophage polarization and impaired $CD8^+$ T-cell activity in non-responders. LASSO regression identified ACAT1 as the top candidate gene linking fatty acid metabolism to immunotherapy resistance. ACAT1 knockdown inhibited macrophage M2 polarization and enhanced $CD8^+$ T-cell effector function. Metabolomic profiling identified oleic acid as the most significantly altered fatty acid. Oleic acid supplementation and high-oleate diet restored macrophage M2 polarization, impaired $CD8^+$ T-cell cytotoxicity, and induced resistance to anti-PD-1 therapy. Depletion of macrophages largely abolished high-oleate diet-mediated tumor promotion and immunotherapy resistance

Mechanistically, ACAT1 knockdown reduced acetylation of nucleophosmin (NPM1). Immunofluorescence demonstrated altered NPM1 subcellular localization after ACAT1 depletion. Further Co-IP, ChIP-seq analysis, and ChIP-PCR showed that NPM1 cooperates with MYC to bind the SCD1 promoter and promote SCD1 transcription, thereby enhancing endogenous oleic acid synthesis. Analysis of single-cell RNA-sequencing datasets identified SLC27A4 as the only fatty acid transporter positively associated with macrophage M2 polarization. Stable isotope tracing demonstrated that although oleic acid uptake was comparable between M1 and M2 macrophages, its metabolic fate differed substantially. M1 macrophages preferentially incorporated oleate into phospholipids and triglycerides, whereas M2 macrophages preferentially utilized oleic acid through b-oxidation to fuel the tricarboxylic acid cycle.

Conclusion: Fatty acid, especially oleic acid metabolic reprogramming is a key driver of immunotherapy resistance in HCC. ACAT1 promotes oleic acid synthesis by acetylating NPM1 and facilitating NPM1-MYC-dependent transcription activation of SCD1. SLC27A4 further mediates oleic acid-driven immunosuppressive macrophage reprogramming through altered metabolic routing.

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Disclosure of Interest: N/A

P-134 IMMUNE RELATED PATHOLOGICAL FEATURES AND PREDICTIVE SCORE IN INTRAHEPATIC CHOLANGIOCARCINOMA TREATED WITH COMBINED CONVERSION IMMUNOTHERAPY

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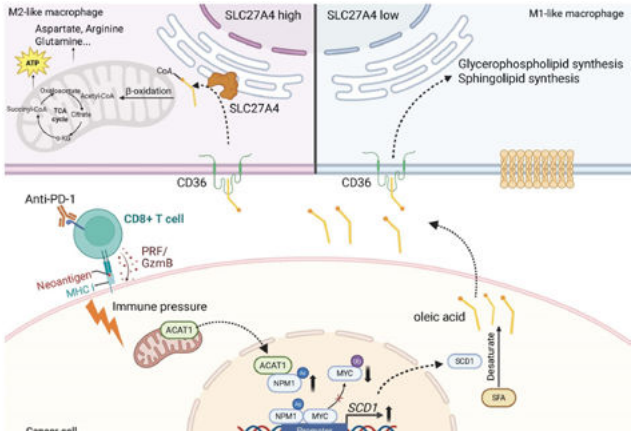
Abstract: Immune checkpoint inhibitor (ICI) based combined neoadjuvant/conversion therapy (NAT) is increasingly utilized in the management of initially unresectable intrahepatic cholangiocarcinoma (iCCA). Reliable biomarkers in predicting treatment and survival outcome remain underdeveloped. Here we assessed immune-related pathological features (irPF) in pre-treatment biopsy specimens of initially unresectable iCCA treated by ICI based conversion therapy. A predictive scoring system (immune therapy predictive score, iTPS) was developed to predict the patients' oncological outcome. We evaluated thirteen irPF (tumor infiltrating lymphocyte, mature tertiary lymphoid structure, lymphoid aggregate, dense plasma cell infiltration, granuloma, neutrophil, foamy macrophage, necrosis, cholesterol cleft, hemosiderin deposition, giant cell formation, neovascularization and mature fibrosis) in hematoxylin-eosin (HE) stained biopsy specimen slides from 95 iCCA patients. Cox regression analysis was used to analyze the correlation between these features and recurrence-free survival (RFS) and overall survival (OS). Features showing correlation with survival were selected for iTPS to develop a binary iTPS scheme. Four features (immature fibrosis, tumor-infiltrating lymphocytes, lymphoid aggregate and hemosiderin) were included in iTPS. A binary iTPS scheme showed patients with low iTPS displaying significantly better RFS (HR:1.83; CI: 1.02~3.27, P=0.04) and OS (hazard ratio [HR]:12.9; 95% confidence interval [CI]: 3.07~54.18, P<0.001). In conclusion, we developed an iTPS scheme based on routine HE-stained pretreatment biopsy slides. The iTPS can predict the RFS and OS of iCCA patients treated by combined ICI-based conversion therapy. iTPS is a good candidate predictive biomarker in iCCA and provides a new perspective in understanding the tumor immune microenvironment in immunotherapy.

Disclosure of Interest: N/A

Image:



P-136 MARGIN-ENRICHED CD4+ CENTRAL-MEMORY T CELLS AFFECT MACROPHAGES VIA ANXA1-FPR1 SIGNALING AXIS TO PROMOTE TUMOR PROGRESSION IN INTRAHEPATIC CHOLANGIOCARCINOMA

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Introduction: Intrahepatic cholangiocarcinoma (iCCA), as the second most prevalent primary hepatic tumors, accounts for about 10%-20% of all primary liver cancer, ranking behind hepatocellular carcinoma (HCC)(1). Currently, surgical resection remains the most frequent treatment option for iCCA, whereas, 60% patients can experience tumor recurrence or metastasis(2, 3). With the development of single-cell transcriptomics and spatial transcriptomic technology, we could explore the pivotal role of tumor microenvironment in tumor progression at the single-cell level(4). The existing research uncovered the tumor margin was considered a complex and active region, and immune escape and tumor invasion could occur at the tumor margin(5, 6). However, the immune

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microenvironment and the tumor-marginal immune signature in iCCA have not yet been investigated. Exploring potential mechanisms is important for improving treatment efficiency and preventing iCCA progression.

Methods: To figure out the composition of immune cells in different areas of iCCA, we firstly performed mass cytometry (cytometry by time of flight, CyTOF) on 30 samples from iCCA tumor, paratumor and margin tissue. We performed single-cell RNA-seq (scRNA-seq) analysis to further elucidate the molecular characteristics, biofunctions and cellular interactions of CD4+ Tcm cells in iCCA, and the distribution and cellular neighborhoods of CD4+ Tcm cells were discovered via spatial transcriptomic analysis. Flow cytometry, immunohistochemistry (IHC) and immunofluorescence staining (IF) were performed to validate the enrichment of CD4+ Tcm in margin zones of iCCA. Western blotting (WB) and qRT-PCR were used to detect the HIF1α, FOSL2, and ANXA1 expression in CD4+ Tcm, respectively. The expression of CCL19 in iCCA tissue and FPR1 in macrophages was also evaluated by WB and qRT-PCR. The metabolic state of CD4+ Tcm was measured by Oxygen Consumption Rate (OCR) and Extracellular Acidification Rate (ECAR). In vitro experiments, such as CCK8 assay, wound-healing assay, transwell migration assay, and EDU assay, were used to determined the proliferation, migration, invasion and motility ability of tumor cells. The size and weight of tumor were evaluated via in vivo experiments.

Results: There was a specific immune profile in the margin zone of iCCA, and we found that a specific subset of CD4+ central memory T cells (Tcm) is significantly enriched in the margin area based on CyTOF data. ScRNA-seq analysis further discovered that margin-enriched CD4+ Tcm exhibited upregulated ANXA1 expression and were recruited by CCL19+ fibroblasts via the CCL19-CCR7 signaling axis. We found that the FOSL2 expression was significantly upregulated and CD4+ ANXA1+ Tcm had the top 3 hypoxia-related scores. The positive correlation of HIF1α, FOSL2 and ANXA1 were computed via the bulk RNA-seq analysis. The level of ANXA1 in CD4+ ANXA1+ Tcm was regulated by the HIF1α-FOSL2-ANXA1 signaling pathway. The T cell activation-related genes (CD69 and CD28) were infrequently expressed in CD4+ ANXA1+ Tcm in the tumor margin zone, and the dysfunction and naïve scores of CD4+ ANXA1+ Tcm were high in all CD4+ T cell subsets. Combined with the CIBERSORT analysis, CD4+ ANXA1+ Tcm cells in the tumor margin zone was resting. The degree of CD4+ ANXA1+ Tcm enrichment in the margin zone of iCCA was correlated with clinical prognosis. Patients with enriched CD4+ ANXA1+ Tcm cells in the tumor margin exhibited a worse prognosis. We found the intracellular interactions between CD4+ ANXA1+ Tcm cells and macrophage and the strong links between the numbers of these two celltypes. Specifically, CD4+ ANXA1+ Tcm cells could recruit macrophages to the tumor margin and regulate the M2-type macrophage polarization via the ANXA1-FPR1 signaling axis. We found CD163 highly expressed on macrophages at the tumor margin. Additionally, the immunosuppressive and chemokine-related scores of macrophages in margin zones were significantly higher than those in paratumor zones. According to the tumor-related gene sets, all of the angiogenesis-, hypoxia-, inflammation-, invasion-, metastasis-, proliferation- and EMT-related scores of tumor cells in the FPR1+ macrophage neighborhood were higher than those cells in others. Macrophages treated with ANXA1 exhibited enhanced tumor cell proliferation, migration and invasion, which was evaluated by in vitro experiments. Furthermore, the counts of M2-type macrophages in the tumor margin zone and the tumor sizes were found to be associated with the ANXA1-FPR1 signaling pathway, as indicated by in vivo experiments.

Conclusion: Our study systematically characterized the features and distribution of CD4+ ANXA1+ Tcm cells in the margin zone of iCCA. We investigated the potential mechanisms by which CD4+ ANXA1+ Tcm cells affected tumor progression, and provided novel understanding of the function of these CD4+ ANXA1+ Tcm cells in iCCA. Furthermore, the new identification of CD4+ ANXA1+ Tcm in iCCA not only added a biomarker to predict patient prognosis but may also develop a novel therapeutic strategy to significantly improve patients' outcomes.

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Disclosure of Interest: N/A

Epidemiology, Staging and Prognosis

P-052 SIMPLIFIED BALAD SCORE AS A BIOMARKER FOR FIRST-LINE IMMUNE CHECKPOINT INHIBITOR SELECTION IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background/Aim: Although the choice of first-line immune checkpoint inhibitor (ICI) regimens for unresectable hepatocellular carcinoma (uHCC) is often influenced by factors such as proteinuria and bleeding risk, clear criteria for selecting between regimens have not been established. We focused on a simplified score based on the BALAD score (BALAD-S), a prognostic score for HCC calculated from bilirubin, albumin, AFP, AFP-L3, and PIVKA-II, and investigated its utility in selecting first-line ICI regimens.

Patients and Methods: This retrospective study included 752 patients with Child–Pugh A and BCLC-B/C uHCC who received first-line systemic therapy with either atezolizumab plus bevacizumab (AB) (n=645) or durvalumab plus tremelimumab (DT) (n=107) between 2020 and the end of 2025. Patients lacking data required for BALAD-S score calculation were excluded. The BALAD-S score was calculated as a simplified additive score based on serum bilirubin, albumin, AFP, AFP-L3, and PIVKA-II. Prognostic outcomes were compared according to BALAD-S score, retrospectively.

Results: Patients were stratified into two groups according to the BALAD-S score: ≤2 (L group) and ≥3 (H group).

In the L group, 426 patients received AB and 63 received DT. Median progression-free survival (PFS, months) was 10.5 (95% CI 8.3–11.7) vs. 4.3 (95% CI 2.4–5.9) for AB vs. DT, respectively (p<0.001). Median overall survival (OS, months) was 28.3 (95% CI 25.4–34.9) vs. 19.4 (95% CI

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17.0–27.8) (p=0.049), with a hazard ratio (HR) for OS of 1.50 (95% CI 1.00–2.26) for DT relative to AB. No significant differences were observed in major baseline factors, including Child–Pugh score, mALBI grade, or tumor stage.

In the H group (AB:DT = 219:44), median PFS was 5.3 (95% CI 4.0–6.7) vs. 7.0 (95% CI 3.0–16.0) (p=0.210). Median OS was 16.4 (95% CI 13.4–18.0) vs. 27.3 (95% CI 15.8–NA) (p=0.022), with an HR for OS of 0.53 (95% CI 0.30–0.91) for DT relative to AB. Baseline characteristics were generally balanced between groups, except for PIVKA-II levels (median 1306.0 vs. 3348.5 mAU/mL, p=0.010). A significant interaction was observed between BALAD-S group and treatment regimen for OS (interaction p=0.005).

Conclusion: The therapeutic outcomes of AB and DT differed according to the BALAD-S score. The BALAD-S score may serve as a useful indicator for selecting first-line ICI regimens in patients with uHCC. These findings suggest that BALAD-S may function not only as a prognostic marker but also as a predictive biomarker for ICI regimen selection.

Disclosure of Interest: Honoraria

P-053 UNMASKING THE BURDEN OF LIVER CANCER IN FRANCE: NATIONWIDE INCIDENCE, PREVALENCE AND MORTALITY OF HCC AND ICCA FROM REAL-WORLD DATA (2015–2021)

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Introduction: French epidemiological data on primary liver cancer (PLC) remain limited, as cancer registries (FRANCIM) lack national coverage and do not distinguish hepatocellular carcinoma (HCC) from intrahepatic cholangiocarcinoma (iCCA), the most common subtypes. Using the National Health Data System (SNDS), this study provides the first nationwide estimates of incidence, prevalence, and mortality of PLC, by cancer type (HCC and iCCA) between 2015 and 2021.

Methods: PLC Cases were identified via ICD-10 codes C22 (PLC), C22.0 (HCC), or C22.1 (iCCA) within a chronic liver disease (CLD) cohort derived from the 2% representative sample of the SNDS (ESND) between 2015 and 2021. Crude and age-standardized rates of incidence, prevalence and mortality were estimated overall and by subtype, using the total ESND population as the reference, and stratified by age, sex, social deprivation index of the municipality of residence (FDep) and department of residence. The world standard population was used for direct age standardization (where computation was possible). Results were extrapolated to the entire French population using INSEE data.

Results: In 2021, the age-standardized incidence rate (ASIR) was 11.4 per 100,000 person-years (PY) for all PLC (i.e., 16,241 new cases in France), 6 per 100,000 PY for HCC (8,291 new cases), and 2.3 per 100,000 PY for iCCA (3,451 new cases), with no significant change between 2015 and 2021. In contrast, age-standardized prevalence rate (ASPR) rose significantly: from 30.3 to 36.8/100,000 PY for PLC overall, and from 15.6 to 20.6/100,000 PY for HCC between 2015 and 2021. For iCCA, an increase was observed only at the end of the period, the ASPR reaching 4.8 per 100,000 PY in 2021. In 2021, an estimated 49,545 patients were living with PLC in France. For all PLC, in 2021, the age-standardized mortality rate (ASMR) was 5.1/100,000 PY, higher than in 2015, reaching 2.3/100,000 PY for HCC and 1.8/100,000 PY for iCCA, with no significant difference over time for each subtype.

HCC and iCCA showed strikingly divergent profiles. HCC disproportionately affected men (ASIR 10.5 vs. 2.0/100,000 PY; ASMR 4.0 vs. 0.7/100,000 PY in women), while iCCA showed no sex difference. Both subtypes showed increasing crude incidence, prevalence and mortality rates with age, most markedly for iCCA particularly after 75 years. For HCC, crude incidence and prevalence rates were significantly higher in the most deprived municipalities (FDep Q5 vs. Q1, p=0.05 and p=0.003, respectively), a gradient absent regarding mortality and for iCCA. Marked geographic disparities were also observed, likely reflecting regional variation in risk factor distribution.

Conclusion: This large representative study confirms the substantial burden of liver cancer in France and reveals divergent patterns between HCC and iCCA. Striking disparities by sex, age, social deprivation, and geography highlight the urgent need to address underlying inequalities in risk exposure, access to prevention strategies and cancer care.

Disclosure of Interest: N/A

P-054 NEUTROPHIL-TO-LYMPHOCYTE RATIO AND EXTRAHEPATIC SPREAD PREDICT RESPONSE AND SURVIVAL IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Introduction: Identifying patients unlikely to respond to atezolizumab plus bevacizumab (AB) remains a critical challenge in unresectable hepatocellular carcinoma (uHCC). We aimed to develop and externally validate a simple risk scoring system using baseline neutrophil-to-lymphocyte ratio (NLR) and extrahepatic spread (EHS) to predict treatment outcomes.

Methods: We included 304 patients with uHCC receiving first-line AB from multiple Korean centers, forming discovery (n=220) and validation (n=84) cohorts. Study outcomes included objective response rate (ORR) assessed by modified Response Evaluation Criteria in Solid Tumors , overall survival (OS), and progression-free survival (PFS). Multivariable analysis identified high NLR (>4.575) and EHS as independent predictors of nonresponse. The NLR-EHS score assigned 2 points for high NLR and 1 point for EHS (range, 0–3).

Results: In the discovery cohort, the score achieved an area under the receiver operating characteristic curve (AUC) of 0.749 (95% CI, 0.688–0.810) for predicting nonresponse, with ORR decreasing progressively: 67.3%, 47.7%, and 8.2% for low- (0), moderate- (1-2), and high- (3) risk groups, respectively ($p < 0.001$). External validation confirmed comparable discrimination (AUC, 0.705; 95% CI, 0.603–0.806), with a consistent ORR gradient of 77.8%, 54.2%, and 22.2% across risk groups ($p < 0.001$). The score maintained prognostic value for OS in both discovery (HR 1.28; $p = 0.003$) and validation cohorts (HR 1.45; $p = 0.007$). High-risk patients had notably inferior median OS (6.9 vs. 17.1 months in validation).

Conclusion: The NLR-EHS score is a simple, practical tool for stratifying nonresponse risk and survival in uHCC patients receiving AB, facilitating early identification of high-risk patients who may benefit from alternative strategies.

Disclosure of Interest: N/A

P-055 GENOMIC PROFILES AS DETERMINANTS OF THERAPEUTIC EFFICACY IN HEPATOCELLULAR CARCINOMA: TOWARDS PRECISION MEDICINE

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Background: As therapeutic options for hepatocellular carcinoma (HCC) expand, optimizing treatment selection remains a clinical challenge. We hypothesized that patient-specific mutational landscapes and associated biological characteristics significantly influence treatment efficacy and tumor burden.

Methods: We analyzed 28 patients treated for HCC between January 2025 and January 2026 who had available tumor biopsy samples. Targeted Next-Generation Sequencing (NGS) was performed to identify genomic alterations. These profiles were correlated with etiology, pathological features, initial tumor markers, and therapeutic responses across systemic and localized modalities. Genomic instability was assessed using the HRD sum score.

Results: Mutations in TERT promoter (42.9%), TP53 (35.7%), ARID1A (25.0%), and CTNNB1 (25.0%) were most frequent. Mutational profiles varied by etiology; NBNC HCC showed a significantly higher prevalence of CTNNB1 mutations compared to others (46.2% vs. 6.7%). CTNNB1 mutations were exclusively found in CK19-negative HCC (36.8% vs. 0.0%), while CK19-positive tumors showed higher TP53 mutations (44.4%) and RIT1 amplifications (22.2%). Baseline tumor burden was highest in TP53 and FGF-amplified cases (Median AFP 4,513, PIVKA-II 1,930). HRD sum score showed a positive correlation trend with PD-L1 CPS (r=0.26, p=0.32).

Treatment response was genotype-specific. TP53 mutations predicted primary resistance to ICI (PD-Ref 43.3%, AFP increase +4,848) but high sensitivity to HAIC (PD-Ref 5.9%, PR >35%). For CTNNB1 mutants, TKIs generally resulted in stable disease (SD) with minimal marker fluctuations; however, Lenvatinib showed superior intrahepatic efficacy (PR 33.3%) compared to other TKIs. Furthermore, CTNNB1 mutants showed poor response to ICI (PD-Ref 30.0%) but exhibited significant tumor marker reduction after HAIC, despite an overall high SD rate. Notably, a patient with CD274 amplification achieved a confirmed Partial Response (PR) with a decline in AFP levels from 13585 to 9517 ng/mL during Durvalumab/Tremelimumab treatment. AXIN1 mutations and RIT1 amplifications were consistently associated with refractory disease, with AXIN1 mutants showing rapid progression and an AFP/PIVKA-II surge under ICI. ARID1A mutants exhibited response dissociation, showing better extrahepatic control (Complete Response) under ICI despite intrahepatic progression.

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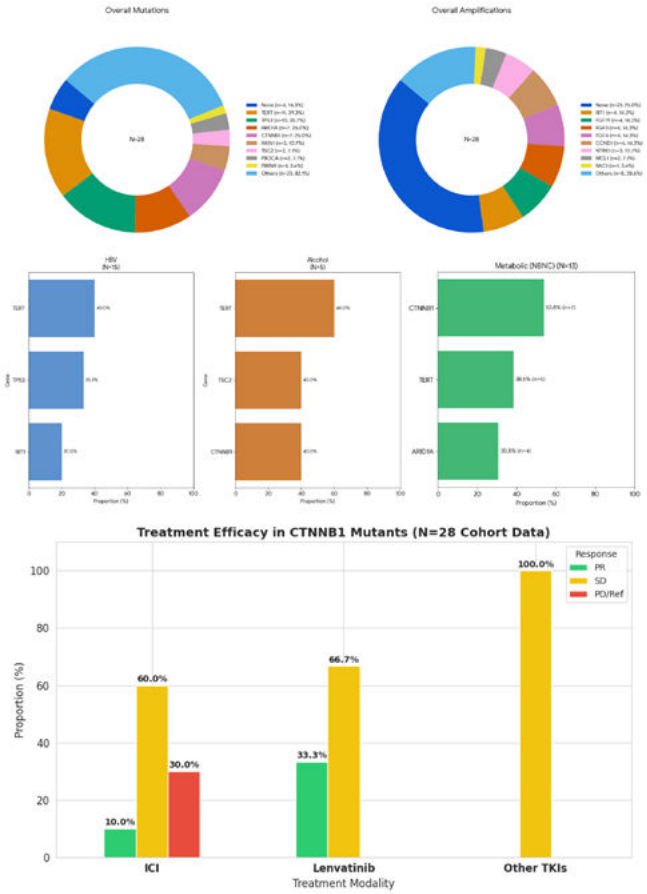
Conclusions: Genomic profiling via targeted NGS, including HRD scoring, provides critical insights into HCC tumor burden and treatment-specific outcomes. Integration of mutational data and PD-L1 expression into clinical decision-making enables optimized, personalized treatment strategies. Furthermore, longitudinal genomic monitoring via follow-up biopsy could be pivotal in navigating subsequent lines of therapy as tumor characteristics evolve.

Disclosure of Interest: N/A

Image:



P-056 LONG-TERM SURVIVAL AFTER HEPATIC RESECTION FOR HEPATOCELLULAR AND INTRAHEPATIC CHOLANGIOCARCINOMA: POPULATION-BASED ANALYSIS IN S.KOREA

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Background: Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the two major types of primary liver cancer, accounting for approximately 70% and 15% of all cases, respectively. South Korea remains a high-incidence region for both malignancies. Despite advances in surgical and imaging techniques, long-term survival outcomes and their changing trends over time have not been fully evaluated in population-based studies. This study aims to analyze survival rates and their influencing factors among patients with HCC and ICC who underwent hepatic resection in Korea.

Methods: Using the Korea Central Cancer Registry, we analyzed data from 43,537 patients who underwent hepatectomy between 2004 and 2018. Patients were categorized by time period (2004–2008, 2009–2013, 2014–2018), and 5-year survival rates were estimated using the Kaplan–Meier method. Multivariable Cox proportional hazards models identified prognostic factors associated with survival.

Results: A total of 36,380 patients with HCC and 7,157 with ICC underwent liver resection. Both cancers showed a male predominance, more pronounced in HCC. Major hepatectomy was frequent, particularly in ICC, which was associated with longer hospital stays, higher medical costs than HCC. Over time, the proportion of patients residing in metropolitan areas declined, more than half of surgeries continued to be performed there, indicating persistent geographic disparity between residence and treatment location. Surgeries at high-volume centers increased, hospital stays shortened, and 5-year survival improved in HCC but remained unchanged in ICC. Multivariable analysis identified male sex, advanced age, major hepatectomy, surgical region as independent predictors of poorer survival, with low income adversely affecting survival only in HCC.

Conclusion: Postoperative survival following hepatectomy has improved for HCC but remains unchanged for ICC. Better outcomes were observed for surgeries performed in metropolitan areas, likely reflecting differences in institutional experience and resources. These findings highlight persistent disparities in treatment outcomes and underscore the need for regionally balanced healthcare resources and further studies to refine prognostic determinants in primary liver cancers surgery.

Disclosure of Interest: N/A

P-057 CONTRACEPTIVE USE IN RELATION TO GALLBLADDER CANCER RISK: FINDINGS FROM THE CHILE BILIARY LONGITUDINAL STUDY

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Introduction: Gallbladder cancer (GBC) occurs predominantly in women, unlike other biliary tract cancers, suggesting that sex hormones may contribute to carcinogenesis. However, evidence linking contraceptive use with GBC risk remains inconsistent. We examined the association between contraceptive use and high-grade dysplasia (HGD) and GBC risk in a high-risk population of women with gallstones.

Methods: The Chile Biliary Longitudinal Study enrolled 4,711 women aged 50-74 years with ultrasound-confirmed gallstones from south-central Chile between 2016 and 2019. Ever contraceptive use, mode of delivery (pills, other, none), and duration of use (0-1; >1-4; 5-9; ≥10 years) were self-reported at baseline. Incident HGD/GBC cases were identified through pathology reports and linkage with national death registries. Multivariable-adjusted Cox proportional hazards models estimated hazard ratios (aHRs) and 95% confidence intervals (CIs) for associations between contraceptive (ever use, mode of use, and duration) and HGD/GBC risk. Confounders, including ethnicity (Mapuche/non-Mapuche), number of gallstones, waist-to-height ratio, region (Araucania/Maule), parity, and menopausal hormone therapy (MHT), were selected using logistic regression for factors associated with exposure and Cox regression models for associations with outcome.

Results: Over a median follow-up of 4.8 years (range 2.0-7.7), 120 women (2.5%) were diagnosed with HGD/GBC. The median age at diagnosis was 64 years, 34% of cases occurred among women identifying as Mapuche, and 62% reported ever contraceptive use. Ever use of contraceptives was associated with increased HGD/GBC risk (aHR 1.8, 95% CI 1.2–2.8). Among women with duration data, high risks were observed for >1-4 years of contraceptive use (aHR 2.3, 95% CI 1.3–3.9) and 5-9 years of use (aHR 2.8, 95% CI 1.6–4.9) but not for ≥10 years (aHR 1.3, 95% CI 0.7-2.2), compared with non-use. Most women reported pills as the mode of contraceptive delivery, and the association for pill use compared with non-use was similar to the overall association (aHR 1.5, 95% CI 1.0–2.3).

Conclusions: Among women with gallstones, ever use of contraceptives was associated with increased HGD/GBC risk. Analyses by duration showed higher risks at intermediate durations but not with longer use, differing from patterns observed for some hormone-related cancers. These results support a potential hormone-related mechanism in GBC development and may help identify women at high risk.

Disclosure of Interest: N/A

P-058 THREE-DIMENSIONAL MARGIN ASSESSMENT PREDICTS LOCAL TUMOR PROGRESSION AFTER STEREOTACTIC MICROWAVE ABLATION OF SMALL HCC ≤3 CM

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Introduction: Local tumor progression (LTP) remains the main cause of treatment failure after microwave ablation (MWA) of small hepatocellular carcinoma (HCC). Adequate ablative margins are considered critical; however, conventional two-dimensional assessment is imprecise and the widely used 5 mm safety threshold may oversimplify a potentially continuous risk relationship. Three-dimensional quantitative ablation margin assessment (3D-QAM) enables accurate measurement of the minimal ablation margin (MAM) and may improve risk stratification.

Methods: This retrospective single-center study included 175 lesions in 115 patients with HCC ≤3 cm treated with CT-guided stereotactic MWA between 2016 and 2022. MAM was assessed using 3D-QAM based on co-registered pre- and post-ablation imaging. Associations between MAM and LTP were evaluated using multivariable logistic regression. Model performance was assessed by receiver operating characteristic (ROC) analysis and internally validated using bootstrap resampling. Sensitivity analyses included generalized estimating equations (GEE) to account for clustering of lesions within patients.

Results: LTP occurred in 36 of 175 lesions (20.6%). Lesions with LTP had significantly smaller MAM compared with those without progression (2.9 vs. 4.7 mm, $p < 0.001$). In multivariable analysis, MAM was a strong independent protective factor (odds ratio 0.68 per millimeter increase, $p < 0.001$). Right-sided lesion location was associated with increased LTP risk (odds ratio 2.75, $p = 0.045$), whereas multifocality was not significant. ROC analysis demonstrated moderate discrimination (AUC 0.70), with an optimism-corrected AUC of 0.73 after internal validation. The probability of LTP decreased continuously with increasing MAM, without evidence of a strict threshold effect. Results remained consistent in sensitivity analyses using GEE.

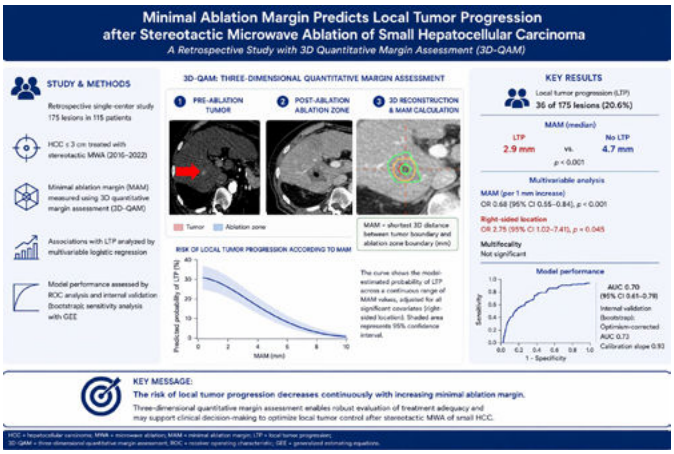
Conclusion: The minimal ablation margin is the key determinant of local tumor progression after stereotactic MWA of small HCC. Risk decreases continuously with increasing margin size, supporting a shift from fixed safety thresholds toward margin-based risk stratification. Three-dimensional quantitative margin assessment enables robust evaluation of treatment adequacy and may support intra- and post-procedural decision-making to optimize local tumor control.

Disclosure of Interest: N/A

Images:

Variable	B	S.E.	Wald test	df	P Value	Odds Ratio	95% CI	
							-	+
Multifocality	0.595	0.424	1.967	1	0.161	1.814	0.789	4.167
MAM (mm)	-0.381	0.106	12.989	1	**<.001**	0.683	0.556	0.841
Right Sided LL	1.01	0.505	4.002	1	**0.045**	2.746	1.021	7.389

Table 2 Multivariable Logistic Regression Identifying Independent Predictors of Local Tumor Progression (LTP). B = Regression Coefficient; S.E. = Standard Error; df = Degree of Freedom; CI = Confidence Interval; MAM = minimal ablation margin; mm = Millimeter; LL = Lesion Location.



P-059 OPEN HEPATECTOMY VS. LAPAROSCOPIC HEPATECTOMY FOR PATIENTS WITH SUBCUPSULAR HEPATOCELLULAR CARCINOMA

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Introduction: The proximity of hepatocellular carcinoma (HCC) to the liver capsule may increase risks of intraoperative tumor disruption and dissemination, yet comparative long-term outcomes of laparoscopic (LH) vs open hepatectomy (OH) for subcapsular HCC remain poorly defined.

Method: Consecutive patients who underwent curative-intent resection for imaging-defined subcapsular HCC (tumor ≤0.1 cm from the liver capsule on preoperative CT/MRI) between January 2015 and January 2021 at a single high-volume center were identified from a prospectively maintained database. Patients who underwent LH were compared with those who had OH. Propensity score matching (PSM) was used to adjust for baseline differences. Survival was assessed using Kaplan–Meier analysis and Cox proportional hazards regression.

Results: Of 4098 patients, 1815 with subcapsular HCC were included (LH, n=548; OH, n=1267). After PSM, 530 well-matched pairs were analyzed. The LH group had significantly shorter median RFS (16.6 vs 37.5 months; HR 1.43, 95% CI 1.22 to 1.67; P<0.001) and OS (37.5 vs 59.7 months; HR 1.25, 95% CI 1.003 to 1.55; P<0.05) compared with the OH group. The survival disadvantage associated with LH was most pronounced in patients with tumors larger than 5 cm, right-lobe tumors, or those requiring right hemihepatectomy.

Conclusion: In this study, LH was associated with inferior long-term RFS and OS compared with OH for patients with subcapsular HCC. These findings suggest that the open approach may be preferable for optimizing oncologic outcomes in this specific tumor subgroup, particularly for larger or right-sided lesions, despite the short-term recovery benefits of laparoscopy.

Disclosure of Interest: N/A

P-060 GENDER-DIMORPHISM LINKED DISTINCT GUT MICROBIAL SIGNATURE IN HEPATOCELLULAR CARCINOMA PATIENTS.

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Introduction: Hepatocellular carcinoma (HCC) commonly developed from cirrhotic liver and intensely influenced by gut-liver axis and dysbiotic gut worsen the HCC through multiple pathways. Increasing evidence indicated gender-based gut microbiome composition, potentially contributing to male and female differently in HCC susceptibility and clinical trajectories.

Methods: Fecal samples from male (n=38) and female (n=32) patients with HCC were collected and differential microbiome taxonomic profiling was performed using V3-V4 16S rRNA sequencing on Illumina MiSeq. Biomarker ability and correlation analyses were performed targeting gender-specific gut microbial species.

Results: Gender-specific gut microbial profiling showed defiling variations between male and female HCC patients at each taxonomical level, starting form phylum till species. Toal four phyla and ten genre showed significant gender-specific differentiation. Toal 18 species showed differential ability between the male and female HCC patients, and 10 species showed reasonable differential biomarker ability. Toal six species (P. copri, B. wexlerae, A. butyriciproducens, D. longicatena, C. perfringens, and A. histaminiformans) showed AUROCs upto 0.73 in Male HCC patients. Whereas four species (E. faecium, L. reuteri, C. celatum, and B. dentium) presented AUROCs up to 0.75. Gender-specific microbial biomarkers presented strong negative correlation.

Conclusion: This study signify microbial gender-based dimorphism in HCC, highlighting the gut microbiome as a gender-dependent biological variable. Critically, this necessitates the gender-specific nursing protocols of adoption to target the gender-specific distinct dysbiotic profiles to optimize microbial stability and improve clinical prognoses in the HCC management.

Disclosure of Interest: N/A

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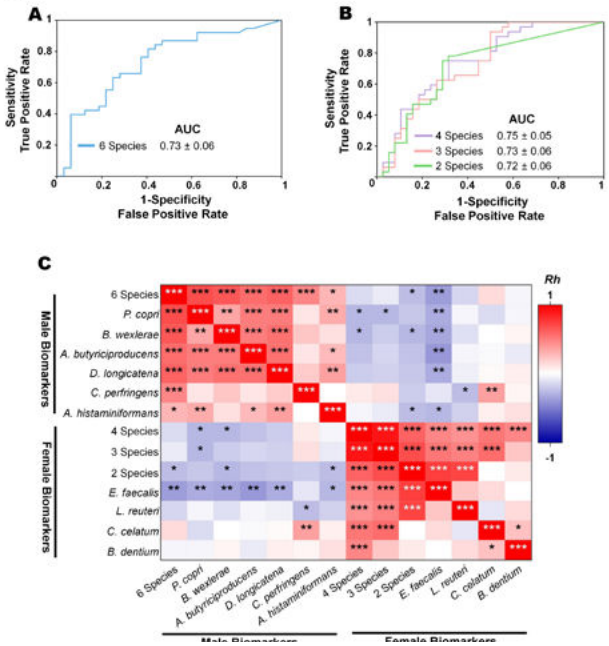
Image:

Figure 1



P-061 CLINICALLY SIGNIFICANT PORTAL HYPERTENSION, RATHER THAN ALBI GRADE, IS THE MOST RELEVANT PROGNOSTIC FACTOR IN PATIENTS RECEIVING SYSTEMIC THERAPY FOR HEPATOCELLUAR CARCINOMA.

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Introduction: In recent clinical trials of patients with advanced hepatocellular carcinoma (HCC) treated with systemic therapy, Child-Pugh A score has traditionally been used as an eligibility criterion. However, the proportion of patients with cirrhosis in these trials has not been reported, and this score has been extrapolated to non-cirrhotic populations. On the other hand, the prognostic performance of the ALBI score has shown discordant effects in these clinical trials. We aimed to compare the roles of different prognostic models in patients with advanced HCC, particularly Child–Pugh A patients with or without cirrhosis.

Methods: A prospective, multicenter cohort study was conducted between 2018 and 2024 in Argentina, Chile, Brazil, and Colombia, including patients with BCLC stage A, B or C HCC treated with systemic therapy. We estimated the Kaplan-Meier product and the mean instantaneous risk of death (hazard ratio, HR) with 95% confidence intervals (95% CI) using a Cox proportional hazards model.

Results: Among 306 patients who initiated systemic therapy at BCLC stage B (27%) and C (73%), treatments included sorafenib 60.5% (n=185), atezolizumab + bevacizumab 39.7% (n=91), lenvatinib 9.1% (n=28), and nivolumab 0.6% (n=2). Cirrhosis was present in 83.3% (n=255), Child-Pugh A in 79.1% (n=242), and ALBI grades 1, 2, and 3 in 11.4%, 31.2%, and 57.4%, respectively. Median overall survival was 16.0 months (95% CI 12.9–18.3). Patients with cirrhosis had worse survival (median 13.6 months) compared to those without cirrhosis (21.7 months) [HR 1.74 (95% CI 1.11–2.75; P=0.016)], particularly those with clinically significant portal hypertension (CSPH) [HR 1.53 (95% CI 1.11–2.12)]. Patients with cirrhosis and Child-Pugh A vs B had better survival (median 18.3 vs 9.0 months; HR 2.33, P<0.0001). When focusing on Child-Pugh A patients (n=242; Table 1), the ALBI score did not discriminate prognosis, both in the overall cohort and in those with or without cirrhosis. In the final multivariable Cox model among Child-Pugh A patients with or without cirrhosis, variables independently associated with survival were atezolizumab + bevacizumab [HR 0.64 (95% CI 0.42–0.99)], adjusted for serum alpha-fetoprotein ≥400 ng/mL and presence of CSPH.

Conclusion: Accurate reporting of the proportion of patients with cirrhosis, particularly those with CSPH, is important because both are independent prognostic determinants and may be unbalanced if not included as stratification factors.

Disclosure of Interest: Honoraria

Image:

Table 1. Comparison between Child Pugh A patients with and without cirrhosis.

VARIABLE	*Without cirrhosis n=51 (21.1%)*	*With cirrhosis n=191 (78.9%)*	*P values*
Age, years (± SD)	66 ± 13.8	66 ± 8.7	0.76
Gender, Male, n (%)	38 (74.5)	148 (77.5)	0.65
Obesity, n (%)	7 (14.3)	41 (23.8)	0.15
Comorbidities, n (%)	33 (64.7)	114 (59.7)	0.51
Etiology of liver disease, n (%)			
Viral/non-viral	16 (31.3)/35 (68.7)	79 (41.4)/112 (58.6)	0.19
Hepatitis C	10 (19.6)	68 (35.6)	0.03
MASLD	12 (23.5)	58 (30.4)	0.33
Alcoholic liver disease	5 (9.8)	22 (11.5)	0.8
Hepatitis B	6 (11.8)	11 (5.6)	0.12
Cryptogenic	2 (3.9)	21 (11.0)	0.35
Cholestatic (PBC, PSC)	2 (3.9)	3 (1.6)	0.43
Other	13 (25.5)	1 (0.5)	<.0001
Child Pugh A5/A6, n (%)	43 (86.0)/7 (14.0)	134 (70.2)/57 (29.8)	0.02
ALBI score, n (%)			
1	23 (45.1)	48 (25.1)	<.0001
2	19 (37.2)	130 (68.1)	
3	9 (17.6)	13 (6.8)	
Mild Ascites, n (%)	-	9 (4.7)	0.12
HE grades I-II, n (%)	-	1 (0.5)	0.61
Large gastroesophageal varices, n (%)	-	46 (24.1)	<.0001
ECOG 0-1, n (%)	49 (98.0)/1 (2.0)	186 (97.4)/5 (2.6)	0.80
Median total Bilirubin, mg/dl (IQR)	1.0 (0.5-1.0)	1.0 (0.7-1.2)	0.01
Median Albumin, g/dl (IQR)	3.9 (3.6-4.3)	3.6 (3.6-4.0)	0.02
Median INR, (IQR)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	0.18
Median serum AFP, ng/ml (IQR)	9.6 (3.2-410)	144.0 (15-1371)	0.007
AFP ≥400 ng/ml, n (%)	9 (18.0)	48 (25.1)	0.29
Macrovascular tumor invasion, n (%)	8 (16.0)	55 (28.8)	0.07
Metastatic disease, n (%)	25 (50.0)	69 (36.1)	0.07
BCLC, n (%)			
A/B	10 (23.8)	56 (32.2)	0.29
C	32 (76.2)	118 (67.8)	

Abbreviations: AFP: alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer staging; CSPH: clinically significant portal hypertension; ECOG: Eastern Cooperative Oncology Group performance status; HE: hepatic encephalopathy; HCC: hepatocellular carcinoma, INR: international normalized ratio; IQR: interquartile range.

P-062 SAA DYNAMICS IDENTIFY DISTINCT RESPONSE SUBTYPES IN HEPATOCELLULAR CARCINOMA PATIENTS UNDERGOING IMMUNOTHERAPY

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Introduction: Immune checkpoint inhibitor (ICI) therapy has become a cornerstone in the treatment of advanced hepatocellular carcinoma (HCC). However, reliable biomarkers for predicting and monitoring clinical response remain an unmet need. The identification of biomarkers capable of distinguishing heterogeneous patient outcomes is critically important to optimize immunotherapy.

Methods: A multi-omics exploratory analysis of pretreatment samples from HCC patients was performed to identify potential biomarkers. Furthermore, a retrospective validation cohort of HCC patients who received at least one cycle of immunotherapy between 2016 and 2021 was analyzed. Patients were stratified into subgroups based on the baseline levels and on-treatment kinetics of the circulating inflammatory marker Serum Amyloid A (SAA). The correlations between SAA-defined subgroups and clinicopathological features, survival outcomes, and peripheral immune cell profiles were evaluated.

Results: Multi-omics analysis revealed significantly higher pretreatment expression of the SAA gene family in patients who later experienced progressive disease on immunotherapy. In the validation cohort, the optimal prognostic cutoff for baseline SAA was 32 mg/L. Meaningful on-treatment kinetics were defined as an initial increase in SAA levels by >30% followed by a return to baseline

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before the next treatment cycle. Univariate analysis showed that both low SAA baseline and these specific kinetics were significantly associated with superior progression-free survival (PFS) and overall survival (OS). In multivariate analysis, the combination of SAA baseline and kinetics emerged as an independent prognostic factor for both OS (p=0.001) and PFS (p<0.001). This favorable SAA profile was also associated with an elevated proportion of peripheral CD8+ T cells.

Conclusion: A low baseline SAA level combined with characteristic on-treatment kinetic patterns is associated with superior outcomes in unresectable HCC patients treated with immunotherapy. Dynamic SAA tracking provides a practical and non-invasive approach to identify distinct response subtypes and monitor treatment efficacy in real time.

Disclosure of Interest: N/A

Images:

Table 1. The association between SAA baseline status and early kinetics with the clinicopathologic characteristics and uni- and multivariate analyses for OS and PFS (n=384).

Clinicopathological variables	SAA baseline (log₂=5)			SAA early kinetics			OS				PFS			
	High (n=131)	Low (n=253)	p	M-type (n=227)	non-M-type (n=157)	p	Uni. p	Mul. analysis HR (95% CI)	Mul. analysis p		Uni. p	Mul. analysis HR (95% CI)	Mul. analysis p	
Age (year)			0.631			0.840	0.066	-	-		0.140	-	-	
⩽50	59 (45.0)	106 (41.9)		99 (43.6)	66 (42.0)									
>50	72 (55.0)	147 (58.1)		128 (56.4)	91 (58.0)									
Gender			0.120			0.052	0.240	-	-		0.250	-	-	
Male	119 (90.8)	214 (84.6)		190 (83.7)	143 (91.1)									
Female	12 (9.2)	39 (15.4)		37 (16.3)	14 (8.9)									
BMI			0.471			1.000	**0.036**	-	0.191		0.330	-	-	
⩽24	99 (75.6)	181 (71.5)		166 (73.1)	114 (72.6)									
>24	32 (24.4)	72 (28.5)		61 (26.9)	43 (27.4)									
RECIST			0.217			**<0.001**	**<0.001**	-	-		**<0.001**	-	-	
CR	0 (0.0)	2 (0.8)		2 (0.9)	0 (0.0)									
PR	57 (43.5)	118 (46.6)		116 (51.1)	59 (37.6)									
SD	42 (32.1)	93 (36.8)		83 (36.6)	52 (33.1)									
PD	27 (20.6)	31 (12.3)		21 (9.3)	37 (23.6)									
NA	5 (3.8)	9 (3.6)		5 (2.2)	9 (5.7)									
Tumor size (cm)			**0.012**			**<0.001**	**0.002**	-	0.303		**0.012**	-	0.280	
⩽7	17 (13.0)	62 (24.5)		62 (27.3)	17 (10.8)									
>7	114 (87.0)	191 (75.5)		165 (72.7)	140 (89.2)									
Tumor number			0.058			0.342	**<0.001**	1.20-2.52	**0.003**		**<0.001**	1.24-2.30	**<0.001**	
Single	24 (18.3)	70 (27.7)		60 (26.4)	34 (21.7)									
Multinodular	107 (81.7)	183 (72.3)		167 (73.6)	123 (78.3)									
PVTT			**0.045**			**0.005**	**<0.001**	1.15-2.52	**0.004**		**<0.001**	1.19-1.98	**<0.001**	
No	77 (58.8)	176 (69.6)		163 (71.8)	90 (57.3)									
Yes	54 (41.2)	77 (30.4)		64 (28.2)	67 (42.7)									
Extrahepatic metastasis			**0.001**			**0.049**	**<0.001**	-	0.331		**<0.001**	1.12-2.17	**0.008**	
No	100 (76.3)	226 (89.3)		200 (88.1)	126 (80.3)									
Yes	31 (23.7)	27 (10.7)		27 (11.9)	31 (19.7)									
BCLC stage			**0.005**			**0.001**	**<0.001**	-	-		**<0.001**	-	-	
B	57 (43.5)	150 (59.3)		139 (61.2)	68 (43.3)									
C	74 (56.5)	103 (40.7)		88 (38.8)	89 (56.7)									
ECOG-PS			0.922			1.000	**0.015**	-	0.139		**0.038**	-	0.223	
0	76 (58.0)	144 (56.9)		130 (57.3)	90 (57.3)									
1	55 (42.0)	109 (43.1)		97 (42.7)	67 (42.7)									
Child-Pugh			**0.005**			**0.020**	**0.011**	-	-		**<0.001**	-	-	
A5 points	105 (80.2)	230 (90.9)		206 (90.7)	129 (82.2)									
A6 or B7 points	26 (19.8)	23 (9.1)		21 (9.3)	28 (17.8)									
HBsAg			0.179			0.505	0.960	-	-		0.35	-	-	
Negative	21 (16.0)	27 (10.7)		31 (13.7)	17 (10.8)									
Positive	110 (84.0)	226 (89.3)		196 (86.3)	140 (89.2)									
Anti-HCV			1.000			0.779	0.54	-	-		0.99	-	-	
Negative	129 (98.5)	248 (98.0)		222 (97.8)	155 (98.7)									
Positive	2 (1.5)	5 (2.0)		5 (2.2)	2 (1.3)									
AFP (ng/mL)			0.904			0.253	**0.022**	-	0.233		0.084	-	-	
⩽400	57 (43.5)	107 (42.3)		91 (40.1)	73 (46.5)									
>400	74 (56.5)	146 (57.7)		136 (59.9)	84 (53.5)									
ALT (U/L)			0.544			1.000	0.340	-	-		0.300	-	-	
⩽50	78 (59.5)	141 (55.7)		129 (56.8)	90 (57.3)									
>50	53 (40.5)	112 (44.3)		98 (43.2)	67 (42.7)									
AST (U/L)			0.171			**0.013**	**0.001**	-	0.135		**0.005**	-	0.149	
⩽40	29 (22.1)	74 (29.2)		72 (31.7)	31 (19.7)									
>40	102 (77.9)	179 (70.8)		155 (68.3)	126 (80.3)									
LDH (U/L)			**<0.001**			**<0.001**	**<0.001**	-	0.881		**0.005**	-	0.540	
⩽300	84 (64.1)	209 (82.6)		191 (84.1)	102 (65.0)									
>300	47 (35.9)	44 (17.4)		36 (15.9)	55 (35.0)									
Alb (g/L)			**<0.001**			**0.001**	**0.037**	-	0.879		**0.010**	-	0.395	
⩽40	76 (58.0)	93 (36.8)		83 (36.6)	86 (54.8)									
>40	55 (42.0)	160 (63.2)		144 (63.4)	71 (45.2)									
TBil (umol/L)			0.773			0.835	0.17	-	-		0.550	-	-	
⩽20	111 (84.7)	210 (83.0)		191 (84.1)	130 (82.8)									
>20	20 (15.3)	43 (17.0)		36 (15.9)	27 (17.2)									
NLR			**<0.001**			**0.001**	0.200	-	-		0.050	-	-	
⩽3	54 (41.2)	178 (70.4)		154 (67.8)	78 (49.7)									
>3	77 (58.8)	75 (29.6)		73 (32.2)	79 (50.3)									
PLR			**<0.001**			**<0.001**	0.150	-	-		0.040	-	-	
⩽200	78 (59.5)	215 (85.0)		189 (83.3)	104 (66.2)									
>200	53 (40.5)	38 (15.0)		38 (16.7)	53 (33.8)									
CRP (mg/L)			**<0.001**			**<0.001**	**<0.001**	1.03-2.19	**0.035**		**<0.001**	-	0.071	
⩽3	2 (1.5)	115 (45.5)		96 (42.3)	21 (13.4)									
>3	129 (98.5)	138 (54.5)		131 (57.7)	136 (86.6)									
SAA baseline status			-			**<0.001**	**<0.001**	-	-		**<0.001**	-	-	
High	-	-		37 (16.3)	94 (59.9)									
Low	-	-		190 (83.7)	63 (40.1)									
SAA early kinetics			**<0.001**			-	**<0.001**	1.04-1.93	**0.026**		**<0.001**	1.13-1.91	**0.004**	
M-type	37 (28.2)	190 (75.1)		-	-									
non-M-type	94 (71.8)	63 (24.9)		-	-									

Abbreviations: OS, overall survival; **PFS**, progression-free survival; ***Uni***, univariate analysis; ***Mul***, multivariate analysis; ***HR***, hazard ratio; **95% *CI***, 95% confidence interval; **BMI**, body mass index; **RECIST**, response evaluation criteria in solid tumors version; **CR**, complete response; **PR**, partial response; **SD**, stable disease; **PD**, progression disease; **PVTT**, portal vein tumor thrombus; **BCLC**, Barcelona Clinic Liver Cancer; **ECOG-PS**, Eastern Cooperative Oncology Group performance status; **HBsAg**, Hepatitis B surface antigen; **Anti-HCV**, Hepatitis C antibody; **AFP**, alpha-fetoprotein; **ALT**, alanine transaminase; **AST**, aspartate transferase; **LDH**, lactate dehydrogenase; **Alb**, albumin; **TBil**, total bilirubin; **NLR**, neutrophil lymphocyte ratio; **PLR**, platelet lymphocyte ratio; **CRP**, C-reactive protein; **SAA**, serum amyloid A.

P-063 MASLD AND THE RISK OF HEPATOCELLULAR CARCINOMA IN ANTIVIRAL-NAÏVE CHRONIC HEPATITIS B: POTENTIATING EFFECT OF ALCOHOL CONSUMPTION IN A LONGITUDINAL COHORT

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic hepatitis B are major causes of chronic liver disease. However, The impact of concurrent MASLD on hepatocellular carcinoma (HCC) risk in antiviral treatment–naïve CHB patients remains unclear. This study aimed to investigate this association.

Methods: We analyzed 949 antiviral treatment–naïve CHB patients who underwent transient elastography. MASLD was defined as a controlled attenuation parameter ≥248 dB/m plus at least one metabolic risk factor. The primary outcome was incident HCC, with antiviral therapy during follow-up adjusted as a time-varying covariate.

Results: Over 7,743 person-years of follow-up (median 4.3 years), 43 patients (4.5%) developed HCC. MASLD was associated with a higher risk of HCC compared with the non-steatosis group, although the association was not statistically significant (aHR 1.68, 95% CI 0.67–4.18), consistent with findings in the propensity score–matched cohort. In subgroup analyses, MASLD was associated with a significantly increased HCC risk among patients who consumed alcohol (aHR 5.28, 95% CI 1.35–20.61). Older age (≥60 years), current smoking, and elevated serum AFP levels were also independently associated with increased HCC risk.

Conclusions: In antiviral treatment–naïve CHB patients, MASLD showed a trend toward increased HCC risk. However, among those who consumed alcohol, MASLD was significantly associated with higher HCC risk, suggesting a potential interaction between MASLD, alcohol consumption, and CHB.

Disclosure of Interest: N/A

P-064 EVOLVING HEPATOCELLULAR CARCINOMA LANDSCAPE: EPIDEMIOLOGY, TREATMENT ALLOCATION AND DOWNSTAGING LIMITS – THE NIGUARDA EXPERIENCE

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Background and aim: The epidemiology and management of hepatocellular carcinoma (HCC) are rapidly evolving due to the routinary use of antiviral therapies and the introduction of immune checkpoint inhibitors (ICIs). Multidisciplinary tumor boards (MDTBs) play a central role in treatment allocation by integrating liver function, tumor burden, and patient performance status. This study aimed to assess temporal changes in clinical presentation, treatment strategies, and outcomes of HCC at first diagnosis in a real-world setting.

Methods: We conducted a retrospective single-center study including consecutive HCC patients referred to Niguarda Hospital between July 2024 and August 2025. Clinical, etiological, tumor features, treatments, and outcomes were analyzed.

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Results: One hundred patients were included (87% male; median age 70 years old). A shift toward metabolically driven liver disease was observed, with metabolic-associated steatotic liver disease (MASLD) and metabolic-associated alcohol-related liver disease (MetALD) each accounting for 16% of cases. Comorbidities were frequent, including diabetes (40%) and prior myocardial infarction (18%). Most patients (53%) were diagnosed at an early stage (BCLC 0: 20%; BCLC A: 33%), with preserved liver function (median ALBI −2.2) and low alpha-fetoprotein levels (median 4 ng/mL). MDTB discussion guided 96% of treatment decisions. 48% patients were candidate to curative treatment (LT, Resection, Ablation or SRBT), while the remaining patients were evaluated for disease-control therapies. 9% of patients in the overall cohort were evaluated for best supportive care due to advanced disease or being unfit for any therapeutic intervention. During follow-up, recurrence occurred in 33% within one year, emerging as a major determinant of clinical course. Recurrent HCC was more aggressive, shifting to non-curative strategies, including systemic therapy (15%) and best supportive care.

Considering only patients potentially eligible for transplantation (n = 65; age < 75 years, without any significant comorbidities potentially contraindicated LT), 43 met the Milan criteria, whereas 22 were beyond Milan. Of these 22 patients, 11 were also beyond the expanded (UCSF) criteria, notably, 63% had a Metroticket score < 50%. Best supportive care was indicated in 25% of patients due to decompensated liver disease precluding any active treatments Systemic therapy was initiated in all the patients (7/11) with a not favorable Metroticket score. Of these, five were still receiving treatment at the time of analysis, while one discontinued due to hepatic decompensation and subsequently died 20 months after initial diagnosis. Only two patients (18%) were successfully downstaged to within Milan criteria and listed for liver transplantation; one has already been transplanted, while the other remains on the waiting list.

In this real-world cohort, HCC is increasingly metabolically driven and frequently diagnosed at an early stage, enabling access to curative treatments in a substantial proportion of patients. However, recurrence remains the main determinant of outcome, while aggressive downstaging strategies—including "super downstaging" approaches—may expand transplant eligibility in a limited selection of patients.

Disclosure of Interest: N/A

P-065 NON-CIRRHOTIC HCC: MASLD-DRIVEN, LATE PRESENTATION, AND WORSE OVERALL SURVIVAL COMPARED WITH CIRRHOTIC HCC

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Background: Hepatocellular carcinoma (HCC) accounts for over 80% of primary liver cancers worldwide, with a subset of cases occurring in patients without cirrhosis. Non-cirrhotic HCC is increasingly linked to metabolic liver disease, including metabolic-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), and often lacks routine surveillance. This study compared etiology, clinical presentation, and outcomes of patients with non-cirrhotic versus cirrhotic HCC in Saudi Arabia.

Methods: Data were obtained from the King Faisal Specialist Hospital and Research Centre HCC Registry. Demographic, aetiological, and clinical characteristics were compared between patients with and without cirrhosis. Survival up to 36 months was estimated using the Kaplan-Meier method, with mortality data supplemented through the National Death Registry.

Results: Among 432 patients diagnosed with HCC, 88.2% exhibited underlying cirrhosis (Table 1). Compared with cirrhotic patients, those with non-cirrhotic HCC were diagnosed at an older median age (68.0 vs 64.0 years) and included a higher proportion of males (78.4% vs 68.2%). Aetiology varied significantly by cirrhosis status. MASLD/MASH was the predominant cause in non-cirrhotic HCC (51.0% vs. 33.1%), whereas hepatitis C virus was more prevalent in cirrhotic cases, and hepatitis B virus was more common among non-cirrhotic patients. Despite exhibiting better-preserved liver function (Child-Pugh A: 72.5% vs 54.9%), non-cirrhotic patients were less frequently diagnosed at early BCLC stages (0–A: 29.4% vs 42.2%) and were more often outside the Milan criteria (60.8% vs 36.0%). Receipt of locoregional therapies was significantly lower in non-cirrhotic patients (31.1% vs. 58.8%; $p < 0.001$). Overall survival was poorer in the non-cirrhotic group, with 1- and 3-year survival probabilities of 0.62 and 0.42, respectively, compared to 0.72 and 0.52 in cirrhotic patients.

Conclusion: Non-cirrhotic HCC in Saudi Arabia is predominantly MASLD-related and is associated with later-stage presentation and poorer survival compared with cirrhotic HCC. These findings highlight potential gaps in surveillance and access to locoregional therapies and support the need for improved risk-based screening strategies.

Disclosure of Interest: N/A

Image:

Table 1. Sociodemographic and Tumer Characteristics and risk factors by liver Cirrhosis status

	Liver Cirrhosis		
	Yes	No	Test
N	381 (88.2%)	51 (11.8%)	
Age at Diagnosis	64.0	68.0	0.080
Gender			
Male	260 (68.2%)	40 (78.4%)	0.138
Female	121 (31.8%)	11 (21.6%)	
Smoking Status			
Never	306 (80.3%)	46 (90.2%)	0.293
Current	34 (8.9%)	3 (5.9%)	
Former	34 (8.9%)	1 (2.0%)	
Unknown	7 (1.8%)	1 (2.0%)	
HCC History in Family			
Yes	12 (3.1%)	0 (0.0%)	0.110
No	368 (96.6%)	50 (98.0%)	
Unknown	1 (0.3%)	1 (2.0%)	
HCC etiology (4 groups)			
HBV	78 (20.5%)	14 (27.5%)	0.009
HCV	100 (26.2%)	6 (11.8%)	
MASLD/MASH	126 (33.1%)	26 (51.0%)	
Others	77 (20.2%)	5 (9.8%)	
HCC Etiology			
Hep B	78 (20.5%)	14 (27.5%)	0.001
Hep C	100 (26.2%)	6 (11.8%)	
MASLD/MASH	126 (33.1%)	26 (51.0%)	
Hemochromatosis	1 (0.3%)	0 (0.0%)	
Autoimmune Hepatitis	7 (1.8%)	0 (0.0%)	
PFIC	3 (0.8%)	0 (0.0%)	
PBC	4 (1.0%)	0 (0.0%)	
PCS	0 (0.0%)	1 (2.0%)	
Alcoholic cirrhosis	14 (3.7%)	0 (0.0%)	
Cryptogenic	30 (7.9%)	0 (0.0%)	
Fibrolamellar	4 (1.0%)	3 (5.9%)	
/Unkown	14 (3.7%)	1 (2.0%)	
Diagnosis method			
Biopsy	19 (5.0%)	8 (15.7%)	0.003
Imaging (CT or MRI)	361 (95.0%)	43 (84.3%)	
BCLC Stage			
Very early stage	44 (11.5%)	5 (9.8%)	0.429
Early stage(A)	117 (30.7%)	10 (19.6%)	
Intermediate stage(B)	63 (16.5%)	9 (17.6%)	
Advanced stage(C)	64 (16.8%)	14 (27.5%)	
Terminal stage (D)	51 (13.4%)	7 (13.7%)	
Unknown	42 (11.0%)	6 (11.8%)	
Albumin Bilirubin			
Grade 1	96 (25.2%)	19 (37.3%)	0.297
Grade 2	221 (58.0%)	25 (49.0%)	
Grade 3	48 (12.6%)	6 (11.8%)	
Unknown	16 (4.2%)	1 (2.0%)	
Listed for transplant	2.598 (2.728)	2.549 (2.419)	0.902
Child-Pugh Classifications			
Child A	209 (54.9%)	37 (72.5%)	<0.001
Child B	131 (34.4%)	9 (17.6%)	
Child C	40 (10.5%)	2 (3.9%)	
Unknown	1 (0.3%)	3 (5.9%)	
Diabetes			
Yes	209 (54.9%)	30 (58.8%)	0.592
No	172 (45.1%)	21 (41.2%)	
Hypertension			
Yes	177 (46.5%)	29 (56.9%)	0.313
No	200 (52.5%)	22 (43.1%)	
Unknown	4 (1.0%)	0 (0.0%)	
Milan Criteria			
Within score	201 (52.8%)	15 (29.4%)	0.002
Outside score	137 (36.0%)	31 (60.8%)	
Unknown	43 (11.3%)	5 (9.8%)	
HCC Mets status			
Yes	43 (11.3%)	12 (23.5%)	0.043
No	333 (87.4%)	38 (74.5%)	
Unknown	5 (1.3%)	1 (2.0%)	
Performance Status			
Fully active	175 (45.9%)	22 (43.1%)	0.494
Restricted physically	69 (18.1%)	14 (27.5%)	
Ambulatory	31 (8.1%)	5 (9.8%)	
limited selfcare	21 (5.5%)	3 (5.9%)	
Completely disabled	9 (2.4%)	0 (0.0%)	
Unknown	76 (19.9%)	7 (13.7%)	
First Treatment at KFSHRC			
Locoregional therapies	200 (58.8%)	14 (31.1%)	0.001
Surgery	58 (17.1%)	8 (17.8%)	
Systemic therapy	30 (8.8%)	9 (20.0%)	
Combined therapy	3 (0.9%)	2 (4.4%)	
Supportive/ Palliative	49 (14.4%)	12 (26.7%)	

Continuous variables are reported as median (IQR) and compared using the Mann–Whitney U test; categorical variables are compared using χ^2 or Fisher's exact test, as appropriate

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P-066 18F-FDGAL UPTAKE ON PET/CT CORRELATES WITH TUMOR DIFFERENTIATION AND PREDICTS MORTALITY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) can be diagnosed without a biopsy in patients with cirrhosis. This leaves tumor pathology unavailable, limiting prognostic information. The positron emission tomography (PET) tracer [18F]-fluoro-2-deoxy-D-galactose (18F-FDGal) is, like galactose, almost only metabolized in hepatocytes. We hypothesized that the accumulation of 18F-FDGal in HCC correlates with histological differentiation and prognosis.

Methods: This clinical study included 30 patients with histology-proven HCC who underwent an 18F-FDGal PET/CT scan conducted at our tertiary liver center.

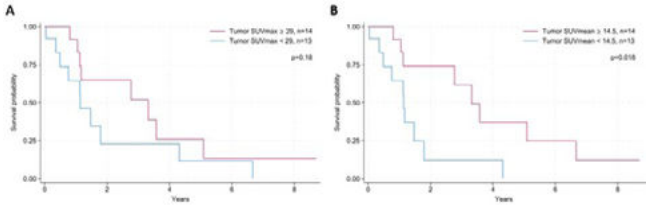
The patients either had known tumor differentiation (n = 17) or were diagnosed with HCC less than 12 months prior to the 18F-FDGal PET/CT scan (n = 27). A whole-body PET/CT scan was performed approximately 1 hour after a bolus injection a median of 105 MBq 18F-FDGal. The maximum and average standardized uptake values (SUVmax and SUVmean) were calculated in tumors and liver tissue without tumor.

Results: The SUVmax and SUVmean for poorly differentiated tumors were significantly lower than for well- and moderately differentiated tumors pooled as one group ($p = 0.01$ and $p = 0.04$). The tumor-to-liver ratio for poorly differentiated tumors was lower when compared to well- and moderately differentiated tumors when comparing SUVmax in the tumor to SUVmax in the liver ($p = 0.03$). Patients with a tumor SUVmean < 14.5 had a mortality rate that was 3.5 times higher than patients with a tumor SUVmean ≥ 14.5 ($p = 0.02$).

Conclusion: The SUVmean of 18F-FDGal in metabolic active HCCs correlated with histological differentiation and overall survival.

Disclosure of Interest: N/A

Image:



P-067 CLINICAL CHARACTERIZATION OF GALLBLADDER CANCER IN A MEXICAN COHORT: INSIGHTS FROM A REAL-WORLD DATABASE

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Introduction: Gallbladder cancer (GBC) is associated with high mortality, exceeding 70% of diagnosed cases, largely due to late and incidental diagnosis (Ferlay et al., 2024; Roa et al., 2022). In routine clinical practice, diagnosis and monitoring often rely on non-specific tumor markers such as carbohydrate antigen 19-9 (CA 19-9), which lack adequate sensitivity and specificity for GBC. As a result, a substantial proportion of patients (pts) may not be accurately identified or monitored using current biomarker strategies. Despite the high burden of disease in Latin America, real-world evidence describing how these biomarkers perform in clinical settings, as well as their impact on patient identification and management, remains limited—particularly in heterogeneous populations such as Mexico. This analysis addresses the urgent need to better characterize GBC in real-world settings and to identify gaps in current biomarker-driven diagnostic strategies that may contribute to missed or delayed patient identification in this population.

Methods: We conducted a retrospective analysis of 245 patients with GBC between 2014 and 2023 at Instituto Nacional de Cancerología (INCan), México. The analysis included demographic variables (age, sex, place of origin), clinical variables (body mass index, tobacco and alcohol use, prior diagnosis of gallstones), oncological variables (TNM staging, clinical stage, serum CA 19-9 levels, treatments before and after admission), and therapeutic variables (surgery, chemotherapy, and radiation therapy). Descriptive analyses, Kaplan–Meier survival estimates, and regression/correlation analyses were performed. Geographic distribution was assessed.

Results: The mean age at diagnosis was 61.1 ± 10.6 years, with a median of 62 years (IQR: 53–69), and female predominance (6:1). Interestingly, higher rates of alcohol use, particularly among women, were reported. Most cases were referred from the central and southern regions of the country, and 66% of patients reported advanced disease (stage IV). Cholelithiasis was associated with increased risk stratification. A significant proportion of patients (49%) had normal CA 19-9 levels, indicating limited diagnostic utility; however, CA 19-9 retained prognostic value and was associated with survival outcomes during chemotherapy.

Conclusion: In real-world practice, reliance on CA 19-9 may contribute to under-recognition of GBC, as many patients present with normal levels despite advanced disease. While CA 19-9 remains prognostic, its limited diagnostic sensitivity highlights a critical gap in current approaches. These findings emphasize the need for improved biomarkers and earlier identification strategies in high-risk populations.

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Disclosure of Interest: N/A

P-068 LIVER FUNCTION STRATIFICATION USING ALBI AND CHILD–PUGH IN ADVANCED HEPATOCELLULAR CARCINOMA: A REAL-WORLD STUDY

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Introduction: Patients with advanced hepatocellular carcinoma (HCC) and impaired liver function are frequently excluded from clinical trials. The Child–Pugh (CP) classification is commonly used to guide treatment eligibility but may inadequately capture heterogeneity in hepatic reserve. The albumin–bilirubin (ALBI) score offers a more objective assessment of liver function. This study aimed to evaluate whether ALBI further stratifies liver function beyond CP class and its association with treatment duration, attrition, and overall survival (OS) in a real-world HCC cohort.

Method: We conducted a retrospective study of patients with advanced HCC who received at least one line of systemic therapy at two tertiary centers between 2021 and 2025. Baseline liver function was assessed using CP class and ALBI score at initial consultation. Treatment duration across first- to third-line therapies and OS were evaluated. Associations between liver function, treatment exposure, number of treatment lines, and survival were analyzed using non-parametric tests and Spearman correlation. ALBI was analyzed as both a categorical and continuous variable.

Results: Fifty-three patients were included. At baseline, 69.8% were CP A, 24.5% CP B, and 5.7% CP C; ALBI grades were 34.0% grade 1, 58.5% grade 2, and 7.5% grade 3. Among CP A patients, 59.5% were reclassified as ALBI grade 2 or 3, indicating substantial discordance. Median first-line treatment duration was 4.5 months (IQR 1.9–12.0) and did not differ by CP class or ALBI grade. Attrition was high, with 34% receiving second-line and 15% third-line therapy. Median OS was 13.0, 31.4, and 8.3 months for CP A, B, and C patients, respectively, with marked heterogeneity in CP C. ALBI grade did not predict treatment duration or survival when analyzed categorically or continuously. Survival correlated with number of treatment lines (Spearman rho = 0.59, $p = .0007$), reflecting attrition and selection bias. A small subset of CP C patients achieved measurable treatment duration, most of whom were ALBI grade 2, highlighting heterogeneity within advanced liver dysfunction.

Conclusion: In this real-world HCC cohort, ALBI revealed clinically relevant heterogeneity within CP classes but was not independently associated with treatment duration or survival. High attrition across treatment lines underscores the dominant impact of liver function and clinical decline on treatment sequencing. ALBI may support more nuanced assessment of treatment feasibility in selected patients with advanced liver dysfunction, though prospective validation is warranted.

Disclosure of Interest: N/A

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P-069 RISK FACTORS, CLINICAL CHARACTERISTICS, AND OUTCOMES OF CHOLANGIOCARCINOMA IN EGYPTIAN PATIENTS: A MULTICENTRE RETROSPECTIVE STUDY

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Introduction: Cholangiocarcinoma (CCA) represents 3% of gastrointestinal malignancies. Discrepancy in incidence of CCA between different regions reflects discrepancies in risk factors, presentation and treatment options. CCA is a rising health concern in Egypt, particularly in the Nile Delta region, with increasing annual incidence. Often associated with liver cirrhosis, chronic HCV infection, Schistosomiasis, and environmental factors

The aim of this study is to explore the characteristics, risk factors, treatments and outcomes of CCA among Egyptian patients.

Methods: This multicentre retrospective study included 102 patients recruited consecutively between January 2015 and January 2024 from Oncology and Endemic Medicine departments, Cairo university; National Cancer Institute, Menoufia University; and Assiut University. Demographic, clinical, laboratory and imaging data and treatment outcomes were collected from the clinics' registries. Diagnosis of CCA was based on the National Comprehensive Cancer Network (NCCN) guidelines. Classification of CCA was done according to the 11th revision of the international classification of diseases (ICD-11) into Intrahepatic cholangiocarcinoma (iCCA), Perihilar cholangiocarcinoma (pCCA), and Distal cholangiocarcinoma (dCCA). Overall Survival was calculated from date of diagnosis to date of death or study end.

Results: This multicentre study comprised 102 patients with CCA, predominantly males (59.8%) and residing in urban areas (79.4%), Their median age of 60 [26-82] years. The recorded risk factors for CCA were obesity (29.4%), cigarette smoking (24.5%), Diabetes mellitus (21.6%) and viral hepatitis C (13.7%). Perihilar lesions were the predominant kind of CCA, succeeded by the intrahepatic variant. CCA predominantly presented as a malignant biliary stricture (64.4%). Distal CCA affected only 2.9% of the patients. Malignant Lymphadenopathy or distant metastases affected 56.3% of patients. The leading treatment modality was chemotherapy (91.2%) followed by surgery (27.5%) Cisplatin-gemcitabine was the most used chemotherapy regimen.

Mortality was significantly higher in patients with urban residency, the presence of intrahepatic cholangiocarcinoma, and the administration of Surgery and cisplatin-gemcitabine treatment were associated with reduced mortality rates.

The Median overall survival was 31.4 months. Intrahepatic cholangiocarcinoma was the independent factor affecting mortality by multivariate analysis.

Conclusion: CCA in Egyptian patients commonly presents at an advanced stage, with perihilar tumors being the predominant subtype. Despite widespread use of chemotherapy, outcomes remain suboptimal. Intrahepatic CCA is associated with poorer survival, highlighting the need for improved early detection and tailored therapeutic strategies.

Disclosure of Interest: N/A

P-070 REFINING POST-TRANSPLANT RECURRENCE RISK STRATIFICATION IN HEPATOCELLULAR CARCINOMA USING MACHINE LEARNING

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Introduction: Post-transplant recurrence remains the major oncological challenge after liver transplantation for hepatocellular carcinoma (HCC). Although expanded transplantation criteria increase patient eligibility, their ability to identify patients with durable recurrence-free survival (RFS) remains uncertain. This study compared the prognostic performance of major transplantation criteria and developed a machine-learning model to improve post-transplant recurrence risk stratification.

Method: A retrospective cohort of 1,509 patients with pathologically confirmed HCC who underwent deceased-donor liver transplantation between 2005 and 2022 was analyzed. Overall survival (OS) and RFS were compared across transplantation criteria using Kaplan–Meier analysis. Patients were randomly assigned to training (70%) and test (30%) cohorts. Four survival prediction models were developed and evaluated: least absolute shrinkage and selection operator–Cox regression (LASSO-Cox), random survival forest (RSF), extreme gradient boosting with accelerated failure time objective (XGBoost-AFT), and survival support vector machine (Survival SVM). Model performance was assessed using the concordance index (C-index) and time-dependent receiver operating characteristic analysis.

Result: Patients additionally included beyond the Milan criteria by either the Fudan or UCSF criteria demonstrated significantly worse RFS despite maintaining acceptable OS. Six variables were selected for model development: tumor number, maximum tumor diameter, microvascular invasion, alpha-fetoprotein, aspartate aminotransferase, and gamma-glutamyl transferase. Among the evaluated algorithms, the RSF model achieved the best predictive performance, with a test-set C-index of 0.762 and 1-, 2-, and 3-year AUCs of 0.816, 0.814, and 0.801, respectively. RSF-based risk stratification identified distinct recurrence-risk groups with significantly different outcomes.

Conclusion: Expanded transplantation criteria capture a broader patient population but are associated with increased recurrence risk among patients beyond the Milan criteria. A six-variable RSF model provides accurate individualized post-transplant recurrence risk assessment and may facilitate risk-adapted surveillance and adjuvant treatment strategies.

Disclosure of Interest: N/A

Images:

Table 2. Survival outcomes and event distribution in the overall cohort and across transplantation criteria

	All (n = 1509)	Milan (n = 640)	UCSF (n = 750)	Fudan (n = 815)	Hangzhou (n = 754)	5-5-500 (n = 751)	Asan (n = 903)	Up-to-7 (n = 825)
Overall survival rate								
1-year	90.0% (88.5%-91.5%)	95.3% (93.6%-96.9%)	95.0% (93.5%-96.6%)	94.8% (93.3%-96.3%)	95.2% (93.7%-96.7%)	94.8% (93.2%-96.4%)	94.4% (92.9%-95.9%)	95.1% (93.6%-96.6%)
2-year	78.8% (76.7%-80.9%)	89.7% (87.4%-92.1%)	89.2% (87.0%-91.5%)	89.0% (86.8%-91.2%)	90.4% (88.3%-92.5%)	90.2% (88.1%-92.4%)	88.6% (86.6%-90.7%)	89.8% (87.8%-91.9%)
3-year	71.9% (69.6%-74.2%)	86.7% (84.1%-89.4%)	86.0% (83.5%-88.5%)	85.4% (83.0%-87.9%)	86.9% (84.5% - 89.3%)	87.0% (84.6%-89.4%)	84.6% (82.3%-87.0%)	86.3% (84.0%-88.7%)
5-year	65.1% (62.7%-67.6%)	82.4% (79.5%-85.5%)	81.7% (79.0%-84.6%)	80.5% (77.8%-83.3%)	82.7% (80.0%-85.5%)	83.4% (80.7%-86.1%)	80.0% (77.4%-82.7%)	82.3% (79.7%-85.0%)
10-year	58.3% (55.7%-61.0%)	75.5% (71.9%-79.2%)	74.4% (71.1%-77.9%)	72.9% (69.6%-76.3%)	74.9% (71.6%-78.4%)	75.1% (71.7%-78.6%)	72.3% (69.2%-75.6%)	74.4% (71.1%-77.7%)
Recurrence-free survival rate								
1-year	80.3% (78.3%-82.4%)	93.7% (91.8%-95.7%)	93.3% (91.5%-95.1%)	92.5% (90.7%-94.4%)	93.3% (91.5%-95.1%)	94.0% (92.2%-95.7%)	91.6% (89.8%-93.4%)	93.4% (91.7%-95.1%)
2-year	70.8% (68.5%-73.2%)	89.4% (87.0%-91.9%)	88.5% (86.1%-90.8%)	87.3% (85.0%-89.7%)	88.8% (86.5%-91.1%)	89.4% (87.2%-91.7%)	85.7% (83.4%-88.1%)	88.6% (86.4%-90.9%)
3-year	67.3% (64.9%-69.8%)	87.5% (84.9%-90.2%)	86.4% (83.9%-89.0%)	85.0% (82.5%-87.6%)	87.1% (84.6%-89.6%)	88.1% (85.8%-90.5%)	83.7% (81.2%-86.2%)	86.8% (84.5%-89.2%)
5-year	64.1% (61.6%-66.6%)	85.2% (82.4%-88.1%)	84.2% (81.5%-86.9%)	82.6% (80.0%-85.4%)	85.3% (82.7%-87.9%)	86.4% (84.0%-89.0%)	81.0% (78.4%-83.7%)	84.7% (82.2%-87.3%)
10-year	61.1% (58.5%-63.9%)	82.2% (79.0%-85.5%)	81.0% (78.0%-84.1%)	79.4% (76.4%-82.5%)	81.7% (78.6%-84.8%)	82.9% (80.0%-86.0%)	77.8% (74.9%-80.8%)	80.9% (77.9%-83.9%)
Number of recurrences	542 (35.9%)	104 (16.3%)	132 (17.6%)	156 (19.1%)	128 (17.0%)	116 (15.4%)	185 (20.5%)	144 (17.5%)
Number of deaths	613 (40.6%)	158 (24.7%)	192 (25.6%)	223 (27.4%)	189 (25.1%)	178 (23.7%)	242 (26.8%)	208 (25.2%)
Number of recurrence-related deaths	436 (71.1%)	75 (47.5%)	97 (50.5%)	117 (52.5%)	94 (49.7%)	83 (46.6%)	135 (55.8%)	106 (51.0%)

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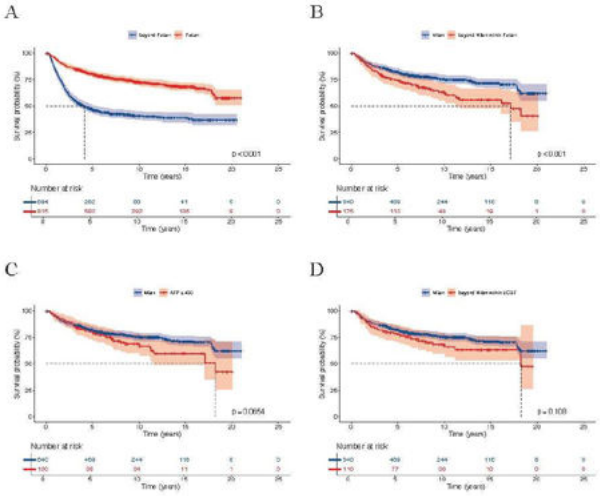

Figure 2
Kaplan-Meier curves of OS under different transplantation criteria. (A) Patients within the Fudan criteria vs. those beyond the Fudan criteria; (B) Patients beyond the Milan criteria but within the Fudan criteria vs. those within the Milan criteria; (C) Patients beyond the Milan criteria but within the Fudan criteria with AFP ≤ 400 ng/mL vs. those within the Milan criteria; (D) Patients beyond

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P-129 DEFINITION, RISK FACTORS, AND OUTCOMES OF EARLY AND LATE RECURRENCE AFTER CURATIVE RESECTION FOR INTRAHEPATIC CHOLANGIOCARCINOMA

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Background: Recurrence of intrahepatic cholangiocarcinoma (ICC) is generally associated with poor prognosis. We aimed to define early recurrence, reveal differences in risk factors between early and late ecurrence, and provide insights to guide individualized treatment strategies

Methods: This retrospective cohort study included consecutive patients with ICC who underwent curative resection at Zhongshan Hospital, Fudan University, between 2009 and 2016. The optimal cutoff time point for distinguishing early and late recurrence was determined using the minimum P value approach based on post-recurrence survival (PRS) and overall survival (OS). Immunohistochemistry was performed to evaluate the expression of immune markers. Univariable and multivariable Cox proportional hazards regression models were applied to identify clinicopathological and microenvironmental factors associated with each recurrence group.

Results: Among 1,024 ICC patients, 730 experienced recurrence and were stratified by time to recurrence. A 12-month cutoff most effectively distinguished between early and late recurrence, with early recurrence showing markedly poorer PRS and OS. Compared with late recurrence, early recurrence exhibited a significant association with microvascular invasion (MVI), whereas late recurrence was more strongly correlated with nodal metastasis. Among 599 patients with immunohistochemical data, high levels of CD3+ and CD4+ T cells were associated with a protective effect against early recurrence, whereas increased Foxp3+ regulatory T cells, CD68+ macrophages, and CD66b+ neutrophils served as risk factors for early recurrence. By contrast, the predictive value of immune markers in patients with late recurrence appeared to be remarkably limited.

Conclusion: We defined early and late recurrence in resected ICC and identified distinct tumour and microenvironmental characteristics for each type of recurrence. These findings provide insights into the prediction of recurrence timing and offer a clinical framework for reducing postoperative recurrence in ICC.

Disclosure of Interest: N/A

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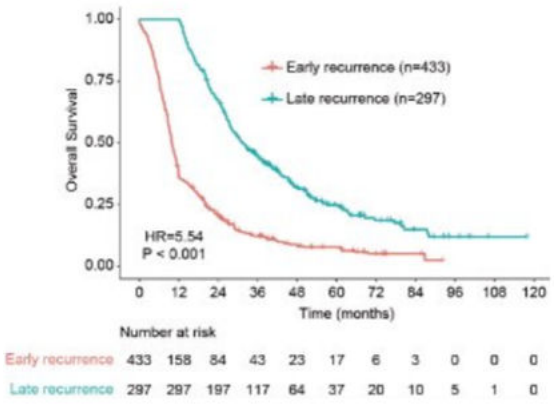

P-130 DEVELOPMENT AND VALIDATION OF A STROMAL-IMMUNE SIGNATURE TO PREDICT PROGNOSIS IN INTRAHEPATIC CHOLANGIOCARCINOMA

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Background: Intrahepatic cholangiocarcinoma (iCCA) is a highly desmoplastic tumor with poor prognosis even after curative resection. We investigated the associations between the composition of the iCCA stroma and immune cell infiltration and aimed to develop a stromal-immune signature to predict prognosis in surgically treated iCCA.

Patients and methods: We recruited 359 iCCA patients and performed immunohistochemistry to detect α-smooth muscle actin (α-SMA), CD3, CD4, CD8, Foxp3, CD68, and CD66b. Aniline was used to stain collagen deposition. Survival analyses were performed to detect prognostic values of these markers. Recursive partitioning for a discrete-time survival tree was applied to define a stromal-immune signature with distinct prognostic value. We delineated an integrated stromal-immune signature based on immune cell subpopulations and stromal composition to distinguish subgroups with different recurrence-free survival (RFS) and overall survival (OS) time.

Result: We defined four major patterns of iCCA stroma composition according to the distributions of α-SMA and collagen: dormant (α-SMAlow/collagenhigh), fibrogenic (α-SMAhigh/collagenhigh), inert (α-SMAlow/collagenlow), and fibrolytic (α-SMAhigh/collagenlow). The stroma types were characterized by distinct patterns of infiltration by immune cells. We divided patients into six classes. Class I, characterized by high CD8 expression and dormant stroma, displayed the longest RFS and OS, whereas Class VI, characterized by low CD8 expression and high CD66b expression, displayed the shortest RFS and OS. The integrated stromal-immune signature was consolidated in a validation cohort.

Disclosure of Interest: N/A

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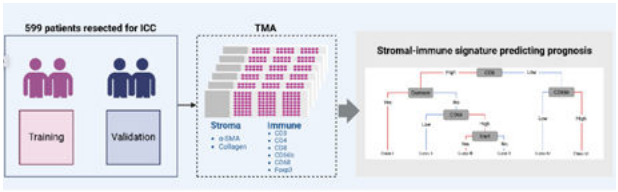

P-133 BALANCING TUMOR CONTROL AND GRAFT SAFETY IN PRETRANSPLANT IMMUNE CHECKPOINT INHIBITION FOR HEPATOCELLULAR CARCINOMA BEYOND THE MILAN CRITERIA AT TRANSPLANTATION: A SINGLE-CENTER RETROSPECTIVE COHORT STUDY

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Introduction: Pretransplant immune checkpoint inhibitors (ICIs) are increasingly incorporated into bridging or downstaging strategies for patients with hepatocellular carcinoma (HCC) being considered for liver transplantation (LT).1 However, evidence regarding post-transplant oncologic outcomes, graft safety, and prognostic factors remains limited, particularly among recipients who remain beyond the Milan criteria at LT.2 We evaluated post-LT outcomes among ICI-exposed recipients and explored factors associated with HCC recurrence and acute rejection.

Methods: We retrospectively analyzed 342 patients with HCC beyond the Milan criteria who underwent deceased-donor LT between January 2019 and December 2024, including 101 who received pretransplant ICI therapy. HCC recurrence was assessed using cumulative-incidence functions and Fine–Gray competing-risk regression, with death without recurrence treated as a competing event. Among ICI-exposed recipients, biopsy-confirmed acute cellular rejection was evaluated using Firth logistic regression. Early postoperative peripheral blood lymphocyte subsets were also analyzed in relation to recurrence and rejection.

Results: The study included 342 LT recipients with HCC beyond the Milan criteria, of whom 101 (29.5%) received pretransplant ICI therapy (Table 1). During a median follow-up of 24.2 months, 114 patients (33.3%) developed HCC recurrence, and AFP >400 ng/mL was independently associated with a higher recurrence risk (SHR 1.89, 95% CI 1.29–2.78; P=0.001; Figure 1A). ICI exposure was not significantly associated with recurrence in the overall cohort (SHR 0.74, 95% CI 0.47–1.16; P=0.182), but was associated with a lower recurrence risk in patients with AFP >400 ng/mL (SHR 0.41, 95% CI 0.19–0.90; P=0.026; Figure 1B, C). In the ICI-exposed group, 26 patients (25.7%) developed recurrence and 12 (11.9%) developed biopsy-confirmed acute rejection. The incidence of acute rejection was higher among patients with an ICI washout period ≤30 days than among non-ICI recipients and those with a washout period >30 days (20.5% vs 5.8% and 5.3%, P=0.004 and P=0.029, respectively; Figure 1D). No rejection-related retransplantation or death occurred. Higher B-lymphocyte parameters and lower NK-cell levels were associated with recurrence, whereas a higher CD8+ T-cell proportion was associated with acute rejection.

Conclusion: Among LT recipients with HCC beyond the Milan criteria, pretransplant ICI exposure was not significantly associated with HCC recurrence overall. In ICI-exposed recipients, a washout interval

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≤30 days was associated with an increased risk of biopsy-confirmed acute rejection, although no rejection-related graft loss or death occurred. Early postoperative immune profiles were associated with subsequent oncologic and graft outcomes. These findings support individualized pretransplant ICI use based on tumor-related risk, treatment timing, and post-transplant immune status.

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Disclosure of Interest: N/A

Images:

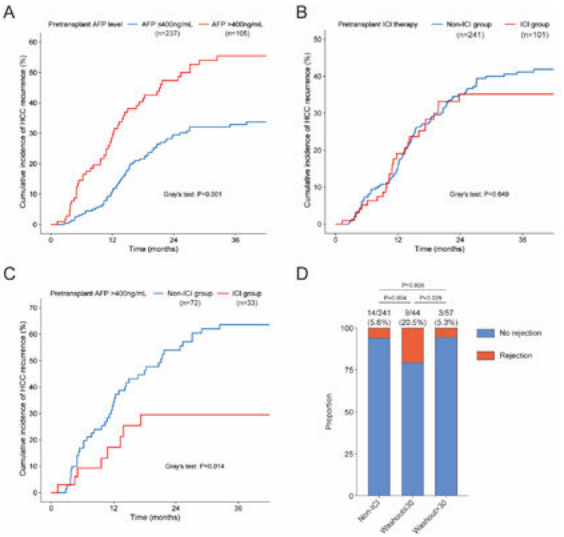

Table 1

Clinical characteristics of hepatocellular carcinoma recipients undergoing liver transplantation.

Variables	Overall (n=342)	Recurrence (n = 114)	No recurrence (n = 228)	P
Age, years, median (IQR)	56 (49-63)	54 (47-63)	56 (50-63)	0.095
Male, n (%)	304 (88.9)	106 (93.0)	198 (86.8)	0.089
Diagnosis, n (%)				
HBV	292 (85.4)	101 (88.6)	191 (83.8)	0.259
HCV	4 (1.2)	1 (0.9)	3 (1.3)	>0.99
Alcohol	10 (2.9)	1 (0.9)	9 (3.9)	9
Other	36 (10.5)	11 (9.6)	25 (11.0)	0.174
Child-Pugh class, n (%)				0.852
A	183 (53.5)	64 (56.1)	119 (52.2)	
B	111 (32.5)	31 (27.2)	80 (35.1)	0.490
C	48 (14.0)	19 (16.7)	29 (12.7)	0.142
MELD score, median (IQR)	12 (8-13)	9 (7-13)	11 (8-14)	0.322
AFP level, ng/mL, median (IQR)				0.086
≤400, n (%)	237 (69.3)	63 (55.3)	174 (76.3)	<0.00
>400, n (%)	105 (30.7)	51 (44.7)	54 (23.7)	1
Number of tumors, n (%)				
1	55 (16.1)	16 (14.0)	39 (17.1)	
2	49 (14.3)	15 (13.2)	34 (14.9)	
3	33 (9.6)	6 (5.3)	27 (11.8)	0.466
>3	205 (60.1)	77 (67.5)	128 (56.1)	0.662
Maximum diameter, cm, median (IQR)	4.5 (3-7)	5.5 (3.1-9.5)	4 (3-6)	0.052
Tumor differentiation, n (%)	192 (56.1)	47 (41.2)	145 (63.6)	0.043
I-II,	150 (43.9)	67 (58.8)	83 (36.4)	0.001
III-IV				<0.00
Vascular invasion, n (%)	121 (35.4)	28 (24.6)	93 (40.8)	1
None	162 (47.4)	57 (50.0)	105 (46.1)	
Microvascular	59 (17.3)	29 (25.4)	30 (13.2)	
Macrovascular	234 (68.4)	82 (71.9)	152 (66.7)	0.003
Locoregional therapy, n (%)	216 (63.2)	77 (67.5)	139 (61.0)	0.491
TACE	80 (23.4)	24 (21.1)	56 (24.6)	0.005
RFA	23 (6.7)	11 (9.6)	12 (5.3)	0.324
RT	153 (44.7)	44 (38.6)	109 (47.8)	0.234
Targeted therapy	101 (29.5)	26 (22.8)	75 (32.9)	0.470
ICI therapy	26 (7.6)	12 (10.5)	14 (6.3)	0.127
Acute rejection, n (%)	131 (38.3)	85 (74.6)	46 (20.2)	0.106
Death, n (%)				0.054
				0.149
				<0.00
				1

P values indicate comparisons between the recurrence and no recurrence groups.

AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor; LT, liver transplantation; MELD, Model for End-stage Liver Disease; RFA, radiofrequency ablation; RT, radiotherapy; TACE, transarterial chemoembolization.

P-137 PERIOPERATIVE CIRCULATING TUMOR DNA ANALYSIS FOR RECURRENCE RISK ASSESSMENT, EARLY RELAPSE DETECTION, AND ADJUVANT THERAPY RESPONSE EVALUATION IN LIVER CANCER

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Introduction: Recurrence after curative hepatectomy is the main cause of poor outcomes in liver cancer, yet clinicians still lack sensitive perioperative tools to assess recurrence risk, catch early relapse, and judge adjuvant treatment response. We evaluated perioperative circulating tumor DNA (ctDNA) as such a tool in patients undergoing hepatectomy for liver cancer.

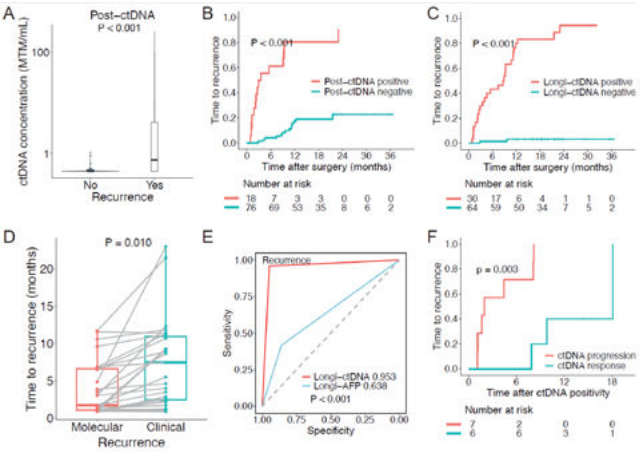
Methods: We prospectively enrolled 94 patients with liver cancer treated with curative hepatectomy. ctDNA was quantified by personalized next-generation sequencing from perioperative plasma samples (n=430).

Results: Higher preoperative ctDNA burden correlated with microvascular invasion (median: 82.0 vs 3.3 MTM/mL, P<0.001), and patients who relapsed showed significantly higher ctDNA burden than those who did not (median: 103.3 vs 7.6 MTM/mL, P<0.001). ctDNA clearance was noted in 81.2% of patients after curative hepatectomy, and patients who remained postoperative ctDNA-positive showed higher recurrence risk (HR=10.38, P<0.001), especially early recurrence (within one year) when compared with those who were postoperative ctDNA-negative (77.8% vs 15.8%, P<0.001). During follow-up, persistent longitudinal ctDNA positivity was similarly predictive of recurrence (HR=53.59, P<0.001), with an AUC of 0.942 (sensitivity 93.1%, specificity 95.4%). In hepatocellular carcinoma, longitudinal ctDNA outperformed alpha-fetoprotein (AFP) for predicting recurrence (AUC 0.953 vs 0.638, P<0.001). Longitudinal ctDNA analysis detected radiologically evidenced recurrence with a median lead time of 1.7 months compared with standard-of-care surveillance. Among patients who received adjuvant therapy, those with a ctDNA response (decreased or stable ctDNA burden) experienced a longer interval from ctDNA positivity to recurrence (HR=0.08, P=0.003).

Conclusion: Perioperative ctDNA dynamics provide robust prognostic value after hepatectomy, detect molecular relapse before it becomes radiologically apparent, and mirror adjuvant treatment response. Incorporating dynamic ctDNA into postoperative care could enable earlier, biomarker-guided intervention in liver cancer.

Disclosure of Interest: N/A

Image:



P-138 PROFILING CIRCULATING TUMOR DNA FOR RECURRENCE PREDICTION AND PREVENTION IN HEPATOCELLULAR CARCINOMA FOLLOWING LIVER TRANSPLANTATION

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Introduction: Sensitive biomarkers for recurrence risk stratification, recurrence surveillance and adjuvant therapy guidance are of unmet need for patients with hepatocellular carcinoma (HCC) undergoing liver transplantation (LT). Herein, we explored the potential of profiling circulating tumor DNA (ctDNA) for prediction and prevention of recurrence in HCC after LT.

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Methods: HCC patients (n=91) who underwent LT were prospectively enrolled. ctDNA was assayed using next-generation sequencing from perioperative plasma (n=408). Associations between ctDNA status with clinicopathological parameters, tumor recurrence, and adjuvant treatment effect were analyzed.

Results: Higher preoperative ctDNA burden correlated with microvascular invasion (median: 45.0 vs 5.1 MTM/mL, P=0.003) and recurrence (156.2 vs 7.7 MTM/mL, P<0.001). ctDNA clearance was noted in 87.7% patients after LT and patients who kept positive postoperative ctDNA showed higher recurrence risk (HR=8.86, P<0.001), especially early recurrence (within 1 year; 75.0% vs 10.1%, P<0.001). During follow-up, positive longitudinal ctDNA was similarly predictive of recurrence (HR=36.50, P<0.001). The AUC of longitudinal ctDNA for predicting recurrence was 0.930, significantly higher than alpha-fetoprotein (0.655, P<0.001). Longitudinal ctDNA detected radiologically evidenced recurrence with a median lead time of 5.1 months compared to standard-of-care surveillance. Among patients who received adjuvant therapy, those with positive postoperative ctDNA could benefit (HR=0.11, P=0.003) and those with decreased ctDNA burden following treatment experienced longer interval from ctDNA positivity to recurrence (HR=0.17, P=0.006).

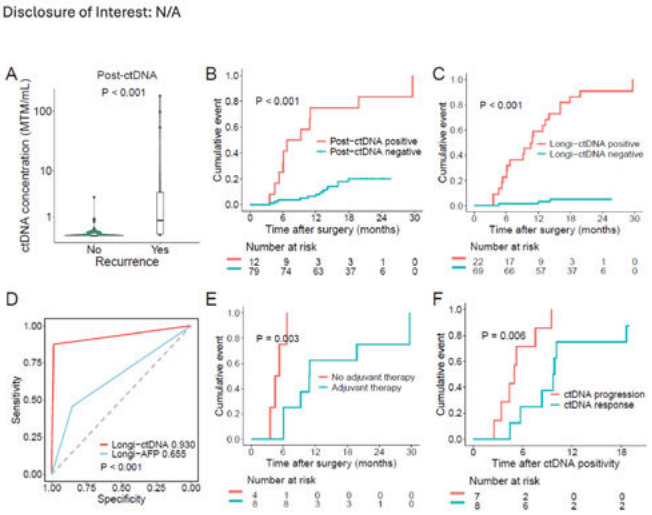
Conclusion: Serial ctDNA analysis demonstrates strong prognostic value, capable of heralding tumor recurrence prior to radiological recurrence and measuring treatment efficacy. Its integration into clinical practice of HCC provides unique opportunities for adjuvant therapy decision-making following LT.

(A) The association of post-ctDNA burden with recurrence status. (B) Kaplan–Meier analysis of TTR for patients stratified by post-ctDNA status. (C) Kaplan–Meier analysis of TTR for patients stratified by longi-ctDNA status. (D) Receiver operating characteristic curves comparing the predictive value of longi-ctDNA and longi-AFP for recurrence. (E) Kaplan–Meier analysis of TTR for patients with post-ctDNA positivity stratified by adjuvant therapy administration. (F) Kaplan–Meier analysis of the interval between molecular recurrence and clinical recurrence stratified by ctDNA dynamic changes.

Abbreviations: ctDNA, circulating tumor DNA; HCC, hepatocellular carcinoma; Longi-AFP, longitudinal alpha-fetoprotein; Longi-ctDNA, longitudinal ctDNA; LT, liver transplantation; Post-AFP, postoperative alpha-fetoprotein; Post-ctDNA, postoperative ctDNA; TTR, time to recurrence.

Disclosure of Interest: N/A

Image:



Surveillance and Diagnosis

P-071 TEMPORAL, REGIONAL, AND DEMOGRAPHIC PATTERNS OF ABDOMINAL IMAGING IN HEPATOCELLULAR CARCINOMA PATIENTS IN THE UNITED STATES: 2016 – 2024

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Introduction: The use of diagnostic imaging and the incidence of hepatocellular carcinoma (HCC) have both increased in the US over the last two decades. However, a systemic analysis of imaging modality usage in HCC patients, particularly in four US regions, is lacking. This study examines temporal trends in the use of diagnostic imaging in HCC patients across US regions.

Methods: A retrospective cohort study was conducted using Optum Clinformatics DataMart in the US. Between Jan 2016 and Dec 2024, we identified adults (>= 18 years) who underwent at least one abdominal magnetic resonance imaging (MRI), MRI with gadoxetate, computed tomography (CT), or ultrasound and had an HCC diagnosis (within ±6 months). Annual rates per 100,000 patients for each imaging modality in HCC patients were calculated and stratified by age, gender, race, and four US regions (Midwest, Northeast, South and West),

Results: From 2016 to 2024, all four imaging modalities demonstrated consistent upward trends in patients with hepatocellular carcinoma (HCC) in all US geographical regions.

Region: In the Midwest, MRI rates increased from 24 to 77 per 100,000 (221% increase), CT from 31 to 74 (139% increase), and ultrasound from 19 to 47 (147% increase). The Northeast showed the highest baseline rates, with MRI increasing from 45 to 104 per 100,000 (131% increase), CT from 57 to 103 (81% increase), and ultrasound from 42 to 78 (86% increase). In the South, MRI rates rose from 29 to 85 per 100,000 (193% increase), CT from 39 to 92 (136% increase), and ultrasound from 25 to 56 (124% increase). The West demonstrated similar patterns with MRI increasing from 34 to 77 per 100,000 (126% increase), CT from 39 to 85 (118% increase), and ultrasound from 29 to 57 (97% increase). MRI with gadoxetate rates remained relatively stable across all regions (range: 4–15 per 100,000).

Age: Patients aged 65+ comprised the majority of HCC cases across all regions and modalities. By 2024, rates per 100,000 for MRI in this age group reached: Northeast (254), Midwest (223), West (179), and South (176); CT in this age group reached: Northeast (248), Midwest (215), West (200), and South (195). The 45-64 age group showed stable rates, while 18-44 remained lowest (1-5 per 100,000) for all modalities.

Gender: Males consistently demonstrated higher rates than females across all regions, with approximately 2:1 to 3:1 male-to-female ratios. Male MRI rates by 2024 were 108-145 per 100,000 whereas for females, rates were consistently lower: 45-66 per 100,000.

Race: White patients showed the highest rates across most regions by 2024, except Northeast where the rates were slightly higher for black patient while rates in Asian patients varied widely for the four modalities.

Conclusion: From 2016 to 2024, abdominal MRI, CT, and ultrasound use among patients with HCC increased across all US regions; CT remained the most commonly used modality, while MRI showed the greatest growth, and MRI with gadoxetate remained stable. Imaging utilization was highest among patients aged ≥65 years, higher in males than females, and highest in White patients, with regional variation across Black and Asian patients, supporting demographic- and region-specific imaging capacity planning in HCC care.

Disclosure of Interest: Stocks

Image:



Figure: Temporal trends in the use of MRI, MRI with gadoxetate, CT, Ultrasound in HCC patients by four US regions

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P-072 INFLUENCE OF DIFFERENT VARIABLES ON SERUM PIVKA-II CONCENTRATION IN A COHORT OF PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE IN THE ABSENCE OF HEPATOCELLULAR CARCINOMA

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INTRODUCTION: PIVKA-II (Protein Induced by Vitamin K Absence or Antagonist-II) is a promising biomarker for hepatocellular carcinoma (HCC) screening in patients with advanced chronic liver disease (ACLD)1. However, identifying factors that may affect its serum concentration independently of HCC is essential to ensure its reliable clinical use. A preliminary study by our group revealed statistically significant differences in PIVKA-II levels between patients with normal vs abnormal glomerular filtration rate (GFR), International Normalized Ratio (INR) and serum albumin levels2.

The aim of this study was to further evaluate the influence of these and other clinical variables on PIVKA-II serum concentration in a larger cohort of patients enrolled in our center's HCC surveillance program.

MATERIALS AND METHODS: Consecutive patients with ACLD aged 18-80 years, with alcohol-related liver disease, metabolic dysfunction-associated steatotic liver disease, and/or hepatitis C virus infection, between July 2024 and April 2025, were included. Thirty eight relevant clinical and laboratory data were collected prospectively.

All patients underwent baseline ultrasound and laboratory testing, as well as two additional ultrasounds at 6 and 12 months to confirm the absence of focal lesions. PIVKA-II was quantified using an electrochemiluminescence immunoassay (Cobas e801, Roche), and its median value and 95th percentile (P95) were calculated in the study population at the basal time.

Statistical analysis was performed using R software. The association between baseline characteristics and a PIVKA level > P95 was assessed by fitting univariate and multivariate logistic regression models. Predictive performance was evaluated using the area under the ROC curve (AUC).

RESULTS: The study comprised 334 cirrhotic patients (76% male, mean age 64.1). Clinical characteristics are summarized in Table 1.

The median PIVKA-II concentration was 24.2 ng/mL (Interquartile range: 17.7-59.2) and P95 was found to be 529.6 ng/mL. Results are expressed as odds ratios (OR) with 95% confidence interval (95%CI) and p-values in Figure 1.

In a multivariate analysis, creatinine demonstrated a positive association with PIVKA-II >529.6 ng/mL (p<0.001, OR=4.65, 95%CI=2.10-10.28), while albumin showed an inverse association (p=0.007, OR= 0.848, 95%CI= 0.75-0.95). The model exhibited good discriminatory performance with an AUC of 0.782 (95%CI: 0.670-0.893).

CONCLUSIONS: Our findings in a larger cohort confirm that several factors significantly influence PIVKA-II levels, consistent with our previous study. Consideration of these variables is essential for accurate interpretation of PIVKA-II in clinical practice.

ACKNOWLEDGMENTS: We extend our gratitude to Roche Diagnostics® for the complimentary provision of consumables for PIVKA-II determination.

REFERENCES:

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Disclosure of Interest: N/A

Images:

	N	
Etiology of liver disease	**334**	
Alcohol-related		191 (57%)
VHC		103 (31%)
Metabolic dysfunction-associated steatotic liver disease		26 (8%)
Other		14 (4%)
Child-Pugh	**334**	
A (score 5-6)		316 (94.6%)
B (score7-9)		18 (5.4%)
MELD score	**327**	
Mean (SD)		8.78 (3.19)
Esophageal varices	**328**	
No		182 (55.5%)
Yes		146 (44.5%)
Prior complications	**334**	
No		206 (61.7%)
Yes		128 (38.3%)
Carvedilol	**334**	
No		207 (62%)
Yes		127 (38%)
Diuretics	**334**	
No		248 (74.3%)
Yes		86 (25.7%)
Oral anticoagulants	**334**	
No		307 (91.9%)
Yes		27 (8.1%)

Table 1. Clinical characteristics.

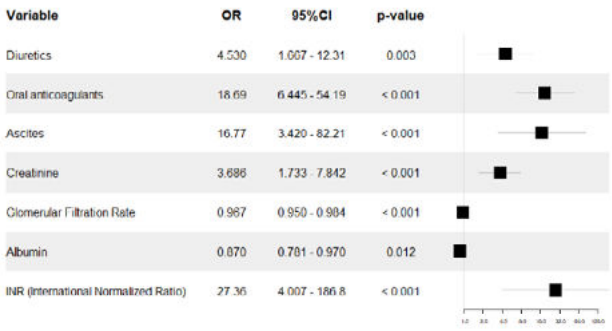

Figure 1. Forest plot showing the effect of different variables on PIVKA-II concentration.

P-073 A NOVEL PROGNOSTIC MODEL INTEGRATING THE ASAP SCORE AND NEUTROPHIL-TO-LYMPHOCYTE RATIO IN ADVANCED HEPATOCELLULAR CARCINOMA TREATED WITH ATEZOLIZUMAB PLUS BEVACIZUMAB: A MULTICENTER COHORT STUDY

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Background/Aim: The ASAP score, comprising age, sex, alpha-fetoprotein, and protein induced by vitamin K absence-II, was originally developed for early hepatocellular carcinoma (HCC) detection and has recently shown potential prognostic relevance. Therefore, we aimed to evaluate the utility of the ASAP score for risk stratification in a multicenter cohort of patients with advanced HCC treated with atezolizumab plus bevacizumab.

Methods: Consecutive patients with unresectable HCC receiving first-line atezolizumab plus bevacizumab at Seoul National University Hospital (SNUH) were retrospectively analyzed, with external validation performed in an independent cohort from the Catholic Medical Center (CMC) of Korea. Cutoff values were determined using X-tile software. Associations between baseline variables, including the ASAP score, and overall survival (OS) and progression-free survival (PFS) were assessed using multivariable Cox models, and independently associated variables were integrated to derive a combined risk stratification model, which was evaluated using Kaplan–Meier estimates and Cox proportional hazards analyses.

Results: X-tile analysis identified 6.4 as the optimal cutoff for the ASAP score. In multivariable Cox analyses for OS and PFS the ASAP score and neutrophil-to-lymphocyte ratio (NLR) were the only baseline variables independently associated with both outcomes. Patients were therefore stratified using a combined ASAP–NLR model into a low-risk group (ASAP <6.4 and NLR <3.2) and a high-risk group (ASAP ≥6.4 and/or NLR ≥3.2). In the SNUH cohort, the median OS was 21.4 months in the low-risk group and 9.8 months in the high-risk group, with the high-risk group showing significantly worse OS (adjusted hazard ratio [aHR] 2.24; 95% confidence interval [CI] 1.54–3.25; P < 0.001) and PFS (aHR 1.77; 95% CI 1.30–2.39; P < 0.001). In the external CMC cohort, this risk stratification remained prognostically relevant, with a longer median OS in the low-risk group than in the high-risk group (23.6 vs. 13.4 months), and the high-risk group showing significantly worse OS (HR 1.34; 95% CI 1.34–3.28; P < 0.001) as well as PFS (HR 1.66; 95% CI 1.16–2.38; P = 0.006).

Conclusion: The combined ASAP–NLR model demonstrated effective risk stratification for survival outcomes in patients with advanced HCC receiving atezolizumab plus bevacizumab, with consistent findings in an external validation cohort, supporting its potential utility in real-world clinical practice.

Disclosure of Interest: N/A

P-074 PREVALENCE AND CLINICAL CORRELATES OF PORTAL VEIN THROMBOSIS IN HEPATOCELLULAR CARCINOMA

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Background: Portal vein thrombosis (PVT) is a frequent and clinically significant complication of hepatocellular carcinoma (HCC), often reflecting advanced tumor biology, vascular invasion, and limited therapeutic options. However, contemporary data describing the prevalence, management patterns, and outcomes of PVT in patients with HCC remain limited. We aimed to assess the prevalence and care outcomes of PVT in patients with HCC.

Methods: We conducted a retrospective analysis of a prospectively maintained HCC registry including adult patients (>18 years) diagnosed with HCC according to radiological or histopathological criteria. All patients diagnosed between 2020 and 2025 at King Faisal Specialist Hospital and Research Centre, a major tertiary referral center in Saudi Arabia, were included. PVT was identified on baseline imaging and classified as present or absent. Descriptive statistics and analyses were used to assess PVT prevalence across liver function, tumor stage, and treatment subgroups, where clinical, laboratory, and tumor characteristics were compared by PVT status. Overall survival was evaluated using Kaplan-Meier analysis, and Cox proportional hazard models were used to assess the association between PVT and mortality risk.

Results: PVT was identified in 14.3% of patients with HCC, of whom only 19.4% were listed for liver transplantation. The presence of PVT indicated poorer liver function, as only 25.8% of these patients were classified as Child-Pugh A. A significantly higher proportion of patients with PVT were outside the Milan criteria compared with those without PVT (63.0% vs. 35.0%, p < 0.001), with over 25% having extra-hepatic metastases. Baseline treatment allocation differed, with patients with PVT receiving less locoregional therapy and more supportive or palliative care than those without PVT. After adjusting for age and sex, PVT was independently associated with an increased mortality risk (adjusted hazard ratio 2.7; 95% CI 1.93–3.84).

Conclusion: This analysis showed that PVT is associated with advanced liver disease and poorer prognosis in patients with HCC. Patients with PVT show lower eligibility for liver transplantation and reduced use of curative locoregional therapies. Importantly, PVT independently predicted a higher mortality risk after adjusting for age and sex, underscoring the need for improved risk stratification and management strategies for this high-risk subgroup.

Disclosure of Interest: N/A

Image:

Table 1. Sociodemographic and Tumor Characteristics and risk factors by PVT status

	Portal Vein Thrombosis		
	Yes	No	Test
N	62 (14.3%)	372 (85.7%)	
Age at Diagnosis	65.0	64.0	0.114
Gender			
Male	41 (66.1%)	261 (70.2%)	0.523
Female	21 (33.9%)	111 (29.8%)	
BCLC Stage			
Very early stage	5 (8.1%)	45 (12.1%)	0.007
Early stage(A)	9 (14.5%)	117 (31.5%)	
Intermediate stage(B)	10 (16.1%)	62 (16.7%)	
Advanced stage(C)	20 (32.3%)	58 (15.6%)	
Terminal stage (D)	12 (19.4%)	48 (12.9%)	
Unknown	6 (9.7%)	42 (11.3%)	
Albumin Bilirubin			
Grade 1	11 (17.7%)	104 (28.0%)	0.163
Grade 2	39 (62.9%)	209 (56.2%)	
Grade 3	11 (17.7%)	43 (11.6%)	
Unknown	1 (1.6%)	16 (4.3%)	
Listed for transplant			
Yes	12 (19.4%)	174 (46.8%)	<0.001
No	44 (71.0%)	141 (37.9%)	
Missing	6 (9.7%)	57 (15.3%)	
Child-Pugh Classifications			
Child A	16 (25.8%)	230 (61.8%)	<0.001
Child B	39 (62.9%)	103 (27.7%)	
Child C	7 (11.3%)	35 (9.4%)	
Unknown	0 (0.0%)	4 (1.1%)	
Milan Criteria			
Within score	20 (32.3%)	196 (52.7%)	<0.001
Outside score	39 (62.9%)	130 (34.9%)	
Unknown	3 (4.8%)	46 (12.4%)	
HCC Mets status			
Yes	16 (25.8%)	40 (10.8%)	<0.001
No	43 (69.4%)	328 (88.2%)	
Unknown	3 (4.8%)	4 (1.1%)	
Performance Status			
Fully active	20 (32.3%)	180 (48.4%)	0.092
Restricted physically	14 (22.6%)	68 (18.3%)	
Ambulatory	6 (9.7%)	30 (8.1%)	
limited selfcare	2 (3.2%)	22 (5.9%)	
Completely disabled	1 (1.6%)	8 (2.2%)	

P-075 PROGNOSTIC VALIDATION OF PERINEURAL INVASION IN RESECTED CHOLANGIOCARCINOMA: A RETROSPECTIVE STUDY

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Introduction: Cholangiocarcinoma (CCA) is a malignant tumor with increasing incidence and poor prognosis. Currently, surgical resection is the only curative treatment in CCA. However, high recurrence rate decreases the survival of the resected CCA. Prognostic factors exploration could increase the early detection of recurrence. Perineural invasion (PNI) has been validated to be poor prognostic factor in malignancies. Herein, we aim to investigate the PNI as a prognostic factor in resected cholangiocarcinoma.

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Methods: Patients with CCA underwent surgical resection have been retrospectively collected at the Second Affiliated Hospital of Nanchang University, between January 2019 and October 2025. The patients were categorized into PNI-positive group and PNI-negative group according to pathological diagnosis. Median event free survival (EFS) and overall survival (OS) were performed by Kaplan-Meier analysis. Univariate and multivariate Cox regression analyses were used to identify independent prognostic factors of EFS and OS. Moreover, the value of adjuvant therapy was evaluated in both groups.

Results: 113 patients were recruited, including 67 PNI-positive CCA patients (59.3%). The median EFS of PNI-positive patients was significantly lower than PNI-negative ones (9 months versus 15 months, p=0.041). The median OS of PNI-positive patients was significantly shorter than PNI-negative ones (24 months versus 35 months, p=0.013). PNI-positive correlated with poor differentiation (p=0.033), and positive nodular metastasis (p=0.003). PNI-positive validated to be poor prognostic factor in both EFS and OS by Cox regression analyses. Moreover, adjuvant therapy indicated the trend of better EFS (p=0.123) and OS (p=0.041) in PNI-positive patients.

Conclusion: PNI-positive indicates worse EFS and OS in resected cholangiocarcinoma, and these patients might benefit from adjuvant therapy.

Disclosure of Interest: N/A

P-076 Hepatocellular carcinoma surgical resection changes plasmatic bacterial RNA signatures.

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Background: Hepatocellular carcinoma (HCC) develops in the context of chronic liver disease and inflammation. Gut dysbiosis in HCC is characterized enrichment of pro-inflammatory taxa, leading to increased intestinal permeability and translocation. Increasing evidence highlights the gut microbiota as a key modulator of hepatocarcinogenesis. The presence of microbial signatures in cancer-related samples has gained increasing attention and its use as tumor biomarkers is still an emerging field.

Research aim: Detection and comparison of bacterial RNA in plasma samples of HCC patients before and after surgical treatment to identify possible plasma tumor biomarkers.

Methods: Plasma was collected prior and at least 20 days after surgery from 20 patients with HCC who underwent liver transplantation or resection. Clinical and histological characteristics were obtained from medical records. Cell free RNA (cfRNA) was isolated from plasma, and a low input library was generated and sequenced. RT-qPCR was used for validation. Reads obtained from plasma samples were compared against curated non-human RNA reference databases. For each patient and each sample, the top 20 most abundant taxa were selected. Relative abundances were calculated, and differential representation between pre-surgery and post-surgery samples was estimated as log2 fold change. Bacterial genera were classified as gut or non-gut derived. Statistical analysis, heatmaps and plots were generated in R 4.5.2.

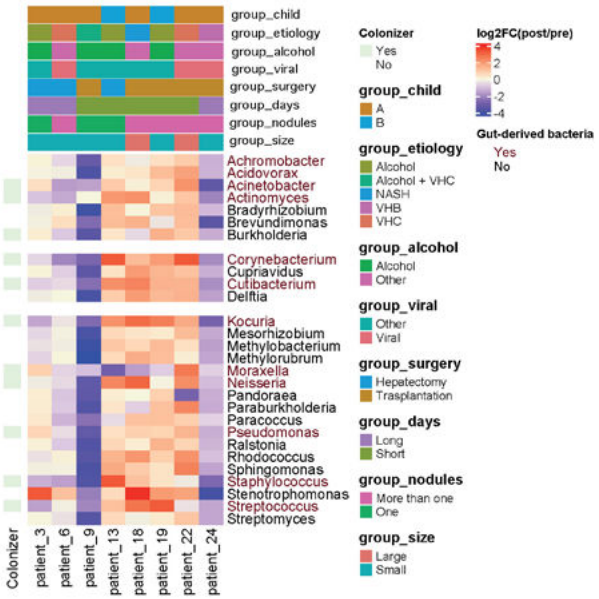
Results: Plasma cfRNA pre- and post-surgery was sequenced from 8 patients (5 transplanted and 3 resected patients). Analysis revealed marked interindividual heterogeneity in postoperative bacterial RNA dynamics. Patients with worse hepatic function (Child Pugh B) showed an independent relative enrichment of gut-derived bacteria. Gut-derived bacteria were also more abundant in postoperative plasma in patients sampled within 50 days after surgery (short interval). Indeed, patients undergoing liver transplantation tended to show higher gut-derived bacterial RNA. Pre-surgery plasma analyses revealed a consistent association between tumor burden (both tumor size and number of nodules) and gut-derived bacterial enrichment.

Conclusions: This study demonstrates the feasibility of detecting and characterizing bacterial RNA signatures. The integration of microbial profiles with clinical data may provide novel insights into host–microbiome interactions in cancer and support the development of minimally invasive biomarkers.

Disclosure of Interest: N/A

Images:

	Patients (n=8)
Age (media, SD)	61,5 ± 8,0
Gender	
Male	8 (100%)
Female	0
Comorbidities	
Diabetes mellitus type 2	5 (62.5%)
Dyslipidaemia	1 (12.5%)
Obesity	3 (37.5%)
Underlying liver disease	
No liver disease	0
Chronic hepatitis	1 (12.5%)
Cirrhosis	7 (87.5%)
- HCV	*3 (37.5%)*
- HBV	*1 (12.5%)*
- Alcohol	*4 (50%)*
- NASH	*1 (12.5%)*
Child-Pugh	
A	6 (75%)
B	2 (25%)
C	0
Alpha-fetoprotein (UI/mL) (median, IQR)	3,51 (1,78–3,92)
> 10 UI/mL	1 (12.5%)
< 10 UI/mL	5 (62.5%)
N.A.	2 (25%)
BCLC	
0	6 (30%)
A	12 (60%)
B	2 (10%)
C	0
Tumor burden	
One nodule	3 (37.5%)
Multinodular	5 (62.5%)
> 3 nodules	*2 (40%)*
≤ 3 nodules	*3 (60%)*
Tumor size (cm) (median, IQR)	1,85 (1,45–2,40)
Differentiation degree	
Well differentiated	0
Moderately differentiated	8 (100%)
Poorly differentiated	0
Tumor capsule invasion	0
Microscopic vascular invasion	1 (12.5%)
Satellitosis	2 (25%)
HCC treatment	
Liver transplantation	11 (55%)
Hepatic resection	9 (45%)
Previous treatment of actual HCC	2 (25%)
Previous HCC (relapse)	3 (37.5%)
Days between plasma samples (median, RIQ)	33 (29,5–77,5)



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P-077 DIAGNOSTIC PERFORMANCE OF PIVKA-II IN COMPARISON WITH AFP, CA 19-9, CA 72-4 AND HE4 IN HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) remains a major global health burden, with prognosis strongly dependent on early detection. Conventional biomarkers such as alpha-fetoprotein (AFP) show limited sensitivity and specificity, particularly in early-stage disease. Recently, PIVKA-II (protein induced by vitamin K absence-II) has emerged as a promising biomarker with potential to improve diagnostic accuracy. The present study evaluates its role in comparison with AFP and additional tumor markers.

Methods: Serum levels of PIVKA-II, AFP, CA 19-9, CA 72-4, and HE4 were measured in patients with HCC and in control subjects. Blood samples were collected under standardized conditions and analyzed using immunochemical methods. Diagnostic performance was assessed using ROC curve analysis, including calculation of AUC, sensitivity, and specificity. Correlations between biomarker levels and selected clinical parameters were also evaluated.

Results: PIVKA-II demonstrated higher diagnostic accuracy compared to AFP alone, with superior AUC values. The combination of PIVKA-II and AFP significantly improved sensitivity for HCC detection compared to either marker individually. CA 19-9, CA 72-4, and HE4 showed limited specificity for HCC but contributed to differential diagnostic assessment. Statistically significant differences in biomarker levels between HCC patients and controls were observed ($p < 0.05$).

Conclusion: PIVKA-II represents a valuable biomarker for the diagnosis of hepatocellular carcinoma, particularly when used in combination with AFP. Its incorporation into diagnostic algorithms may enhance early detection and improve patient stratification in clinical practice.

Disclosure of Interest: N/A

P-078 CIRCULATING HYPERMETHYLATED RASSF1A AS A POSSIBLE MARKER OF HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS C PATIENTS

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Introduction: Hepatocellular carcinoma (HCC) is a major global health burden and represents the fourth leading cause of cancer-related mortality worldwide. Epigenetic alterations, particularly DNA methylation, play a critical role in hepatocarcinogenesis. This study aimed to evaluate plasma levels of methylated RASSF1A as a non-invasive diagnostic biomarker for HCC in patients with post-hepatitis C virus (HCV) cirrhosis.

Methods: Plasma methylated RASSF1A levels were assessed in 120 participants divided into three equal groups: HCC patients with chronic HCV infection, post-HCV cirrhotic patients without HCC, and age- and sex-matched healthy controls. Methylation-sensitive restriction enzyme digestion followed by real-time quantitative polymerase chain reaction was used to assess the expression levels of RASSF1A methylation.

Results: HCC patients exhibited significantly higher circulating levels of hypermethylated RASSF1A compared with cirrhotic and control groups. Significant associations were observed between RASSF1A levels and several clinico-pathological parameters. Receiver operating characteristic curve analysis demonstrated good diagnostic performance in distinguishing HCC from cirrhosis.

Conclusion: Liquid biopsy is presented as promising technique for diagnosis and following up of patients. Circulating hypermethylated RASSF1A may serve as a non-invasive diagnostic indicator for distinguishing HCC in HCV cirrhotic patients and evaluating their progression. Nonetheless, it is imperative to standardize procedures, techniques, and data analysis to incorporate this method into regular investigations.

Disclosure of Interest: N/A

Image:

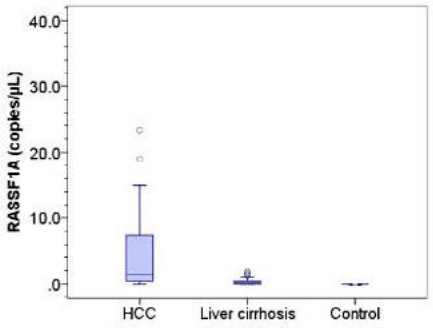

Figure 1: Median levels of RASSF1A in HCC, liver cirrhosis and control groups

P-079 METHYLATION-BASED CTDNA MONITORING FOR RECURRENCE RISK STRATIFICATION IN RESECTED COLORECTAL CANCER LIVER METASTASES: INTERIM ANALYSIS OF THE CLIMB STUDY

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Background: Colorectal cancer liver metastasis (CRCLM) carries a substantial risk of postoperative recurrence despite curative-intent hepatectomy, while conventional imaging is insufficiently sensitive for minimal residual disease (MRD). Circulating tumor DNA (ctDNA) is a promising biomarker for MRD. We employed a blood-based multi-target DNA methylation assay to characterize ctDNA kinetics and explore its potential clinical utility in postoperative surveillance and treatment decisions in CRCLM.

Methods: This study is a prospective observational cohort with 2-year follow-up period, enrolling CRCLM patients undergoing curative hepatectomy and standard postoperative management. Plasma was collected preoperatively and at postoperative months (POM) 1, every 3 months, analyzed by a blood-based multi-target DNA methylation assay. Primary endpoint was recurrence-free survival (RFS) with a minimum of 35 recurrence events, calculated based on the Schoenfeld method. Univariate and multivariate Cox regression analyses were performed to identify independent prognostic factors for RFS.

Results: This interim analysis included 41 evaluable patients; 16 (39.0%) developed recurrence over a median follow-up of 6.9 (1.0-16.7 months). Preoperative ctDNA was detectable in 75.6% overall and 61.0% of chemotherapy-naive patients, with detection rates positively associated with tumor burden. POM1 ctDNA positivity showed a numerically higher recurrence risk (HR, 13.2; 95% CI, 1.7-106.0, $p = 0.002$). The most recent longitudinal ctDNA measurement also stratify recurrence risk (HR, 3.8; 95% CI, 1.0-13.9, $p= 0.034$), reinforcing the association between ctDNA positivity and recurrence. Both univariate and multivariate Cox regression analyses, adjusted for sex, age, tumor size, tumor number, preoperative ctDNA, recent longitudinal ctDNA, consistently identified POM1_ctDNA as a significant prognostic factor for relapse.

Conclusions: This interim analysis suggests methylation-based ctDNA as a promising dynamic biomarker for patients with resected CRCLM, with potential utility in postoperative risk stratification. Given the limited sample size and relative short follow-up duration, these preliminary findings warrant further validation upon completion of the study and in larger multicenter prospective cohorts.

Disclosure of Interest: N/A

P-139 SINGLE-VESICLE EXTRACELLULAR VESICLE SURFACE PROFILING IDENTIFIES IL1RAP-CENTERED SIGNATURES FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE

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Introduction: Hepatocellular carcinoma (HCC) surveillance remains challenging in individuals with high-risk liver disease. Circulating extracellular vesicles (EVs) carry parental-cell surface proteins

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and are promising liquid biopsy targets, but bulk profiling may obscure disease-relevant vesicle subsets1. We used a 550-plex proximity barcoding assay (PBA) to profile circulating EV surface proteins at single-vesicle resolution and identify signatures associated with HCC tumor-bearing status and postoperative surveillance2.

Methods: Paired peripheral blood samples collected at HCC diagnosis and 5 and 30 days after surgery were obtained from 30 patients at Zhongshan Hospital, Fudan University, as the discovery cohort. An independent testing cohort included 10 patients from the Second Affiliated Hospital of Hainan Medical University. Single-EV surface proteomic profiling was performed using a 550-probe PBA panel. Pseudo-bulk differential analysis integrated edgeR, limma, and DESeq2 under strict paired designs with multiple-testing correction. Candidate proteins, dual-positive EV phenotypes, biomarker correlations, and protein-based classifiers were evaluated. Classifiers were trained only in the discovery cohort and tested in the independent Hainan cohort. Single-vesicle bioinformatic analysis was used to infer EV subpopulation composition and putative cellular origin.

Results: PBA-based single-EV profiling revealed remodeling of the circulating EV surface proteome in tumor-bearing HCC, with IL1RAP emerging as the dominant candidate signal. In the discovery cohort, 14 EV surface proteins were enriched in tumor-bearing samples compared with postoperative samples, using an adjusted P value threshold of 0.05 and a fold-change cutoff of >1.25. IL1RAP was enriched in tumor-bearing samples, correlated with HCC stage (r=0.462, p=0.0302), and independently discriminated tumor-bearing status, with AUCs of 1.000 in the training cohort and 0.894 in the testing cohort. In machine-learning analysis, the IL1RAP and EFNB2 protein combination achieved AUCs of 0.900 in training and 1.000 in testing, and the top testing-set models converged on this combination. At the dual-positive EV level, IL1RAP+ADIPOQ+ EVs showed the most pronounced enrichment in tumor-bearing samples among four significantly enriched dual-positive EV populations. Single-vesicle subpopulation analysis further showed IL1RAP enrichment within a T cell-associated EV population, providing clues to the cellular origin and intercellular communication context of the HCC-associated EV signal. Additional PBA-derived findings included stage-associated NOTCH3 and ADIPOQ signals, four-protein principal component separation of tumor-bearing and postoperative samples, and correlations of TNFSF11 with alpha-fetoprotein (r=0.565, p=0.0061) and PIVKA-II/DCP (r=0.325, p=0.139).

Conclusion: Single-EV profiling revealed clinically relevant heterogeneity within circulating EV populations in tumor-bearing HCC. IL1RAP-centered EV signatures linked tumor-bearing status, disease stage, classification performance, and T cell-associated EV subpopulations. These findings warrant further validation for HCC surveillance and support EV as a framework for studying tumor-associated intercellular communication.

Reference: [1]Liang, I. Y. et al. HCC EV ECG score: An extracellular vesicle-based protein assay for detection of early-stage hepatocellular carcinoma. Hepatology 77, 774–788, doi:10.1002/hep.32692 (2023), [2] Wu, D. et al. Profiling surface proteins on individual exosomes using a proximity barcoding assay. Nat Commun 10, 3854, doi:10.1038/s41467-019-11486-1 (2019).

Disclosure of Interest: N/A

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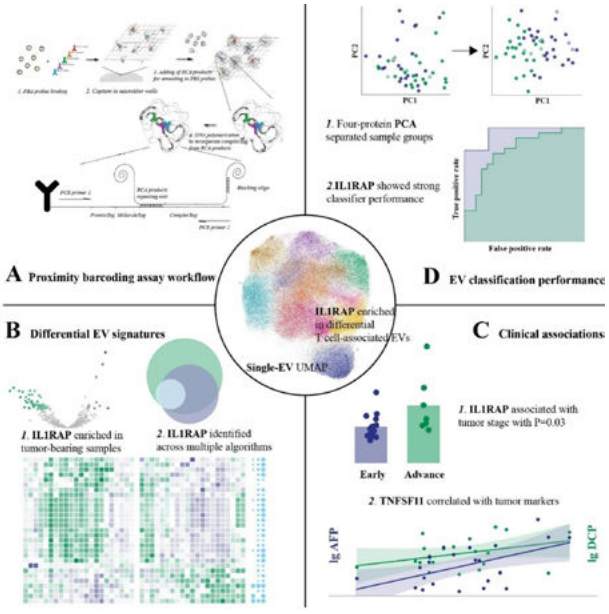

Therapy & Miscellaneous

P-080 Real-World Outcome of Atezolizumab Plus Bevacizumab in Patients with Hepatitis C Virus-Related Hepatocellular Carcinoma: A Study of 334 Patients

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Introduction: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, particularly in regions with a high hepatitis C virus (HCV) burden. The combination of atezolizumab plus bevacizumab is the standard first-line systemic therapy for unresectable HCC (uHCC). Real-world data from large cohorts, especially in patients with HCV-related HCC, are needed to validate the efficacy, safety, and applicability of this regimen. In this study, we report the treatment outcomes of a large cohort of patients with HCV-related uHCC who received atezolizumab plus bevacizumab as first-line systemic therapy.

Methods: This retrospective observational study included patients with HCV-related uHCC treated with atezolizumab plus bevacizumab in the Egyptian National Program for HCC Surveillance and Management between 2022 and 2025. Treatment response was assessed according to modified RECIST criteria. The primary endpoints were the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).

Results: 850 patients started treatment (652 males [76.7%], mean age 64 ± 7 years, 99.3% Child-Pugh A, 45.6% with portal vein thrombosis, and 89.3% BCLC stage C).

Of these, 197 (23.18%) died within the first 6 months (mostly before the first assessment), 77 (9.06%) discontinued treatment (mainly due to adverse events, primarily hepatic decompensation), and 210 (24.71%) did not reach the first CT evaluation time point.

Of the 334 evaluable patients, 23 (6.89%) achieved a complete response (CR), 116 (34.73%) a partial response (PR), 124 (37.13%) stable disease (SD), and 71 (21.26%) progressive disease (PD). The ORR was 41.62%, and DCR was 78.74%. Median OS in this group was 28.77 months, and median PFS was 14.3 months (95% CI: 12.37–17.03).

Conclusion: In this large Egyptian real-world cohort of patients with HCV-related uHCC, atezolizumab plus bevacizumab demonstrated meaningful antitumor activity among evaluable patients. However, the high early mortality rate highlights the challenges of advanced-stage disease presentation in routine clinical practice.

Disclosure of Interest: N/A

Images:

Table 1: Baseline patient characteristics (n=850)

Variables		Results
Gender	Female	198 (23.29%)
	Male	652 (76.71%)
Age , years		64 ± 7 (Range 29-96)
Co-morbidities	Total	177 (20.82)
	Hypertension	112
	Diabetes mellitus	94
	Cardiac	8
	Renal	1
Received treatment for HCV	SOF/DCV ±RBV	760 (96.45)
	Others	28 (3.55)
	Missing	62
Performance status	PS 0	618 (68.29%)
	PS 1	287 (31.71%)

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Performance status	**PS 0**	618 (68.29%)
	PS 1	287 (31.71%)
Child Pugh score	**A5**	685 (80.59%)
	A6	159 (18.71%)
	B7	6 (0.71%)
Liver on Ultrasound	**Cirrhosis**	786 (92.58)
Portal vein (Available for 789)	**Thrombosed**	360 (45.63)
AFP median (IQR) ng/ml		202 (12.2-1211)
AFP>400		364 (42.82%)
Hemoglobin g/dl		12.43 ± 1.79
Platelets x1000/mm3		196 ± 94
White cells x1000/mm3		6.69 ± 4.45
INR		1.14 ± 0.30
Bilirubin total mg/dl		1.02 ± 1
Albumin g/dl		3.89 ± 0.61
AST IU/ml		48 ± 39
ALT IU/ml		39 ± 30
Creatinine mg/dl		1.15 ± 1.63

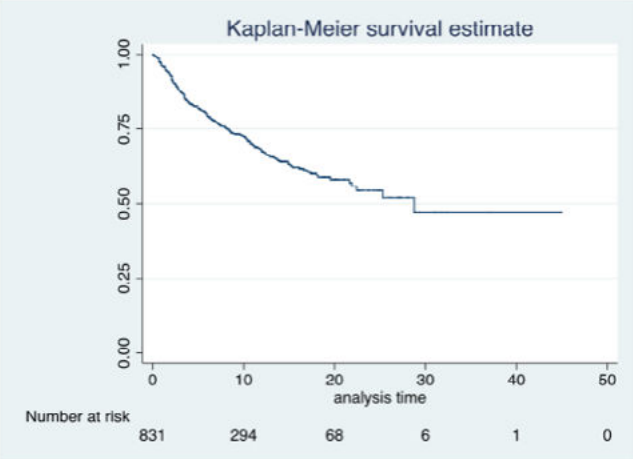

Figure 1: Overall survival of patients
Overall survival (615/850, 72.35%) = median survival time is 28.77 months

P-081 MODEL TO PREDICT OF HEPATIC DECOMPENSATION DURING IMMUNE CHECKPOINT INHIBITOR THERAPY FOR HEPATOCELLULAR CARCINOMA

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Background: Immune checkpoint inhibitors (ICI) have significantly improved survival outcome for patients with unresectable hepatocellular (uHCC). However, due to high prevalence of pre-existing advanced liver dysfunction, a significant fraction of ICI-treated uHCC patients will experience early hepatic decompensation and liver-related death. The objective of this study was develop and internally validate a clinical prediction tool for early death or new/worsening decompensation under ICI therapy for uHCC.

Methods: All U.S. Veteran patients who received first-line (1L) Atezolizumab/Bevacizumab, Atezolizumab monotherapy, STRIDE, or durvalumab monotherapy were identified in the U.S. Veterans Administration Corporate Data Warehouse between 10/2020 and 2/2024. Manual chart abstraction confirmed uHCC diagnosis, characterized immediate pre-1L tumor characteristics (number, tumor diameters, macrovascular invasion, extrahepatic spread, prior locoregional therapy or resection), evidence of portal hypertension (ascites, endoscopy, imaging), spleen size, prior hepatic decompensations (ascites, variceal hemorrhage, encephalopathy), Child-Turcotte-Pugh (CTP), ALBI score/grade, ECOG performance status, and baseline labs. Chart abstraction further identified time to death and post-treatment decompensations including new/worsening ascites (clinical diagnosis/paracenteses/imaging), variceal hemorrhage (endoscopically/clinically confirmed), hepatic encephalopathy, SBP (laboratory confirmed), and HRS. After 70%:30% random sampling, generalized linear models to predict 90-day death or decompensation were trained by elastic-net and step-wise regression and internally validated for AUROC, calibration and decision-curve analysis to compare net benefit using modified ALBI grade as a reference.

Results: 367 patients undergoing 1L atezolizumab/bevacizumab (n = 245), STRIDE (n = 101), atezolizumab (n = 16) or durvulamab (n = 5) monotherapy were abstracted. Median age was 70 (IQR 66-74); 98.9% were male; 211 (57.5%) were white, 99 black (27.0%) and 31 (8.4%) Hispanic; etiology of liver disease was ALD/ALD+HCV/HCV/MASH/HBV in 16.3%/25.6%/33.5%/21.0%/1.1% (60.2% viral); baseline CTP class was A/B/C 76.0%/23.4%/0.5%; 182 (49.5%) had experienced any hepatic decompensation prior to 1L ICI; median tumor number was 4 [IQR 1-5], largest tumor size 5.5cm [2.7 - 11.1cm], TTD 11.5cm [5.3 - >20cm] , 127 had macrovascular invasion (34.6%, 13% VP4) and 84 extrahepatic spread (22.9%); and BCLC 0/A/B/C/D stage was 1.4%/7.1%/30.0%/59.9%/ 1.6%. 109 (29.7%) died or developed worsening decompensation within 90 days (17 variceal hemorrhage, 57 new/worsening ascites, 9 SBP, 3 HRS, 25 hepatic encephalopathy, with 68 deaths). Univariate predictors of death/decompensation included CTP class, splenomegaly, portal hypertension, prior decompensation, MVI, prior locoregional therapy, serum albumin, bilirubin, AST, sodium and alkaline phosphatase. After training, compared to ALBI grade, models based on serum albumin, alkaline phosphatase, portal hypertension, total tumor diameter, and presence of VP3/4 MVI showed superior discrimination, calibration and net-benefit for prediction outcomes (Figure 1).

Conclusion: Death and worsening decompensation within 90 days of initiation of ICI therapy for uHCC is relatively frequent and can be reasonably predicted with a parsimonious set of readily available clinical and laboratory values. After external validation, such predictive models may be utilized to stratify patients needing closer hepatology management during ICI therapy.

Disclosure of Interest: Research/Education grant

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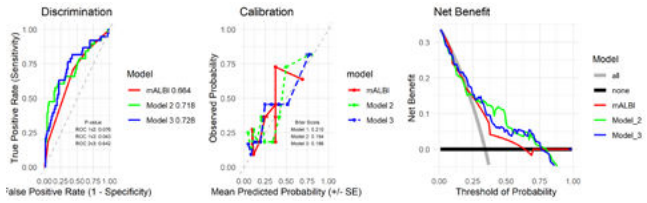

P-082 BODY SURFACE AREA–ADJUSTED BEVACIZUMAB EXPOSURE AND CLINICAL OUTCOMES IN ATEZOLIZUMAB PLUS BEVACIZUMAB THERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA: A NATIONWIDE REAL-WORLD STUDY

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Background: In atezolizumab plus bevacizumab (Atezo/Bev) therapy for hepatocellular carcinoma (HCC), the bevacizumab (Bev) dose is determined based on body weight. However, weight-based dosing may not fully account for inter-individual differences in body habitus, such as height. This study aimed to evaluate Bev exposure using a body surface area (BSA)–based metric and to identify the optimal exposure range.

Methods: A total of 1,516 patients who received Atezo/Bev therapy at 30 institutions in Japan between September 2020 and July 2025 were retrospectively analyzed. The median age was 74 (68–80) years, with 1,208 males and 308 females. Etiology was viral/non-viral in 751/765 patients. Child–Pugh scores (5/6/≥7) were 874/438/204, and BCLC stages (≤B/≥C) were 670/846. Median AFP was 30.3 (5.5–594.0) ng/mL, and median follow-up was 14.0 (6.9–25.3) months. Standard BSA was calculated using the DuBois formula based on ideal body weight (BMI =22), from which standard Bev dose (mg/m²) was derived. Actual Bev dose (mg/) was calculated using measured body weight. The ratio of actual to standard Bev dose (mg/m²) was defined as the Bev–BSA index (BBI), and its clinical impact was retrospectively evaluated.

Results: Median progression-free survival (PFS) and overall survival (OS) were 7.4 (6.7–7.9) months and 20.5 (19.0–22.4) months, respectively. In spline analysis adjusted for age, sex, performance status, etiology, Child–Pugh class, macrovascular invasion, extrahepatic spread, AFP, and treatment line, hazard ratios (HR) for OS fell below 1 within a BBI range of 106–121%. Based on this, patients were categorized into Under (<106%), Target (106–121%), and Over (>121%) groups. Median PFS was 6.6, 10.3, and 5.5 months ($p < 0.001$), and median OS was 19.2, 24.8, and 16.4 months ($p = 0.014$) in the Under, Target, and Over groups, respectively. Objective response rates were 29.7%, 33.3%, and 16.7% ($p = 0.025$), while disease control rates were 75.8%, 80.7%, and 71.7%

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(p = 0.071), with no significant differences in adverse events among groups. Multivariable analysis identified performance status ≥2 (HR 1.44), Child–Pugh class B or higher (HR 1.44), macrovascular invasion (HR 1.33), AFP ≥100 ng/mL (HR 1.37), ≥3rd-line therapy (HR 1.29), and BBI Target (HR 0.81) as significant factors for PFS. For OS, age ≥75 years (HR 1.16), performance status ≥2 (HR 2.02), Child–Pugh class B or higher (HR 2.02), macrovascular invasion (HR 1.49), AFP ≥100 ng/mL (HR 1.44), ≥3rd-line therapy (HR 1.30), and BBI Target (HR 0.85) were independent predictors.

Conclusions: BSA-adjusted bevacizumab dosing was associated with improved efficacy without increased toxicity in patients with unresectable HCC treated with Atezo/Bev. This approach may contribute to dose optimization in Atezo/Bev therapy for HCC.

Disclosure of Interest: Honoraria

P-083 TISLELIZUMAB PLUS DONAFENIB COMBINED WITH TRANSARTERIAL CHEMOEMBOLIZATION IN PATIENTS WITH RESECTED HIGH-RISK HEPATOCELLULAR CARCINOMA (TIDE): UPDATED RESULTS FROM A PHASE II TRIAL

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Introduction: There is no established adjuvant therapy for patients with high risk of hepatocellular carcinoma (HCC) after curative resection. The TIDE trial was conducted to assess the efficacy and safety of adjuvant tislelizumab plus donafenib with transarterial chemoembolization (TACE) in high-risk HCC patients. 1-year recurrence free survival (RFS) data have been previously presented at ESMO 2024, and this time the main results of the trial.

Methods: In this prospective, single-arm, phase II study, HCC patients who underwent curative resection and had a single tumor larger than 5 cm in diameter with microvascular invasion (MVI) were recruited. Eligible patients underwent one cycle of TACE a month after surgery. Subsequently, within a week following TACE, they began treatment with tislelizumab (200 mg intravenously every 3 weeks) and donafenib (100 mg orally twice daily). This regimen was maintained for one year, unless interrupted by disease recurrence or intolerable toxicity. The primary endpoint was the cumulative 3-year recurrence-free survival (RFS) rate, while the secondary endpoints were overall survival (OS) and the incidence of adverse events.

Results: A total of 30 patients were enrolled from December 9, 2022, to December 13, 2023. The median tumor size was 7.5cm, 63% were infected with HBV, and 43% had cirrhosis. As of Apr 1, 2026, the median duration of follow-up was 33.2 months. 11 patients relapsed, of whom 2 patients died due to disease progression, and 1 patient died from a cerebral hemorrhage after a fall. The median RFS and OS time have not been reached. The 1-, 2-, 3- year RFS rates were 86.7% (95% CI, 75.3%-99.7%) and 63.3% (95% CI, 43.6%-77.8%), 60.0% (95% CI, 40.5%-75.0%) respectively. The incidence of grade 3 TRAEs stood at 20.0%, including rash, hand-foot skin reactions, and immune-related pneumonia. One patient experienced grade 4 elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). No patients encountered grade 5 TRAEs.

Conclusions: The 3-year RFS rate was 60%, which achieved the primary endpoint. The combination of tislelizumab plus donafenib and TACE appears to be a promising adjuvant therapy for patients with high-risk HCC after curative resection. Furthermore, no significant safety concerns were observed.

Disclosure of Interest: N/A

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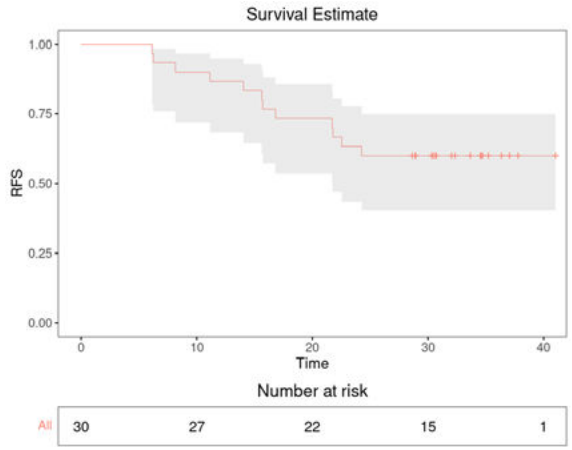

P-084 META-ANALYSIS COMPARING REAL-WORLD EFFECTIVENESS OF LENVATINIB VS OTHER TYROSINE KINASE INHIBITORS IN UNRESECTABLE HEPATOCELLULAR CARCINOMA AFTER ATEZOLIZUMAB + BEVACIZUMAB.

Qi Zhao, **MD, MPH** [1] , Fernando Rodriguez [2], MSc, Abby Paine [2], PhD, Wilson Ngai, PharmD, MSc [1]

[1] Eisai Inc., [2] Source Health Economics

Introduction: Current guidelines (NCCN, ESMO, BCLC) recommend tyrosine kinase inhibitors (TKI) as treatment options for patients with unresectable hepatocellular carcinoma (uHCC) who progress after first-line (1L) immunotherapy (IO). However, evidence is largely from sorafenib(SOR)-treated populations and comparative randomized controlled trial evidence post-IO is limited, thus optimal TKI-choice is unclear. To address the critical need for comparative efficacy data in this setting, a targeted literature review (TLR) and meta-analysis (MA) were conducted to compare the efficacy of lenvatinib (LEN) vs SOR, cabozantinib (CAB), and regorafenib(REG) in uHCC following IO in real-world clinical practice.

Methods: A TLR was conducted in PubMed to identify real-world studies reporting outcome data for LEN vs SOR, CAB or REG as per pre-defined PICOS criteria. Feasibility assessment determined whether evidence was appropriate for MA, evaluating comparability of patient characteristics, outcome definitions, and sample size across studies. Pooled estimates were derived from study-level data using fixed- and random-effects models. Overall survival (OS), progression-free survival(PFS), objective response rate (ORR), and disease control rate (DCR) were evaluated. Propensity score matched data were utilized, when available, to reduce confounding between treatment cohorts. Statistical significance was defined as a 95% confidence interval (CI) that does not include 1.0 (i.e. $p < 0.05$).

Results: Of the 13 identified real-world studies, 6 publications representing 5 unique studies were included in the MA (4 LEN vs SOR [N = 50–428], 2 LEN vs CAB [N = 107–302]). All were observational studies post-atezolizumab (ATEZ) + bevacizumab (BEV; 4 retrospective, 1 prospective). One study was identified for LEN vs REG, precluding MA. In the MA, LEN showed a nominally significant increase in OS, PFS, ORR and DCR vs SOR, along with a nominally significant OS benefit vs CAB (Table). Comparisons of safety outcomes vs all comparators, and PFS, ORR and DCR vs CAB were not possible due to insufficient data.

Conclusions: In MA of observational studies in uHCC post-ATEZ+BEV, LEN demonstrated longer OS, PFS and higher ORR and DCR vs SOR, and longer OS vs CAB. Consistent direction of effect across studies and robustness of statistical modelling support reliability of results. However, results should be interpreted with caution due to limited comparative evidence vs REG and CAB, potential for selection bias in observational data, and some variability in reporting of baseline characteristics and response assessment.

Disclosure of Interest: N/A

Image:

Meta-analysis results of LEN vs TKIs in uHCC post 1L ATEZ+BEV

Endpoints	LEN vs SOR Pooled HR/OR (95% CI)	LEN vs CAB Pooled HR/OR (95% CI)
OS	0.65 (0.49, 0.86)**	0.72 (0.65, 0.81)***
PFS	0.48 (0.40, 0.59)***	–
ORR	2.23 (1.08, 4.63)*	–
DCR	2.47 (1.38, 4.43)**	–

*p<0.05; **p<0.01; ***p<0.001.

P-085 REAL-WORLD FOUR-YEAR OUTCOMES OF ATEZOLIZUMAB–BEVACIZUMAB IN HEPATOCELLULAR CARCINOMA: RESULTS FROM THE CHIEF FRENCH COHORT

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Background: While atezolizumab–bevacizumab is a first-line therapy for unresectable HCC, long term results are not available from the phase 3 trial.

Methods: Data from 880 HCC patients treated with AtezoBev across 32 French centres were prospectively collected in the CHIEF cohort. OS and PFS were estimated using Kaplan–Meier methods, with multivariable Cox models identifying predictors; quality of life was assessed using EORTC QLQ-C30 and QLQ-HCC18.

Results: At a median follow-up of 48.0 months (95% CI, 39.4–57.2), the cohort reflected real-world complexity, with 22% Child-Pugh B and 58% alcohol-related liver disease, alongside a high prevalence of portal hypertension, including esophageal varices (EV) in 55%, prior decompensation in 20%, and prior variceal bleeding in 7%.

In the overall cohort, 12-month OS was 61.8% (95% CI 58.7-65.1), 24-month OS was 41.4% (38.3-44.8), and 48-month OS was 28.8% (25.8-32.1). Median PFS was 10 months. The best ORR by mRECIST was 42.2% (CR 11.0%, PR 31.2%), with CR achieving a median OS not reached and a median PFS of 35.7 months. On multivariable analysis, ALBI 2 (HR 1.63, p=0.003) and vascular invasion (HR 1.39, p=0.027) were independent predictors of mortality; ALBI remained independently prognostic for PFS (grade 2: HR 1.34, p=0.035; grade 3: HR 1.74, p=0.021).

Curative-intent conversion was achieved in 37 patients (4.2%), including 9 liver transplants, 19 resections, and 9 ablative therapies. Among responders, 39% of complete responders and 19% of partial responders proceeded to curative treatment. Overall survival was not reached in patients who underwent curative-intent therapy. Quality of life remained globally stable during treatment, with global health status scores declining only modestly from 60.6 at baseline to 57.8 at last evaluation, and a median time to deterioration of 11.8 months.

Conclusions: This 4-year CHIEF update provides the longest prospective real-world follow-up of AtezoBev, confirming durable benefit with a survival plateau near 29% at 48 months. Some responses enabled conversion to curative-intent treatment. Quality of life remained preserved, supporting good tolerability in routine practice.

Disclosure of Interest: Advisory Board

P-086 CLINICAL OUTCOMES OF RESPIRATORY-GATED PENCIL BEAM SCANNING PROTON BEAM THERAPY FOR HCC: A LARGE-SCALE PSM ANALYSIS

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Introduction: The 2025 BCLC update recognizes external beam radiotherapy, including proton beam therapy (PBT), as a curative alternative for hepatocellular carcinoma (HCC). However, large-scale evidence evaluating optimal respiratory motion management and the safety of stereotactic body PBT (SBPT) remains limited.

Methods: We evaluated 1,680 patients with intrahepatic HCC treated with PBT (2015-2024): Group A (breath-hold; n = 264), group B (respiratory-gated passive scattering [RG-PS]; n = 355), and group C (RG with pencil beam scanning [RG-PBS]; n = 1,061). Propensity score matching (PSM) adjusted for baseline imbalances. Hepatic toxicity was evaluated by albumin–bilirubin (ALBI) score deterioration (≥ 0·50 increments) within 4 months post-PBT. Within group C, SBPT (≤ 5 fractions; n = 268) was compared with moderate hypo-fractionation (> 5 fractions; n = 268) post-PSM.

Results: After PSM, 3-year in-field local control (approximately 90%), progression-free survival, and overall survival were comparable across groups (all P > 0·05). Group A carried a significantly higher risk of ALBI score deterioration than group C before PSM (odds ratio [OR] 1·74; P < 0·001) and after PSM (OR 1·73; P = 0·01). Conversely, group C demonstrated comparable hepatic safety to group B post-PSM (OR 1·30; P = 0·25). Within group C, SBPT achieved survival outcomes and hepatic toxicity profiles equivalent to moderate hypo-fractionation (all P > 0·05).

Conclusion: RG-PBS provides excellent long-term local control equivalent to traditional techniques while offering superior liver preservation compared with breath-hold strategies. Furthermore, PBS-based SBPT is a safe, efficient curative modality that overcomes interplay effect concerns, maintaining oncological durability without compromising hepatic reserve.

Disclosure of Interest: N/A

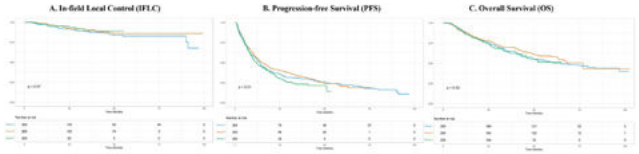
Images:

Table 1. Baseline patient and treatment characteristics among patients receiving proton beam therapy using end–exhale breath–hold (BH, group A), respiratory–gated passive scattering (PS, group B), and respiratory–gated pencil beam scanning (PBS, group C)

Variables	Overall (n=1680)	Group A* (n=264)	Group B (n=355)	Group C (n=1061)	P
Age (years)	64·0 (58·0–71·0)	59·0 (53·0–65·0)	66·0 (60·0–73·0)	65·0 (58·0–72·0)	<0·001
Male sex	1407 (83·8%)	238 (90·2%)	277 (78·0%)	892 (84·1%)	<0·001
Etiology					<0·001
– HBV	1190 (70·8%)	221 (83·7%)	240 (67·6%)	729 (68·7%)	
– HCV	151 (9·0%)	23 (8·7%)	39 (11·0%)	89 (8·4%)	
– NBNC	334 (19·9%)	20 (7·6%)	73 (20·6%)	241 (22·7%)	
– Co-infection	5 (0·3%)	0 (0·0%)	3 (0·8%)	2 (0·2%)	
mALBI grade					0·58
– grade 1	1169 (69·5%)	189 (71·6%)	234 (65·9%)	746 (70·3%)	
– grade 2a	235 (14·0%)	35 (13·3%)	54 (15·2%)	146 (13·8%)	
– grade 2b	250 (14·9%)	35 (13·3%)	59 (16·6%)	156 (14·7%)	
– grade 3	26 (1·5%)	5 (1·9%)	8 (2·3%)	13 (1·2%)	
Tumor size (cm)	2·6 (1·5–5·3)	2·8 (1·5–5·0)	2·0 (1·4–3·5)	3·0 (1·6–6·5)	<0·001
PVTT	401 (23·9%)	74 (28·0%)	52 (14·6%)	275 (25·9%)	<0·001
BDI	60 (3·6%)	14 (5·3%)	10 (2·8%)	36 (3·4%)	0·23
BCLC stage					0·0002
– stage 0	534 (31·8%)	79 (29·9%)	138 (38·9%)	317 (29·9%)	
– stage A	527 (31·4%)	88 (33·3%)	123 (34·6%)	316 (29·8%)	
– stage B	71 (4·2%)	5 (1·9%)	14 (3·9%)	52 (4·9%)	
– stage C	543 (32·3%)	91 (34·5%)	78 (22·0%)	374 (35·2%)	
– stage D	5 (0·3%)	1 (0·4%)	2 (0·6%)	2 (0·2%)	
AFP (ng/mL)	7·0 (3·2–47·5)	7·7 (3·1–70·2)	5·9 (2·9–23·9)	7·4 (3·4–52·8)	0·005
PIVKA–II (mAU/mL)	29·0 (20·0–109·8)	27·5 (19·0–60·0)	27·0 (20·0–67·5)	31·0 (21·0–180·5)	<0·001
Treatment naive	274 (16·3%)	41 (15·5%)	66 (18·6%)	167 (15·7%)	0·42
Re–irradiation	69 (4·1%)	13 (4·9%)	18 (5·1%)	38 (3·6%)	0·36
BED_{10} (gray)	109·6 (86·4–109·6)	109·6 (100·0–109·6)	109·6 (109·6–109·6)	109·6 (75·0–109·6)	<0·001
Treatment aim					<0·001
– definitive PBT alone	335 (19·9%)	51 (19·3%)	111 (31·3%)	173 (16·3%)	
– consolidative	523 (31·1%)	88 (33·3%)	90 (25·4%)	345 (32·5%)	
– salvage	459 (27·3%)	81 (30·7%)	124 (34·9%)	254 (23·9%)	
– palliative	359 (21·4%)	42 (15·9%)	30 (8·5%)	287 (27·0%)	
Interval TACE–PBT					<0·001
– PBT alone	498 (29·6%)	66 (25·0%)	122 (34·4%)	310 (29·2%)	
– within 2 months	905 (53·9%)	159 (60·2%)	149 (42·0%)	597 (56·3%)	
– over 2 months	277 (16·5%)	39 (14·8%)	84 (23·7%)	154 (14·5%)	
PBT period					<0·001
– 2022–2024	104 (6·2%)	93 (35·2%)	10 (2·8%)	1 (0·1%)	
– 2016–2017	270 (16·1%)	95 (36·0%)	152 (42·8%)	23 (2·2%)	
– 2018–2019	509 (30·3%)	49 (18·6%)	141 (39·7%)	319 (30·1%)	
– 2020–2021	797 (47·4%)	27 (10·2%)	52 (14·6%)	718 (67·7%)	

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non–B non–C; ; mALBI, modified albumin–bilirubin; PVTT, portal vein tumor thrombosis; BDI, bile duct invasion; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha–fetoprotein; PIVKA–II, prothrombin induced by vitamin K absence or antagonist–II; BED_{10}, biologically effective dose calculated using an α/β of 10 gray; PBT, proton beam therapy; TACE, trans-arterial chemo-embolization

Group A*; 213 patients received PS, while 51 patients were treated with PBS



P-087 LIVER RESECTION VERSUS TRANS-ARTERIAL CHEMOEMBOLIZATION FOR HUGE HEPATOCELLULAR CARCINOMA (>10CM): A NATIONWIDE PROPENSITY SCORE ADJUSTED ANALYSIS

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Background and Aims: The treatment of hepatocellular carcinoma (HCC) > 10 cm remains controversial. The ongoing debate regarding the treatment of patients with HCC > 10 cm is partly due to the necessity of tailoring treatment to individual patient conditions. This study aims to address the important controversy regarding the management of large HCC, focusing on providing insights into the comparative effectiveness of liver resection (LR) and Transarterial Chemoembolization (TACE).

Method: Patients registered in the Korean Primary Liver Cancer Registry (KPLCR) were selected. The KPLCR is a random sample consisting of approximately 15% of patients newly diagnosed with primary liver cancer registered in the Korean Central Cancer Registry (KCCR), which is a nationwide cancer registry and includes more than 95% of all cancer cases in Korea. The study design utilizes data from the KPLCR covering the years 2008 to 2017 to investigate the treatment outcomes for HCC larger than 10 cm. Starting with 15,307 cases, the study identified 9,310 HCC patients with follow-up data, excluding those with missing initial treatment data (n=5,863) and follow-up loss (n=132). From these, 7,662 patients with single HCC were selected, further excluding cases with multiple HCC (n=1,394) and distant metastasis (n=254). This refined the cohort to 504 patients with HCC tumors larger than 10 cm, who were then divided into two treatment groups: 122 patients underwent liver resection (LR), and 382 patients received TACE.

Results: After PSM, the baseline characteristics showed no significant differences between the LR group (n=99) and the TACE group (n=99). Before propensity score matching (PSM), the hazard ratio (HR) for LR was 3.41 (95% CI: 2.62-4.43, p<0.001), indicating a significantly better survival probability for the LR group compared to the TACE group. After PSM, the HR for LR was slightly

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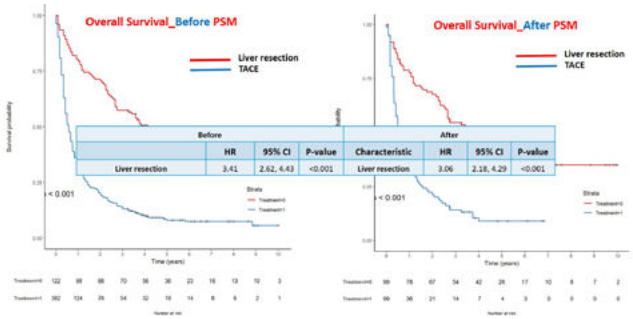
reduced to 3.06 (95% CI: 2.18-4.29, p<0.001), but the survival advantage of LR over TACE remained highly significant. Before PSM, the HR for LR was 3.29 (95% CI: 2.59-4.17, p<0.001), indicating a markedly better recurrence-free survival (RFS) for the LR group compared to the TACE group. After PSM, the HR for LR increased slightly to 3.37 (95% CI: 2.43-4.68, p<0.001), maintaining the significant survival advantage of LR over TACE.

Conclusion: This study provides a comprehensive analysis of treatment outcomes for HCC > 10 cm, comparing LR and TACE using data from the KPLCR. The results indicate that LR is associated with significantly better OS and RFS compared to TACE, both before and after PSM.

Disclosure of Interest: N/A

Image:



P-088 SURVIVAL TRENDS IN TRANSARTERIAL CHEMOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA: A POOLED ANALYSIS

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Introduction: Transarterial chemoembolization (TACE) is the standard for intermediate-stage hepatocellular carcinoma (HCC), but whether survival outcomes have improved over time remains unclear, particularly given regional disparities in patient selection and distinct advances in technique. Therefore, this study aims to evaluate temporal trends and regional variations in overall survival (OS) after TACE for HCC.

Methods: The primary individual patient data (IPD) analysis included 9,111 treatment-naïve patients with unresectable HCC, Child-Pugh class A5–B7, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1 who received TACE. Data were collected from 31 tertiary centers across China between January 2010 and June 2019. The analysis was supplemented by a global systematic review of the literature (MEDLINE, EMBASE, and Cochrane Library, 2009–2023), encompassing 621 studies, 701 cohorts, and 154,948 patients. Median follow-up was 15.8 months, with 74.3% deaths.

Results: In the IPD cohort, median OS was 18.0 months (95% CI, 17.3-18.6), with 1-, 2-, 3-, and 5-year rates of 61.6%, 41.6%, 29.9%, and 16.3%. Overall, OS showed no significant temporal change (slope: -0.152 months/year, 95%CI: -0.731–0.428, p=0.563), and survival improved significantly over time in Ideal patients (ECOG PS 0, Child-Pugh A5-B7, no macrovascular invasion or extrahepatic spread; slope: 1.896 months/year, 95%CI: 0.399–3.393, p=0.019), with a median OS of 33.9 months, while broader populations showed no significant improvement. These trends were consistent in both observed and adjusted analyses using Cox direct standardization and machine learning-based counterfactual prediction. Both interrupted time series and survival analyses showed comparable survival between drug-eluting beads and conventional TACE. Systematic review confirmed these patterns (weighted median OS: 21.1 months), with no temporal survival improvement overall, and subgroup analysis revealed survival improvements were observed exclusively in Western countries and Japan/South-Korea, where the proportion of early/intermediate-stage HCC patients progressively increased over time, whereas no improvement was observed in China. Sensitivity analyses supported these findings.

Conclusions: Survival in TACE-treated patients appear to be stable over years, rigorous patient selection emerges as the principal driver to improve temporal survival, a finding unchanged by novel embolic devices.

Disclosure of Interest: N/A

P-089 DIFFERENTIAL TOXICITY PROFILES FROM FIRST-LINE IMMUNOTHERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA: A COMPARATIVE ANALYSIS OF ATEZOLIZUMAB PLUS BEVACIZUMAB VERSUS DURVALUMAB PLUS TREMELIMUMAB

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Introduction: Atezolizumab plus bevacizumab (A+B) and durvalumab plus tremelimumab (D+T) are established first-line standards of care in unresectable hepatocellular carcinoma (HCC). Risk of toxicity is a key consideration in choosing treatment. In this non-randomised, observational study we aimed to compare incidence and clinical impact of adverse events attributable to treatment (trAEs) including immune-related adverse events (irAEs).

Methods: We analysed two multinational cohorts of Child–Pugh A patients (pts) with unresectable HCC treated with frontline A+B or D+T between 01/2022 and 12/2025, when both regimens were concurrently reimbursed. We assessed median follow-up (using reverse Kaplan-Meier); incidence, severity (grade ≥3), duration of toxicity and proportion of permanent treatment discontinuation were assessed using logistic regression following propensity score matching (PSM).

Results: A total of 632 pts were included (A+B n=454; D+T n=178). Median follow-up was 10.6 and 13.8 months for D+T and A+B, respectively (p<0.001), and median treatment exposure was 2.78 and 4.07 months, respectively (p<0.001). Compared to A+B, D+T-treated pts were older (median age 72 vs 67 years), more frequently male (86% vs 76%), with non-viral aetiology (54% vs 36%), and less frequently had extrahepatic disease (29% vs 44%) or BCLC stage C (60% vs 75%).

Frequency of all-grade trAEs was similar across regimens (58.6% A+B vs. 57.3% D+T), with grade ≥3 toxicity occuring in 22.2% and 19.7% respectively. The risk of overall and grade ≥3 trAEs was comparable between the two regimens (D+T vs A+B: OR 0.95, 95% CI 0.67–1.35; p=0.768; and OR 0.86, 95% CI 0.55–1.31; p=0.477) with consistent results across multivariable and PSM analyses (OR 0.89, 95% CI 0.50–1.55; p=0.669). D+T was associated with a higher incidence of grade ≥3 irAEs, particularly gastrointestinal (7.3% vs 1.8%; p<0.001) and dermatologic events (3.9% vs 0.7%; p=0.007), whereas severe hepatotoxicity was more frequent with A+B (3.3% vs 1.1%). In univariable analysis, D+T was associated with increased odds of any-grade irAE (OR 1.67, 95% CI 1.18–2.38; p=0.004) and grade ≥3 irAE (OR 1.92, 95% CI 1.20–3.04; p=0.006), with consistent results after adjustment and PSM (OR 2.65, 95% 1.35-5.49; p=0.006). The median duration of grade ≥3 trAEs was comparable between cohorts (25 days [IQR 4.0–71.5] with A+B vs 29.5 days [IQR 21.8–57.5] with D+T). Among patients with grade ≥3 trAEs, treatment discontinuation due to toxicity occurred in 24.8% of A+B-treated pts and 45.7% of D+T-treated pts (p=0.031).

Conclusions: In this observational study, D+T and A+B showed comparable incidence of trAEs, with D+T being associated with higher incidence of irAEs. These estimates persisted following robust PSM adjustments. Although duration of trAEs was similar across cohorts, permanent discontinuations due to toxicity were more frequent in the D+T cohort.

Disclosure of Interest: N/A

Image:

Characteristic	AB N = 454[1]	DT N = 178[1]	p-value[2]
Age, years	67 (60, 74)	72 (65, 77)	<0.001
Sex			0.003
Male	343 (76%)	153 (86%)	
Female	111 (24%)	24 (14%)	
Performance status			0.11
0	249 (55%)	110 (62%)	
1	205 (45%)	68 (38%)	
Aetiology			<0.001
Viral	252 (64%)	80 (46%)	
Non-viral	141 (36%)	93 (54%)	
Child–Pugh score (class A)			0.6
5	309 (68%)	125 (70%)	
6	145 (32%)	53 (30%)	
Portal vein thrombosis			0.6
Yes	138 (31%)	51 (30%)	
No	306 (69%)	120 (70%)	
Unknown	1 (0.2%)	1 (0.6%)	
Extrahepatic disease	196 (44%)	50 (29%)	<0.001
BCLC stage			0.001
A	17 (3.8%)	9 (5.3%)	
B	95 (21%)	59 (35%)	
C	336 (75%)	102 (60%)	
ALBI grade			>0.9
1	208 (49%)	80 (48%)	
2	211 (50%)	84 (51%)	
3	5 (1.2%)	1 (0.6%)	

[1] Median (Q1, Q3); n (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

P-090 COMPARISON OF HEPATOTOXICITY SEVERITY ACROSS DIFFERENT IMMUNE CHECKPOINT INHIBITOR-BASED THERAPIES IN HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW

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Introdcuction: The aim of this study was to investigate the incidence and spectrum of hepatotoxicity associated with immune checkpoint inhibitor (ICI)-based regimens in patients with hepatocellular carcinoma (HCC).

Methods: We analyzed 81 prospective trials comprising 103 treatment arms and 9,768 patients treated with ICI monotherapy or in combination with systemic and/or locoregional therapies. The primary outcome was hepatic adverse events (AEs), defined as aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin elevations, or immune-related hepatitis (ir-hepatitis). Secondary outcomes included events requiring immunosuppressive therapy or treatment discontinuation. Multivariable meta-regression was performed to identify factors associated with hepatotoxicity.

Results: AST elevation was the most common hepatic AE, with pooled incidences of 24% (95% CI, 20–30%) for any-grade and 5% (95% CI, 4–7%) for grade ≥3 events. Ir-hepatitis occurred in 3% (95% CI, 2–4%) and 2% (95% CI, 1–3%) for any-grade and grade ≥3 events, respectively. Compared with ICI monotherapy, ICI plus systemic therapy (any-grade AST elevation: OR 2.01; 95% CI, 1.13–3.58; grade ≥3: OR 1.85; 95% CI, 1.03–3.31) and triple therapy incorporating locoregional treatment (any-grade AST elevation: OR 5.74; 95% CI, 2.53–13.04; grade ≥3: OR 7.48; 95% CI, 3.32–16.82) were associated with increased hepatotoxicity. Events requiring immunosuppressive therapy and treatment discontinuation occurred in 5.0% (95% CI, 4–8%) and 2.0% (95% CI, 2–3%), respectively.

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Conclusion: Treatment intensification, particularly with ICI plus systemic and triple therapy regimens, was associated with an increased risk of both any-grade and grade ≥3 hepatotoxicity.

Disclosure of Interest: N/A

P-091 MULTICENTER PROPENSITY-WEIGHTED COMPARISON OF HEPATIC ARTERIAL INFUSION CHEMOTHERAPY AND TYROSINE KINASE INHIBITORS IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA PREVIOUSLY TREATED WITH ATEZOLIZUMAB–BEVACIZUMAB

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Background/Aim: Following the failure of first-line atezolizumab–bevacizumab (AB), the optimal second-line strategy for advanced hepatocellular carcinoma (HCC) remains undefined. The 2025 BCLC recommendations emphasize individualized decision-making under the CUSE framework. This study aimed to compare the clinical outcomes of hepatic arterial infusion chemotherapy (HAIC) and tyrosine kinase inhibitors (TKIs) in this setting.

Methods: This multicenter retrospective study included 90 patients (HAIC, n=51; TKIs, n=39) from four tertiary centers who experienced disease progression after AB. Baseline characteristics, including higher tumor burden and portal vein tumor thrombosis (PVTT) in the HAIC group, were adjusted using inverse probability of treatment weighting (IPTW). Tumor response was assessed via mRECIST by blinded radiologists. Primary endpoints were progression-free survival (PFS) and overall survival (OS).

Results: HAIC yielded significantly higher objective response rates (35.3% vs. 5.1%, $P=.002$) and disease control rates (66.7% vs. 25.6%, $P<.001$) compared to TKIs. In the IPTW-weighted analysis, HAIC was associated with significantly longer PFS (7.1 vs. 3.4 months; $P<.001$), although OS did not differ significantly between the groups (10.5 vs. 6.3 months; $P=.31$). Notably, the TKI group had a substantially higher rate of treatment discontinuation due to toxicity compared to the HAIC group (53.8% vs. 15.7%).

Conclusions: As a second-line treatment after AB failure, HAIC provides superior radiologic response and longer PFS compared to TKIs. While no definitive OS benefit was observed, these findings support HAIC as an effective investigational salvage option, particularly for patients with liver-dominant disease requiring robust intrahepatic control.

Disclosure of Interest: N/A

Images:

Table 1. Baseline Characteristics of the Overall Patient Population

Variable	2nd HAIC (n=51)	2nd TKI (n=39)	Total (n=90)	*p*-value	SMD
Age	61.2 ± 11.7	61.8 ± 9.9	61.5 ± 10.9	.78	.05
Sex				.64	
Male	40 (78.4)	33 (84.6)	73 (81.1)		.15
Female	11 (21.6)	6 (15.4)	17 (18.9)		.15
Etiology				.93	
HBV	36 (70.6)	28 (71.8)	64 (71.1)		.03
HCV	4 (7.8)	2 (5.1)	6 (6.7)		.11
Alcohol	6 (11.8)	4 (10.3)	10 (11.1)		.05
Other	5 (9.8)	5 (12.8)	10 (11.1)		.10
Total bilirubin (mg/dL)	1.3 ± 1.3	1.4 ± 1.8	1.3 ± 1.5	.92	.07
Albumin (g/dL)	3.6 ± 0.6	3.6 ± 0.6	3.6 ± 0.6	.78	.00
ALBI grade				.42	
1	12 (23.5)	14 (35.9)	26 (28.9)		.28
2	35 (68.6)	23 (59.0)	58 (64.4)		.20
3	4 (7.8)	2 (5.1)	6 (6.7)		.11
ALT (U/L)	52.8 ± 58.3	32.3 ± 35.1	43.9 ± 50.4	.04	.41
AST (U/L)	117.5 ± 142.2	61.2 ± 39.9	93.1 ± 113.2	.01	.51
INR	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	.58	1.00
Creatinine (mg/dL)	0.9 ± 1.0	0.8 ± 0.2	0.9 ± 0.8	.54	.13
AFP (ng/mL)	15926.3 ± 23497.5	7272.6 ± 16570.8	12176.4 ± 21119.3	.04	.40
PIVKA-II (mAU/mL)	59579.2 ± 110425.1	33738.2 ± 79287.5	48381.4 ± 98490.3	.20	.27
ECOG				.63	.05
0	34 (66.7)	27 (69.2)	61 (67.8)		.13
1	16 (31.4)	10 (25.6)	26 (28.9)		.17
2	1 (2.0)	2 (5.1)	3 (3.3)		
Child-Pugh class				.67	
A	46 (90.2)	37 (94.9)	83 (92.2)		.18
B	5 (9.8)	2 (5.1)	7 (7.8)		.18
mUICC stage				.04	
II	1 (2.0)	1 (2.6)	2 (2.2)		.04
III	9 (17.6)	3 (7.7)	12 (13.3)		.30
IVa	22 (43.1)	9 (23.1)	31 (34.4)		.43
IVb	19 (37.3)	26 (66.7)	45 (50.0)		.60
BCLC				1.00	
B	3 (5.9)	2 (5.1)	5 (5.6)		.04
C	48 (94.1)	37 (94.9)	85 (94.4)		.04
Up to 7 criteria				.01	
<7	6 (11.8)	14 (35.9)	20 (22.2)		.57
≥7	45 (88.2)	25 (64.1)	70 (77.8)		.57
PVTT				.01	
No	17 (33.3)	25 (64.1)	42 (46.7)		.63
Yes	34 (66.7)	14 (35.9)	48 (53.3)		.63
Extrahepatic disease					
No	22 (43.1)	8 (20.5)	30 (33.3)	.04	.49
Yes	29 (56.9)	31(79.5)	60 (66.7)		.49

Data are given as n (%) or mean ± standard deviation. HAIC, hepatic arterial infusion chemotherapy; TKI, tyrosine kinase inhibitor; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, albumin-bilirubin; ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; ECOG, Eastern Cooperative Oncology Group; mUICC, Modified Union for International Cancer Control; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombus; SMD, absolute standardized mean differences.

Table 2. Treatment Responses by Second-Line Therapy of Hepatocellular Carcinoma

	2nd HAIC (n=51)	2nd TKI (n=39)	*p*-value
Treatment response			<.001
CR	0 (0.0)	0 (0.0)	
PR	18 (35.3)	2 (5.1)	
SD	16 (31.4)	8 (20.5)	
PD	16 (31.4)	25 (64.1)	
NA	1 (2.0)	4 (10.3)	
ORR	18 (35.3)	2 (5.1)	.002
DCR	34 (66.7)	10 (25.6)	<.001

Values are presented as number (%). ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not applicable; HAIC, hepatic arterial infusion chemotherapy; TKI, tyrosine kinase inhibitor.

Table 3. Weighted Cox regression analysis of overall survival

	HR (95% CI)	*p*-value
Treatment (HAIC vs TKI)	0.61 (0.36 – 1.02)	.06
Age	0.98 (0.97 – 1.00)	.34
Sex (Male)	1.31 (0.55 – 2.62)	.47
ECOG (≥1)	1.62 (1.11 – 2.37)	.01
Child-Pugh B	3.46 (1.68 – 7.13)	<.001
PVTT	0.78 (0.55 – 1.69)	.90
Up to seven ≥7	2.73 (1.37 – 5.44)	.004

HR < 1 indicates survival benefit in favor of HAIC. Weighted Cox proportional hazards regression with IPTW adjustment was applied. HR, hazard ratio; HAIC, hepatic arterial infusion chemotherapy; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; PVTT, Portal vein tumor thrombus.

Table 4. Weighted Cox regression analysis of progression free survival

	HR (95% CI)	*p*-value
Treatment (HAIC vs TKI)	0.47 (0.30 – 0.73)	<.001
Age	0.99 (0.97 – 1.00)	.25
Sex (Male)	1.07 (0.49 – 2.34)	.87
ECOG (≥1)	1.56 (1.03 – 2.35)	.03
Child-Pugh B	2.65 (1.20 – 5.84)	.02
PVTT	1.04 (0.64 – 1.68)	.87
Up to seven ≥7	1.75 (0.99 – 3.09)	.05

HR < 1 indicates survival benefit in favor of HAIC. Weighted Cox proportional hazards regression with IPTW adjustment was applied. HR, hazard ratio; HAIC, hepatic arterial infusion chemotherapy; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; PVTT, Portal vein tumor thrombus.

Table 5. Weighted logistic regression analysis of treatment response (ORR and DCR)

Outcome	Variable	OR (95% CI)	*p*-value
ORR	Treatment (HAIC vs TKI)	14.34 (3.00–68.48)	.001
	PVTT	1.00 (0.33–3.03)	1.00
	Up to seven ≥7	0.74 (0.17–3.29)	.70
DCR	Treatment (HAIC vs TKI)	6.55 (2.47–17.42)	<.001
	PVTT	1.08 (0.44–2.66)	.87
	Up to seven ≥7	0.59 (0.19–1.86)	.37

OR > 1 indicates higher odds of treatment response in favor of HAIC. IPTW-weighted logistic regression with stabilized weights was applied. IPTW, inverse probability of treatment weighting; HAIC, hepatic arterial infusion chemotherapy; OR, odds ratio; CI, confidence interval; ORR, objective response rate; DCR, disease control rate.

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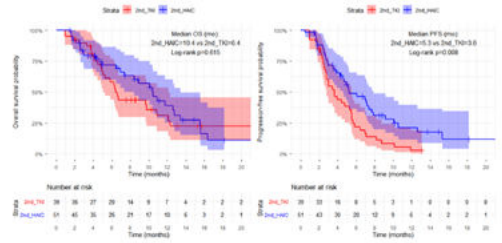

Fig 3. Overall survival comparison and B. Progression free survival between patients treated with second-line HAIC and second-line TKIs using the Kaplan-Meier curve. HAIC, hepatic arterial infusion chemotherapy; TKI, tyrosine kinase inhibitor; OS, overall survival, PFS, progression-free survivial.

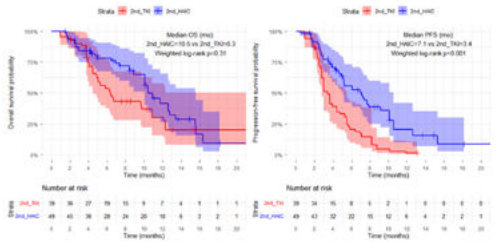

Fig 4. IPTW-weighted Kaplan–Meier curves for OS and PFS in patients treated with HAIC versus TKIs following AB therapy failure. Weighted Cox proportional hazards regression was applied with IPTW to adjust for baseline differences. OS and PFS were compared between treatment groups using weighted log-rank tests. OS, overall survival; PFS, progression-free survival; IPTW, inverse probability of treatment weighting; HAIC, hepatic arterial infusion chemotherapy; TKI, tyrosine kinase inhibitor; AB, atezolizumab–bevacizumab.

P-092 BEYOND THE ALGORITHM: TUMOR-BOARD DETERMINANTS OF TREATMENT-STAGE MIGRATION ACROSS THE BCLC STAGES (2020–2024)

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Introduction: The multidisciplinary tumor board (MTB) is pivotal in tailoring treatment for hepatocellular carcinoma (HCC), particularly when evidence-based first-line options supported by overall survival (OS) data are unsuitable because of patient-, technical-, or context-related factors or when multiple treatment options show OS benefit but lack direct comparative evidence. The BCLC algorithm incorporates the Complexity, Uncertainty, Subjectivity, and Emotion (CUSE) framework, which helps make explicit the trade-offs underlying each clinical decision and structures MTB deliberations trough treatment-stage migration (TSM), allowing deviation from linear, stage-based recommendations. Although this is part of implicit real-world practice, the determinants of TSM remain poorly characterized.

Methods: We retrospectively analyzed all cases discussed by the BCLC-MTB between January 2020 and December 2024. Eligible cases involved adult HCC patients presented for treatment decision-making. Data collected included BCLC stage, prior therapies, TSM decision, and underlying rationale.

Results: A total of 800 cases were reviewed by the MTB, 368 were eligible cases (295 patients), 27.7% (n=102) involved TSM. The median age of TSM cases was 70 [64-76] years, and 30.4% of them were treatment naïve.

TSM was most frequent in BCLC-B (56.9%) and BCLC-A (33.3%) stages. Globally, the principal reasons for migration were technical infeasibility (31.4%), untreatable progression (17.7%), and reduction in tumor burden (11.8%). Main reasons for TSM differed based on BCLC stage: In BCLC-A cases (n=34) it was technical infeasibility ± comorbidity in 64.7%; in BCLC-B, untreatable progression was involved in 39.7% of the cases. Comorbidities and/or advanced age influenced 17.6% of TSM decisions, particularly among BCLC-A cases in which they were implied in one third of the cases (29.4%).

Globally, treatment proposed by MTB was performed in 85.6% of the cases (87.1% in non-TSM vs 81.4% in TSM cases; p=0.15). Radiological progression (12 cases) and comorbidities (11 cases) were the main reasons for not executing the plan in the overall cohort. In 9 cases treatment was not performed due to hepatic decompensation.

Conclusions: One-third of HCC cases discussed at the MTB required TSM, most commonly driven by technical or patient-related constraints. These results emphasize the key importance of multidisciplinary discussion in tailoring therapy, adapting recommendations to the priorities agreed upon by patients and physicians, as well as to the intended treatment goals. They also highlight the need to integrate the rationale for TSM into clinical trial design and survival modeling.

Disclosure of Interest: Honoraria

P-093 REAL-WORLD OUTCOMES OF PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED WITH DURVALUMAB PLUS TREMELIMUMAB WHO MET OR DID NOT MEET THE INCLUSION CRITERIA FOR THE PHASE 3 HIMALAYA TRIAL

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Introduction: The phase 3 HIMALAYA trial established durvalumab plus tremelimumab (Dur/Tre) as a standard first-line systemic therapy for unresectable hepatocellular carcinoma (HCC). In routine clinical practice, Dur/Tre is frequently administered to patients who would not have fulfilled the original trial eligibility criteria—most notably those with gastroesophageal varices or elevated risk of gastrointestinal bleeding for whom bevacizumab is contraindicated. Real-world outcomes in this broader, heterogeneous population remain incompletely characterized.

Methods: This multicenter retrospective study enrolled 412 patients with unresectable HCC who initiated Dur/Tre between March 2023 and August 2025 at 30 Japanese institutions. Patients were stratified by adherence to HIMALAYA trial inclusion criteria: the HIMALAYA group (n=92; 22.3%) and the non-HIMALAYA group (n=320; 77.7%). The primary endpoint was overall survival (OS) and the secondary endpoint was progression-free survival (PFS), both measured from treatment initiation. Kaplan–Meier estimates were compared using the generalized Wilcoxon test; multivariable Cox proportional hazards models identified independent predictors; and inverse probability weighting (IPW) was applied to adjust for baseline covariate imbalances. Immune-mediated adverse events (AEs) were graded per NCI-CTCAE v5.0.

Results: Median follow-up was 9.1 (4.2–15.4) months. Median PFS was 5.4 months (95% CI, 3.0–7.2) in the HIMALAYA group versus 3.0 months (95% CI, 2.6–3.4) in the non-HIMALAYA group (p=0.012). Multivariable analysis identified portal vein invasion (HR, 1.509; 95% CI, 1.049–2.170; p=0.027) as an independent predictor of inferior PFS, and BMI ≥25 kg/m² as independently associated with favorable PFS (HR, 0.780; 95% CI, 0.612–0.993; p=0.044). Median OS was 19.4 months (95% CI, 17.8–26.3) in the HIMALAYA group versus 15.4 months (95% CI, 12.7–21.2) in the non-HIMALAYA group (p=0.014). ECOG-PS ≥1 (HR, 1.878; 95% CI, 1.253–2.814; p=0.002) and albumin–bilirubin (ALBI) grade ≥2 (HR, 2.032; 95% CI, 1.319–3.318; p=0.001) independently predicted worse OS, whereas HIMALAYA eligibility status was not an independent predictor of either endpoint. After IPW adjustment, PFS remained significantly shorter in the non-HIMALAYA group (HR, 1.424; 95% CI, 1.037–1.954; p=0.029), whereas IPW-adjusted OS did not differ significantly between groups (HR, 1.326; 95% CI, 0.853–2.062; p=0.211). Overall response rate and disease control rate were 31.4% and 64.0% in the HIMALAYA group versus 13.9% and 42.8% in the non-HIMALAYA group (both p<0.001). Endocrine dysfunction of any grade occurred more frequently in the HIMALAYA group (14.1% vs. 6.6%; p=0.030), as did grade ≥3 events (5.4% vs. 0.6%; p=0.007). Subgroup analysis suggested that non-HIMALAYA patients with ALBI grade 1 may achieve OS outcomes comparable to those in the HIMALAYA group.

Conclusion: In this large real-world cohort, patients with unresectable HCC treated with Dur/Tre who met phase 3 HIMALAYA eligibility criteria demonstrated favorable survival outcomes. Patients who did not meet eligibility criteria also showed encouraging prognoses, particularly those with preserved hepatic function (ALBI grade 1). ECOG-PS and ALBI grade—rather than formal trial eligibility per se—emerged as the dominant independent determinants of survival, underscoring the primacy of performance status and hepatic functional reserve in guiding patient selection for Dur/Tre in real-world clinical practice.

Disclosure of Interest: Honoraria

Posters

P-094 PATIENTS WITH HEPATOCELLULAR CARCINOMA SHOULD BENEFIT FROM SALVAGE TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT WHEN INDICATED

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Introduction: The role of salvage/rescue transjugular intrahepatic portosystemic shunt (TIPS) in patients with hepatocellular carcinoma (HCC) remains controversial. This study aimed to evaluate outcomes in patients with active HCC undergoing salvage/ rescue TIPS.

Methods: This retrospective multicenter study across 18 centers included consecutive patients with active HCC between 2010 and 2025 who underwent salvage (persistent bleeding despite therapy) and rescue (early rebleeding within 5 days) TIPS for acute variceal bleeding. Mortality at 42 days, overall survival (OS), and HCC-related outcomes were analyzed.

Results: 49 patients with active HCC were included. Viral hepatitis was the main etiology (61%); 78% had prior AVB. Median MELD score was 14, 22% were Child-Pugh C, and 47% ALBI grade 3. Median largest tumor diameter was 29 mm; 59% had a single lesion, 16% macrovascular invasion, and 6% extrahepatic metastases. Most patients were BCLC stage A (47%), and 65% were within Milan criteria.

At 42 days, 61% of patients had died. In univariate analysis, older age was the only factor associated with 42-day mortality (HR 1.10, p = 0.01); no liver function parameters or HCC-related features were significantly associated with early mortality.

Median OS was 17 months and was 24 months in patients within the Milan criteria compared to 9 months with those outside the criteria (p = 0.14). In univariate analysis, prothrombin time (HR 0.97, p = 0.04), presence of ascites at the time of TIPS (HR 2.39, p = 0.02), and pre-TIPS hepatic venous pressure gradient (HR 1.06, p = 0.039) were associated with mortality.

Rebleeding occured in 10% of patients, hepatic encephalopathy in 39%, and cardiac failure in 6%, and no tumor dissemination was observed at imaging during HCC surveillance. Following salvage/rescue TIPS, 55% of patients received HCC therapy, including liver transplantation (n = 11), ablation (n=4, all achieving complete response (CR)), locoregional therapies (n = 9; 58% CR, 14% partial response, 14% stable disease, and 14% progressive disease), and systemic treatments (n = 3).

Conclusion: These preliminary data suggest that liver function parameters may influence prognosis more than tumor characteristics. HCC should not been considered as a definite contraindication for rescue TIPS. Validation in a larger cohort, currently being collected, is warranted.

Disclosure of Interest: N/A

P-095 EFFICACY AND SAFETY OF ATEZOLIZUMAB PLUS BEVACIZUMAB (ATEZO/BEV) IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC) AND COMORBIDITIES: POST-HOC FINAL ANALYSIS OF THE ATHECA STUDY

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Introduction: Atezo/Bev is the standard of care for uHCC. In clinical practice, patients often present with multiple comorbidities, such as hypertension, diabetes, dyslipidemia or cardiovascular disease, which may raise concerns regarding treatment tolerability and safety. We evaluated the safety and efficacy of Atezo/Bev in the subgroups of patients with comorbidities.

Methods: ATHECA was a phase IIIb, open-label, Spanish, multicenter study (NCT04732286) that enrolled patients with uHCC and no prior systemic therapy. This exploratory analysis evaluated outcomes based on the presence of comorbidities (hypertension, diabetes, dyslipidemia and cardiovascular disease). Overall Survival (OS) was calculated with the Kaplan-Meier method. Data are based on the final analysis (Clinical cut-off date 26 April 2024) with a median follow-up of 29.2 months (mo).

Results: Out of 99 evaluable patients in the ITT population, 73% (n=73) had at least one comorbidity, with 61% having 1 or 2 comorbidities and 12%, having 3 or more. Hypertension was the most prevalent condition affecting 57% (n=57) of patients. The median Overall Survival (mOS) for the total population was 24.8 mo, showing consistency across subgroups. Patients with 1-2 comorbidities achieved a mOS of 22.78mo (12-mo OS: 72.3% (58.8% - 82.0%); 24-mo OS: 47.3% (33.5% - 59.9%)) and patients with >3 comorbidities had a mOS of 31.17mo (12-mo OS: 66.7% ((33.7% - 86.0%); 24-mo OS: 55.6% (23.1% - 79.0%). Patients without these comorbidities had a mOS of 29.98 mo (12-mo OS: 69.8% (48.6% - 83.6%); 24-mo: 61.2% (39.7% - 77.1%)). The incidence of grade 3-4 adverse events was 22.2%, 27.9% and 58.3% of patients with 0, 1-2 and >3 comorbidities, respectively. Grade 3-4 hemorrhagic events occurred in 3.7% (n=1), 6.6% (n=4) and 0% of patients, respectively.

Conclusion: This analysis of ATHECA study shows that in patients with common comorbidities such as hypertension, diabetes, dyslipidemia or controlled cardiovascular disease, adequate management supports consistent efficacy and safety outcomes with the combination.

Disclosure of Interest: Honoraria

Image:

Table 1:

Condition	1-2 comorbidities (N=61)	3 or more comorbidities (N=12)
Hypertension, n (%)	45 (73.8)	12 (100.0)
Diabetes, n (%)	22 (36.1)	12 (100.0)
Dyslipidemia, n (%)	10 (16.4)	10 (83.3)
Cardiovascular disease, n (%)	10 (16.4)	2 (16.7)

Posters

P-096 SEQUENTIAL THERAPY PATTERNS AND PROGNOSTIC IMPACT OF FIRST-LINE TREATMENT RESPONSE IN UNRESECTABLE HEPATOCELLULAR CARCINOMA PATIENTS WITH FAILURE OF ATEZOLIZUMAB PLUS BEVACIZUMAB

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Background/Hypothesis: Optimal subsequent treatment strategies following first-line Atezolizumab plus bevacizumab (Atezo/Bev) in unresectable hepatocellular carcinoma (HCC) remain unclear, particularly beyond the second-line treatment settings. We evaluated patterns of sequential treatment after Atezo/Bev and examined the impact of both treatment response to the preceding systemic therapy and the type of systemic agents used at each subsequent treatment line on survival outcomes.

Materials and Methods: In this single-center retrospective cohort study, we analyzed 353 patients with unresectable HCC, who received Atezo/Bev ≥3 cycles (May 2022–December 2023) and underwent subsequent treatment. At each treatment line, overall survival (OS) and progressive-free survival (PFS) were evaluated by type of systemic agents and stratified by the best response to the prior therapy (progressive disease [PD] vs. non-PD groups).

Results: Of the total patients, 307 (87.0%) received second-line systemic therapy, and 279 (90.9%) of them underwent the initial response evaluation. Tyrosine kinase inhibitors (TKIs) constituted most of the second-line therapy (lenvatinib or sorafenib in >80% of the patients). Median OS was comparable between lenvatinib and sorafenib (9.5 vs. 8.3 months; P=NS), whereas lenvatinib was significantly associated with longer median PFS (5.4 vs. 2.8 months; P<0.05). Survival outcomes after second-line treatment did not differ between patients achieving PD and non-PD after first-line Atezo/Bev (median OS, 7.8 vs. 9.4 months; and median PFS, 3.7 vs. 4.2 months; both Ps=NS). In the third-line settings, TKIs predominated and showed comparable survival outcomes with immune checkpoint inhibitors (ICIs) (median OS and PFS, 6.9 vs. 4.0 months; and 1.7 vs. 1.8 months, respectively; Ps=NS). Furthermore, treatment response of second-line systemic treatment showed no significant association with survival outcomes of subsequent therapy (median OS and PFS for PD vs. non-PD groups, 7.4 vs. 6.1 months and 1.8 vs. 1.6 months, respectively; Ps=NS).

Conclusions: TKIs were predominant subsequent therapies after first-line Atezo/Bev for HCC, with second-line lenvatinib achieving longer PFS than sorafenib, while survival outcomes were similar between TKIs and ICIs in later-line settings. Survival after subsequent treatment was not significantly influenced by response to prior treatment. Further multi-center prospective studies are warranted to determine the optimal treatment sequence after Atezo/Bev.

Disclosure of Interest: N/A

P-097 PERCUTANEOUS CRYOABLATION FOR HEPATOCELLULAR CARCINOMA IN ANATOMICALLY CRITICAL LOCATIONS: CLINICAL OUTCOMES AND SAFETY

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Introduction: Cryoablation offers distinct advantages for treating tumors in anatomically critical locations; however, clinical evidence regarding latest cautery-enabled cryoablation systems remains sparse.

Purpose: To evaluate the clinical outcomes of cryoablation for hepatocellular carcinoma (HCC), particularly in anatomically critical locations such as perivascular or subcapsular portion.

Methods: This retrospective study included patients with HCC who underwent percutaneous cryoablation between June 2023 and October 2025. Cryoablation was performed under ultrasound guidance, supplemented by fusion imaging and contrast-enhanced ultrasound as required. Technical and clinical outcomes, including local tumor progression (LTP), intrahepatic distant recurrence (IDR), extrahepatic recurrence (ER) and post-procedural complications, were evaluated. Factors associated with LTP were evaluated using multivariable Cox proportional hazards regression analysis.

Results: A total of 149 HCCs (mean size, 1.6 ± 0.5 cm) in 139 patients (mean age, 65.5 ± 9.6 years; 112 men [80.6%]) were analyzed. Technical success was achieved in 145 lesions (97.3%). During a median follow-up of 21 months (range, 4–32 months), LTP occurred in 20 lesions (13.8%), with a median LTP-free survival of 28 months. Most HCCs were situated in critical locations, including perivascular (68.5%, 102/149) or subcapsular (30.2%, 45/149) areas. The rates of LTP, IDR and ER at 2-year were 14.4%, 58.2%, and 10.2%, respectively. On a multivariable analysis, a tight ablative margin (<5 mm) was the only independent factors associated with LTP (hazard ratio, 14.34; 95% confidence interval [CI], 3.95–51.97; p < 0.001), whereas perivascular tumor location was not associated with LTP. Post-procedural complications occurred in 25.9% (36/139) of patients, all of which were minor (SIR Grade 1 or 2) with no major complications or deaths. Common minor events included transient portal vein thrombosis (12.2%, 17/139) and hemoperitoneum (11.5%, 16/139), Notably, no significant bile duct dilatation was observed despite the proximity to critical structures.

Conclusion: Percutaneous cryoablation provides acceptable technical success and effective local tumor control for HCCs in anatomically critical locations, with a low risk of major complications.

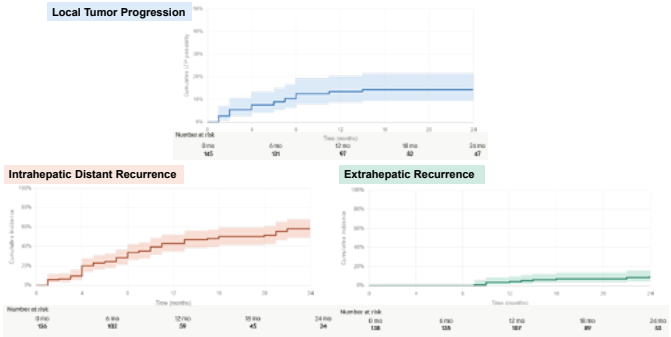
Disclosure of Interest: N/A

Images:

Comparison of Clinical and Procedural Variables Between Patients With and Without Local Tumor Progression

Characteristic		LTP (+) (n=20)	LTP (-) (n=125)	P value
Age		61.8 ± 8.4	65.4 ± 9.8	0.22
Male		12 (60.0)	104 (83.2)	0.25
Tumor size ≥2 cm		6 (30.0)	30 (24.0)	0.94
AFP		12.9 ± 16.0	50.8 ± 265.2	0.48
Number of needles				0.77
	1	6 (30.0)	36 (28.8)	
	2	12 (60.0)	79 (63.2)	
	3	2 (10.0)	10 (8.0)	
Margin < 5mm		17 (85.0)	26 (20.8)	<0.001
Irregular ablation shape		2 (10.0)	7 (5.6)	0.20
Location				0.49
Perivascular		15 (75.0)	84 (67.2)	
Non-perivascular		5 (25.0)	41 (32.8)	

Cumulative Incidence of Local Tumor Progression, Intrahepatic Distant Recurrence, and Extrahepatic Recurrence After Percutaneous Cryoablation for Hepatocellular Carcinoma



P-098 CONVERSION SURGERY AFTER IMMUNOTHERAPY IN INITIALLY UNRESECTABLE HEPATOCELLULAR CARCINOMA: A FRENCH MULTICENTRIC RETROSPECTIVE STUDY

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Introduction: Hepatocellular carcinoma (HCC) is often diagnosed at an advanced stage, precluding upfront resection.

Immunotherapy has reshaped the management of unresectable HCC, achieving significant tumour response rates and enabling potential conversion to surgery. However, multicentric data on perioperative safety and survival outcomes after resection in this setting remain limited.

Methods: A multicentric retrospective study was conducted across ten French University Hospitals between 2019 and 2024. Patients with initially unresectable HCC who received immunotherapy followed by surgical resection after achieving a radiologic tumour response were included. Primary endpoints were overall survival (OS) and disease-free survival (DFS). Secondary endpoints included postoperative morbidity (Clavien ≥ III), 90-day mortality, and pathological response.

Results: Forty patients were included (85% male; median age 59 years; median BMI 26.0 Kg/m^2).

Posters

Before treatment, 67.5% were classified as BCLC stage C (VP4 n = 4, VP3 n = 8, VP2 n = 5, nodal metastases n = 7), and 5.1% as Child-Pugh B7. The median size of the largest lesion was 89 mm (range 60 – 120), with a median number of 3.5 nodules. All patients received a median of 11 cycles of immunotherapy (range 6 –18) before surgery. An objective radiological complete response was achieved in 3 patients and 25 (62.5%) presented an objective radiological partial response. After immunotherapy, 33% of patients were reclassified as BCLC A, 43% as BCLC C, and liver function remained preserved in all but one case (Child-Pugh B7). Major hepatectomy was performed in 33 patients (82.1%). The overall rate of major complications (Clavien ≥ III) was 24%, with no 90-day mortality. Median hospital stay was 7 days, including a median of 2.6 days in intensive care. Complete pathological response (100% necrosis) was observed in 17 patients (42.5%). With a median follow up of 23.8 months, OS rates were 97.5% at 3 months, 94.5% at 12 months ans 81% at 36 months. DFS rates were 94.5% at 3 months, 54.5% at 12 months and 54% at 36 months.

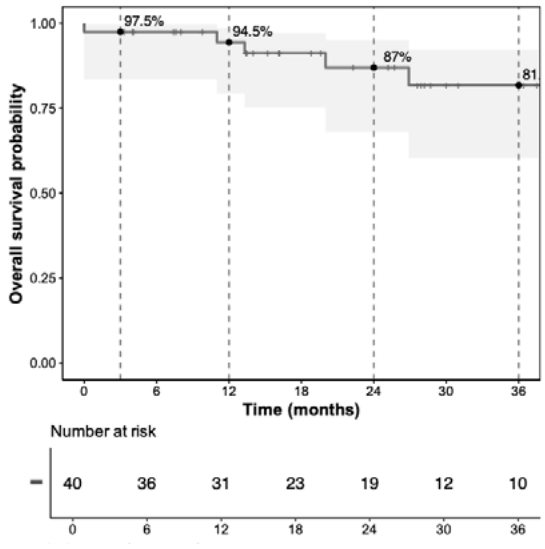
Conclusion: Conversion surgery after immunotherapy for initially unresectable HCC is feasible and safe in experienced centers, showing low postoperative morbidity and encouraging 2-year survival outcomes.

These results support the curative potential of hepatic resection following combined immunotherapy and highlight the need for larger comparative studies to validate its long-term benefit.

Disclosure of Interest: N/A

HCC caracteristics after immunotherapy

	Patients (n = 40)
BCLC grades (%)	
A	13 (33.3)
B	9 (23.1)
C	17 (43.6)
Tumour shrinkage (%)	34 (85.0)
Number of cycles (median [IQR])	11.00 [6.00, 15.50]
Maximal nodule size, mm (median [IQR])	45.00 [23.00, 69.25]
Regression of vascular invasion (%)	15 (37.5)
Radiological response according recist 1.1 (%)	
CR	3 (7.5)
PR	25 (62.5)
SD	10 (25.0)
PD	2 (5.0)
Milan criteria	
IN	8 (21.6)
OUT	32 (78.4)
AFP score	
<2	16 (47.0)
>2	24 (53.0)
AFP, ng/ml	15 (37.5)



P-099 OUTCOMES OF ATEZOLIZUMAB PLUS BEVACIZUMAB FOR HEPATOCELLULAR CARCINOMA: IMPACT OF RELATIVE BEVACIZUMAB EXPOSURE

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Background and Aims: Bevacizumab in atezolizumab plus bevacizumab (Atezo/Bev) therapy for unresectable hepatocellular carcinoma (HCC) is administered according to body weight. However, the clinical impact of relative bevacizumab exposure on efficacy and safety remains unclear. We investigated the association between relative bevacizumab exposure and treatment outcomes in patients with HCC treated with Atezo/Bev.

Methods: A total of 1,217 patients with HCC who received Atezo/Bev between September 2020 and July 2025 were included. Median age was 74.0 (69.0–80.0) years, 980/237 were male/female, performance status was 0/1/≥2 in 1009/181/27, liver disease etiology was viral/non-viral in 586/622, Child–Pugh score was 5/6/7/≥8 in 726/349/111/31, and BCLC stage was ≤A/B/≥C in 122/447/648 patients. Median AFP was 21.0 (5.0–347.5) ng/mL, and median observation period was 15.7 (9.1–27.3) months. Patients were classified into the higher relative bevacizumab exposure (HRE) and lower relative bevacizumab exposure (LRE) groups according to whether bevacizumab exposure was above or below that expected at a reference BMI of 25 kg/m², which was adopted as a pragmatic threshold for relative dose assessment. Survival was evaluated using a 9-week landmark analysis after bevacizumab initiation. Patients initially classified into the HRE group who interrupted or discontinued bevacizumab within 9 weeks were reassigned to the LRE group.

Results: Median progression-free survival (PFS) and overall survival (OS) were 10.0 (9.2–10.9) months and 24.7 (21.9–26.0) months, respectively. Best response by RECIST version 1.1 was complete response/partial response/stable disease/progressive disease in 5.5%/29.9%/53.0%/11.7%, with an objective response rate of 33.4% and a disease control rate (DCR) of 83.5%. DCR was significantly higher in the HRE group than in the LRE group (87.0% vs. 82.1%, p=0.004). Adverse events did not differ significantly between the groups. Both PFS and OS were significantly longer in the HRE group than in the LRE group (PFS: 12.0 [10.5–13.8] vs. 9.3 [8.3–10.2] months, p=0.017; OS: 26.0 [24.4–30.7] vs. 23.2 [20.3–25.7] months, p=0.032). In multivariable analysis, Child–Pugh score ≥7 (HR 1.37 [1.13–1.66], p=0.001), first-line treatment (HR 0.81 [0.71–0.93], p=0.003), and LRE classification (HR 1.17 [1.01–1.35], p=0.035) were independently associated with PFS. For OS, Child–Pugh score ≥7 (HR 1.94 [1.56–2.42] p<0.001), BCLC stage ≥C (HR 1.21 [1.02–1.44], p=0.032), first-line treatment (HR 0.84 [0.72–0.99], p=0.042), performance status ≥1 (HR 1.27 [1.01–1.59], p=0.041), and LRE classification (HR 1.20 [1.00–1.43], p=0.048) were significant factors. In spline analysis, the hazard ratio for OS was below 1.0 at a BMI range of 23–28 kg/m².

Conclusions: Higher relative bevacizumab exposure was safe and associated with improved survival outcomes in patients with HCC treated with Atezo/Bev.

Disclosure of Interest: Honoraria

P-100 TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT AS A BRIDGING STRATEGY TO HEPATOCELLULAR CARCINOMA TREATMENT IN PATIENTS WITH REFRACTORY ASCITES OR HYDROTHORAX

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Introduction: The use of TIPS in patients with active hepatocellular carcinoma (HCC) remains controversial. This study aimed to assess outcomes after TIPS performed for refractory ascites or hydrothorax.

Material and methods: We conducted a retrospective multicenter study across 15 centers, including consecutive patients with active HCC who underwent TIPS for refractory ascites or hydrothorax between 2007 and 2025. The primary endpoint was overall survival (OS), while secondary endpoints included ascites resolution and oncological outcomes following HCC-directed treatments after TIPS.

Results: A total of 54 patients with active HCC undergoing TIPS for refractory ascites (n = 49) or hepatic hydrothorax (n = 5) were included. Mean age was 65 years; 69% had alcohol-related liver disease, 41% had a history of acute variceal bleeding (AVB), and 94% presented varices the day of TIPS. Median MELD score was 12, 79% of patients were classified as Child-Pugh B and 30% presented with ALBI grade 3. The median largest tumor diameter was 25 mm. Multifocal disease was present in 56% of patients, and 9% had macrovascular invasion (25% Vp3 and 25% Vp4). Most patients were classified as BCLC stage A (52%), and 80% were within the Milan criteria.

Median overall survival was 24 months. Ascites resolution following TIPS was achieved in 56% of patients within a median time of 2 months. Vascular invasion (HR 4.06, p=0.014), >3 lesions (HR 2.93, p=0.027) and metastasis (HR 10.6, p=0.004) were associated with increased mortality, whereas being within Milan criteria (HR 0.30, p=0.011) and receipt of HCC treatment (HR 0.15, p=0.02) were associated with improved survival. Ascites control was not directly associated with survival but significantly increased access to HCC treatment (HR 2.72, p=0.04).

Following TIPS placement, 52% of patients received HCC-directed therapy, including liver transplantation (n = 8), ablation (n = 9; 7 complete responses and 2 progressive diseases), locoregional therapies (n = 6; 3 complete responses and 3 partial responses), and systemic treatments (n = 4). During follow-up, AVB occurred in 6% of patients, hepatic encephalopathy in 39%, and cardiac failure in 2%. New extrahepatic metastases developed in three patients but these patients presented active HCC under systemic treatment.

Conclusion: In selected HCC patients, TIPS allows control of ascites in a substantial proportion of cases, thereby enabling the implementation of curative or palliative treatment for HCC

Disclosure of Interest: N/A

P-101 THE EFFICACY AND SAFETY OF 24H-FOLFOX VERSUS 46H-FOLFOX HEPATIC ARTERIAL INFUSION CHEMOTHERAPY IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Introduction: Hepatic arterial infusion chemotherapy (HAIC) with oxaliplatin and fluorouracil has already been recommended as one of the strategies for patients with unresectable hepatocellular carcinoma (HCC), especially for the ones with huge HCC, or macrovascular invasion. However, the standard 46-FOLFOX HAIC makes the patients intolerant and negative emotions. Reducing time might release these adverse events. Herein, we aim to investigate the efficacy and safety of 24h-FOLFOX HAIC versus 46h-FOLFOX HAIC in patients with unresectable HCC.

Methods: Patients with unresectable HCC treated with 24h-FOLFOX HAIC were retrospectively enrolled in in second affiliated hospital of Nanchang University between January 2024 and August 2025. Baseline matched participants treated with 46h-FOLFOX HAIC were collected simultaneously. The evaluation of efficacy was according to modified RECIST (mRECIST), and the primary outcomes were objective response rate (ORR) and disease control rate (DCR). Secondary outcomes included progression-free survival (PFS) and overall survival (OS).

Results: Fifteen patients with unresectable HCC were enrolled in 24h-FOLFOX HAIC group, and twenty-eight patients with baseline matched unresectable HCC were collected in 46h-FOLFOX HAIC group. 26.67% of patients got partial response (PR), 60.00% of patients was stable disease (SD), and 13.33% of patients experienced progression disease (PD) in 24h-FOLFOX HAIC group. Therefore, the ORR was 26.67%, and DCR was 86.67% in 24h-FOLFOX HAIC group. 25.00% of patients got PR, 53.57% of patients was SD, and 21.43% of patients suffered PD in 24h-FOLFOX HAIC group. Therefore, the ORR was 25.00%, and DCR was 78.57% in 46h-FOLFOX HAIC group. There was no difference between two groups when comparing ORR (p=1.00) and DCR (p=0.81). The median PFS (mPFS) was 326 days in 24h group compared to 187 days in 46h group (p=0.44). The median OS (mOS) was not reached in 24h group compared to 371 days group in 46h group (p=0.157). 24h-FOLFOX HAIC group suffered higher rate of hypertension than 46h-FOLFOX HAIC group (p=0.025). 24h-FOLFOX HAIC group also had the trend of higher rate of fever, abdominal pain, nausea, elevated ALT or AST, although no significant difference.

Conclusion: The efficacy of 24h-FOLFOX HAIC was comparable with 46h-FOLFOX HAIC in patients with unresectable. The adverse effects of 24h-FOLFOX HAIC group had the trend of higher adverse events than 46h-FOLFOX HAIC group, which might be an alternative option for patients that were intolerant with 46h-FOLFOX HAIC.

Disclosure of Interest: N/A

P-102 CLINICAL IMPACT OF A COMPREHENSIVE RESPIRATORY TRAINING PROGRAM IN STEREOTACTIC BODY RADIATION THERAPY FOR LIVER TUMORS: IMPLICATIONS FOR BREATH-HOLD ELIGIBILITY, MARGIN REDUCTION, AND BREATHING REGULARITY

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Introduction: In radiation therapy (RT) for liver tumors, managing respiratory motion is essential to enhance targeting accuracy and minimize toxicity to surrounding normal organs. Effective respiratory training, particularly when utilizing breath-hold (BH) techniques, may facilitate improved motion control and enable margin reduction. We established a comprehensive respiratory training program (CRTP) and evaluated its clinical impact in patients undergoing hepatic stereotactic body radiation therapy (SBRT).

Methods: The CRTP was initiated in March 2025 at a single institution. It consisted of a respiratory control education video provided one week before computed tomography simulation, followed by video-guided respiratory training led by an experienced medical physicist immediately prior to simulation. BH eligibility was defined as a breath-hold duration ≥ 15 seconds and diaphragmatic reproducibility within 5 mm across five consecutive breath-holds. Patients who met the BH criteria were assigned to the BH-RT group, while the remaining patients were allocated to the amplitude-gated RT (AG-RT) group. To evaluate the impact of the CRTP, BH allocation rates and internal target volume (ITV) margins were compared with historical baseline data from 2023. Additionally, paired breathing pattern assessments, including baseline shift, interval standard deviation (SD), and duty cycle, were performed for the AG-RT group immediately before and after the CRTP using an external respiratory monitoring system during a 3-minute free-breathing period.

Results: A total of 324 patients (2023, no-CRTP) and 234 patients (2025, CRTP) who underwent hepatic SBRT were analyzed. The BH allocation rate significantly increased from 38.6% (125/324) to 60.3% (141/234) ($p < 0.001$). The ITV margin for the entire cohort significantly decreased from 7.5 ± 2.8 mm in the no-CRTP cohort to 6.4 ± 3.4 mm in the CRTP cohort ($p < 0.001$). This reduction was more pronounced in the BH-RT group, where the margin decreased from 6.5 ± 3.6 mm to 5.1 ± 3.5 mm ($p < 0.001$). In the paired AG-RT group analysis (n = 88), the CRTP significantly reduced baseline shift (0.51 ± 0.64 to 0.07 ± 0.25 counts/3 min, $p < 0.001$, Cohen's d = 0.673) and interval SD (1.09 ± 0.58 to 0.81 ± 0.48 sec, $p < 0.001$, Cohen's d = 0.469), while the duty cycle remained unchanged (55.6 ± 11.9% vs. 54.0 ± 12.8%, p = 0.396).

Conclusion: The CRTP significantly increased the BH allocation rate and improved respiratory regularity in the AG-RT group, as demonstrated by reduced baseline shift and interval SD. These improvements were associated with a significant reduction in the ITV margin. These findings suggest that incorporating the CRTP into clinical workflows may enhance the precision of hepatic SBRT.

Disclosure of Interest: N/A

P-103 ATEZOLIZUMAB PLUS BEVACIZUMAB (ATEZO/BEV) IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC) TREATED IN SPAIN ACCORDING TO MACROVASCULAR INVASION (MVI): POST-HOC FINAL ANALYSIS OF THE ATHECA STUDY

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Introduction: Macrovascular invasion (MVI) including portal vein tumor thrombosis represents a high-risk feature associated with poor prognosis in uHCC. We evaluated the safety and efficacy of Atezo/Bev according to MVI baseline status.

Methods: ATHECA was a phase IIIb, single arm, open-label, multicenter study (NCT04732286), that enrolled patients with uHCC who had received no prior systemic therapy. This analysis focuses on the presence of MVI at baseline, as assessed by an external independent review. Patients with vascular invasion of the portal or hepatic veins were eligible for inclusion. Survival outcomes were estimated using the Kaplan-Meier method. Data are based on the final analysis (Clinical cut-off Date 26 April 2024) ; median follow-up of 29.2 months (mo).

Results: Out of 99 evaluable patients in the ITT population, 24 (24.2%) had MVI at baseline. Furthermore, 41.7% (n=10) also had esophageal (EG) varices at screening, of whom 40% (n:4) had been treated, and 50% (n:12) had extrahepatic spread (EHS). In comparison, among patients without MVI, the incidence of EG varices was 29.3% (n:22), of which 31% (n:7) had been treated, and 44% (n:33) presented EHS. The median Overall Survival (mOS) was 11.24 mo (95% CI: 7.72–NE) for patients with MVI, compared to 29,98 mo (95% CI: 21.02 - NE) in patients without MVI. Estimated OS rates in the MVI group were 44.3% (23.2% - 63.6%) at 12-mo, 33,2 % (14.4% - 53.5%) at 24-mo and 22.2% (7.2% - 42.2%) at 36-mo, versus 78.5% (67.3% - 86.2%), 57.3% (44.7% - 68.0%) and 38% (18.8% - 57.1%) respectively in the non-MVI group. The safety profile in patients with MVI was manageable and consistent with that of the overall population. Treatment-related grade 3-4 events occurred in 37.5% (n:9) of patients with MVI and 28% (n:21) of those without MVI. No grade 3-4 or 5 hemorrhagic adverse events were reported in the MVI group whereas in patients without MVI grade 3-4 and 5 occurred in 6.7% (n:5) and 2.7% (n:2) of patients, respectively.

Conclusion: Atezo/Bev demonstrates a favorable benefit-risk profile in patients with uHCC and MVI. Despite the poor prognosis associated with MVI, Atezo/Bev provides clinically meaningful survival and a favorable safety profile in patients with vascular involvement.

Disclosure of Interest: Honoraria

P-104 OPTIMIZING YTTRIUM-90 RADIOEMBOLIZATION IN HEPATOCELLULAR CARCINOMA: EFFICACY, DOSIMETRY, AND RESPONSE ASSESSMENT USING MRECIST AND LI-RADS TRA.

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INTRODUCTION: Transarterial radioembolization with yttrium-90 (TARE-Y90) is an established therapeutic modality for hepatocellular carcinoma (HCC), offering curative and palliative potential. Personalized dosimetry and the advent of systemic immunotherapies have significantly reshaped TARE-Y90's current indications and role. This study aimed to: 1) evaluate TARE-Y90 efficacy and safety in a contemporary, consecutive HCC patient cohort; 2) assess concordance between modified Response Evaluation Criteria in Solid Tumors (mRECIST) and LI-RADS Treatment Response Assessment (LI-RADS TRA) criteria for defining treatment response; and 3) determine the minimal median absorbed dose and estimated absorbed dose to 70% of tumor volume (D70) for radiological response.

METHODS: This retrospective analysis involved a single-center cohort of HCC patients treated with yttrium-90 glass microspheres from January 2017 to June 2025. Data included baseline clinical characteristics, treatment response (according to mRECIST and LI-RADS Radiation TRA criteria at 3 months and thereafter), dosimetric variables, and follow-up. All therapeutic decisions were made within a multidisciplinary tumor board.

RESULTS: The cohort comprised 80 patients (94% male), with a median age of 69.2 years. Most (87%) had liver cirrhosis, primarily alcohol-related (65%), followed by hepatitis C (15%) and MASLD (8%). Liver function, assessed by the ALBI score, showed ALBI-1 in 79% and Child-Pugh A5 in 88%. At TARE-Y90, 39% were Milan criteria within (MILAN-IN), 25% BCLC-B, and 36% BCLC-C. TARE-Y90 was used as first-line therapy in 73.8%. The vascular approach was segmentectomy in 74% and lobectomy in 26%. Median administered activity was 2.39 GBq, with a median absorbed dose of 473 Gy.

Concordance for defining response between mRECIST and LI-RADS Radiation TRA criteria was substantial (kappa = 0.675). In contrast, concordance for defining progression demonstrated almost perfect agreement (Kappa = 0.899)

Thresholds for total absorbed dose and D70 for mRECIST response were 367 Gy and 281.5 Gy at 3 months, and 302 Gy and 104.5 Gy at 6 months, respectively. Median duration of response was 9.33 months [range 2.30-22.30]. Overall survival rates were 78% at 1 year, 52% at 2 years, and 40% at 3 years. Survival at 3 years differed according to BCLC-stage: 60% and 30% in BCLC-B and BCLC-C patients respectively. Baseline ALBI score was significantly associated with survival (HR 3.709, p=0.018), as well as tumor dose (HR 0.997, p=0.013) and bilobar disease (HR 2.364, p=0.042).

CONCLUSION: TARE-Y90 demonstrates sustained efficacy and safety in HCC, validating specific dosimetric thresholds for radiological response crucial for personalized therapy. While mRECIST and LI-RADS TRA exhibit substantial concordance for response, their near-perfect agreement for progression assessment highlights their distinct clinical utility. The baseline ALBI score is a significant prognosticator, emphasizing the critical role of liver function. These findings reinforce TARE-Y90's value and inform optimization strategies in evolving HCC management.

Disclosure of Interest: Honoraria

P-105 POST-PROGRESSION OUTCOMES AND PREDICTORS OF SURVIVAL IN ADVANCED HEPATOCELLULAR CARCINOMA TREATED WITH FIRST-LINE IMMUNE CHECKPOINT INHIBITORS

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Introduction: The optimal therapeutic strategy following progression on first-line (1L) immune checkpoint inhibitors (ICIs)-based regimens in advanced hepatocellular carcinoma (HCC) remain poorly defined. This study aimed to evaluate long-term outcomes of patients treated with 1L ICIs and to identify factors associated with post-progression survival (PPS).

Methods: We retrospectively analysed patients with advanced HCC who received and subsequently progressed on 1L ICI-based therapy at IRCCS Humanitas Research Hospital between 2016 and 2025. Overall survival (OS), progression-free survival (PFS), and PPS were estimated using the Kaplan–Meier method. PPS predictors were identified using univariable and multivariable Cox proportional hazards models, with statistical significance set at p<0.05.

Results: The analysis included 122 patients (median age 71 years; 81% male; 76% BCLC stage C; 26% with portal vein thrombosis (PVT)). 1L regimens comprised combinations of anti-PD-1 and anti-CTLA-4 (28.7%), anti-PD-1 and anti-VEGF (31.2%), anti-PD-1 and tyrosin-kinase inhibitor (TKI) (27.1%) or anti-PD-1 monotherapy (9.8%). Median OS and PFS from initiation of 1L therapy were 13.6 (95%CI 5.9-38.2) and 5.8 months (95%CI 1.8-11.1). The 4-year OS was 20.6% (95%CI: 13.2-29.1) and was strongly influenced by best overall response (BOR; CR 67%, PR 40%, SD 14.0%, PD 5.0%).

Among the 95 patients alive post-progression, 57 (60%) received best supportive care (BSC) while 38 (40%) underwent 2L treatment, predominantly TKIs (76%), followed by ICIs (10%) and other treatments (14%). Median PPS was 7.2 months (95%CI 2.2-19.6), significantly longer in patients receiving 2L therapy vs BSC (18.6 vs 3.3 months; HR 0.26, 95%CI 0.16-0.43, p <0.001), with no statistical difference between TKIs and ICIs (HR 0.96, 95%CI, 0.28-3.31, p=0.95). In multivariate Cox regression stratified by BCLC stage, ECOG PS<2 (HR 0.50, 95%CI 0.28-0.89, p=0.018) and absence of PVT (HR 0.44, 95%CI 0.23-0.83; p=0.012) were independently associated with improved PPS, while PD as BOR to 1L was a strong predictor of worse outcomes (HR 3.66, 95%CI 1.77-7.55, p<0.001). A time-dependent analysis suggested a trend toward reduced mortality risk with post-progression treatment, although did not reach statistical significance (TKI, HR 0.95, 95%CI 0.90-1.00, p=0.09).

Conclusions: 1L ICIs-based regimens provided durable long-term survival in patients with advanced HCC. Notably, outcomes after progression were strongly influenced by the initial best response to ICIs, supporting its role as a key factor in tailoring post-progression management.

Disclosure of Interest: N/A

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P-106 YOUNGER AGE AND CLINICAL OUTCOMES IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC) TREATED WITH CAMRELIZUMAB + RIVOCERANIB VS SORAFENIB (CARES-310)

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Background: Cancer incidence in adults under 50 is rising globally, particularly in gastrointestinal cancers (Siegel RL et al. Cancer J Clin 2025). Early-onset cancer in young adults under age 40 has become a universal research priority (Ben-Aharon I, et al. Nat Rev Cancer 2025 and Danielson L, et al. Trends Cancer 2024). The global uHCC trial, CARES-310 (NCT03764293) showed overall survival (OS) of camrelizumab + rivoceranib compared to sorafenib (mOS, 23.8 months [mo], vs 15.2 mo, hazard ratio [HR] 0.64, one-sided p<0.0001 with median age 58.0 years (n=272) and 56.0 years (n=271), respectively.

Methods: We performed a post-hoc analysis of the CARES-310 study evaluating younger age survival outcomes (intention-to-treat) and safety assessed by age groups of <50 years and ≥50 years where mOS and median progressive free survival (mPFS) were estimated using the Kaplan-Meier method with confidence intervals (CI) calculated using Brookmeyer and Crowley method. Macrovascular invasion and/or extrahepatic metastasis, geographical region, and baseline AFP stratified hazard ratios and the corresponding 95% CIs. The one-sided p-value was calculated based on log-rank test. Outcome trends were evaluated in those <40 years.

Results: In the ≥50 group, mOS for cam + rivo (n=194) was 23.9 mo (95% CI, 21.3, 30.3) compared to sor (n=192) 15.2 mo (95% CI, 13.0, 18.9) [HR 0.6 (0.47, 0.77)], p<0.0001. In the <50 group, the mOS for cam + rivo (n=78) was 21.5 mo (95% CI, 16.1, 38.6) compared to sor (n=79) 15.2 mo (95% CI, 11.1, 23.5) [HR 0.7 (0.47, 1.06)], p=0.445. In the <40 group, the limited patient numbers hinder model assumption and indicate that study results are not robust. Inclusion of the <40 group was to appreciate the number of young patients treated for uHCC in this age group. In the <40 group, the median age was 34 years (range 23-39) for cam + rivo vs median 36 years (range 23-39) for sor. In the<40 group, mOS for cam + rivo (n=23), was 24.2 mo (95% CI, 15.2, NE) compared to sor (n=29) 15.2 mo (95% CI, 9.2, NE). Of note, the <40 group is not consistent with study results even though cam + rivo had a longer mOS than sor. Similar clinical benefits for mPFS were observed for cam + rivo in the age subgroups. In the ≥50, mPFS for cam + rivo was 6.2 mo (95% CI, 5.5, 9.2) compared to sor 3.7 mo (95% CI, 3.5, 4.6) [HR 0.56 (0.45, 0.72)], p<0.0001. In the <50 group, mPFS for cam + rivo was 5.5 mo (95% CI, 3.7, 6.3) compared to sor 2.7 mo (95% CI, 1.9, 3.7) [HR 0.53 (0.37, 0.77)], p=0.0004. To appreciate the younger age group, in the <40 group, mPFS for cam + rivo was 5.5 mo (95% CI, 1.8, 7.4) compared to sor 2.2 mo (95% CI, 1.9, 3.7). The analysis demonstrates a treatment effect in the overall population, with the subgroup age analyses explored for consistency of treatment effect across age subgroups. In the safety population, grade 3 or 4 treatment related adverse events (TRAEs) occurring ≥5% was higher in the ≥50 vs <50 group for cam + rivo was hypertension 40.7% vs 32.1%, increased AST 19.6% vs 12.8%, increased ALT 14.9% vs 11.5%, palmar-plantar erythrodysaesthesia syndrome (PPES) 13.9% vs 7.7%, decreased platelet count 13.4% vs 9%, increased GGT and blood bilirubin 10.8% vs 10.3% and 3.8%, respectively. In the <40 group, select grade 3 or 4 TRAEs for cam + rivo and sor were hypertension 17.4% vs 13.8% and PPES 13.0% and 13.8%, respectively.

Conclusion: These results suggest meaningful clinical benefit of cam + rivo as first-line therapy for patients with uHCC who have not received prior systemic therapy compared to sor regardless of age.

Disclosure of Interest: N/A

P-107 REAL-LIFE SAFETY AND EFFICACY OF IMMUNOTHERAPY FOR ADVANCED BILIARY TRACT CARCINOMA IN A NATIONAL MULTICENTRIC COHORT

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Background: Biliary tract cancer (BTC) is a heterogeneous group of malignancies, with most cases diagnosed at advanced stages. Recent phase III trials have demonstrated that adding immune checkpoint inhibitors (ICIs) to gemcitabine and cisplatin improves survival, leading to their incorporation into first-line treatment. However, real-world data remain scarce.

Methods: We conducted a multicenter observational study, including patients with advanced BTC treated with ICI-based regimens and chemotherapy. Clinical, demographic, and treatment data were retrospectively collected. Overall survival (OS) was estimated using the Kaplan-Meier method, and prognostic factors were assessed using multivariate Cox regression. A historical control cohort including patients who did not receive ICI was described and analyzed using propensity score matching.

Results: A total of 152 patients were included in the ICI cohort, with a median age of 66.5 years; 57.9% were male, and 68.4% presented with metastatic disease. The most frequent primary sites were intrahepatic cholangiocarcinoma (52.6%) and gallbladder carcinoma (23.7%). Durvalumab plus gemcitabine/cisplatin was the most common regimen (95.4%). After a median follow-up of 8.3 months, 84 patients (55.2%) had died, and the median OS was 15.5 months (95% CI: 12.3–21.5). Maintenance therapy was administered to 37.5% of patients, predominantly as ICI monotherapy. Multivariate analysis identified ECOG performance status >0 (HR 3.91, p=0.026), neutrophil-to-lymphocyte ratio ≥3 (HR 1.98,

p=0.017), and vascular invasion (HR 1.83, p=0.006) as independent negative prognostic factors. Safety was favorable, with only 10 cases of grade ≥2 ICI-related adverse events. The historical control group showed a median OS of 14.5 months. In the propensity score–matching analysis, the ICI cohort treatment improved survival compared with the historical cohort (HR 0.61; 95% CI, 0.39–0.93; p = 0.025).

Conclusions: This real-world cohort demonstrates that ICI combined with chemotherapy in advanced BTC yields survival outcomes comparable to those observed in pivotal trials, even in a more diverse population beyond trial eligibility. Some patients may experience long-term benefits, emphasizing the need for biomarkers and improved access to treatment.

Disclosure of Interest: Research/Education grant

P-108 COMPARATIVE SURVIVAL OUTCOMES OF SBRT AND TARE IN INTERMEDIATE-STAGE HEPATOCELLULAR CARCINOMA: A POPULATION-BASED STUDY

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Background: For patients with intermediate-stage hepatocellular carcinoma (HCC), both stereotactic body radiation therapy (SBRT) and transarterial radioembolization (TARE) are commonly utilized locoregional therapies. Comparative population-based data evaluating survival outcomes between these modalities remain limited.

Methods: We conducted a retrospective analysis of patients with non-metastatic T2-T3 HCC, approximating intermediate-stage HCC without tumor in the vein, who underwent SBRT or TARE were identified from the SEER Reseasrch Plus database. Baseline demographic, socioeconomic, tumor, and treatment characteristics were compared between groups. Overall survival (OS) was evaluated using multivariable Cox proportional hazards regression adjusting for age, tumor size, sex, race, income, residence, AFP status, systemic therapy, ablation, resection, and transplantation.

Results: A total of 507 patients were included, comprising 286 treated with SBRT and 221 treated with TARE. Baseline characteristics were generally balanced between treatment groups. Patients undergoing TARE had a higher proportion of T3 disease (41% vs. 31%, p=0.019), whereas resection was more common among SBRT-treated patients (4.5% vs. 1.4%, p=0.042). Median tumor size and age were similar between groups. On multivariable analysis, treatment modality was not associated with OS (TARE vs. SBRT: HR 1.01, 95% CI 0.80–1.27, p>0.9). Factors associated with worse survival included larger tumor size (HR 1.09 per 10-mm increase, 95% CI 1.05–1.13, p<0.001), female sex (HR 1.30, 95% CI 1.01–1.69, p=0.045), positive AFP (HR 1.77, 95% CI 1.33–2.36, p<0.001). Receipt of systemic therapy (HR 0.70, 95% CI 0.53–0.92, p=0.011) and liver transplantation (HR 0.20, 95% CI 0.09–0.46, p<0.001) were independently associated with improved survival.

Conclusions: In this population-based cohort of patients with intermediate-stage HCC, SBRT and TARE were associated with comparable overall survival after adjustment for clinical and demographic factors. Larger tumor size and positive AFP were independently associated with worse survival, whereas systemic therapy and liver transplantation were associated with improved survival but not by the choice of locoregional treatment modality. These findings suggest that SBRT and TARE are associated with comparable survival among patients with intermediate-stage HCC (1-4).

Disclosure of Interest: Research/Education grant

References: 1.Salem R, Lewandowski RJ, Mulcahy MF, et al.Gastroenterology. 2010;138(1):52-64, 2. Kulik LM, Carr BI, Mulcahy MF, et al. Hepatology. 2008;47(1):71-81, 3. Bujold A, Massey CA, Kim JJ, et al. Journal of Clinical Oncology. 2013;31(13):1631-1639, 4. Wahl DR, Stenmark MH, Tao Y, et al. Journal of Clinical Oncology. 2016;34(5):452-459.

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Images:

Table 1. Baseline Characteristics

Characteristic	SBRT N = 286[1]	TARE N = 221[1]	p-value[2]
Age, mean (SD)	69 (10)	69 (9)	0.7
Tumor size (mm), median (Q1, Q3)	41 (28, 63)	45 (30, 69)	0.08
Sex			0.08
Male	193 (67%)	165 (75%)	
Female	93 (33%)	56 (25%)	
Race			0.8
White	149 (52%)	116 (52%)	
Black	30 (10%)	23 (10%)	
Asian/Pacific Islander	29 (10%)	29 (13%)	
American Indian/Alaskan Native	7 (2.4%)	7 (3.2%)	
Hispanic	70 (24%)	45 (20%)	
Unknown	1 (0.3%)	1 (0.5%)	
Income			0.5
≥120,000	54 (19%)	40 (18%)	
100,000 - <120,000	53 (19%)	42 (19%)	
75,000 - <100,000	108 (38%)	71 (32%)	
50,000 - <75,000	65 (23%)	60 (27%)	
<50,000	6 (2.1%)	8 (3.6%)	
Rural-Urban Residence			0.4
Urban >1 million	189 (66%)	130 (59%)	
Urban >250,000	55 (19%)	49 (22%)	
Urban <250,000	18 (6.3%)	13 (5.9%)	
Rural adjacent to Urban	14 (4.9%)	14 (6.4%)	
Rural not adjacent to Urban	9 (3.2%)	13 (5.9%)	
T stage			0.02
T2	198 (69%)	130 (59%)	
T3	88 (31%)	91 (41%)	
AFP Pretreatment			0.8
Negative/Borderline	81 (28%)	61 (28%)	
Positive	156 (55%)	126 (57%)	
Unknown	49 (17%)	34 (15%)	
Ablation			>0.9
No	261 (91%)	201 (91%)	
Yes	25 (8.7%)	20 (9.0%)	
Resection			0.04
No	273 (95%)	218 (99%)	
Yes	13 (4.5%)	3 (1.4%)	
Systemic			0.6
No	208 (73%)	165 (75%)	
Yes	78 (27%)	56 (25%)	
Transplant			0.7
No	268 (94%)	209 (95%)	
Yes	18 (6.3%)	12 (5.4%)	

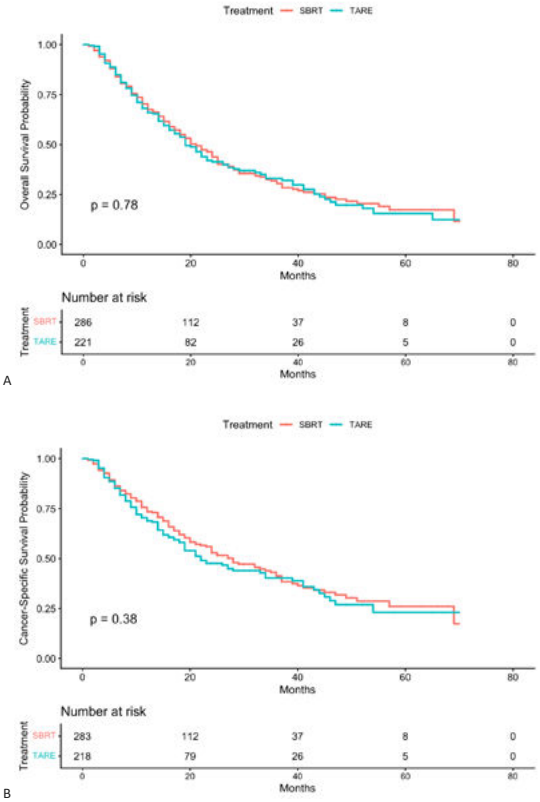
[1]Mean (SD); Median (Q1, Q3); n (%)

Table 2. Multivariable Cox Regression

Characteristic	HR	95% CI	p-value
Treatment modality (SBRT VS TARE)	1.01	0.80, 1.27	>0.9
Age (per year increase)	1.01	1.00, 1.02	0.09
Tumor size (per 10 mm increase)	1.09	1.05, 1.13	<0.001
Female Sex	1.30	1.01, 1.69	0.045
Positive AFP pre-treatment	1.77	1.33, 2.36	<0.001
Ablation	0.97	0.63, 1.47	0.9
Resection	0.63	0.32, 1.23	0.2
Systemic therapy	0.70	0.53, 0.92	0.01
Transplant	0.20	0.09, 0.46	<0.001

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

Figure 1. Overall survival (A) and Cancer Specific Survival (B) among patients with intermediate HCC who received SBRT vs TARE.



P-109 COMPARATIVE SURVIVAL OUTCOMES OF STEREOTACTIC BODY RADIATION THERAPY VERSUS TRANSARTERIAL RADIOEMBOLIZATION IN LOCALLY ADVANCED HEPATOCELLULAR CARCINOMA: A SEER RESEARCH PLUS ANALYSIS, 2016–2023.

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Background: Locally advanced hepatocellular carcinoma (HCC) is associated with poor prognosis and limited curative treatment options. Stereotactic body radiation therapy (SBRT) and transarterial radioembolization (TARE) are both used as liver-directed therapies, but comparative population-level survival data remain limited. This study compared overall survival among patients with locally advanced HCC treated with SBRT versus TARE using the SEER Research Plus database.

Methods: Patients diagnosed with locally advanced HCC between 2016 to 2023 in the SEER Research Plus database were identified. Patient with locally advanced HCC (T3b or T4) without nodal or distant metastasis (N0, M0) and received either SBRT or TARE were included. Baseline demographic, tumor size and pretreatment alpha-fetoprotein positivity (AFP) were compared. Multivariable Cox proportional hazards regression was performed adjusting for age, sex, tumor size, pretreatment AFP, and systemic therapy use. Overall survival was evaluated using Kaplan–Meier analysis with log-rank testing. Overall survival was evaluated using Kaplan–Meier analysis with log-rank testing.

Results: A total of 702 patients were included, of whom 174 received SBRT and 528 received TARE. Median age and sex distribution were similar between the groups. Median tumor size was larger in the SBRT group, 78 mm versus 70 mm, although this difference did not reach statistical significance (p=0.07). There was higher prevalence of White patients in the TARE group and higher prevalence of Asian/Pacific Islander patients in the SBRT group. Pretreatment AFP positivity was more common in the TARE group (72.9% versus 70.7%, p=0.004) and systemic therapy was more frequently used among patients treated with SBRT (31% versus 22%, p=0.01). Median overall survival was 9 (4, 16) months in the SBRT group compared with 12 (6, 20) months in the TARE group. Kaplan–Meier survival analysis demonstrated significantly improved overall survival among patients treated with TARE compared with SBRT, with a log-rank p-value of 0.0002. On multivariable Cox regression, TARE was independently associated with improved overall survival compared with SBR (HR 0.59,

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95% CI 0.36–0.96, p=0.04). Increasing age was not significantly associated with mortality (HR 1.02, 95% CI 1.00–1.05, p=0.11). Female sex was not associated with a statistically significant survival difference (HR 1.26, 95% CI 0.79–1.99, p=0.34). Larger tumor size was associated with worse survival (HR 1.01 per 10-mm increase, 95% CI 0.99–1.01, p=0.18), although this was not statistically significant. Pretreatment AFP positivity was strongly associated with worse survival (HR 2.60, 95% CI 1.69–3.99, p<0.001). Systemic therapy use showed a trend toward worse survival (HR 1.94, 95% CI 1.20–3.15, p=0.07).

Conclusion: In this SEER Research Plus analysis of patients with locally advanced T3b/T4 HCC, TARE was associated with significantly longer overall survival compared with SBRT. This association persisted after multivariable adjustment, with TARE demonstrating a 41% lower hazard of death relative to SBRT. Pretreatment AFP positivity was also independently associated with worse survival. These findings suggest that TARE may provide a survival advantage over SBRT in selected patients with locally advanced HCC, although treatment selection bias and limitations inherent to retrospective registry-based analyses should be considered. Further prospective comparative studies are warranted to better define optimal liver-directed treatment strategies for this high-risk population.

Disclosure of Interest: Research/Education grant

Images:

Table 1. Baseline characteristics

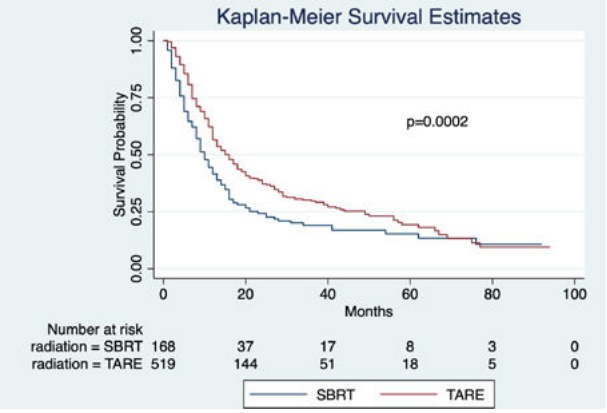
Characteristic	SBRT N = 174	TARE N = 528	p-value
Age, mean (SD)	66 (59, 74)	66 (61, 71)	0.39
Tumor size (mm), median (Q1, Q3)	78 (52, 115)	70 (47, 101)	0.07
Sex			0.55
Male	135 (77.6%)	421 (79.7%)	
Female	39 (22.4%)	107 (20.3%)	
Race			**0.005**
White	77 (44.3%)	298 (56.4%)	
Black	28 (16.1%)	63 (11.9%)	
Asian/Pacific Islander	42 (24.1%)	70 (13.3%)	
American Indian/Alaskan Native	1 (0.6%)	7 (1.3%)	
Hispanic	25 (14.4%)	89 (16.9%)	
Income			0.55
≥120,000	28 (16.1%)	72 (13.6%)	
100,000 - <120,000	38 (22.3%)	104 (19.7%)	
75,000 - <100,000	53 (30.5%)	191 (36.2%)	
50,000 - <75,000	46 (26.4%)	145 (27.5%)	
<50,000	8 (4.6%)	14 (2.7%)	
Rural-Urban Residence			0.73
Urban >1 million	103 (59.2%)	303 (57.4%)	
Urban >250,000	38 (21.8%)	130 (24.6%)	
Urban <250,000	9 (5.2%)	38 (7.2%)	
Rural adjacent to Urban	15 (8.6%)	35 (6.6%)	
Rural not adjacent to Urban	9 (5.2%)	21 (3.9%)	
Positive AFP Pretreatment	123 (70.7%)	385 (72.9%)	**0.004**
Systemic therapy	54 (31%)	114 (22%)	**0.01**
Survival (months)	9 (4, 16)	12 (6, 20)	0.23
Death	146 (83.9)	372 (70.5)	**<0.001**
Cancer-related death	159 (91.4)	474 (89.8)	0.66

Table 2. Multivariable Cox Regression

Characteristic	HR	95% CI	p-value
TARE (vs SBRT)	0.59	0.36, 0.96	0.04
Age (per year increase)	1.02	1.00, 1.05	0.11
Female	1.26	0.79, 1.99	0.34
Tumor size (per 10 mm increase)	1.01	0.99, 1.01	0.18
Positive AFP pre-treatment	2.60	1.69, 3.99	<0.001
Systemic therapy	1.94	1.20, 3.15	0.07

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

Figure 1. Overall survival among patients with locally advanced stage HCC by treatment group.



P-110 SUPPORTIVE CARE NEEDS, NAVIGATION INTERVENTIONS, AND PATIENT-REPORTED WELLBEING AMONG PATIENTS WITH HEPATOBILIARY CANCERS IN A STRUCTURED NAVIGATION PROGRAMME IN INDIA

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Background: Patients with hepatocellular carcinoma (HCC) and biliary tract cancers (BTC) frequently present with advanced disease and poor prognosis, resulting in substantial educational, financial, psychosocial, and treatment-related supportive care needs. Patient advocacy and navigation programs play an important role in addressing these unmet needs by facilitating access to information, care coordination, and supportive services. However, dedicated advocacy initiatives for hepatobiliary cancers remain limited worldwide. We evaluated the supportive care needs, navigation interventions, and baseline patient-reported wellbeing of patients with hepatobiliary cancers enrolled in a structured patient navigation program in India.

Methods: We retrospectively analyzed patients with HCC, gallbladder cancer, and cholangiocarcinoma enrolled in the Jarurat Care Foundation patient navigation program between May 2024 and July 2026. Patients entered the program through clinician, hospital, and caregiver referrals, or social media outreach. Following enrolment, supportive care needs were identified, and individualized support levers were delivered. Support levers are defined as discrete navigation interventions including specialist second opinions, financial guidance, nutrition planning, emotional support, clinical trial matching, and other services. Beginning in May 2026, baseline wellbeing was assessed using validated measures of anxiety/depression (PHQ-4), physical and emotional quality of life, financial toxicity, and patient activation as part of routine navigation. Demographic, clinical, navigation, and wellbeing data were extracted from program records. Descriptive statistics were used to evaluate supportive care needs, support levers delivered, and baseline patient-reported wellbeing.

Results: A total of 188 patients with hepatobiliary cancers were included (Mean age 51.5 years [SD, 11.8; 95% CI, 49.7–53.2]; 47.9% were male), comprising 108 (57.4%) with HCC, 71 (37.8%) with gallbladder cancer, and 9 (4.8%) with bile duct cancers. Patients most frequently requested financial assistance (144 requests), nutritional support (51), emotional support (44), accommodation (21), caregiver support (20), and treatment information (13). In response, 232 individualized support levers were delivered; educational support was the most common intervention (71 levers), followed by financial guidance (55), nutritional support (39), treatment navigation (38), and emotional support (29). Among patients who underwent baseline wellbeing assessment since May 2026, completion varied across instruments because assessments were administered over multiple follow-up calls. Median baseline scores were 2/12 for PHQ-4 (n = 105), 6/10 for physical quality of life (n = 131), 7/10 for emotional quality of life (n = 127), 5/10 for financial toxicity (n = 111), and 3/5 for patient activation (n = 111), demonstrating measurable psychosocial and financial burden at enrolment. Among patients with available longitudinal follow-up, patient-reported wellbeing remained generally stable during navigation support.

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Conclusion: Patients with hepatobiliary cancers have supportive care needs that extend beyond medical treatment. This study demonstrates that a structured patient navigation model is feasible for patients with hepatobiliary cancers and provides a practical approach for delivering individualized supportive care in resource-constrained settings.

Disclosure of Interest: N/A

P-111 CLINICAL OUTCOMES AND DOWNSTAGING POTENTIAL OF IMMUNE CHECKPOINT INHIBITORS IN LARGE HEPATOCELLULAR CARCINOMA: A REAL-WORLD IRISH EXPERIENCE

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Introduction: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality. Immune checkpoint inhibitors (ICIs) have transformed treatment of advanced disease, with atezolizumab plus bevacizumab achieving median overall survival (OS) of 19.2 months in IMbrave150, and the STRIDE regimen (tremelimumab plus durvalumab) achieving median OS of 16.4 versus 13.8 months with sorafenib in HIMALAYA (HR 0.78; p=0.0035) (2,3). Although HCC screening is recommended for cirrhotic patients, some present with large tumours not amenable to surgical or locoregional therapies (4). Limited data exist on outcomes for such patients in the ICI era. Atezolizumab with bevacizumab is the only funded ICI regimen for HCC in Ireland. Here we describe outcomes from an Irish cohort with large HCC (≥15 cm) treated with ICI-based regimens.

Methods: We reviewed a prospectively maintained database at St. Vincent's University Hospital to identify patients with HCC who received ICI-based therapy between January 2023 and January 2026. Clinical, demographic, histopathological, and outcome data were collected. Patients were categorised by dominant lesion size: <15 cm, ≥15 cm, and >20 cm. Overall survival and progression-free survival were estimated using Kaplan–Meier methods and compared using log-rank tests. Results are reported with median survival, hazard ratios (HR), and 95% confidence intervals (CI).

Results: From our cohort of >500 patients, N=63 received immune checkpoint inhibitors: 43 received atezolizumab/bevacizumab (68%), 12 (19%) received durvalumab/tremelimumab, and 8 (13%) received atezolizumab monotherapy. Sixteen patients were female (25%) and 47 were male (75%), with a median age of 67 years. Aetiology included viral hepatitis (N=16), alcoholic liver disease (N=12), and MASLD (N=14). Child–Pugh class was A in 46 patients (73%) and B in 17 (27%), with median ALBI grade of 2. Tumour size was <10 cm in N=41 patients, 10–15 cm in N=10, 15-20 cm in N=8, and >20 cm in N=4. The median AFP level at time of starting ICI was 173 ng/mL. N=25 patients had received prior locoregional therapy, and 8 received second-line tyrosine kinase inhibitor (TKI) therapy. Treatment discontinuation occurred in 36 (57%) patients (19 due to disease progression and 17 due to toxicity).

Median overall survival (OS) was 21 months for tumours <15 cm and 6 months for tumours ≥15 cm (log-rank P = 0.049; HR 0.34, 95% CI 0.12–0.99). Median progression-free survival (PFS) was 6 months for tumours <15 cm and 4 months for tumours ≥15 cm (log-rank P = 0.152). Despite shorter survival in patients with larger tumours, immunotherapy demonstrated clinical activity, including in patients with tumours ≥15 and >20cm. One quarter of patients with HCCs >15cm had disease stability or downstaging on ICI, and were eligible to receive subsequent locoregional therapies

Conclusion: HCC remains a challenging disease, whereby early diagnosis offers the best outcomes (4). Large tumours are particularly complex, with higher symptom burden, impaired liver function, and lower response rates. Immunotherapy plays a key role and demonstrates activity even in patients with large tumours, providing important guidance for clinical management. Increased awareness and regular surveillance for patients with cirrhosis is critical to facilitating early detection. Careful patient selection and multidisciplinary team input are key to enhancing outcomes for patients presenting with large, advanced HCC.

Disclosure of Interest: N/A

P-112 THE ROLE OF MODERN RADIOTHERAPY TECHNIQUES FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA: AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: The practice of radiotherapy (RT) is worldwide transitioning from 3-dimensional conformal RT to modern RT techniques for hepatocellular carcinoma (HCC); however, evidence remains insufficient to determine whether these advanced RT techniques improve treatment outcomes. Therefore, we updated the treatment outcomes of modern RT techniques, including intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), and proton beam therapy (PBT), for patients with liver-confined HCC.

Methods: A systematic review of IMRT, SBRT, and PBT was conducted individually following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to April 2025.

Results: We included 23 IMRT studies comprising 1,479 patients, 22 PBT studies comprising 1,968 patients, and 35 SBRT studies comprising 3,208 patients. When the total doses were converted to the biologically equivalent doses (BED, Gy10), the median BED (mBED) values ranged 48–180 Gy10 (median, 86) for SBRT, 69–110 GyE10 (median, 101) for PBT, and 55–75 Gy10 (median, 67) for IMRT. The pooled 3-year local progression-free survival rates were 64% (95% confidence interval [CI], 45–81%) for IMRT, 89% (95% CI, 86–91%) for PBT, and 86% (95% CI, 82–90%) for SBRT, respectively (p = 0.0076). The pooled 3-year overall survival rates were 19% (95% CI, 11–29%) for IMRT, 55% (95% CI, 48–62%) for PBT, and 65% (95% CI, 57–72%) for SBRT, respectively (p <0.0001). In addition, the pooled survival rates differed significantly according to the mBED using three cutoff points of 65 Gy10, 80 Gy10, and 100 Gy10. The incidence of severe toxicities after modern RT techniques was low.

Conclusions: Modern RT techniques provide remarkable treatment outcomes in patients with HCC. The efficacies of SBRT and PBT were similar and superior to those of IMRT. However, this difference should be interpreted cautiously, as a minimal ablative dose between 65 and 100 Gy10 is required to achieve optimal efficacy for HCC, regardless of the RT techniques.

Disclosure of Interest: N/A

P-113 BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA OUTSIDE CLINICAL TRIALS: CONSENSUS RECOMMENDATIONS

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Background: The combination of atezolizumab and bevacizumab has become the standard first-line systemic therapy for advanced hepatocellular carcinoma (HCC). However, pivotal clinical trials enrolled highly selected populations, excluding patients with comorbidities or clinical conditions frequently encountered in real-world practice that remain areas of uncertainty with limited guidance. The aim of this study is to develop a literature review and consensus recommendations on the use of bevacizumab-containing regimens in special populations with advanced HCC, particularly patients underrepresented or excluded from randomized clinical trials.

Methods: This expert consensus was developed using a structured modified Delphi methodology. A multidisciplinary panel of 10 Brazilian hepatologists and clinical oncologists from different institutions formulated clinical questions using the PICO framework across 10 predefined domains related to bevacizumab safety and use. A PRISMA-informed literature review was conducted, prioritizing clinical guidelines, randomized trials, meta-analyses, and observational studies. Evidence was appraised using the Oxford Centre for Evidence-Based Medicine

(OCEBM) Levels of Evidence. Recommendations were drafted, reviewed, and voted upon through Delphi rounds (consensus=100% concordance; major agreement>80% concordance). Recommendations were graded as strong or weak based on the strength of the evidence.

Results: Consensus recommendations were established for all predefined PICO domains, including anticoagulation, antiplatelet therapy, coagulopathies, liver and renal dysfunction, thrombocytopenia, cardiovascular and cerebrovascular disease, age and body weight extremes, procedural considerations, and digestive bleeding risk (Table). The panel emphasized individualized, multidisciplinary decision-making, careful patient selection, and proactive risk mitigation strategies. Levels of evidence ranged from moderate to low, reflecting the limited representation of these populations in clinical trials.

Conclusions: This expert consensus provides practical, evidence-informed guidance on the use of bevacizumab in special populations with advanced HCC. By addressing common real-world clinical scenarios not adequately covered by existing guidelines, these recommendations aim to promote consistent, safe, and individualized application of bevacizumab-based therapy in routine clinical practice.

Disclosure of Interest: Honoraria

Posters

Image:

Table 1: Clinical contexts, level of evidence available for each context, recommendations based on the level of evidence, and concordance between consensus participants

Subgroups	Level of evidence	Recommendation	Concordance
Anticoagulants	3	weak	Consensus
Hereditary coagulopathies	4	weak	Major agreement
Compensated liver alteration	3	weak	Consensus
Renal impairment or dialysis	4	weak	Consensus
Thrombocytopenia	4	weak	Consensus
Cerebrovascular disease	5	weak	Consensus
Cardiopathies	3	weak	Consensus
Elderly	2	moderate	Major agrément
Obesity	2	moderate	Major agreement
Peri-procedures use (major and minor)	3	moderate	Consensus
Risk of digestive bleeding due to portal hypertension	2	moderate	Consensus

P-114 UNTREATED HBV-INFECTED ADVANCED FIBROSIS, IF HBV-DNA IS DETECTABLE, HAS HCC RISK COMPARABLE TO ANTIVIRALS-TREATED CIRRHOSIS

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Background and Aims: The European Association for the Study of the Liver guideline on hepatitis B virus (HBV) recommends antiviral therapy (AVT) for advanced fibrosis (AdvF) with detectable HBV-DNA, which is a routine AVT criterion applied for liver cirrhosis (LC). Here, we compared hepatocellular carcinoma (HCC) risk between patients with untreated viremic AdvF vs. AVT-treated LC, with external validation.

Methods: We assessed HCC risk for South Korean patients with untreated viremic AdvF not fulfilling conventional AVT criteria (n=302), compared to AVT-treated LC ones (n=1,694). All belonged to Child-Pugh A. LC was defined using gross finding on imaging study or liver stiffness (LS)>11kPa. AdvF was as LS 8~11 kPa without gross LC finding. Multivariable Cox-regressions and propensity-score (PS) matching (2:1) were used for comparison.

Results: In multivariable analyses, untreated viremic AdvF patients demonstrated HCC risk comparable to AVT-treated LC (adjusted hazard ratios [aHRs] 0.66~0.70, all P>0.05), irrespective of LS adjustment. Male, higher FIB-4, lower albumin, and higher bilirubin were independently associated with HCC risk. Likewise, in the Hong Kong cohort, untreated viremic AdvF patients (n=103) showed HCC risk comparable to AVT-treated LC (n=199) (aHR 0.94~0.97, all P>0.05), irrespective of LS adjustment. Male and lower albumin were independently associated with HCC risk. PS-matching confirmed these results in both cohorts (all P>0.05).

Conclusions: Across two independent East-Asian cohorts, untreated viremic AdvF patients demonstrated HCC risk comparable to AVT-treated LC. So, AVT should be considered for viremic AdvF, although conventional AVT criteria are not met. Further prospective studies are required.

Disclosure of Interest: N/A

P-115 COMPARATIVE EFFECTIVENESS OF ABLATIVE THERAPIES FOR HEPATOCELLULAR CARCINOMA: A SINGLE-CENTER ANALYSIS OF RADIOFREQUENCY, MICROWAVE, AND ETHANOL INJECTION TECHNIQUES

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Introduction: Hepatocellular carcinoma (HCC) is the third most common malignancy worldwide and the second leading cause of cancer-related mortality. This study aimed to compare the efficacy of microwave ablation (MWA), radiofrequency ablation (RFA), and percutaneous ethanol injection (PEI), used either as monotherapies or in combination (RFA+PEI and MWA+PEI), in the management of solitary HCC lesions ≤5 cm. Outcomes assessed included survival, recurrence, complications, and cost-effectiveness.

Methods: This retrospective–prospective study included 250 patients with single HCC lesions ≤5 cm, recruited from the National Liver Institute, Menoufia University. Patients were equally allocated into five groups (n=50 each): RFA, MWA, PEI, RFA+PEI, and MWA+PEI. Treatment indications and contraindications were determined according to the Barcelona Clinic Liver Cancer (BCLC) staging system.

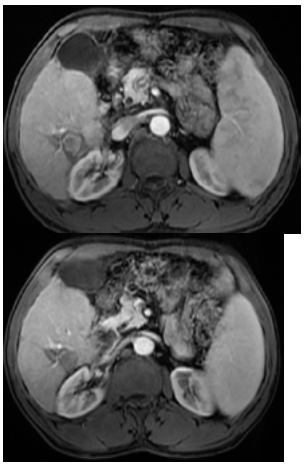
Results: Three patients received antiviral therapy 1–2 years following ablation. The mean procedural costs were 17,340±700, 1,200±900, 1,140±300, 17,500±0.0, and 1,500±0.0 EGP for groups 1 through 5, respectively. Early progression rates were 12%, 8%, 18%, 4%, and 2% across the groups. At 36 months of follow-up, all patients had survived at least six months post-ablation. Mean overall survival durations were 2.44±1.17, 2.59±1.02, 2.69±0.99, 2.91±1.04, and 2.91±1.04 years, respectively. Reported complications were predominantly minor, including pain, nausea, and low-grade fever. One patient developed an abscess and biloma following MWA, another experienced minimal pleural effusion, and two patients in the combination therapy groups developed abdominal wall hematomas.

Conclusions: RFA, MWA, and PEI—whether applied individually or in combination—are effective treatment options for early-stage HCC. The combination of MWA and PEI yielded the most favorable outcomes, with lower recurrence rates and prolonged progression-free survival.

Disclosure of Interest: N/A

Image:

Figure 1. A. TriphasicMRI abdomen (arterial phase) axial cuts is revealing right lobe segment VI focal lesion with homogeneous enhancement, beforeRFA. B. Same lesion (arterial phase) axial cuts one month after RFA.



P-116 THE COMPARISON OF FIRST LINE CHEMOTHERAPY AND PD-1 INHIBITOR COMBINED WITH OR WITHOUT LENVATINIB IN UNRESECTABLE OR METASTATIC BILIARY TRACT CANCER: A REAL-WORLD RETROSPECTIVE STUDY

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Introduction: Biliary tract cancer (BTC) including gallbladder cancer (GBC) and bile duct cancer (intrahepatic, hilar and extrahepatic cholangiocarcinoma [CCA]), is highly aggressive, which is mostly advanced stage at diagnosis, and has a very poor prognosis with a 5-year survival rate less than 5%. The incidence and mortality rate of BTC has been increasing during the past five years. Two phase III clinical trials KEYNOTE-966 and TOPAZ-1 indicated the benefit of chemotherapy and PD-(L)1 inhibitor. A phase II clinical trial, chemotherapy combined with PD1 inhibitor toripalimab and Lenvatinib as first-line treatment for advanced intrahepatic cholangiocarcinoma demonstrated a higher objective response rate (ORR), and a better progression-free survival (PFS). However, the efficacy of triple-drug regimen in real-world study is unknown till now. We aim to retrospectively investigate the effectiveness of chemotherapy and PD-1 inhibitor combined with or without Lenvatinib in unresectable or metastatic BTC.

Methods: Patients diagnosed with unresectable or metastatic BTC were enrolled in the second affiliated hospital of Nanchang University from January 2022 to February 2025, including patients treated with first line chemotherapy and PD-1 inhibitor combined with or without Lenvatinib. The evaluation of efficacy was according to RECIST1.1, and the primary outcomes were objective response rate ORR and disease control rate (DCR). Secondary outcomes included PFS and overall survival (OS).

Results: Of the forty patients enrolled, 20 patients treated with chemotherapy and PD-1 inhibitor combined with Lenvatinib and 20 patients treated with chemotherapy and PD-1 inhibitor without Lenvatinib. In total, 15 (37.5%) received partial response (PR), 22 (55.0%) had stable disease (SD), and 3 (7.5%) experienced progression disease (PD). Therefore, the ORR was 37.5%, and DCR was 92.5%. The median PFS was 7.1 months, and the median OS was 8.9 months.

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For patients treated with chemotherapy and PD-1 inhibitor combined with Lenvatinib, 10 (50.0%) received PR, 9 (45.0%) had SD, and 1 (5.0%) experienced PD. Therefore, the ORR was 50.0%, and DCR was 95%. The median PFS was 6.7 months, and the median OS was 8.4 months.

For patients treated with chemotherapy and PD-1 inhibitor without Lenvatinib, 5 (25.0%) got PR, 13 (65.0%) had SD, and 2 (10.0%) experienced PD. Therefore, the ORR was 25.0%, and DCR was 90.0%. There is a tendency that the ORR is lower compared to the chemotherapy and PD-1 inhibitor combined with Lenvatinib group(p=0.107). The median PFS was 7.1 months, and the median OS was 9.5 months.

Conclusion: First line chemotherapy and PD-1 inhibitor combined with Lenvatinib showed effectiveness in unresectable or metastatic cholangiocarcinoma. Chemotherapy and PD-1 inhibitor combined with Lenvatinib has the trend of higher ORR when compared to chemotherapy and PD-1 inhibitor without Lenvatinib. However, PFS and OS didn't show any improvement.

Disclosure of Interest: N/A

P-117 SALVAGE HEPATECTOMY FOR RECURRENT HEPATOCELLULAR CARCINOMA AFTER RADIOFREQUENCY ABLATION

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Background and Objectives: Although radiofrequency ablation (RFA) is a well-established locore-gional treatment modality for hepatocellular carcinoma (HCC), the optimal strategy to handle local recurrence after ablation is still debated. This study aimed to investigate the role of salvage hepatectomy (SH) as a rescue therapy for recurrent HCC after RFA.

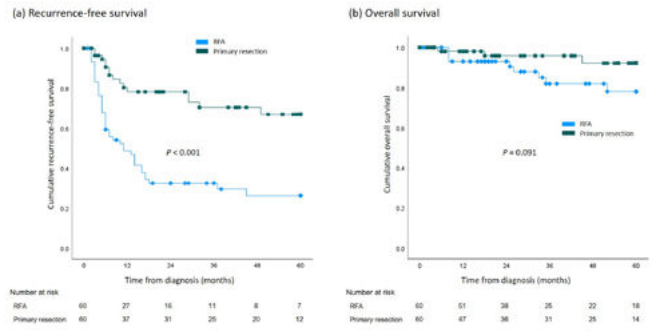
Materials and Methods: Be-tween January 2004 and December 2020, 1161 patients were subject to surgical resection for HCC. Among them, 47 patients who underwent SH for local recurrence after ablation were retrospec-tively analyzed and compared to a propensity-score matched group of controls (n = 47) who re-ceived primary hepatectomy (PH). Short-term and long-term outcomes were analyzed between the two groups.

Results: After matching, operation time, intraoperative blood loss, postoperative hospital stay, and postoperative morbidity rates showed no statistically significant difference. Tumors in the SH group were associated with poor differentiation (SH 9 (19.1%) vs. PH 1 (2.1%), $P < 0.001$). The 5-year disease-free survival rates (31.6% vs. 73.4%, $P < 0.001$) and overall survival rates (80.3% vs. 94.2%, $P = 0.047$) were significantly lower in the SH group. In multivariable analysis, less extensive resection compared to initial plan (hazard ratio (HR) 4.68, $P = 0.024$), higher grade (HR 5.38, $P < 0.001$), negative but close (< 0.1cm) resection margin (HR 22.14, $P = 0.007$), and R1 resection (HR 3.13, $P = 0.006$) were significant predictors for recurrence.

Conclusions: SH for recurrent tumors after ablation shows short-term outcomes equivalent to primary resec-tion. As recurrent tumors show higher grade and more aggressive behavior, more extensive re-sections with wide surgical margins are necessary to prevent recurrence.

Disclosure of Interest: N/A

Image:



P-118 COMPARISON OF REGORAFENIB PLUS PD-1 INHIBITOR AND CONTINUING LENVATINIB PLUS PD-1 INHIBITOR AS SECOND-LINE TREATMENT IN UNRESECTABLE HEPATOCELLULAR CARCINOMA AFTER PROGRESSION OF FIRST-LINE LENVATINIB COMBINED WITH PD-1 INHIBITOR

Saifeng Li [1,2], Qin Wen [1,2], Wenwu Huang [1,2], Zeyu Qiu [1,2], Yanping Li [1,2], Boyi Dai [1,2], Xiongfei Zhang [1,2], Jiawen Liu [1,2], Jingsong Xu [1,2], Sheng Cao [1,2], Yuan Ai [1,2], Long Feng [1]*, Fengming Yi [1]*

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Introduction: Hepatocellular carcinoma (HCC) is a malignant neoplasm with high incidence and mortality in China. The combination of lenvatinib plus PD-1 inhibitors with locoregional therapy has emerged as standard of care in first-line treatment in patients with unresectable HCC. Regorafenib plus PD-1 inhibitor (RP) has been confirmed to be second line treatment although the efficacy is limited. We previously found that continuing lenvatinib plus PD-1 (CLP) inhibitor as second-line treatment after progression of first-line lenvatinib combined with PD-1 inhibitor indicated survival benefit for some patients with unresectable hepatocellular carcinoma in real world. Herein, we aim to compare the efficacy and safety of RP and CLP as second-line treatment in unresectable hepatocellular carcinoma after progression of first-line lenvatinib combined with PD-1 inhibitor.

Methods: Patients with unresectable hepatocellular carcinoma were prospectively enrolled in the Second Affiliated Hospital of Nanchang University from January 2024 to December 2025. The efficacy was conducted according to the RECIST1.1. The primary endpoints included objective response rate (ORR) and progression free survival (PFS). The secondary endpoint was disease control rate (DCR), overall survival (OS). Treatment-related adverse events were evaluated according to Common Terminology Criteria for Adverse Events 5.0.

Results: 117 patients with unresectable hepatocellular carcinoma who received first-line lenvatinib plus PD-1 inhibitor were collected, and 35 patients received second-line therapy. 22 patients (62.9%) received second-line treatment with regorafenib plus PD-1 inhibitor, 13 patients (37.1%) continued to receive lenvatinib plus PD-1 inhibitor. In the CLP group, 2 (15.4%) were evaluated as partial response (PR), 5 (38.5%) had stable disease (SD), and 6 (46.1%) experienced progression (PD). The ORR was 15.4%, and the DCR was 53.9%. Median PFS was 10.6 months, median OS wasn't reached. The RP group showed 3 patients (13.6%) assessed as PR, 9 patients (40.9%) as SD, and 10 patients (45.5%) as PD. The group had an ORR of 13.6%, DCR of 54.5%, median PFS was 8.5 months, and median OS was 8.8 months. No significant difference of ORR and PFS between two groups was observed. CLP group showed the trend of longer OS compared to RP group (p=0.07). All patients experienced at least one adverse event with any grade, and no treatment-related deaths occurred in current study.

Conclusion: The ORR and PFS were comparable between the two patient groups. However, continuing lenvatinib plus PD-1 inhibitor indicated higher OS. Continuing lenvatinib plus PD-1 inhibitors demonstrated favorable regimen, making it a clinically feasible treatment option.

Disclosure of Interest: N/A

P-119 TREATMENT PATHWAYS AND OUTCOMES OF MULTIDISCIPLINARY MANAGEMENT FOR HEPATOCELLULAR CARCINOMA: A 5-YEAR REAL-WORLD STUDY FROM A HIGH-VOLUME CENTER

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Introduction: In the era of rapidly evolving systemic therapy, multidisciplinary team (MDT) management has become central to contemporary hepatocellular carcinoma (HCC) care. We summarized treatment pathways and survival outcomes in a large real-world MDT cohort, with particular focus on patients outside the upfront resection pathway.

Methods: Consecutive HCC patients undergoing initial MDT assessment at West China Hospital from 2019 to 2024 were retrospectively reviewed, with follow-up through December 2025. Patients were categorized as upfront resectable (R), borderline resectable (BR), oncologically unresectable (UR), progression after initial anti-tumor treatment (PIAT), or postoperative recurrence (POR). Overall survival (OS) and event-free survival (EFS) were analyzed using Kaplan–Meier methods.

Results: Among 1,288 patients, 655 were R; 116 BR, 129 UR, 157 PIAT, and 231 POR. The median OS and EFS of R patients reached 89 months 39months, with 5-year OS/EFS rates of 57.5%/40.3%. In BR disease, 50.0% of the patients underwent MDT-guided conversion surgery after neoadjuvant therapy, with superior OS (48 vs 15 months; HR 0.23, $P < 0.001$) and EFS (18 vs 8 months; HR 0.47, $P < 0.001$), which was even comparable to the OS and EFS of R patients. In UR disease, no patients meet the criteria for conversion surgery after system therapies, and the median OS and EFS of this group were 11 and 8 months, with 5-year OS/EFS rates of 5.9%/1.5%. In PIAT disease, median OS and EFS were 13 and 7 months, with a 5-year OS rate of 6.5%. In POR, repeat surgery was associated with longer OS (58 vs 22 months; HR 0.53, $P = 0.045$).

Conclusion: In real-world HCC practice, MDT management supports pathway-specific treatment selection and identifies selected patients who may benefit from conversion or repeat surgery.

Disclosure of Interest: N/A

Posters

P-120 GEMCITABINE, CISPLATIN AND DURVALUMAB IN ADVANCED BILIARY TRACT CANCER: RETROSPECTIVE SINGLE CENTRE REAL-WORLD OUTCOMES AND SUBSEQUENT TREATMENT

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Introduction: Gemcitabine, Cisplatin and Durvalumab (GCD) is the current first-line therapy for treatment of advanced biliary tract cancers (aBTC), demonstrating modest improvement in overall survival (OS) compared to chemotherapy. Real world effectiveness as well as subsequent lines of treatment, especially in the third-line setting and in the context of current standard practices of molecular profiling, remain insufficiently defined.

Methods: A total of 85 patients with aBTC who received first-line GCD at National Cancer Centre Singapore (NCCS) were compared to 109 who received GC alone in a single-centre retrospective study from May 2020 to Feb 2026. Descriptive statistics were used to analyse survival times, treatment response, adverse events (AEs) and molecular tumour characterisation. Kaplan-Meier method was used to estimate OS and progression free survival (PFS) and log-rank test used to compare outcomes.

Results: Clinical characteristics were well balanced between both groups, including primary tumour site, with the majority being intrahepatic and approximately 27% in the gallbladder. Median OS of GCD was 12.4 months (95% CI, 8.9-16.8), comparable to that of GC (12.3 months). 12- and 24-month OS rates were comparable between GCD and GC, at 52.3% vs 52.7% and 21.6% vs 23.9% respectively. Median PFS was also similar to the GC arm at 4.8 months (95% CI, 3.5-6.2). The objective response rate (ORR) with GCD was 32.9%, higher than GC (25.6%). AEs were manageable and expected, with the most common Grade 2 (G2) AE being that of cytopenias (37% ≥G2 neutropenia and 23% ≥G2 thrombocytopenia). Incidence of ≥G2 IRAE was low at 4.7%.

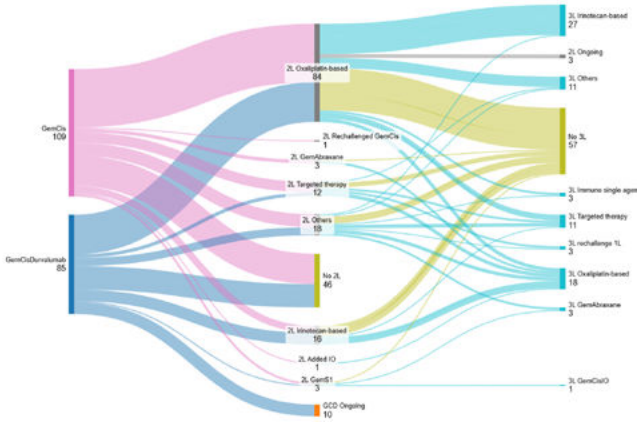
At time of analysis, more patients were still undergoing first and second-line systemic therapy (16.5%) in the GCD cohort. Most patients received Oxaliplatin-based therapy (40%) in the second-line setting post-GCD, followed by Irinotecan-based therapy (11.8%), and 3.5% received targeted therapy. As for those receiving third-line therapy, most naturally received Irinotecan-based therapy (17.6%), and 5.9% received targeted therapy. ORR of oxaliplatin-based therapy was 6%, irinotecan-based therapy 10%, and targeted therapy 50%. Median OS ranged from 5-6 months and PFS ranged from 2-3 months with chemotherapy in the second-line setting, expectedly outstripped by targeted therapy.

56 (65.9%) of the patients who received GCD were molecularly profiled via Multi-Gene Panel Testing (MGPT). 23.2% of profiled patients found an actionable mutation – 6 (10.7%) had FGFR alterations and 7 (12.5%) had IDH1 alterations. Only 5 out of these aforementioned 13 patients received matched targeted therapies, and 3 were in the 3rd line setting, while 1 was in the 5th line setting.

Conclusion: Though there was no difference in OS and PFS between GCD and GC in our cohort, ORR was superior with GCD and results comparable with historical controls. Longer follow up in our cohort (beyond median follow up of 25.7 months) is required to discern if there is any difference in survival, especially since a proportion of GCD patients were still undergoing first-line treatment, reflecting a longer duration of disease control potentially contributed by maintenance Durvalumab. Identifying significant actionable alterations in aCCA patients is pertinent as can be seen by markedly superior response rate and consequently OS/PFS. Costs, platform optimisation and barriers to access to matched therapeutics need to be further explored, to ensure more patients are able to get timely and tailored treatment in an earlier setting.

Disclosure of Interest: N/A

Image:



P-121 PROGNOSTIC VALUE OF BASELINE SIRI AND ALBI GRADE IN PATIENTS WITH ADVANCED BILIARY TRACT CANCER TREATED WITH CHEMO-IMMUNOTHERAPY

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Introduction: Although combination of cisplatin, gemcitabine and durvalumab/pembrolizumab has been established as first-line standard of care for patients with advanced biliary tract cancer (BTC), prognosis remains poor[1,2]. The Systemic Inflammation Response Index (SIRI) reflects systemic inflammation, while Albumin–Bilirubin (ALBI) grade provides insight into liver function, offering complementary prognostic information[3,4]. This study aims to identify prognostic biomarkers by evaluating baseline SIRI and ALBI grade.

Methods: 52 patients affected by advanced BTC treated with first-line chemo-immunotherapy at a single tertiary center were included in the analysis. Baseline SIRI was calculated and patients were divided into high and low groups based on the median value. Overall survival (OS) was estimated using the Kaplan–Meier method and compared between the two groups. The ALBI grade was assessed at baseline, patients were stratified into grade 1 and 2 groups, and differences in OS between these groups were evaluated using Kaplan–Meier method. Univariate Cox proportional hazards assessed the association of baseline SIRI or ALBI with OS.

Results: Patients were stratified into high and low SIRI groups according to median baseline value (2.194; IQR 1.338–3.412). Median OS was significantly shorter in patients with high versus low baseline SIRI value (7.46 vs 14.17 months; long-rank p=0.04). Univariable Cox regression analysis showed a significant association between baseline SIRI and OS (HR 1.14, 95% CI 1.04–1.22). Patients were also grouped according to baseline ALBI grade, with those in ALBI grade 2 group showing significantly shorter OS compared with the ALBI grade 1 group (7.27 vs 14.99 months; long-rank p=0.004). Univariate Cox regression analysis confirmed that baseline ALBI grade was significantly associated with OS (HR 0.35, 95% CI 0.16–0.72).

Conclusions: Our study suggested that higher baseline SIRI was associated with shorter OS. Likewise, poorer ALBI grade correlated with worse outcome. Both SIRI and ALBI grade emerged as independent and complementary prognostic indicators. Validation in larger, prospective cohorts is warranted to confirm their role as prognostic biomarkers.

References:

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Disclosure of Interest: Honoraria

P-122 A REAL-WORLD STUDY OF THE EFFICACY OF SECOND LINE TREATMENT AFTER BEVACIZUMAB PLUS PD-1/PD-L1 INHIBITOR PROGRESSION FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background and aims: Hepatocellular carcinoma (HCC) is a lethal disease with high mortality. Bevacizumab plus PD-1/PD-L1 inhibitor (AB) has become one of the standard regimens for the first-line treatment of unresectable HCC. However, second line treatment after resistance to first-line AB for unresectable HCC is unknow currently. Herein, we aim to investigate the efficacy of second line treatment after AB progression for unresectable HCC.

Methods: Patients diagnosed with unresectable HCC were enrolled in the second affiliated hospital of Nanchang University from September 2020 to December 2025, including patients treated with or without second line after first-line AB progression. Patients were stratified into two groups by second-line treatment: the TKI mono-therapy group and the TKI plus PD-1 inhibitor group. The evaluation of efficacy was according to RECIST1.1 and modified RECIST (mRECIST). The primary

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endpoint was progression free survival (PFS), and secondary endpoints included median overall survival (OS), objective response rate (ORR) and disease control rate (DCR).

Results: A total of 72 patients were enrolled in this study, including 29 patients in the TKI monotherapy group and 43 patients in the TKI plus PD-1 inhibitor group. According to RECIST 1.1, ORR and DCR were 13.79% and 58.62% in the TKI monotherapy group, versus 23.26% and 81.40% in the combination group. The ORR and DCR were 17.24% and 62.07% in the TKI monotherapy group, and 25.58% and 83.72% in the combination group according to mRECIST.

mPFS for all patients was 5.2 months (95% CI: 3.9–6.2). The mPFS in the TKI plus PD-1 inhibitor group was 7.2 months (95% CI: 5.9–9.5), which was significantly longer than 3.4 months (95% CI: 2.8–4.4) in the TKI monotherapy group. In subgroup analysis of TKI plus PD-1 inhibitor group, the lenvatinib plus PD-1 inhibitor (7.4 months) and regorafenib plus PD-1 inhibitor (7.8 months) were associated with longer mPFS, compared with sorafenib plus PD-1 inhibitor (3.9 months).

mOS for all patients was 9.8 months (95% CI: 8.7–12.3). The mOS in the TKI plus PD-1 inhibitor group was 12.3 months (95% CI: 11.5–15.4), significantly longer than 8.7 months (95% CI: 7.5–9.8) in the TKI monotherapy group. Furthermore, subgroup analysis of TKI plus PD-1 inhibitor group demonstrated that the mOS of lenvatinib plus PD-1 inhibitor (12.3 months) and regorafenib plus PD-1 inhibitor (14.5 months) were significantly superior to 8.4 months in the sorafenib plus PD-1 inhibitor.

Conclusion: Second-line treatment after bevacizumab plus PD-1/PD-L1 inhibitor progression could improve overall survival for unresectable hepatocellular carcinoma. Lenvatinib or Regorafenib plus PD-1 inhibitor might be the options for second line treatment.

Disclosure of Interest: N/A

P-123 COMBINATION OF RADIOTHERAPY AND DURVALUMAB/ GEMCITABINE/CISPLATIN THERAPY IMPROVE SURVIVAL IN BILIARY TRACT CANCER (ESPECIALLY EXTRAHEPATIC BILE DUCT CANCER) PATIENTS

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Introduction: Durvalumab (Durva) plus gemcitabine/cisplatin (GP) proved better efficacy compared to GP for advanced biliary tract cancer (BTC) patients in TOPAZ-1 trial. Radiotherapy (RT) has immune-stimulatory effect through several mechanism such as releasing tumor associated antigen etc. However, there is no data about synergistic effect and clinical efficacy of RT plus Durva/GP therapy. Therefore we performed study for describing clinical efficacy of combination of RT plus Durva/GP therapy.

Methods: The clinical course of patients with advanced BTC who received Durva/GP therapy in single cancer center from April 2023 to July 2025 was assessed. Response rate (partial response [PR], stable disease [SD], progressive disease [PD]) per RECIST v1.1 and median progression free survival (PFS), overall survival (OS) were analyzed.

Results: Total 21 BTC patients were treated with Durva/GP therapy. Gallbladder cancer (GBC): Intrahepatic cholangiocarcinoma (IHCCC) : Extrahepatic CCC (EHCCC) patients were 6:8:7. Eight patients (RT group) received several types of RT (PULSAR in 6 patients, TARE in 1 patient, carbon beam therapy in 1 patient). The rate of PR:SD:PD in RT versus (vs) non-RT group were 37.5% vs 15.4% : 62.5% vs 61.5% : 0% vs 23.1%. Median PFS in RT vs non-RT group were 10 vs 5 months ($p = 0.028$) and median OS were 13 vs 10 months ($p = 0.012$). In only EHCCC patients, median PFS, OS of RT group were better than non-RT group with statistically significance (PFS 10 vs 5 months, $p = 0.004$; OS 11 vs 6 months, $p = 0.027$). Almost all patients complained only grade 1/2 nausea and there were no cases with Grade 3/4 adverse effects.

Conclusion: This study demonstrates that radiotherapy can improve clinical efficacy of Durva/GP therapy in advanced BTC, especially EHCCC patients. Further large scaled prospective studies are needed for proving synergistic effect of radiotherapy and Durva/GP therapy to BTC patients.

Disclosure of Interest: N/A

P-124 COMPARISON OF EFFICACY AND SAFETY OF DIFFERENT FIRST LINE TREATMENTS IN BILIARY TRACT CANCER WITH PERITONEAL METASTASIS

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Introduction: Unresectable or metastatic biliary tract cancer (BTC) is a lethal disease with limited survival. Peritoneal metastasis indicates an even worse prognosis. Chemotherapy plus PD-(L)1 is the standard strategy for metastatic BTC. Chemotherapy plus PD-(L)1 combined with targeted therapy has been validated to be another option. However, there is no evidence of the treatment in the BTC peritoneal metastasis (BTCPM). Herein, we aim to investigate the efficacy and safety of different first line treatments of BTCPM.

Methods: Patients diagnosed with BTCPM were recruited in the second affiliated hospital of Nanchang University from February 2019 to April 2025, including patients treated with first line chemotherapy (C), chemotherapy plus targeted therapy (C+T), chemotherapy plus PD-1 inhibitor (C+I), and chemotherapy plus targeted therapy and PD-1 inhibitor (C+T+I). The evaluation of efficacy was according to RECIST1.1, and the primary outcomes was objective response rate (ORR). Secondary outcomes included progression-free survival (PFS) and overall survival (OS). The safety was according to The Common Terminology Criteria for Adverse Events 5.0 (CTCAE 5.0).

Results: Thirty-eight patients with BTCPM were enrolled in current study, including 20 males and 18 females with median age 59 years old. In total, 11 (28.94%) got partial response (PR), 10 (26.32%) had stable disease (SD), and 17 (44.74%) suffered progression disease (PD). Therefore, the ORR was 28.94%, and DCR was 55.26%. The median PFS was 7.87 months, and the median OS was 14.37 months. There was no difference in adverse reactions between different groups.

For the 11 patients in group C, 3 (27.27%) got PR, 2 (18.18%) had SD, and 6 (54.55%) suffered PD. The median PFS was 6.80 months, and the median OS was 12.10 months.

For the 5 patients in group C+T, 2 (40.00%) got PR, 1 (20.00%) had SD, and 2 (40.00%) suffered PD. The median PFS was 13.3 months, and the median OS was 28.3 months.

For the 12 patients in group C+I, 0 (0.00%) got PR, 2 (16.67%) had SD, and 10 (83.33%) suffered PD. The median PFS was 5.7 months, and the median OS was 14.8 months.

For the 10 patients in group C+T+I, 6 (60.00%) got PR, 3 (30.00%) had SD, and 1 (10.00%) suffered PD. The median PFS was 6.8 months, and the median OS was 17.5 months.

Conclusion: Chemotherapy plus targeted therapy and PD-1 inhibitor as first line in treatment of BTCPM showed the trend of higher effectiveness. However, PFS and OS didn't show significant improvement. The additional targeted therapy or PD-1 inhibitor didn't increase any treatment related adverse events.

Disclosure of Interest: N/A

P-131 TENOFOVIR ALAFENAMIDE MONOTHERAPY IS EFFECTIVE IN SUPPRESSING HEPATITIS B VIRUS AFTER LIVER TRANSPLANTATION

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Abstract: Background & Aims: Preventing hepatitis B virus (HBV) recurrence remains essential after liver transplantation (LT). Tenofovir alafenamide (TAF), a first-line nucleos(t)ide analogue for chronic HBV infection, has shown potent antiviral efficacy and improved renal safety, but evidence in LT recipients remains limited. We evaluated the efficacy and safety of TAF monotherapy without hepatitis B immunoglobulin (HBIG) in patients undergoing LT for HBV-related disease.

Approach & Results: In this prospective study, 66 LT recipients with HBV-related disease received TAF monotherapy (25 mg daily) without HBIG prophylaxis. All patients were HBsAg-positive for at least 6 months before transplantation. The primary endpoint was undetectable HBV DNA at 48 weeks after LT. Viral and serologic markers, liver biochemistry, and renal function were assessed during follow-up. At baseline, HBV DNA was detectable in 16.7% of patients. Mean ALT, AST, and creatinine levels were 42.83 U/L, 57.53 U/L, and 75.03 μmol/L, respectively. By week 48, all patients achieved undetectable HBV DNA, which was maintained through week 96. ALT and AST levels declined to 29.50 U/L and 36.01 U/L at week 48 and further decreased to 23.50 U/L and 32.13 U/L at week 96. Mean estimated glomerular filtration rate decreased from 96.40 to 78.78 mL/min/1.73 m^2 at week 48 and remained stable through week 96. No treatment-related serious adverse events were observed.

Conclusions: TAF monotherapy without HBIG was associated with sustained virologic suppression after HBV-related LT and demonstrated a favorable safety profile.

Keyword: Hepatitis B Virus, Liver transplantation, Tenofovir alafenamide

Disclosure of Interest: N/A

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Image:

Table 1. Demographic and laboratory results at baseline and post-transplantation

Parameter	Baseline (n=66)	48week (n=58)	96week (n=58)
Total No. of Patients (N)	66	58	58
Age	52.97(30-73)		
Sex, male (%)	55 (83.3%)	50 (86.2%)	50 (86.2%)
Primary Liver Disease, n (%)			
Hepatitis B Virus-Related Cirrhosis	25 (37.9%)	24 (41.4%)	24 (41.4%)
Liver Cancer	12 (18.2%)	8 (13.8%)	8 (13.8%)
Hepatitis B Virus-Related Cirrhosis plus Liver Cancer	29 (43.0%)	26 (44.8%)	26 (44.8%)
HBsAg status, n (%)			
HBsAb status, n (%)			
Positive	1 (1.5%)	13 (22.4%)	9 (15.5%)
HBeAg status, n (%)			
Positive	13 (19.7%)	0 (0.0%)	0 (0.0%)
HBeAb status, n (%)			
Positive	53 (80.3%)	31 (53.4%)	25 (43.1%)
HBcAb status, n (%)			
Positive	66 (100%)	57 (98.3%)	57 (98.3%)
HBV DNA (Log IU/ml)			
Undetectable HBV DNA, n (%)	55 (83.3%)	58 (100.0%)	58 (100.0%)
Liver Biochemistry			
ALT (U/L)	42.83 (13-203)	29.62(4-169) (n=55)	23.50 (6-69)
AST (U/L)	57.53 (20-242)	36.22 (9-170) (n=55)	32.13 (12-151)
ALP (U/L)	150.56 (43-682)	173.18 (38-784) (n=51)	158.74 (40-741)
TB (μml/L)	42.83 (5.9-422.8)	18.08 (3.9-102) (n=51)	25.95 (5.6-288.6)
DB (μml/L)	18.73 (0.1-321.7)	8.45 (0.4-98.3) (n=51)	15.83 (2-239)
ALB (g/L)	39.52 (21-52)	46.96 (40-55) (n=51)	45.92 (31-53)
Kidney Biochemistry			
eGFR (mL/min/1.73 m²)	96.40 (30-171.2)	78.78 (25-120) (n=55)	78.88 (n=53) (31-118)
Creatinine (μmol/L)	75.03 (44-165)	98.22 (58-203) (n=51)	96.66 (n=56) (65-203)

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; TB, Total Bilirubin; DB, Direct Bilirubin; ALB, Albumin; eGFR, Estimated Glomerular Filtration Rate.

P-135 IMPACT OF ADJUVANT TARGETED THERAPY PLUS IMMUNOTHERAPY ON SURVIVAL AND RECURRENCE IN SPONTANEOUSLY RUPTURED HEPATOCELLULAR CARCINOMA: A PROPENSITY SCORE-MATCHED ANALYSIS

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Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, with over 800 000 deaths annually. Spontaneous rupture is a unique and often fatal complication of HCC, occurring in 3–25% of patients, and is associated with acute hemorrhage, peritoneal dissemination, and high early mortality. Even after successful hepatectomy, patients with spontaneously ruptured HCC (srHCC) have substantially poorer long-term outcomes compared with non-ruptured HCC, mainly due to a higher risk of intrahepatic and peritoneal recurrence. In recent years, adjuvant therapy with tyrosine kinase inhibitors (TKIs) plus immune checkpoint inhibitors (ICIs) has revolutionized the postoperative management of advanced HCC. However, the specific efficacy of this combination in the ruptured HCC population remains poorly defined, as most clinical trials excluded these high-risk patients. Therefore, we conducted this retrospective cohort study to evaluate whether adjuvant targeted ICI therapy confers survival and recurrence benefits in srHCC patients undergoing curative hepatectomy, using propensity score matching to minimize confounding by indication.

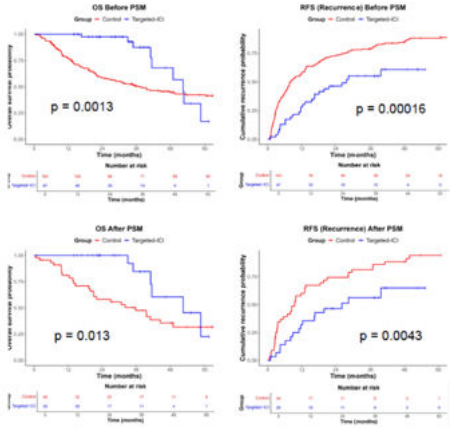
Methods: We retrospectively reviewed 230 patients with spontaneously ruptured HCC who underwent hepatectomy in Zhongshan Hospital. Patients were divided into surgery alone group and surgery plus adjuvant targeted-ICI groups. Exclusion criteria included missing clinicopathological data, loss to follow-up within 3 months, and prior anti-cancer therapy before surgery. PSM was performed at a 1:2 ratio with a caliper of 0.2, matching for sex, age, HBV surface antigen, cirrhosis, total bilirubin (TB), albumin (ALB), prothrombin time (PT), alanine aminotransferase (ALT), Child-Pugh class, alpha-fetoprotein (AFP), tumor size, tumor number, Edmondson histological grade, vascular invasion (VI), extrahepatic metastasis, China Liver Cancer Staging (CNLC), and trans-arterial chemoembolization (TACE) and rupture days. Overall survival (OS) and time to recurrence (TTR) were compared before and after PSM using Kaplan-Meier and log-rank tests. Multivariable Cox regression was applied to identify independent prognostic factors.

Results: Before PSM, 183 control group and 47 targeted-ICI group patients were included. The targeted-ICI group showed significantly better OS (52.57 m vs. 37.00 m, P=0.0013) and TTR (27.80 m vs. 8.00 m, P=0.00016) compared with control group. After PSM, 44 Control and 29 targeted-ICI patients were well-balanced for all covariates (all P>0.05). The OS remained significantly improved in the targeted-ICI group (52.57 m vs. 35.80 m, P=0.013), while the TTR difference was still significant (26.17 m vs. 9.50 m, P=0.0043, Figure 1). Multivariable Cox regression after PSM identified targeted-ICI as an independent protective factor for OS (HR=0.295, 95% CI [0.119-0.733], P=0.0085) and TTR (HR=0.423, 95% CI [0.236-0.758], P=0.0038). Other independent risk factor for poorer TTR was elevated vascular invasion (HR = 1.976, P = 0.0142).

Conclusion: Adjuvant targeted-ICI therapy is associated with improved overall survival and reduced recurrence in patients with spontaneously ruptured HCC after hepatectomy, even after rigorous propensity score matching. These findings suggest that the inherently high recurrence risk of srHCC can be effectively mitigated by postoperative targeted-immunotherapy, and this strategy warrants consideration as an adjuvant standard of care in this challenging population. Nevertheless, given the retrospective nature and single-center design of this study, our results should be interpreted with caution. Future prospective multicenter randomized controlled trials are needed to validate these promising findings and to identify predictive biomarkers for optimal patient selection.

Disclosure of Interest: N/A

Image:



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Clinical Trials in progress

P-125 NEOADJUVANT THERAPY OF SEQUENTIAL TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION, CAMRELIZUMAB AND APATINIB FOR SINGLE LARGE HEPATOCELLULAR CARCINOMA (NEO-START): UPDATED RESULTS FROM A RANDOMIZED CONTROLLED TRIAL

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Introduction: The high recurrence rate after liver resection emphasizes the urgent need for neoadjuvant therapy in hepatocellular carcinoma (HCC) to enhance the overall prognosis for patients. The NEO-START was designed to investigate the efficacy and safety of sequential transcatheter arterial chemoembolization (TACE), camrelizumab and apatinib as a neoadjuvant therapy for single large HCC. Earlier data of this study have been previously presented at ESMO 2025.

Methods: In this phase II randomized controlled trial, 60 patients with a single large (≥10 cm), resectable HCC are randomly assigned in a 1:1 ratio to either the surgery-alone arm (control) or the neoadjuvant-therapy-followed-by-surgery arm. Patients in the neoadjuvant group receive TACE within 1 week after randomization, followed by camrelizumab (200 mg every 2 weeks for 4 cycles), and apatinib (250 mg once daily for 2 months). Patients undergo liver resection after therapy. The primary outcome is the 1-year recurrence-free survival (RFS) rate, and secondary endpoints include pathological remission, overall survival (OS) and the incidence of adverse events (AEs).

Results: A total of 49 patients were enrolled from January 7,2024, to March 28 2026. 24 were randomized to the neoadjuvant group and 25 to the control group. As of April 1, 2026, the median follow-up duration was 12.3 months (IQR 8.3–17.5). 7 recurrences and 2 deaths were observed in the neoadjuvant group, and 12 recurrences and 4 deaths were observed in the control group. The median RFS time was not available in the neoadjuvant group versus 9.3 months (95%CI 4.8-13.8) in the control group, P=0.035. The median OS time has not yet been reached in either group. The 1-year RFS rate was 72.5% in the neoadjuvant group versus 41.1% in the control group. Among the 25 patients in the neoadjuvant group, 24 underwent surgical resection, while 1 patient refused surgery. Major pathological remission (MPR) was observed in 9 patients (9/24, 37.5%), including 4 pathological complete remission (pCR, 16.7%). No patient achieved pCR or MPR in the control group. 12 patient experienced grade 3 alanine aminotransferase or aspartate aminotransferase elevation related to neoadjuvant therapy; no grade 4 or higher AEs occurred. Postoperative complication rates were similar between the two groups.

Conclusion: These results align with earlier reports. Neoadjuvant therapy of sequential TACE, camrelizumab and apatinib showed acceptable safety and significant antitumor activity in patients with single large HCC.

Disclosure of Interest: N/A

P-126 ROSETTA HCC-206: A PHASE 1/2 TRIAL OF FIRST-LINE PUMITAMIG AS MONOTHERAPY OR COMBINED WITH IPILIMUMAB IN ADVANCED OR UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Introduction: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide, with a rising incidence in the United States. Despite recent advances with dual immune checkpoint inhibitor therapy, additional treatment options are needed for unresectable HCC. Pumitamig (BNT327/BMS986545) is an investigational bispecific antibody designed to target both programmed death ligand 1 (PD-L1) and vascular endothelial growth factor A (VEGF-A) in the tumor and tumor microenvironment (TME); binding to PD-L1 on tumor cells aims to restore effector T-cell function and localize VEGF-A neutralization within the TME. Neutralizing local VEGF-A can normalize tumor vasculature and reverse VEGF-A-induced immune suppression. This Phase 1/2 trial will evaluate the safety and efficacy of pumitamig alone or in combination with ipilimumab in patients with first-line advanced or unresectable HCC.

Methods: ROSETTA HCC-206 (NCT07291076) is an ongoing global, randomized, multicenter, open-label, Phase 1/2 trial. Key eligibility criteria include: histologically confirmed diagnosis of locally advanced or unresectable HCC; Eastern Cooperative Oncology Group performance status of 0 or 1; no prior systemic therapy for advanced/unresectable HCC; and measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Key exclusion criteria include: significant bleeding or coagulation disorders or other obvious bleeding risk evidence, an organ transplant or an autoimmune disease.

In Phase 1 of the trial, patients will receive specified doses of pumitamig plus ipilimumab (Cohort 1A and Cohort 1B). In Phase 2, patients will be randomized to one of the treatment arms. The Phase 1 primary endpoints are incidence of adverse events (AE), serious AEs (SAE; per Common Terminology Criteria for Adverse Events v5), AEs meeting protocol-defined dose-limiting toxicity criteria, AEs leading to discontinuation, and AEs leading to death. The Phase 2 primary endpoint is objective response defined as confirmed complete response or partial response by RECIST v1.1 per investigator assessment. The Phase 2 secondary endpoints include incidence of AEs, SAEs, treatment-related AEs, AEs leading to discontinuation, and AEs leading to death. Additional secondary endpoints are end of infusion/trough concentrations of pumitamig, trough concentration of ipilimumab, incidence of antidrug antibodies against pumitamig or ipilimumab, progression-free survival (by RECIST v1.1 per investigator) and duration of response (by RECIST v1.1 per investigator).

Disclosure of Interest: Stocks

P-127 PRODIGE 89 UCGI 44 ALICE (NCT06904170): AN INTEGRATED PHASE II/III RANDOMIZED STUDY COMPARING DURVALUMAB AND TREMELIMUMAB +/- HEPATIC ARTERIAL INFUSION CHEMOTHERAPY WITH GEMOX IN HEPATOCELLULAR CARCINOMA WITH HIGH TUMOR BURDEN

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Introduction: Hepatocellular carcinoma (HCC) is a fatal disease often associated with cirrhosis. The standard of care with atezolizumab-bevacizumab (IMbrave150)1 or D-T (HIMALAYA, STRIDE regimen)2 improves survival data on patients (pts) with high tumor burden, such as Vp4 portal vein thrombosis are disappointing and often excluded from trials (notably, from HIMALAYA). In Asia, HAIC combined with sorafenib has shown overall survival (OS) benefit (SILUS - FOHAIC trials), especially in pts with >50% liver involvement or portal vein thrombosis. The GEMOX regimen (gemcitabine-oxaliplatin) may synergize with immunotherapy by inducing immunogenic cell death and reducing immunoregulatory cells. No prospective study has evaluated this approach in Western populations.

Methods: The ALICE study is a national, multicenter, integrated phase II/III trial comparing D 1500mg - T 300mg alone or combined with HAIC with GEMOX Gem 1000mg/m2 + Oxali 100mg/m2 (every 2 weeks, 4 cycles - one reintroduction possible). Main inclusion criteria are unresectable HCC with high tumor burden BCLC B or C, Child-Pugh A, ECOG PS ≤1, no prior HAIC or liver transplantation. Treatment allocation is balanced using stratified minimisation (tumor burden, ALBI score and HAIC techniques).

Phase II uses a single arm, single stage binomial design with futility at 12 responders/45 pts in the experimental arm (90 total) to reject a 20% ORR and continue to 196 pts (36 month accrual, 18 month follow up), α=5%, 85% power, assumed HR=0.625. Overall power kept at 80% via closed hierarchical α control. Interim Phase II results will be reported only to the DSMB to avoid accrual bias in Phase III.

Results: The study was approved by authorities in August 2025. To date, 6 pts are enrolled.

Conclusion: This integrated design reduces required patient numbers by 45% versus two sequential protocols, providing major methodological and operational advantages and potential practice-changing impact for high tumor-burden HCC.

References: 1.IMbrave150: Exploratory efficacy and safety results of hepatocellular carcinoma (HCC) patients (pts) with main trunk and/or contralateral portal vein invasion (Vp4) treated with atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in a global Ph III study. - ASCO [Internet]. [cité 5 mars 2026]. Disponible sur: https://www.asco.org/abstracts-presentations/198912, 2.Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid. août 2022;1(8):EVIDoa2100070. doi:10.1056/EVIDoa2100070 PubMed PMID: 38319892. **NCT06904170**

Disclosure of Interest: Research/Education grant

P-128 SYMBIOTIC-GI-13: AN OPEN-LABEL, PHASE 1B/2 STUDY OF PF-08634404, A PD-1/VEGF BISPECIFIC ANTIBODY, MONOTHERAPY AND COMBINATION THERAPY IN PATIENTS (PTS) WITH UNRESECTABLE LOCALLY ADVANCED (LA) OR METASTATIC (M) HEPATOCELLULAR CARCINOMA (HCC)

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Introduction: Anti–programmed death (ligand) 1 (PD-[L]1) agents combined with anti–vascular endothelial growth factor (VEGF) agents or anti–cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies are the current first-line treatments (tx) for la/mHCC. With a 5-year survival rate of ≈18% in la/mHCC, there remains a need for new tx options for these pts. Simultaneous bispecific targeting of PD-1 and VEGF has the potential to enhance antitumor activity compared with a combined PD-1/VEGF blockade with single agents. PF-08634404 is a fully human immunoglobulin G4 (IgG4) bispecific antibody targeting PD-1 and VEGF. Phase 1 and 2 studies of PF-08634404 have demonstrated promising antitumor activity with a manageable safety profile in advanced solid tumors.

Methods: Symbiotic-GI-13 (NCT07227012) is an open-label phase 1b/2 study evaluating the safety, pharmacokinetics, and preliminary efficacy of PF-08634404 as monotherapy and in combination with ipilimumab. Adult pts with la/mHCC confirmed by histology/cytology or clinically by AASLD criteria (pts with cirrhosis) are eligible. Pts must have ≥1 measurable (per RECIST 1.1) and untreated lesion, an ECOG PS of 0-1, Child-Pugh Class A, adequate organ function, and have not received prior systemic tx for HCC. Pts with a clinically significant risk of hemorrhage/fistula or active central nervous system metastases will be excluded. In the phase 1b (safety run-in/dose escalation), up to 18 pts will receive PF-08634404 + ipilimumab. In the phase 2 (dose expansion), pts will be randomized to receive PF-08634404 or PF-08634404 + ipilimumab (up to 40 pts per arm). Study tx will be received until protocol-specified discontinuation criteria are met. The primary and secondary objectives/endpoints are reported in the table.

The study is open for enrollment.

This abstract was previously submitted to ESMO GI 2026.

Disclosure of Interest: Advisory Board

Image:

	Phase 1b	**Phase 2**
Primary objectives/endpoints	Safety and tolerability Dose-limiting toxicities	Safety and tolerability Antitumor efficacy Confirmed ORR[a] by investigator
Secondary objectives/endpoints	Antitumor efficacy Confirmed ORR[a] by investigator DOR[a] by investigator PFS[a] by investigator OS Pharmacokinetics Immunogenicity	Antitumor efficacy DOR[a] by investigator PFS[a] by investigator OS Pharmacokinetics Immunogenicity
[a]Per RECIST 1.1		

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