AUA 2026
Washington, DC
MAY 15-18

048IC - Chemotherapy and Immunotherapy for the Urologist and Advanced Practice Provider

Sunday, May 17

Faculty

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AUA 2025
APRIL 26-29 Las Vegas

Prostate Cancer

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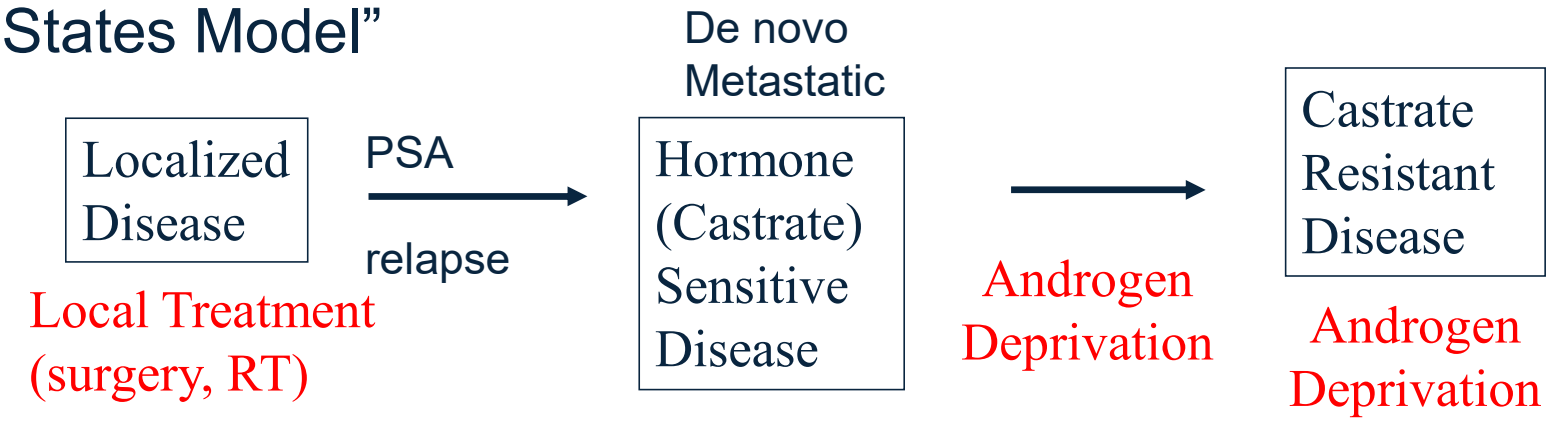
Outline

- Defining advanced prostate cancer
- Androgen Deprivation Therapy
  - Options
  - Side effect management
- Management of Metastatic Hormone Sensitive Prostate Cancer (mHSPC)
- Management of Non-Metastatic Castrate Resistant Prostate Cancer (nmCRPC)
- Management of Metastatic Castrate Resistant Prostate Cancer (mCRPC)

Natural History of Prostate Cancer: "Clinical States Model"



Definition of Castration Resistance

- Castrate level of testosterone (<50 ng/dl) AND one of indications of progression (PSA, radiographic)
  - Rising PSA two consecutive times and >2 ("PSA progression") or
  - **Two** or more **new** lesions on bone scan or progression on CT/MRI by RECIST criteria ("radiographic progression")

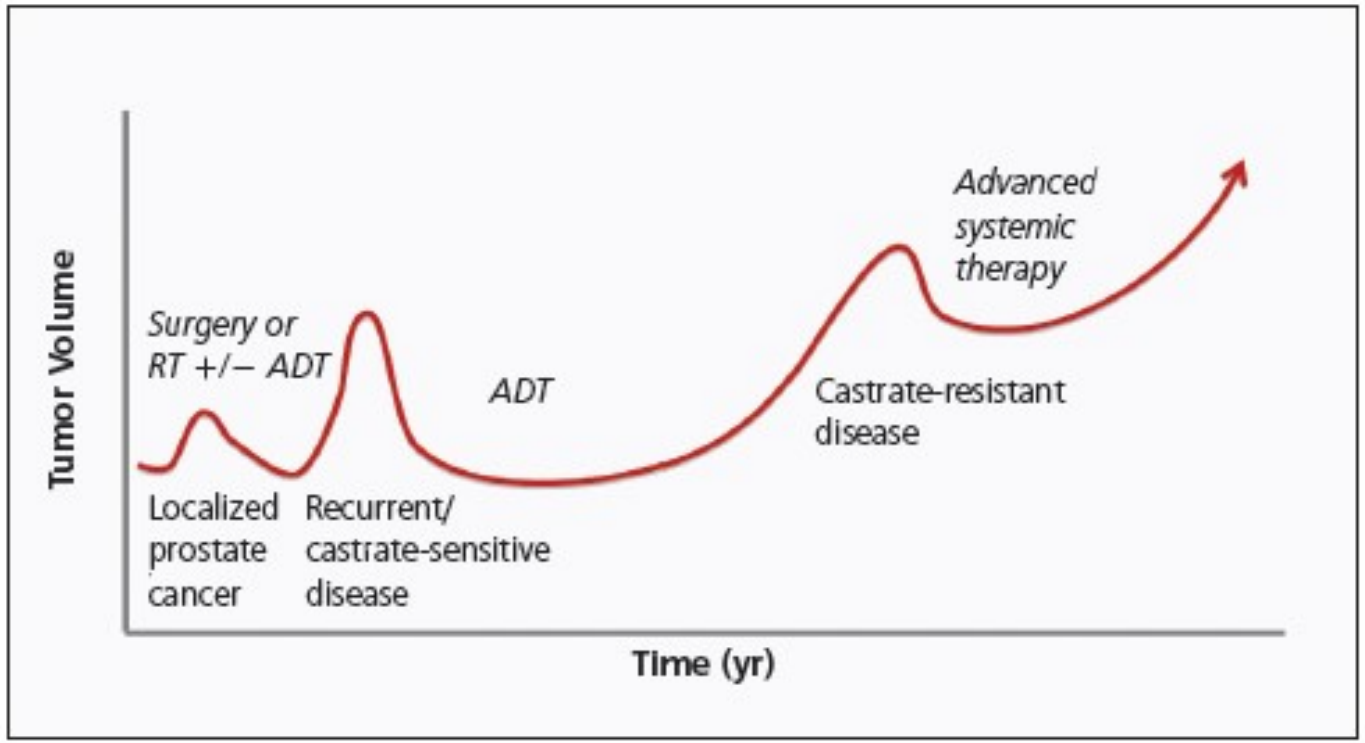


Figure: The Prostate Cancer Continuum. ADT = androgen deprivation therapy. RT = radiation therapy.

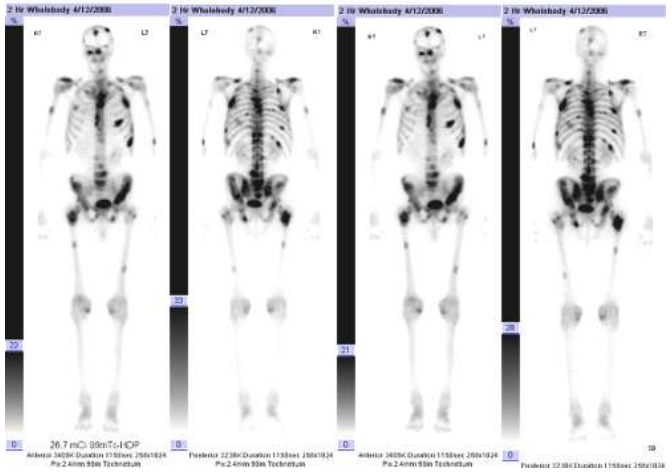
Advanced Prostate Cancer

Recurrent prostate cancer following definitive therapy, locally recurrent disease, systemic recurrence, clinical (symptomatic) recurrence; newly diagnosed distant disease

- Biochemical: PSA recurrence (most common)
- Local: Cancer identified within the prostate (e.g., after XRT)
- Distant: Cancer identified in distant organs (e.g., bone mets)
- Clinical: Local or distant w/ symptoms (e.g., LUTS, pain)

Diagnostics

- CT AP
  - Lymph nodes
    - Pelvic, retroperitoneal
  - Visceral
- Bone scan
  - Eval for lesions of axial skeleton
  - Follow distribution of adult red bone marrow
    - Skull, thorax, pelvis, spine, proximal long bones
  - Bone scans should reveal osteoblastic appearance due to *increased* bone density in the areas of bone mets
- Bone density
- Prostate MRI



Diagnostics

PET imaging with novel tracers

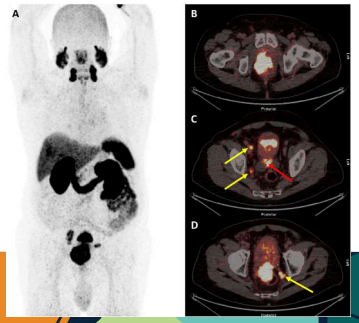
- Prostate-Specific Membrane Antigen (PSMA)
  - Targets PSMA, which is a protein expressed by prostate cancer cells
    - Piflufolastat F 18
    - Gallium 68 PSMA-11
  - Indications: Risk stratification for very high risk localized; patients w/ BCR s/p definitive therapy; work up for progression; before PSMA-targeted radioligand therapy
- F18-Naf
  - Rarely used

Lisney AR, at al. The Role of PSMA PET/CT in the Primary Diagnosis and Follow-Up of Prostate Cancer-A Practical Clinical Review. Cancers (Basel). 2022 Jul 26;14(15):3638

PSMA PET

For nodal staging

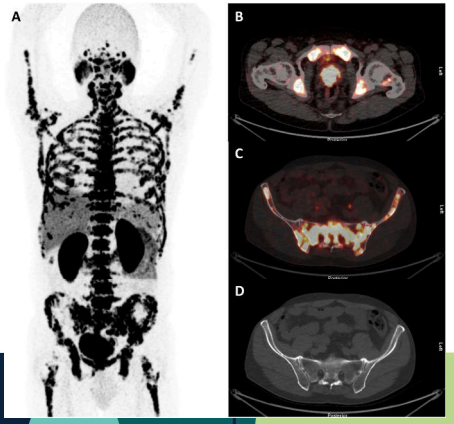
- Sensitivity: 73.7% vs 38.9% (MRI) vs 38.5 % (CT)
- Specificity: 97.5% vs 82.6% (MRI) vs 83.6% (CT)



Ch Eur Urol, 2023

For bone staging

- Sensitivity: 98.0% vs 73.0% (BS)
- Specificity: 96.2% vs 79.1% (BS)

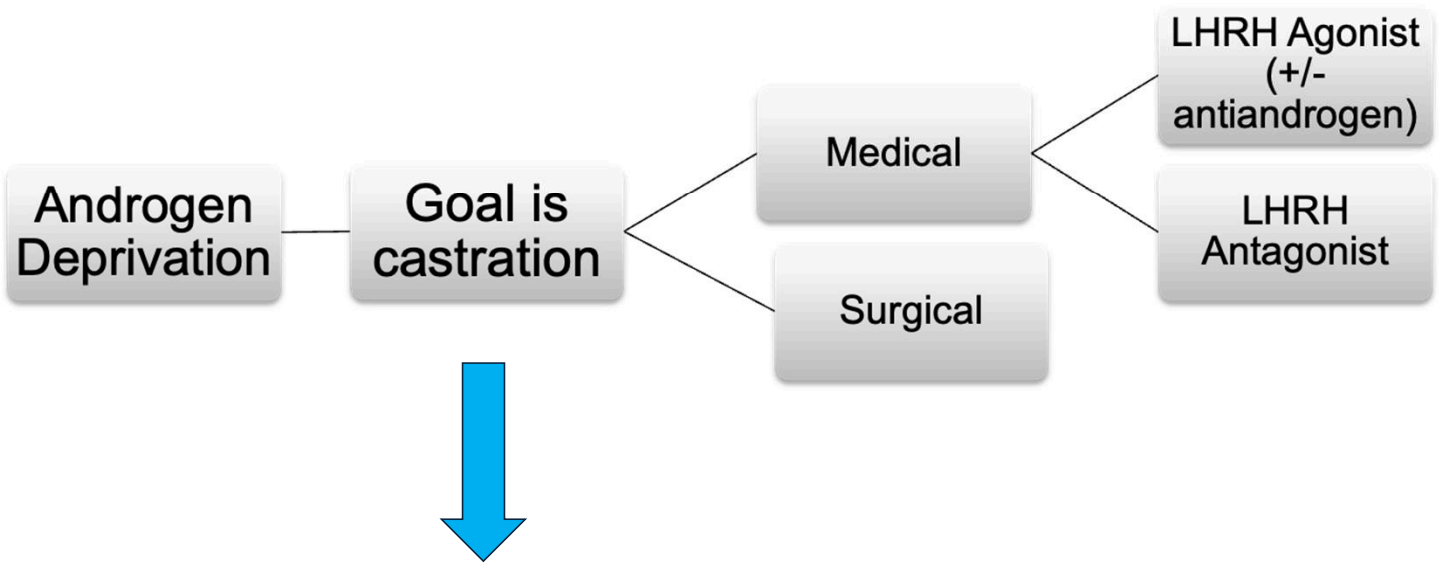


Jochumsen, Sem in Nuc Med, 2023

Advanced Prostate Cancer

- Indications for androgen deprivation therapy (ADT)
  - Symptomatic metastatic disease
  - Asymptomatic metastatic disease
  - BCR only (immediate vs. delayed)
    - PSA > 20 for shorter PSADT
    - PSA > 50
    - Patient preference
    - Arbitrary
  - Continuous vs. intermittent

Androgen Deprivation Therapy



Hormonal Regulation of the Prostate Gland

- Prostate growth depends on presence of androgens
  - Testes and adrenal glands major sources of circulating androgens
- Hormonal regulation of androgen synthesis is mediated through series of biochemical interactions between hypothalamus, pituitary, adrenals, testes
- LHRH from the hypothalamus stimulates release of LH & FSH from the pituitary
- Circulating testosterone and estradiol influence the synthesis of LHRH, LH, & FSH by a negative feedback loop operating at the hypothalamic and pituitary level.

Schally AV, Comaru-Schally AM. Mode of Action of LHRH Analogs. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003.

Androgen Deprivation Therapy: Surgical

- Bilateral orchiectomy
  - Castrate testosterone levels occur 2-12 hours post-op
  - Eliminates > 90% of androgens
  - Low cost, compliance not an issue
  - No testosterone flare
  - Irreversible

Androgen Deprivation Therapy: Medical

- Gonadotropin-releasing hormone (GnRH) agonist
  - Stimulate LH and FSH from pituitary gland to testis
  - Castrate levels of T in 3-4 weeks
  - Most common agent: leuprolide
  - Varying duration depot injections (3, 4 and 6 months most common)
  - If concerned about T surge -> block with antiandrogen (bicalutamide)
- GnRH Antagonist
  - Directly inhibit pituitary LH and FSH release
  - No surge in androgens
  - Agent: degarelix
  - Dosing options:
    - Loading dose 240 mg then 80 mg q month
    - Loading dose 240 mg then LHRH agonist

Meani D, et al.Practical differences between luteinizing hormone-releasing hormone agonists in prostate cancer: perspectives across the spectrum of care. *Therapeutic Advances in Urology*. 2018;10(2):51-63

Gittelman M,, et al: A 1-year, open-label, randomized phase II dose-finding study of degarelix, a novel gonadotropin-releasing hormone (GnRH) receptor blocker, in the treatment of prostate cancer in North America. J Urol 180:1986-1992, 2008

Androgen Deprivation Therapy: Medical

- GnRH Antagonist:
- Relugolix 120 mg daily
  - HERO trial; phase 3 RCT vs leuprolide for 48 weeks
    - Sustained T suppression; 96.7% vs 88.8%
    - Mean T level at day 4: 38mg/dl vs 625 ng/dl
    - Mean T 90 days s/p d/c: 288.4 ng/dl (n=137) vs 58.6 ng/dl (n=47)
    - Eligible patients = BCR, newly dx mCSPC, or advanced localized disease unlikely to be cured by local treatment
    - Few cardiovascular SE

HERO

Cardiovascular Adverse Events

	Relugolix (N = 622)	Leuprolide (N = 308)
Adverse Cardiovascular Events	3.9%	7.1%
Major Adverse Cardiovascular Events (MACE)	2.9%	6.2%
Ischemic Heart Disease	2.4%	1.6%

History of MACE	Yes		No	
N (%)	Relugolix 84 (13.5%)	Leuprolide 45 (14.6%)	Relugolix 538 (86.5%)	Leuprolide 263 (85.4%)
MACE	3.6%	17.8%	2.8%	4.2%
Odds Ratio Leuprolide vs Relugolix (95% confidence interval)	5.8 (1.5, 23.3)		1.5 (0.7, 3.4)	

MACE = non-fatal myocardial infarction + non-fatal stroke + all-cause mortality

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Neal Shore, MD, FACS Carolina Urologic Research Center, SC, USA 26

Shore N et al. Oral relugolix for androgen deprivation therapy in advanced prostate cancer. N Engl J Med 2020; 382:2187-2196

Androgen DeprivationTherapy

- Non-steroidal anti-androgens
  - Block binding of androgen to androgen receptor
  - Rarely used
  - Doesn’t impact serum T
  - If used, then in combination with GnRH tx
  - Most commonly used: bicalutmide

Duration of Hormonal Therapy (ADT)

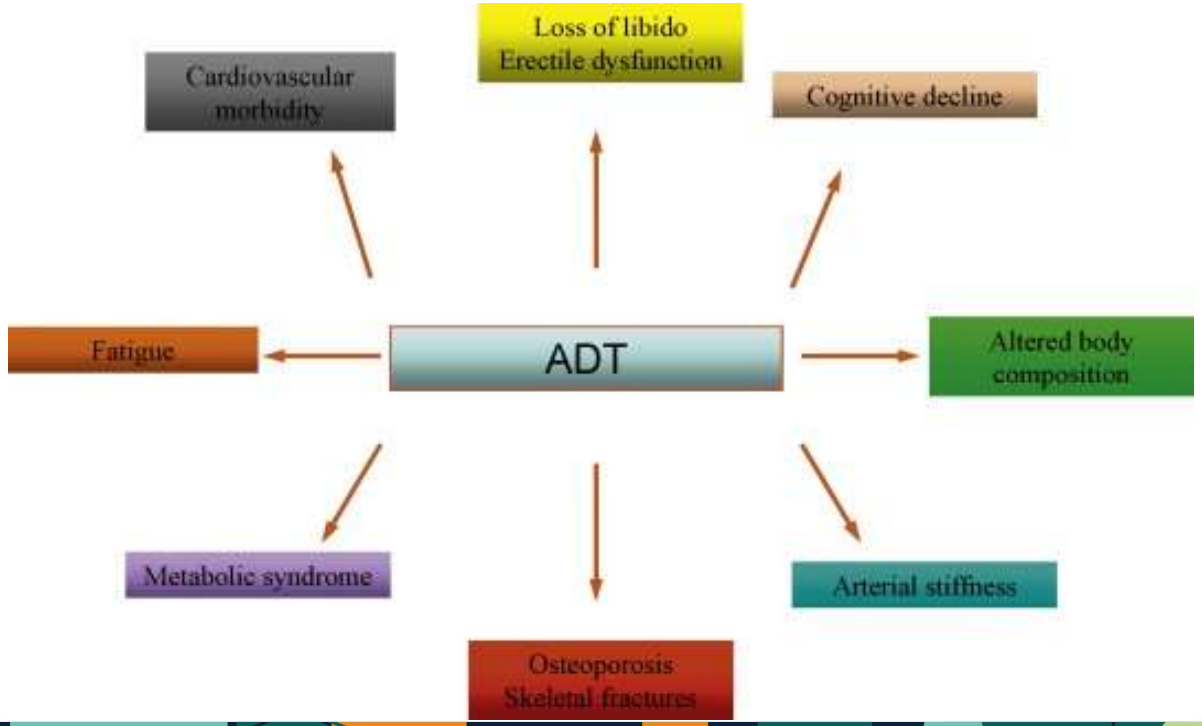
- Intermediate Risk Prostate Cancer
  - 6 months of ADT with Radiation Therapy
- High Risk Prostate Cancer
  - 24-36 months of ADT with Radiation Therapy
- Biochemical Recurrent Prostate Cancer
  - Intermittent or Continuous
- Metastatic Disease
  - Intermittent or Continuous

Intermittent ADT in Metastatic Disease

- SWOG 9346
  - After 7 months of ADT, 1535 patients whose PSA dropped to 4 or below were randomized to IAD vs CAD
  - Median survival 5.1 yrs (IAD) and 5.8 yrs (CAD)
  - Survival results inconclusive
- Several other meta-analyses reported no survival difference between IAD and CAD

Hussain M et al. Intermittent versus continuous androgen deprivation in prostate cancer. NEJM. 2013: 368(14); 1314-1325

Side Effects of Hormonal Therapy



Side Effect Management

Hot flashes

- Data for pharmacologic management is lacking
  - Paraxetine, clonidine
- Physical activity
- Avoid triggers
- Acupuncture

Cognitive Decline

- Physical activity
  - Aerobic & resistance
  - Motor control (balance)
- Mindfulness-based stress relief
- Mental stimulation, brain training

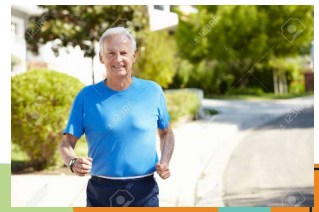
Side Effect Management

Fatigue

- Physical activity
- Sleep hygiene
  - Same night routine
  - Decrease stimulants
- Mindfulness
- Treat contributing factors (e.g., anemia)

Metabolic Syndrome

- Close follow up with PCP
  - Monitor glucose, lipids, A1c
- Physical activity
- Healthy diet
  - Refer to Registered Dietitian



Side Effect Management

Sexual Dysfunction

- PDE5-I
- Vacuum Erection Device
- Intracavernosal injections
- MUSE
- Inflatable penile prosthesis
- Patient/partner communication
- Therapy

Cardiovascular Morbidity

- Smoking cessation
- Minimal alcohol
- Collaborate with cardiology
- Physical activity
- Heart healthy diet

Side Effect Management

Emotional lability

- Individual counseling
- Couples counseling
- Refer to mental health team
- Antidepressants
- Support groups

Evidence-based Practice Resources for Supportive Care Management

- Oncology Nursing Society
- NCCN Guidelines

ADT and Bone Health

- Decreased Bone Density/Bone Health in Presence of ADT
  - Vit D supplementation – 400-1000 IU/day
  - Calcium supplementation – 1000-1200 mg/day
  - Weight bearing exercise
  - DEXA scan
    - Obtain baseline
    - Assess throughout long term ADT (q 2 years)
  - mCRPC w/ bone mets for prevention of skeletal related events
  - Long-term ADT w/ osteoporosis (T score -2.5 or lower)

Bone Antiresorptive Agents

Zoledronic Acid

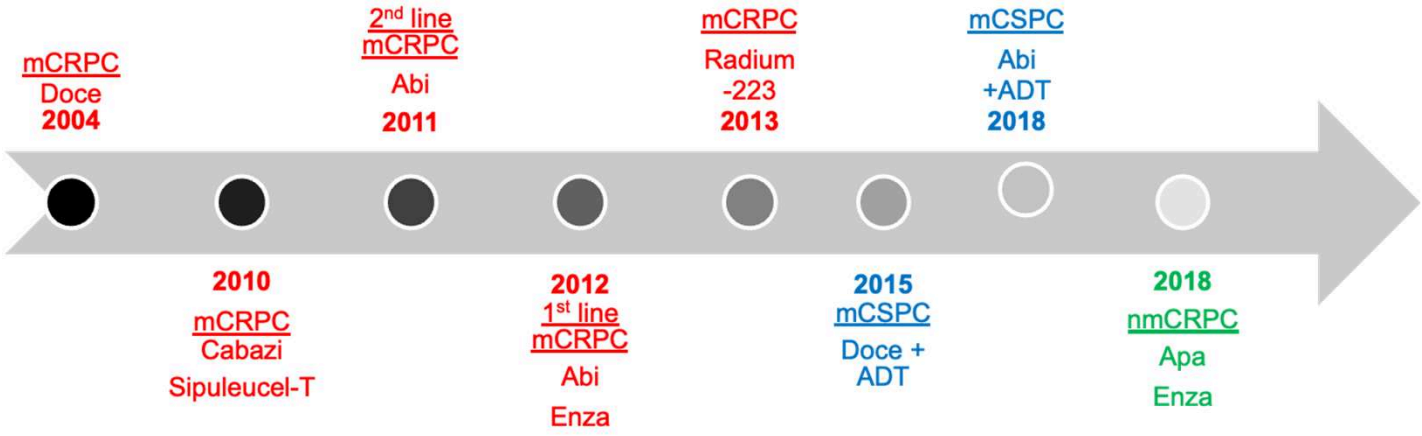
- IV bisphosphonate inhibits bone osteoclasts
- 5 mg annually for osteoporosis; 4 mg q 4 weeks for bone mets
- Monitor renal function

Denosumab

- SQ monoclonal antibody rank-ligand inhibitor
- 60mg q6 mos for osteoporosis; 120 mg q4 weeks for bone mets

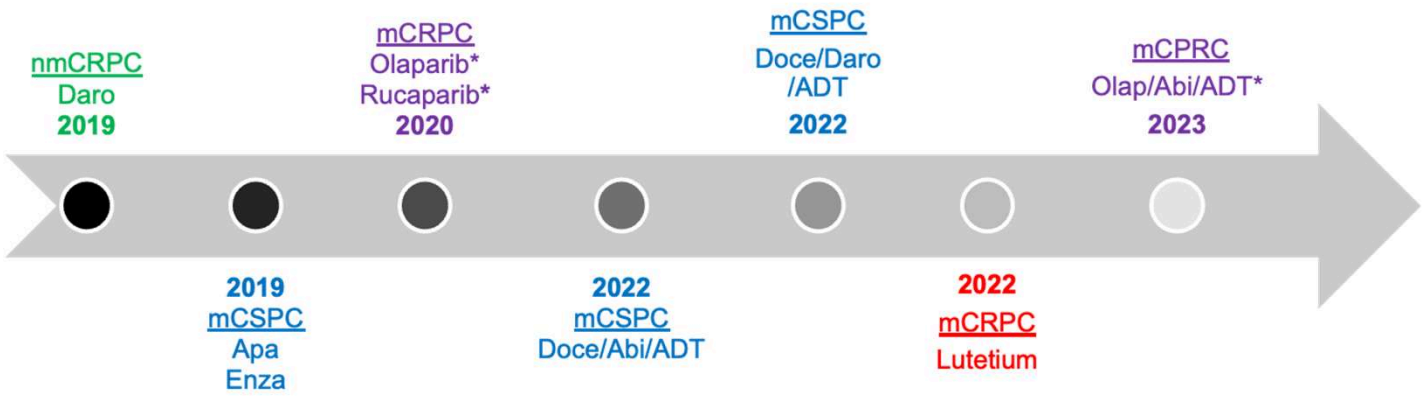
SE: Hypocalcemia, hypophosphatemia, ONJ (Dental eval), renal dysfunction, flu-like symptoms

FDA approvals timeline for advanced prostate cancer



Abbreviations: metastatic castrate resistant prostate cancer (mCRPC), metastatic hormone sensitive prostate cancer (mHSPC), non-metastatic castrate resistant prostate cancer (nmCRPC)

FDA approvals timeline for advanced prostate cancer



Abbreviations: metastatic castrate resistant prostate cancer (mCRPC), metastatic hormone sensitive prostate cancer (mHSPC), non-metastatic castrate resistant prostate cancer (nmCRPC)

Systemic options

Cytotoxic chemotherapy
Docetaxel (Taxotere®)
Cabazitaxel (Jevtana®)

Antiandrogens
Abiraterone (Zytiga®)
Enzalutamide (Xtandi®)
Apalutamide (Erleada®)
Darolutamide (Nubeqa®)

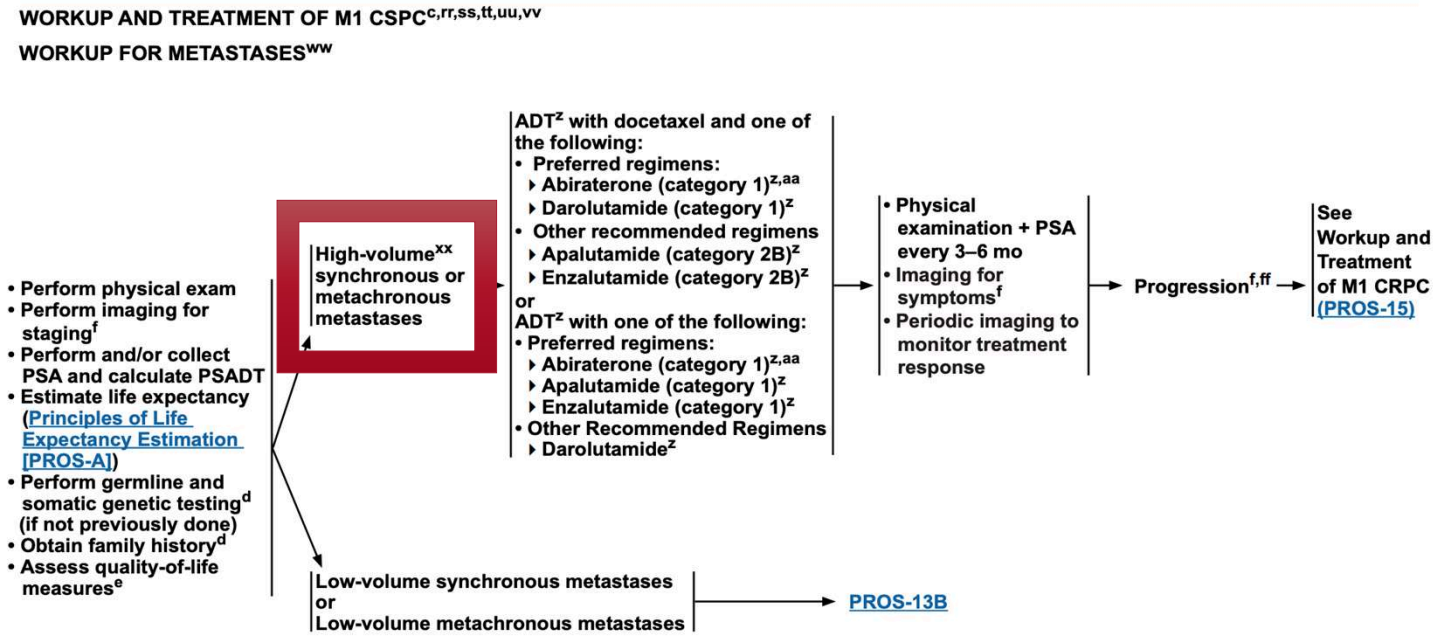
PARP Inhibitors*
Olaparib (Lynparza®)
Rucaparib (Rubraca®)
Talazoparib (Talzenna®) w/ Enza

Immunotherapy
Sipuleucel-T (Provenge®)
Pembrolizumb (Keytruda®)*

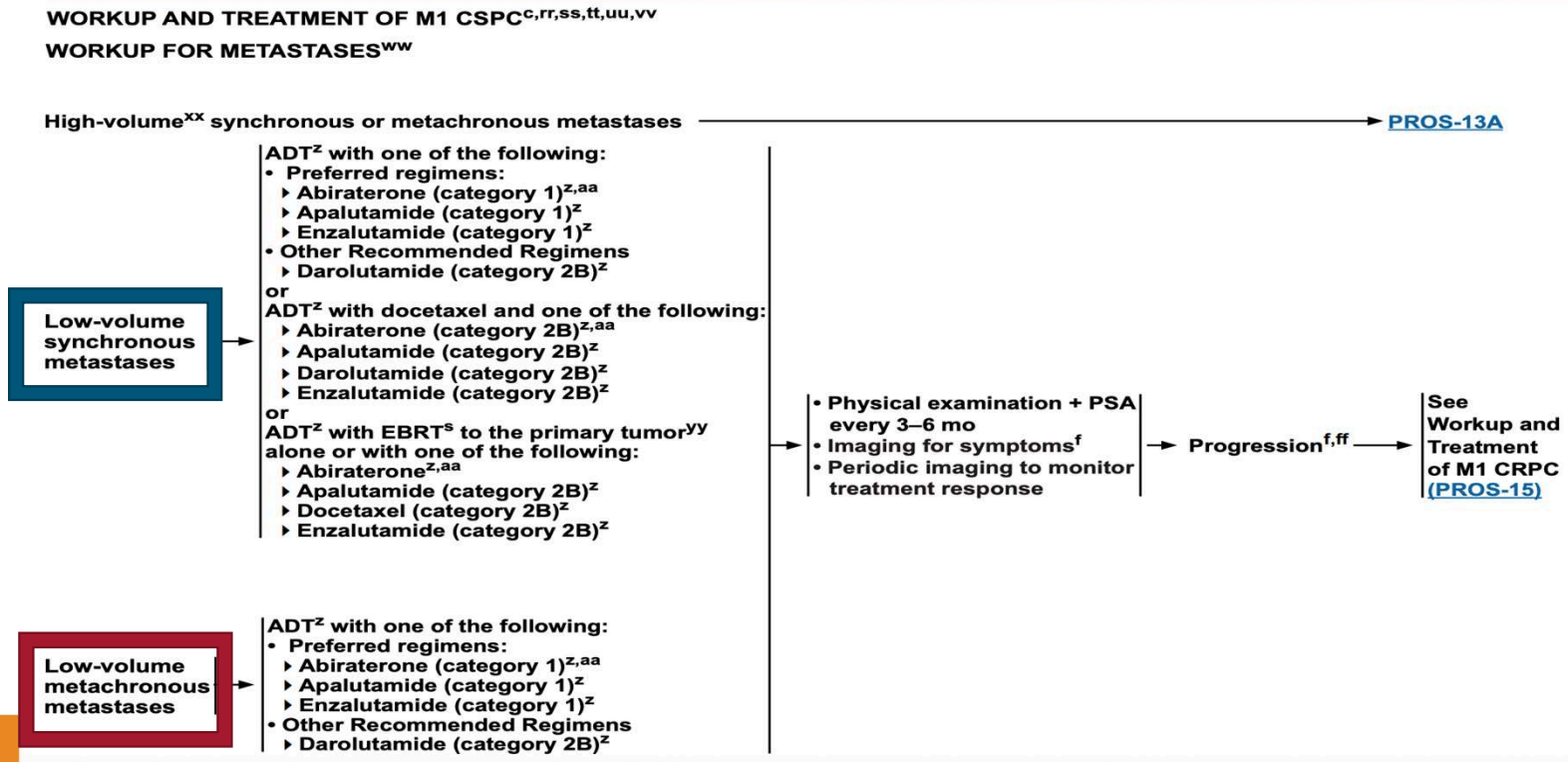
Radiotherapy
Radium-223 (Xofigo®)
Lutetium Lu 177 (Pluvicto®)

Androgen deprivation
Leuprolide (Lupron® , Eligard®)
Degarelix (Firmagon®)
Relugolix (Orgovyx®)

NCCN 1.2025; mCSPC, high volume



NCCN 1.2025; mCSPC, low volume



mCSPC; shout out to history

Docetaxel*

- CHAARTED trial (n= 790)
  - High volume (i.e. visceral mets and/or 4+ bone mets)
  - ADT naïve (or started <120 days)
  - Primary objective = mOS would be 33.3% longer w/ ADT + chemo
  - Increased survival by 13.6 months (from 44 to 57.6 months)
  - 6 cycles every 21 days
  - MOA: Microtubule inhibitor
  - SE: Fatigue, myelosuppression, rash, n/v, LE edema, neuropathy, alopecia, hypersensitivity

Sweeney C et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. NEJM 2015; 373:737-746

Almost unprecedented in oncology that addition of single chemo has this significant of an effect

mCSPC

Abiraterone + prednisone

- LATITUDE (n = 1,200)
  - 2 of 3 risk factors: GG ≥ 8, at least 3 bone mets, or 3 visceral mets
  - ADT naïve
  - ADT + abiraterone 1,000mg vs ADT + placebo
  - Abi associated with 53% lower risk of radiographic POD (POD delayed by 18.2 months)
- STAMPEDE (n = 1,917)
  - 71% improvement in time to treatment failure
    - 37% diff in OS
- MOA: Inhibits CYP17, enzyme needed for androgen synthesis in the testes, adrenals, and tumor
- SE: Mineralocorticoid SE, fatigue, hot flashes, hepatotoxicity, edema, HTN

*LFTs and K q2 weeks x 3 months

Fizazi K et al. Abiraterone plus prednisone in metastatic , castration sensitive prostate cancer. NEJM 2017; 377:352-360
James N et al. Abiraterone for prostate cancer not previously treated with hormone therapy. NEJM 2017; 377:338-351

mCSPC

Apalutamide

- TITAN (n = 1,052)
  - Low and high volume disease, de novo, or prior local tx, or prior docetaxel
  - Apalutamide 240 mg + ADT vs placebo + ADT
  - 33% reduction in risk of death
  - MOA: androgen receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR→ prevents AR translocation, DNA binding, and AR-mediated transcription
  - SE: arthralgia, rash, anorexia, fall, hypothyroidism, fracture, diarrhea

Chi K et al. Apalutamide for metastatic, castration-sensitive prostate cancer. NEJM 2019. 381: 13-24

mCSPC

Enzalutamide

- ARCHES (n = 1,150)
  - mCSPC either de novo or after recurrence following local therapy. Prior ADT and and up to 6 cycles prior docetaxel allowed
  - Enzalutamide 160 mg + ADT vs placebo + ADT
  - Primary endpoint was radiographic progression-free survival
  - Reduced risk of radiographic POD or death by 61%
  - MOA: Inhibits androgen binding to AR and inhibits AR nuclear translocation and interaction with DNA
  - SE: Myalgia, arthralgia, fatigue, hot flash, HTN; seizure warning
- ENZAMET (n = 1,125)
  - ADT + enza vs ADT + standard nonsteroidal antiandrogen
  - OS at 3 years: 80% vs 72%

Armstrong A et al. ARCHES: A randomized, ... ogen dep... n therapy with ... utamide or placebo in men with Metastatic hormone-sensitive prostate cancer ... 2019; 37(32): 2974-2986

Davis *et al. N Engl J Med* 2019; **380**: 121-131

TRIPLETS!

mCSPC

Docetaxel + abiraterone

- PEACE-1 (n= 1,173)
  - De novo disease
  - 4 arms: SOC (ADT alone or + doce); SOC + XRT; SOC + abi/pred; SOC + XRT + abi/pred
  - Primary endpoints were rPFS and OS
  - Triplet therapy reduced risk of death by 25% and risk of rPFS by 50% vs docetaxel + ADT
  - Docetaxel 75 mg/m2 x 6 cycles, abiaraterone 1,00 mg Po daily + prednisone 5 mg BID + ADT
  - SE: HTN, fatigue, PN,

Fizazi K et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive Prostate cancer (PEACE-1); a multicentre, open-label, randomized, phase 3 study with a 2x2 factorial design. Lancet 2022.399(10336) 1695-1707

mCSPC

Docetaxel + darolutamide

- ARASENS (n=1,306)
  - Doce+daro+ADT vs Doce+placebo+ADT
  - Primary endpoint overall survival
  - Triplet therapy reduced risk of death by 32.5% vs Doce+placebo+ADT
  - Docetaxel 75 mg/m2 x 6 cycles, + darolutamide 600 mg BID, +ADT
  - SE: Fatigue, alopecia, neutropenia

Smith M, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. NEJM 2022; 386: 1132-1142

Comparing Metastatic Castrate Sensitive Treatment Options

Agent	Practical Considerations
Docetaxel	De novo high volume disease per CHAARTED Myelosuppression/neuropathy IV chemotherapy requiring frequent visits Limited therapy duration (6 x 21 day cycles) Cost $ Newer data supports use of either antiandrogen vs triplet therapy, not chemo alone
Abiraterone	De novo metastatic disease per LATITUDE and STAMPEDE mineralocorticoid excess syndrome and hepatotoxicity Continuous daily treatment until progression to mCRPC Cost $$$
Apalutamide	De novo metastatic disease or prior local tx per TITAN Rash and CNS effects (dizziness, fatigue, falls) Continuous daily treatment until progression to mCRPC Cost $$$
Enzalutamide	De novo metastatic disease or prior local tx per ARCHES Seizure warning Continuous daily treatment until progression to mCRPC Cost $$$
Doce + abi or daro	De novo metastatic disease per PEACE-1 and ARASENS Multiple therapies can lead to increase toxicity

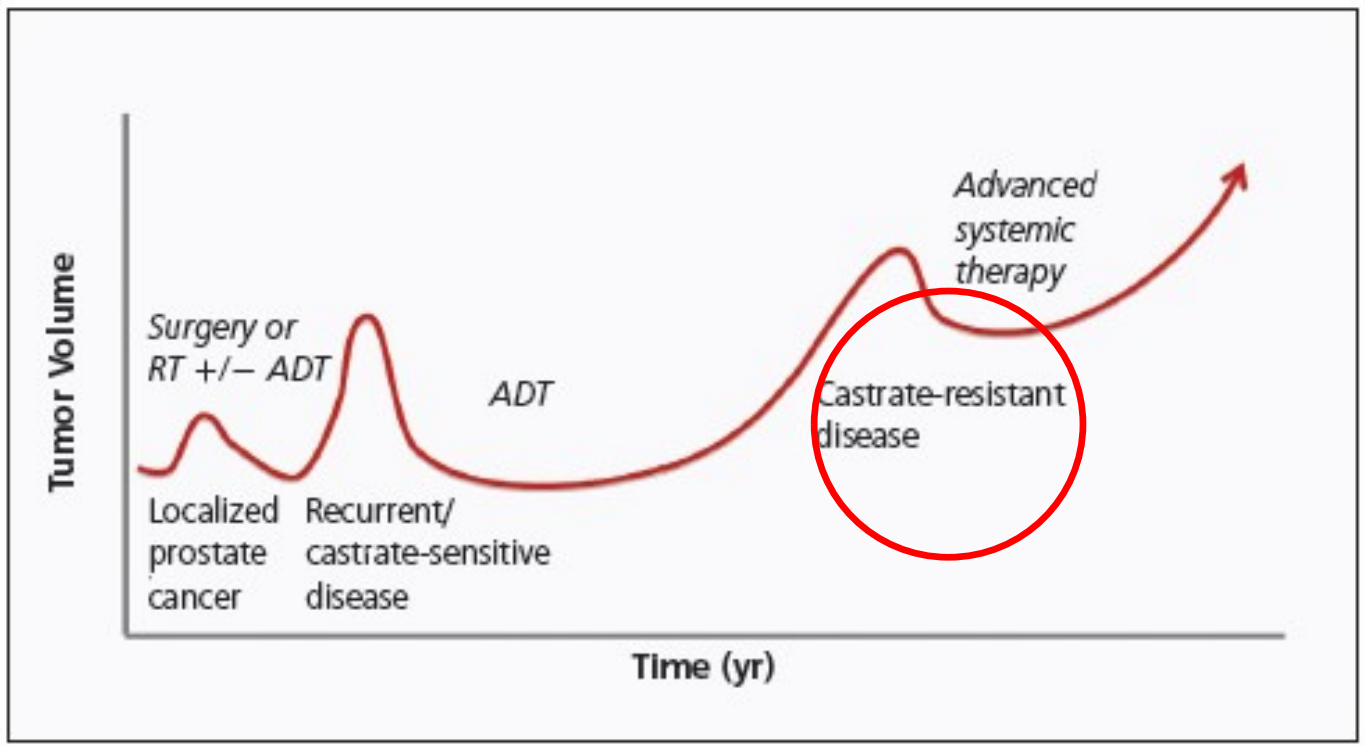
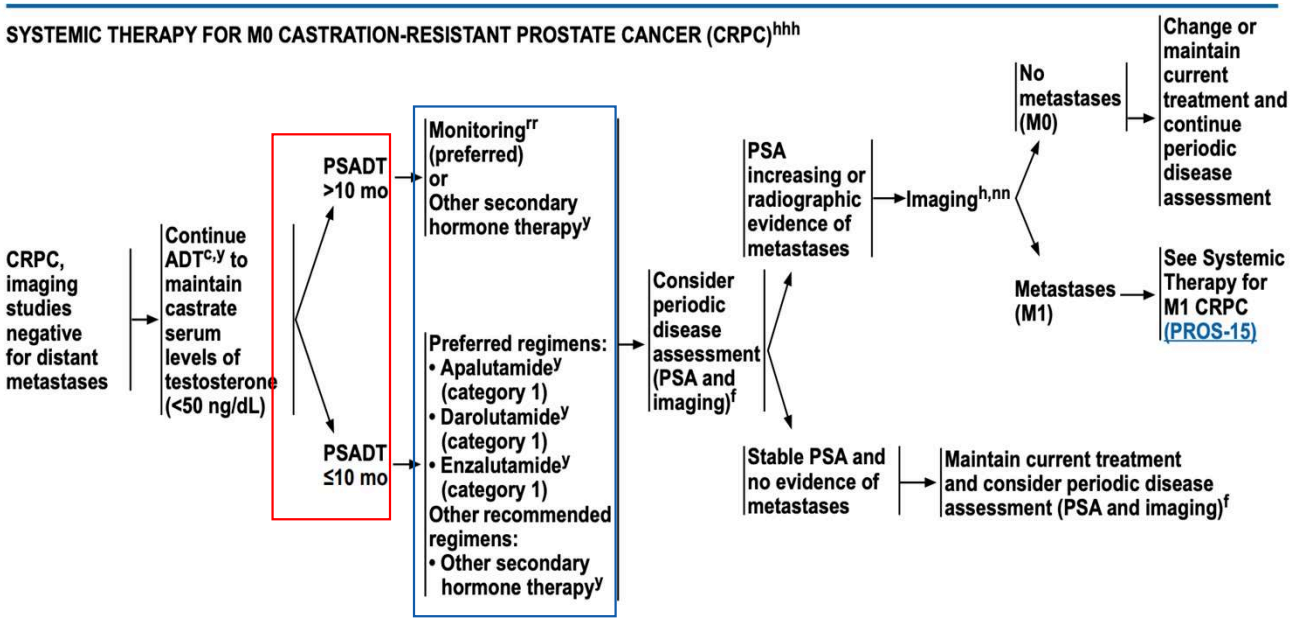


Figure: The Prostate Cancer Continuum. ADT = androgen deprivation therapy. RT = radiation therapy.

NCCN 1.2025; nmCRPC



- Rising PSA
- Castrate T
- Negative imaging

nmCRPC

Enzalutamide

- PROSPER (n = 1,401)
  - Enzalutamide 160 mg + ADT vs placebo + ADT
  - Primary endpoint = mets-free survival
    - 36.6 months vs. 14.7 months
  - Secondary endpoint = median time to subsequent CaP tx
    - 39.6 months vs. 17.7 months
  - MOA: Inhibits androgen binding to AR and inhibits AR nuclear translocation and interaction with DNA
  - SE: Myalgia, arthralgia, fatigue, hot flash, HTN; seizure warning

Sternberg C, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer
N Engl J Med 2020; 382:2197-2206

nmCRPC

Apalutamide

- SPARTAN (n = 1,207)
  - Apalutamide 240 mg + ADT vs. placebo + ADT
  - Primary endpoint = mets-free survival
    - 40.5 months vs. 16.2 months
  - MOA: androgen receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR→ prevents AR translocation, DNA binding, and AR-mediated transcription
  - SE: arthralgia, rash, anorexia, fall, hypothyroidism, fracture, diarrhea

Smith M et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; 378:1408-1418

nmCRPC

Darolutamide

- ARAMIS (n = 1,509)
  - Darolutamide 600 mg BID + ADT vs. placebo + ADT
  - Primary endpoint = mets-free survival
    - 40.4 months vs. 18.4 months
  - MOA: Inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription
  - SE: Fatigue, rash, extremity pain

* Not associated with higher risk of falls, fractures, seizures, HTN compared with placebo

Fizazi K, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019; 380:1235-1246

Comparing Non-Metastatic Castrate Resistant Treatment Options

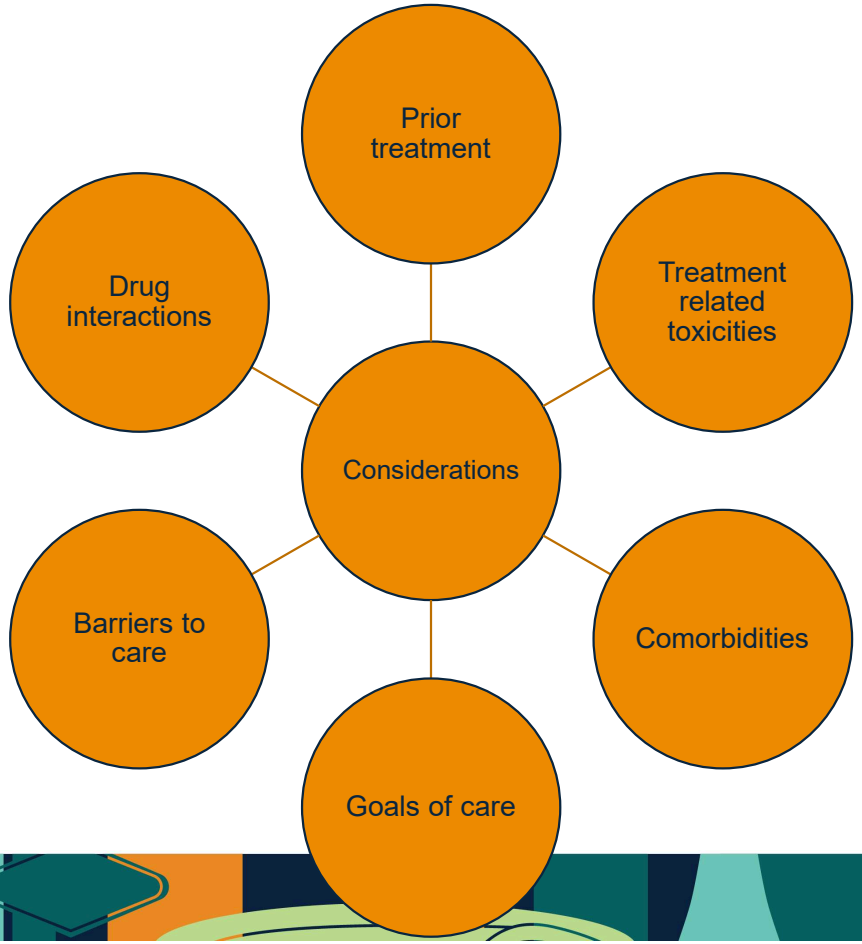
	Enzalutamide	**Apalutamide**	**Darolutamide**
Inclusion	PSA doubling time of < 10 months Baseline PSA ≥2 ng/mL	PSA doubling time of < 10 months Pelvic nodes <2 cm and below aortic bifurcation	PSA doubling time of < 10 months Baseline PSA ≥2 ng/mL, Pelvic nodes <2 cm and below aortic bifurcation
Dose	160 mg daily w/wo food	240 mg daily w/wo food	600 mg twice daily with food
ADEs	Fatigue, hypertension, dizziness, falls, fractures, headache	Fatigue, hypertension, rash, hypothyroidism, fracture	Fatigue, rash, pain in extremities, decrease in neutrophil count, increase in AST, Increase in bilirubin
Cost	$$$	$$$	$$$

AUA 2025
APRIL 26-29 Las Vegas

NCCN 1.2025; mCRPC

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[f,fff,ggg,hhh,iii]

No prior docetaxel/no prior novel hormone therapy[jjj]	Progression on prior novel hormone therapy/no prior docetaxel[jjj]
• Preferred regimens ▸ Abiraterone[z,kkk] (category 1 if no visceral metastases) ▸ Docetaxel[ddd] (category 1) ▸ Enzalutamide[z] (category 1) • Useful in certain circumstances ▸ Niraparib/abiraterone[z,lll,mmm] for *BRCA* mutation (category 1) ▸ Olaparib/abiraterone[z,kkk,lll] for *BRCA* mutation (category 1) ▸ Pembrolizumab for MSI-high (MSI-H)/dMMR[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] (category 1) ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[z]	• Preferred regimens ▸ Docetaxel (category 1)[ddd] ▸ Olaparib for *BRCA* mutation[lll] (category 1) ▸ Rucaparib for *BRCA* mutation[lll] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Niraparib/abiraterone[z,lll,mmm] for *BRCA* mutation (category 2B) ▸ Olaparib for HRR mutation other than *BRCA1/2*[lll] ▸ Pembrolizumab for MSI-H/dMMR or TMB ≥10 mut/Mb[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] (category 2B) • Other recommended regimens ▸ Other secondary hormone therapy[z]
Progression on prior docetaxel/no prior novel hormone therapy[jjj]	**Progression on prior docetaxel and a novel hormone therapy[jjj]**
• Preferred regimens ▸ Abiraterone[z,kkk] (category 1) ▸ Cabazitaxel[ddd] ▸ Enzalutamide[z] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[ddd] ▸ Niraparib/abiraterone[z, lll,mmm] for *BRCA* mutation ▸ Olaparib/abiraterone[z,kkk,lll] for *BRCA* mutation ▸ Pembrolizumab for MSI-H/dMMR[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] • Other recommended regimens ▸ Other secondary hormone therapy[z]	• Preferred regimens ▸ Cabazitaxel[ddd] (category 1) ▸ Docetaxel rechallenge[ddd] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases[ppp] (category 1) ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[ddd] ▸ Olaparib for HRR mutation[lll] (category 1 for *BRCA* mutation) ▸ Pembrolizumab for MSI-H/dMMR, or TMB ≥10 mut/Mb[ddd] ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Rucaparib for *BRCA* mutation[lll] • Other recommended regimens ▸ Other secondary hormone therapy[z]


Prior treatment
Drug interactions
Treatment related toxicities
Considerations
Barriers to care
Comorbidities
Goals of care

mCRPC: Chemotherapy

- Docetaxel
  - Approved in 2004 after showing survival advantage over mitoxantrone (3 months)
  - Microtubule inhibitor
  - Dose: 75mg/m^2 every 3 weeks with prednisone 5 mg BID x 10 cycles
  - SE: Hypersensitivity, myelosuppression, skin rash, alopecia, neuropathy, GI upset

Tannock IF, et al. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004 Oct 7;351(15):1502-12

mCRPC: Chemotherapy

- Cabazitaxel
  - Approved in 2010 after showing survival advantage over mitoxantrone (2.4 months)
  - 2nd line use for men who have already been treated with Docetaxel
  - Microtubule inhibitor
  - Dose: 25mg/m^2 every 3 weeks with prednisone 5mg BID x 10 cycles
  - SE: GI upset, renal insufficiency, neutropenia, hypersensitivity, neuropathy

de Bono JS, et al. TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010 Oct 2;376(9747):1147-54.

mCRPC: Chemotherapy

- Other SE: fatigue, asthenia, anorexia, taste change, arthralgia, alopecia, myelosuppression, electrolyte abnormalities, infusion reactions
- Venous access

mCRPC: Anti-Androgens

- Abiraterone
  - Approved in 2011 for mCRPC s/p Docetaxel after showing survival advantage vs. placebo (3.9 mos.)
  - Approved in 2012 for mCRPC pre-chemo after showing rPFS vs. placebo (8.2 mos.)
  - Oral biosynthesis inhibitor
    - Inhibits CYP17, enzyme needed for androgen synthesis in the testes, adrenals, and tumor
  - Dose: 1,000mg daily with prednisone 5mg BID
  - SE: Myalgia, edema, arthralgia, LUTS, hypokalemia, hepatotoxicity
  - Frequent monitoring for the 1st 3 months (K, LFTs, BP)

de Bono JS, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011 May 26;364(21):1995-2005.

Ryan C et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368:138-148

mCRPC: Anti-Androgens

- Enzalutamide
  - Approved in 2012 for mCRPC s/p docetaxel after showing survival advantage vs. placebo (4.8 mos.)
  - Approved in 2014 for mCRPC pre-chemo after showing rPFS vs. placebo (65% rPFS vs. 14%)
  - Oral androgen receptor inhibitor
    - Inhibits androgen binding to AR and inhibit AR nuclear translocation and interaction with DNA
  - Dose: 160mg daily
  - SE: Myalgia, arthralgia, fatigue, hot flash; seizure warning

Scher HI, et al.; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep 27;367(13):1187-97.

Beer T et al. Enzalutamide in metastatic prostate [illegible] therapy. [illegible] J Med 2014; 37[illegible] 433

Cross resistance

- 20-40% of pts. presents with primary resistance to abi and enza (i.e., no initial PSA response)
- Secondary resistance invariably develops
- Androgen receptor (AR) signaling axis very complex
- Many mechanisms alter the AR-axis signaling process, which leads to disease progression and/or treatment resistance
  - AR amplification, AR overexpression, AR somatic point mutations, AR splice variants, altered intratumoral androgen biosynthesis
  - One example of AR-V7

mCRPC: Immunotherapy

- Sipuleucel-T
  - Approved in 2010 after showing survival advantage over placebo (4.1 mos.)
    - Asymptomatic or minimally symptomatic
  - Autologous cellular immunotherapy
    - Minimum of 50 million CD54+ cells
  - Dose: Pheresis, IV infusion every other week x 3 doses
  - SE: Chills, fever, fatigue, myalgia, infusion reaction
  - PSA changes will not be immediate

Kantoff P, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411-422

mCRPC: Radiopharmaceutical

- Radium 223
  - Approved in 2013 after showing survival advantage vs. placebo (3.6 mos.)
    - Symptomatic bones mets and no visceral mets
  - Alpha particle-emitting radioactive agent
    - Isotope mimics calcium and forms complexes with bone mineral at areas of increased bone turnover
  - Dose: 50kBq/kg IV q 4 weeks x 6 doses
  - SE: Myelosuppression, nausea, diarrhea
  - PSA difficult to follow

Parker C et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369:213-223

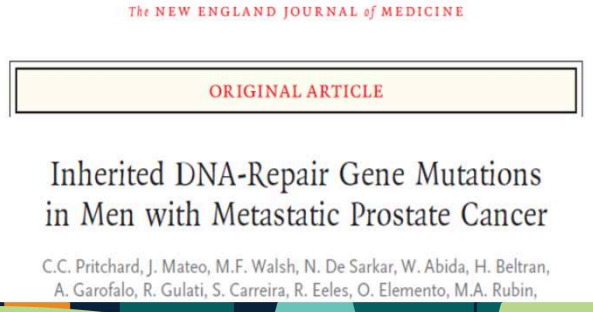
mCRPC: Radiopharmaceutical

- Lutetium Lu-177
  - Approved in 2022 after showing mOS of 15.3 months vs 11.3 months (best supportive care alone)
  - Radioligand; lutetium-177 is linked to a moiety that binds to PSMA and delivers radiation to PSMA-expressing cells
  - Had to have had at least one AR pathway inhibitor, and 1 or 2 prior chemos
  - Must have PSMA positive PET (at least 1 tumor with uptake greater than normal liver)
  - Dose: 7.4 GBq every 6 weeks for 6 doses
  - SE: fatigue, dry mouth, nausea, anemia

Sartor O et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021; 385:1091-1103

Genetics of metastatic prostate cancer

- Sequencing of germline DNA from 692 mPC patients demonstrated 11.8% had mutation in DNA-repair gene
  - BRCA2- 5.3%
  - ATM- 1.6%
  - CHEK2- 1.9%
  - BRCA1- 0.9%
- Germline screening is recommended for all patients with metastatic prostate cancer and for high/very high risk localized. Consider also based on family history, histology, personal h/o other cancers
- Somatic testing


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin,

mCRPC: Special circumstances

- Mutations in BRCA1, BRCA2, ATM, PALB2
  - Consider PARP Inhibitor
  - PROfound study: Olaparib in mCRPC w/ homologous recombination repair (HRR) deficiency s/p abi or enza
  - TRITON 2 study: Rucaparib for patients with BRCA-mutations (germline and/or somatic) s/p antiandrogen and chemo
  - PROpel study: Olaparib + abi/pred; no prior systemic tx for mCRPC
  - TALAPRO-2: Talazoparib + enza vs enza + placebo
- Microsatellite instability (MSI- high of deficient mismatch repair [dMMR])
  - Consider pembrolizumab

Comparing Metastatic Castrate Resistant Treatment Options

Agent	Place in therapy
Sipuleucel-T	Asymptomatic minimally symptomatic, should be used early in therapy when disease burden is lower and immune system intact
Radium 223	Symptomatic bone metastasis only
Abiraterone	May be less effective after enzalutamide treatment
Enzalutamide	May be less effective after abiraterone treatment
Docetaxel	Visceral metastasis present, chemotherapy naïve
Cabazitaxel	Previously treated with docetaxel
Lutetium	Requires PSMA + PET and 2 lines of prior therapy
Pembrolizumab	Microsatellite instability (MSI) – high or deficient mismatch repair (dMMR), second and subsequent lines of therapy
PARP Inhibitors	Mutations in BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, second and subsequent lines of therapy

Practical considerations

- Promoting adherence to PO therapies and treatment schedules
- Evaluating barriers to care
- Providing education about treatments (rationale, schedule, MOA, toxicities, etc.)
- Identifying resources at your institution and elsewhere
- Professional education to keep up with the growing landscape
- Partnering with other disciplines

Future Directions

- Combination therapy
- Correct sequencing
- Gene Expression Testing
- Other agents: PARPi, new antiandrogens targeting splice variants, agents targeting N-terminal domain of AR, radioisotope therapy, etc
- Immunotherapy (in trials)
  - Vaccines + PD-1
  - Combo CPI
  - Targeted therapy + PD-1

FYI re: systemic treatment in non-mets prostate cancer

- Very high risk: EBRT + ADT + abiraterone
  - Other options, but this one is unique given addition of oral antiandrogen
  - In STAMPEDE trial, patients had two of the following: cT3-4, Grade Group 4 or 5 and PSA > 40
- Regional risk group (Any T, N1, M0)
  - EBRT + ADT + abiraterone (for 2 years)
  - EBRT + ADT
  - ADT with or without abiraterone
  - RP + PLND
- nmCSPC (BCR)
  - Monitoring
  - ADT
  - Enzalutamide +/-leuprolide
  - Apalutamide +/- leuprolide

Advanced Prostate Cancer

- There is no cure for metastatic prostate cancer
- Shared decision making is important
- Clinical trials
- Always incorporate best supportive care
- Advanced Care Planning
- Caregivers
- Cancer care is complicated!
- Always let patients know that just because there are multiple treatment options does not mean that they have to exhaust them

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RENAL CANCER

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Mary W. Dunn, MSN, RN, OCN, NP-C

none

Renal Cancer Overview/epidemiology

Account for 2 -3% of all cancer deaths in USA each year

Median age of diagnosis 65, median age of death is 70

Rate increased by 2% per year over the past 65 years

90% renal tumors are RCC, with 85% clear cell type

5 year survival: stage I 96%, II: 82%; III: 64%; IV: 23%

Smoking and obesity possible risk factors, hereditary type RCC (Von Hippel-Lindau disease)

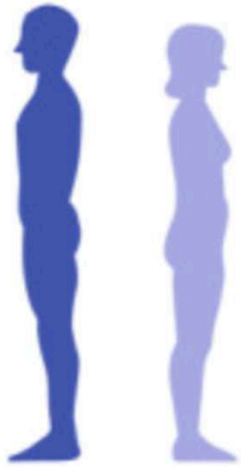
Surgical resection remains the only effective therapy for clinical localized RCC

- Account for 2 -3% of all cancer deaths in USA each year
- Median age of diagnosis 65, median age of death is 70
- Rate increased by 2% per year over the past 65 years
- 90% renal tumors are RCC, with 85% clear cell type
- 5 year survival: stage I 96%, II: 82%; III: 64%; IV: 23%
- Smoking and obesity possible risk factors, hereditary type RCC (Von Hippel-Lindau disease)
- Surgical resection remains the only effective therapy for clinical localized RCC

2024Kidney Cancer Statistics
(new cases)

Estimated New Cases

Male			Female		
Prostate	313,780	30%	Breast	316,950	32%
Lung & bronchus	110,680	11%	Lung & bronchus	115,970	12%
Colon & rectum	82,460	8%	Colon & rectum	71,810	7%
Urinary bladder	65,080	6%	Uterine corpus	69,120	7%
Melanoma of the skin	60,550	6%	Melanoma of the skin	44,410	4%
Kidney & renal pelvis	52,410	5%	Non-Hodgkin lymphoma	35,210	4%
Non-Hodgkin lymphoma	45,140	4%	Pancreas	32,490	3%
Oral cavity & pharynx	42,500	4%	Thyroid	31,350	3%
Leukemia	38,720	4%	Kidney & renal pelvis	28,570	3%
Pancreas	34,950	3%	Leukemia	28,170	3%
All sites	**1,053,250**		**All sites**	**988,660**	

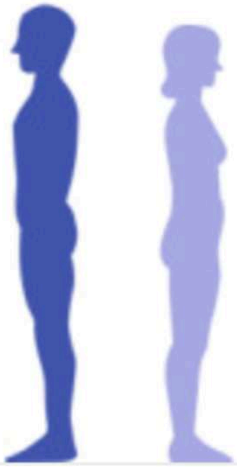


Siegel RL et al. *CA Cancer J Clin 2025 Jan-Feb;74(1):12-49.*

2024 Kidney Cancer Statistics
(mortality)

Estimated Deaths

Male			Female		
Lung & bronchus	64,190	20%	Lung & bronchus	60,540	21%
Prostate	35,770	11%	Breast	42,170	14%
Colon & rectum	28,900	9%	Pancreas	24,930	8%
Pancreas	27,050	8%	Colon & rectum	24,000	8%
Liver & intrahepatic bile duct	19,250	6%	Uterine corpus	13,860	5%
Leukemia	13,500	4%	Ovary	12,730	4%
Esophagus	12,940	4%	Liver & intrahepatic bile duct	10,840	4%
Urinary bladder	12,640	4%	Leukemia	10,040	3%
Non-Hodgkin lymphoma	11,060	3%	Non-Hodgkin lymphoma	8,330	3%
Brain & other nervous system	10,170	3%	Brain & other nervous system	8,160	3%
All sites	**323,900**		**All sites**	**294,220**	



Siegel RL et al. *CA Cancer J Clin 2025 Jan-Feb;74(1):12-49.*

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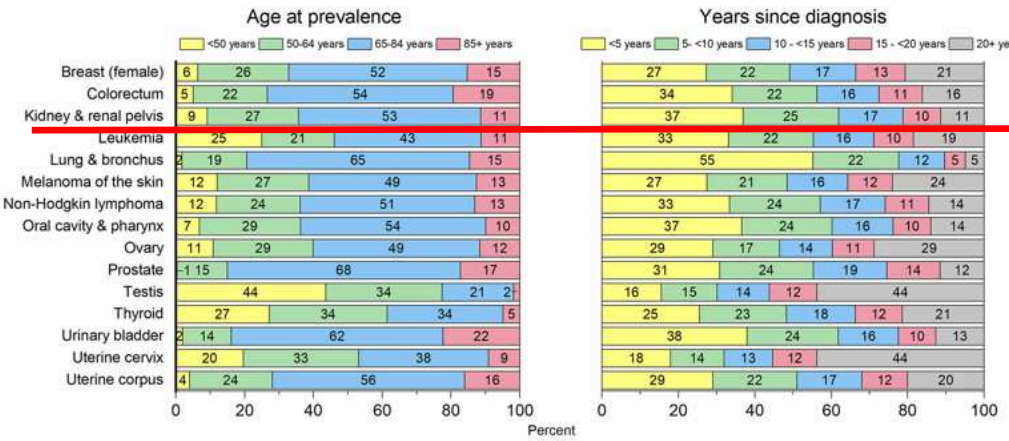
Prevalence by Cancer Type, Years Since Diagnosis, and Age at Prevalence



CA A Cancer J Clinicians, Volume: 72, Issue: 5, Pages: 409-436, First published: 23 June 2022, DOI: (10.3322/caac.21731)

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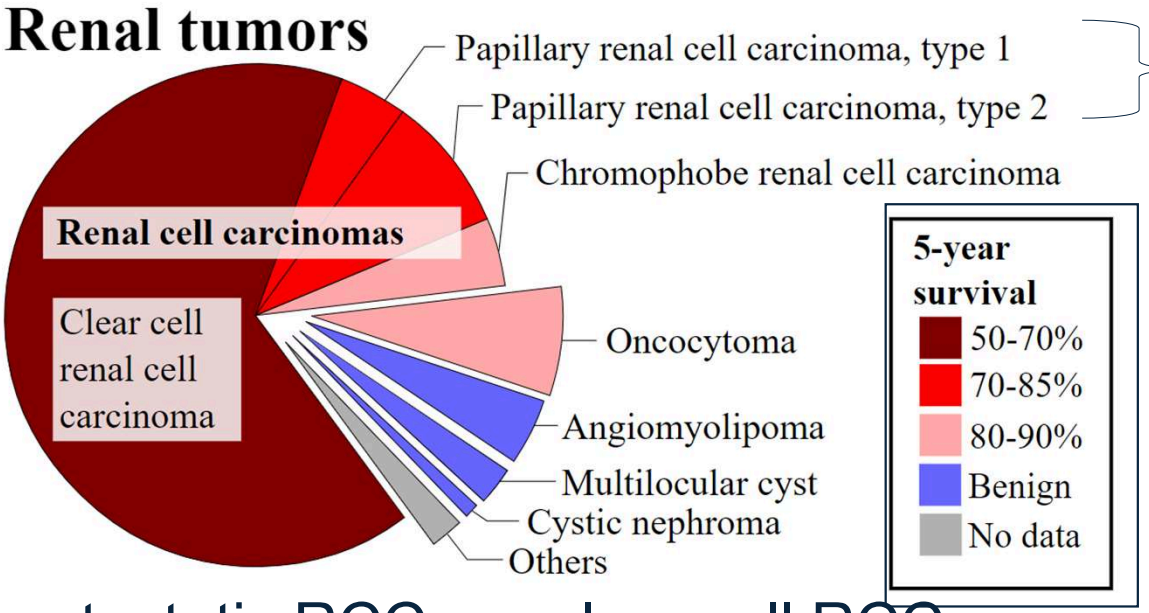
Histologic Classification

- RCC is a heterogeneous disease! ⟹ Clear Cell / Non clear cell



Papillary RCC

- >90% of all metastatic RCC are clear cell RCC

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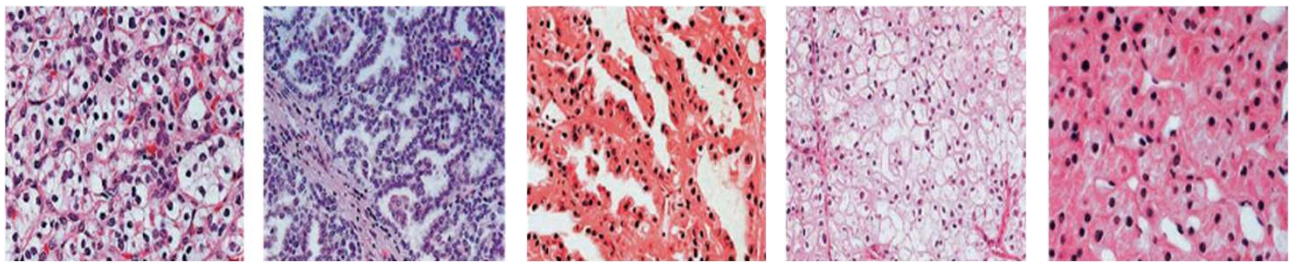
Histological Classification of Human Renal Epithelial Neoplasms

RCC



Type	**Clear cell**	Papillary type 1	Papillary type 2	Chromophobe	Oncocytoma
Incidence (%)	***75%***	*5%*	*10%*	*5%*	*5%*
Associated mutations	***VHL***	*c-Met*	*FH*	*BHD*	*BHD*

BHD=Birt-Hogg-Dubé; FH=fumarate hydratase; VHL=von Hippel-Lindau.

Modified from Linehan WM et al. *J Urol*. 2003;170:2163-2172.

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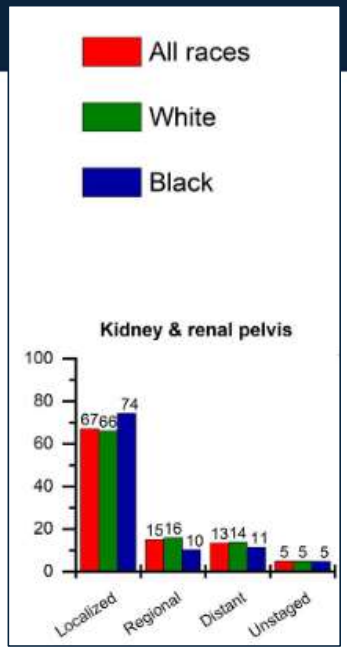
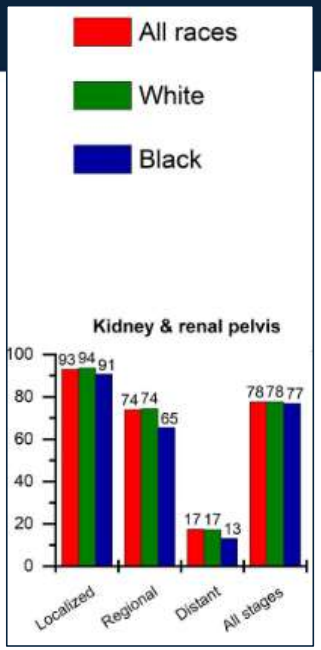
Staging – Renal Cancer

- cT1 – tumor confined to the kidney, measuring <7 cm
  - T1a: ≤ 4cm
  - T1b: 4-7 cm
- cT2 – tumor confined to the kidney, measuring > 7 cm
- cT3 – includes 1 or more of the following
  - Perinephric fat within Gerota's fascia
  - Renal vein or vena caval involvement with tumor thrombus
- cT4 – includes 1 or more of the following
  - Beyond Gerota's fascia
  - Into adjacent organs (spleen, liver, bowel, muscle)



Stage at Presentation
2016 - 2020

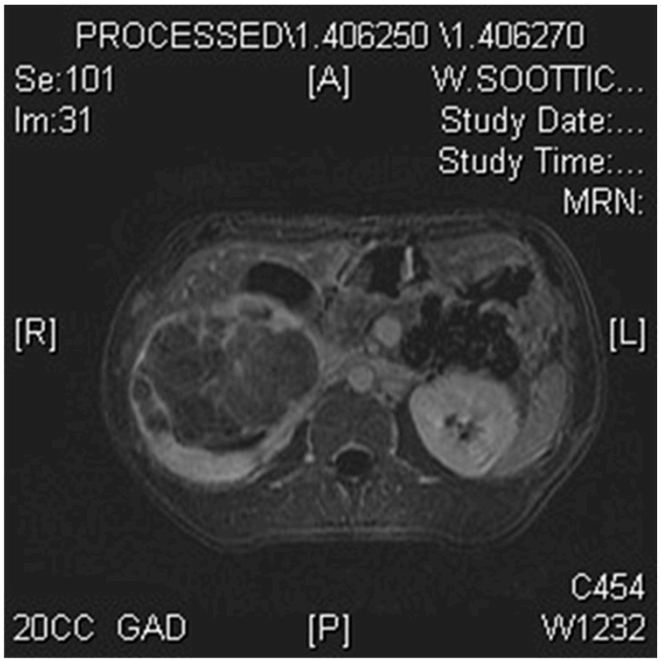


Survival by Stage and Race
2013 - 2019

Approximately 25-30% of Renal Cell Carcinoma is metastatic at presentation

Siegel RL et al. *CA Cancer J Clin 2024 Jan-Feb;74(1):12-49.*

- Small Renal Masses (<4 cm) – Usually incidental findings (MVA, Back pain, Appendicitis, etc)
- Obtain Imaging – CT a/p c and s, or MRI a/p c and s, CMP (assess renal function), chest imaging
- Obtain urine cytology if gross hematuria or microscopic hematuria, or if question of urothelial vs renal cancer



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Chemotherapy

- RCC is only minimally responsive to chemotherapy
- 83 clinic trials involving over 4000 pts, overall response rate is only 6%
- Limited data reveals some response in non-clear cell RCC to Carboplatin, Cisplatin plus Gemcitabine

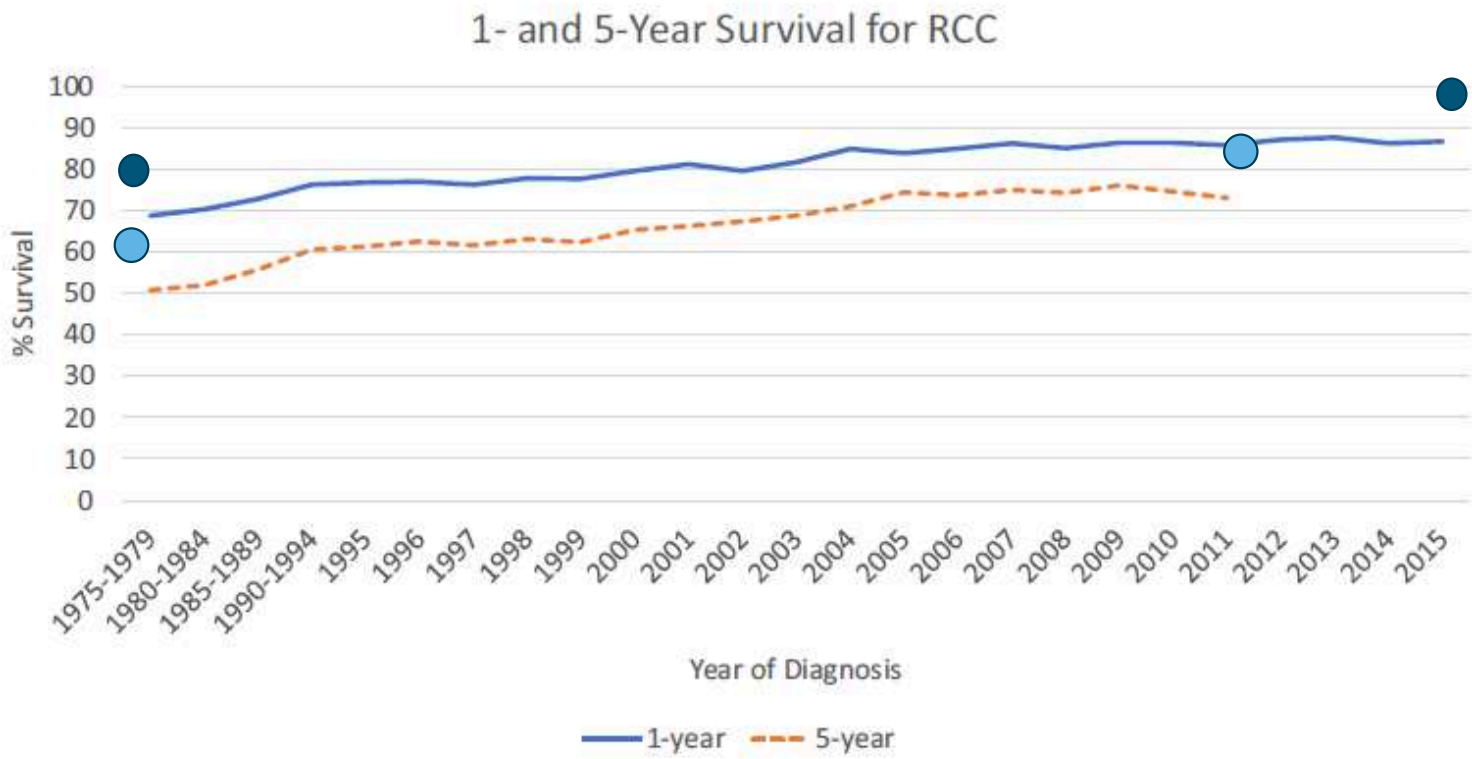

Figure 1. Advances in therapy for RCC have led to increased 1- and 5-year survival rates for patients with RCC.

Huang and Hsieh Semin Nephrol 40:28−41 2020

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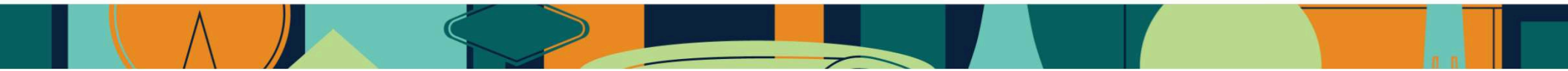
Evidence of an Immunological Role in Combating RCC



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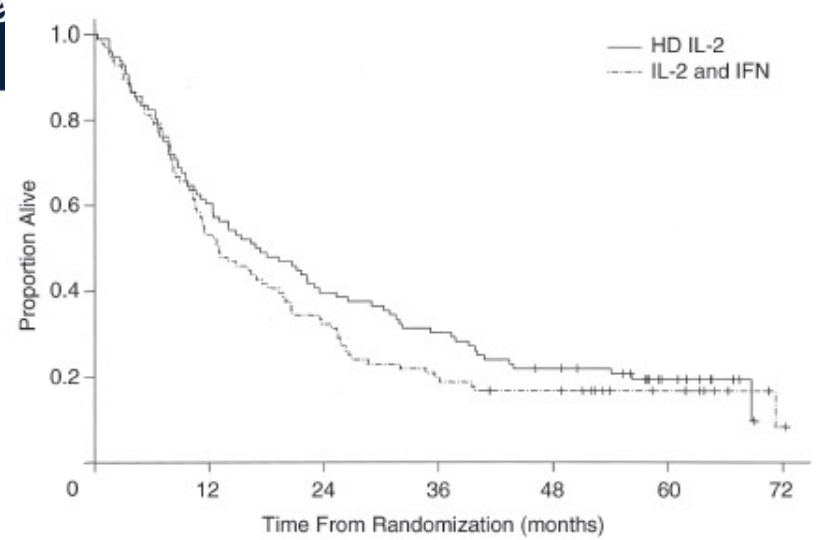
Role of Immunological Responses in Kidney Cancer

- Spontaneous remissions have been documented.
- Abscopal effect: regression of metastases after treatment of primary tumor
- Increased risk of cancer in immunodeficient states
- Tumor infiltrating lymphocytes (TILs)
  - Lymphocytes have been found within tumors.
  - Isolated and expanded TILs have been the focus of experimental therapies.

Cytokines and cytokine regimen used in renal cell carcinoma

- Interferon α
- Interleukin -2
- Interferon α + interleukin -2
- Interferon α + vinblastin
- Interferon α + *cis*- retinoic acid
- Interferon α + interleukin -2+ 5- fluorouracil



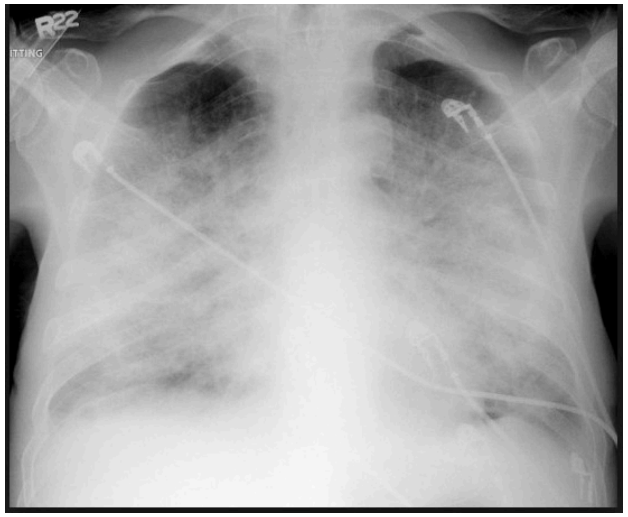
- CR rate 8% v 3%
- Durable CR rate of 7.4% v 0%
- Median OS 17.5 mos v 13 mos
- The only FDA approved therapy to have long-term CR with > 10 year follow-up

- The PROCLAIM database has been capturing data on patients who received HD-IL-2 in more recent years (e.g. 2011-present)
- RR is ~ 15%, CR rate is ~ 5-8%, SD rate ~ 15%

Adverse effects of IL-2
Capillary leak syndrome

Increased capillary permeability

- Fluid retention
- Interstitial edema
- Hypotension
- Intrarenal vasoconstriction
- Acute Kidney Injury



Administration of IL2

- Recommendations for patient management:
  - Monitored bed
  - Central line
  - IVF resuscitation with colloid (hetastarch, albumin)
  - Cooling blanket/acetaminophen (shake n bake)
  - Judicious diuretic use
  - Thoracentesis for symptomatic pleural effusion

Immunotherapy – IL-2

- Lower dose IL-2 IV therapy
  - Only 4% resp rate c/w 16% for std dosing and 11% for SC dosing.
  - Low dose IL-2 and SC dosing had less toxicity
- Repeat IL-2 treatment
  - For pts who respond and then relapse, only 2% will respond to the same IL-2 regimen

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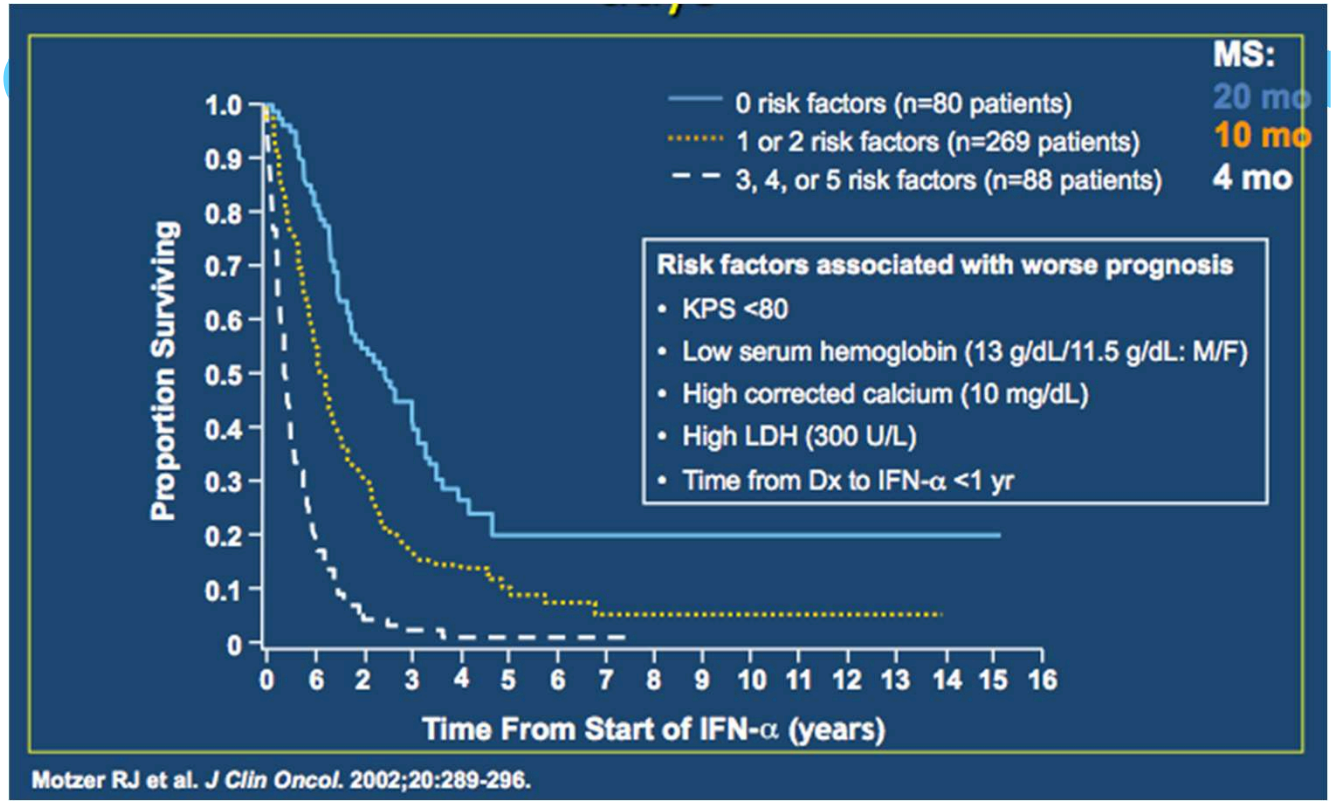
Immunotherapy for Metastatic RCC

- Interferon alpha
  - Approx 15% resp rate
  - Median time to response 4 mo
  - Often short-lived and/or partial responses
  - Largest study to evaluate long-term outcome (Motzer et al, JCO 2002)
    - Retrospective review of 463 pts on 6 trials
    - Median OS 13 mo
    - 14% 2yr PFS

MSK lays


MS:
20 mo
10 mo
4 mo
0 risk factors (n=80 patients)
1 or 2 risk factors (n=269 patients)
3, 4, or 5 risk factors (n=88 patients)
Risk factors associated with worse prognosis
• KPS <80
• Low serum hemoglobin (13 g/dL/11.5 g/dL: M/F)
• High corrected calcium (10 mg/dL)
• High LDH (300 U/L)
• Time from Dx to IFN-α <1 yr
Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 6 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Time From Start of IFN-α (years)
Motzer RJ et al. J Clin Oncol. 2002;20:289-296.

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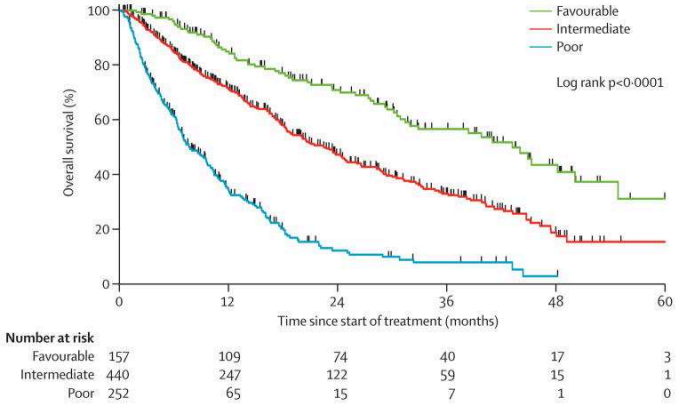
Metastatic Disease: Risk Models

Kevin Zarrabi, MD

- 1st Step: Risk Classification
  - International Metastatic Renal Cell Carcinoma Disease Consortium (IMDC) Risk Model

Prognostic Factors	Risk Groups
KPS less than 80%	Favorable Risk: If patient has 0 factors
Diagnosis to treatment interval less than 1 yr	
Anemia	Intermediate Risk: If patient has 1-2 factors
Hypercalcemia	
Neutrophilia	High Risk: If patient has 3-6 factors
Thrombocytosis	



Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, Mackenzie M, Wood L, Donskov F, Tan MH, Rha SY, Agarwal N, Kollmannsberger C, Rini BI, Choueiri TK. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 2013 Feb;14(2):141-8.

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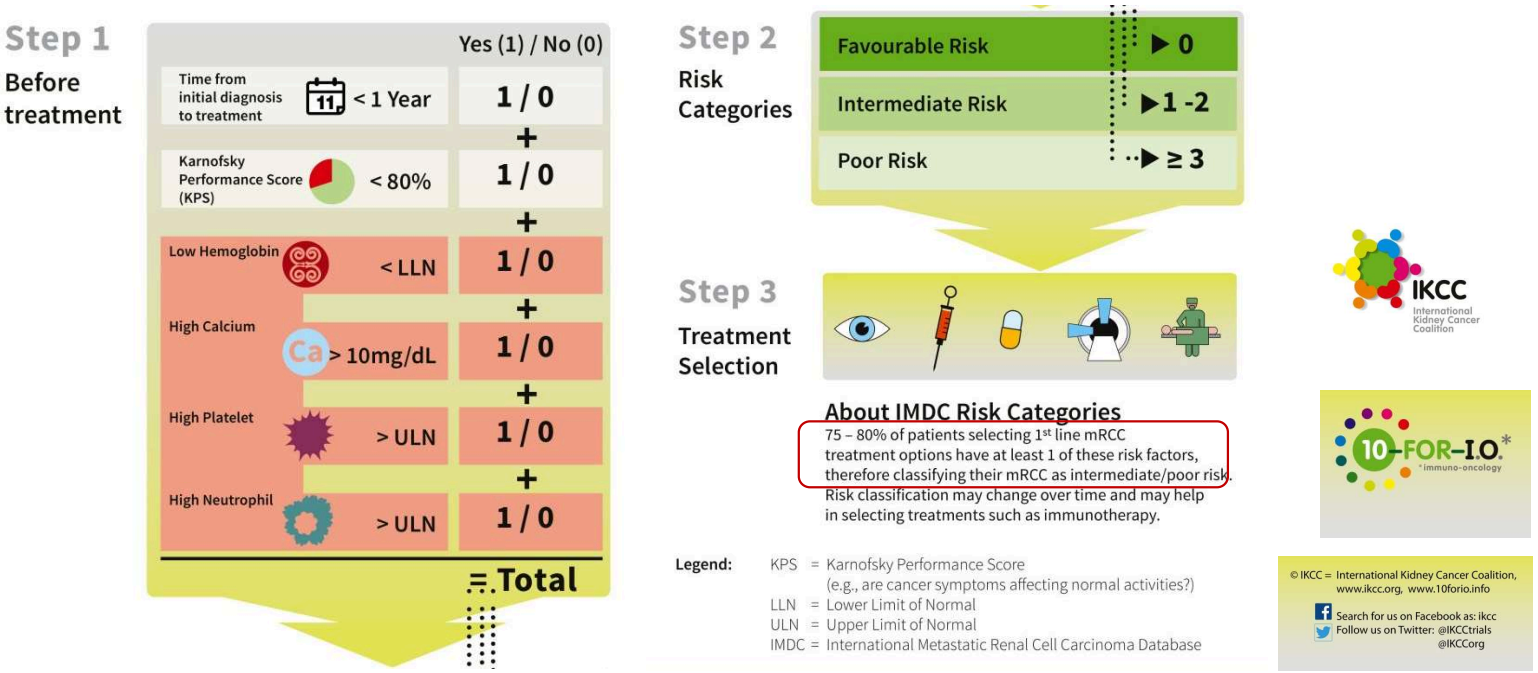
IMDC (Heng) Criteria for Metastatic RCC



About IMDC Risk Categories

75 – 80% of patients selecting 1st line mRCC treatment options have at least 1 of these risk factors, therefore classifying their mRCC as intermediate/poor risk. Risk classification may change over time and may help in selecting treatments such as immunotherapy.

Legend:

KPS = Karnofsky Performance Score (e.g., are cancer symptoms affecting normal activities?)
LLN = Lower Limit of Normal
ULN = Upper Limit of Normal
IMDC = International Metastatic Renal Cell Carcinoma Database

IKCC International Kidney Cancer Coalition

10-FOR-I.O.* *immuno-oncology

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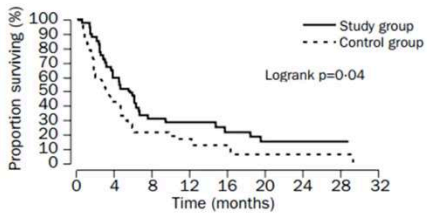
Metastatic Disease: Cytoreductive Nephrectomy

- 2nd Step: Should we remove the kidney/primary tumor?

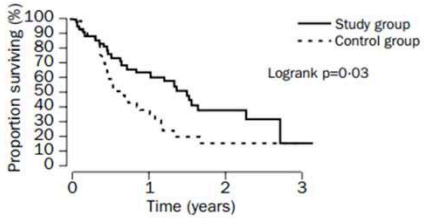
Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial

G H J Mickisch, A Garin, H van Poppel, L de Prijck, R Sylvester, and members of the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group



	Observed number of events	Number of patients at risk							
Study group	32	42	23	12	10	7	4	2	1
Controls	37	42	17	8	5	2	1	1	1

Figure 2: **Kaplan-Meier curves showing time to progression**



	Observed number of events	Number of patients at risk			
Study group	25	42	22	7	1
Controls	30	42	12	2	0

Figure 3: **Kaplan-Meier curves showing overall survival**

Prior to TKI era: Very common (SOC) to pursue cytoreductive nephrectomy.

Cytoreductive Nephrectomy in Patients with Metastatic Renal Cancer: A Combined Analysis

Flanigan et al. SWOG & EORTC, *J Urology 2004; 171: 1071-6.*

Nearly all patients received systemic therapy

CONCLUSIONS:

- Cytoreductive nephrectomy offers surv… advantage (31% decrease death rate, 5.8 mon… advantage)
- Highest benefit in pts with perf…nce status 0
- Minimal surgical complic…, only 5.6% did not proceed on to IFN tre…t after nephrectomy

CRITICISM:

- Mode… …efit
- L… accrual period: 7 years for 246 pts with 80 institutions

Cytoreductive Nephrectomy in The Wrong Patient

- Surgery in poor candidates may worsen outcome
- May limit receipt of systemic therapy (~50% of high risk patients)

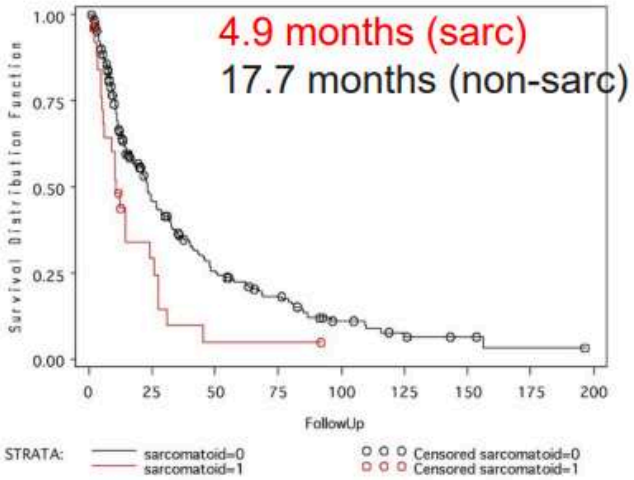


Figure 3. Kaplan-Meier analysis of overall survival (months) of sarcomatoid and nonsarcomatoid groups able to proceed to systemic therapy.

Shuch et al *Cancer* 2008
Tumor factors

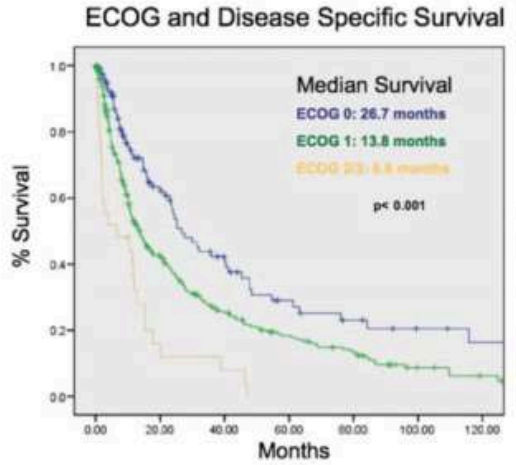


FIGURE 1. This chart illustrates disease-specific survival for patients with renal cell carcinoma who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, and 2.

J Urol 2009
Patient factors

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Metastatic Disease: Cytoreductive Nephrectomy

- **2nd Step: Should we remove the kidney/primary tumor?**
  - Prior to TKI era: Very common (SOC) to undergo cytoreductive nephrectomy.
  - Then came CARMENA and SURTIME

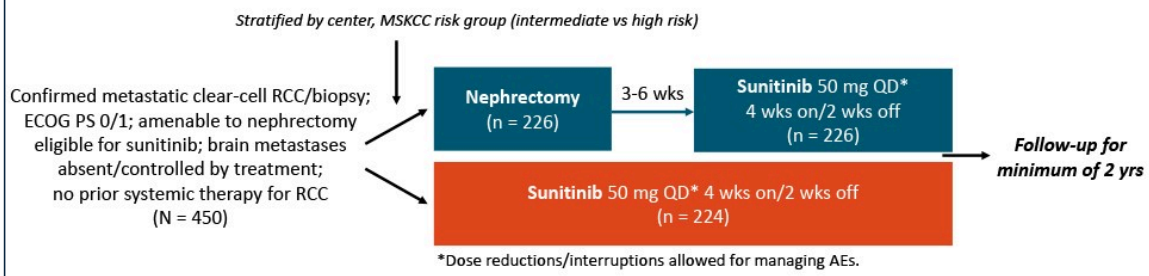
ORIGINAL ARTICLE

Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

Arnaud Méjean, M.D., Ph.D., Alain Ravaud, M.D., Ph.D., Simon Thezenas, Ph.D., Sandra Colas, M.D., Jean-Baptiste Beauval, M.D., Karim Bensalah, M.D., Ph.D., Lionnel Geoffrois, M.D., Antoine Thiery-Vuillemin, M.D., Ph.D., Luc Cormier, M.D., Ph.D., Hervé Lang, M.D., Ph.D., Laurent Guy, M.D., Ph.D., Gwenaelle Gravis, M.D., et al.

Carmena

- Multicenter, randomized, open-label noninferiority phase III trial



- Primary endpoint: OS
- Secondary endpoints: PFS, ORR (RECIST v1.1), clinical benefit, safety

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Metastatic Disease: Cytoreductive Nephrectomy

- 2nd Step: Should we remove the kidney/primary tumor?
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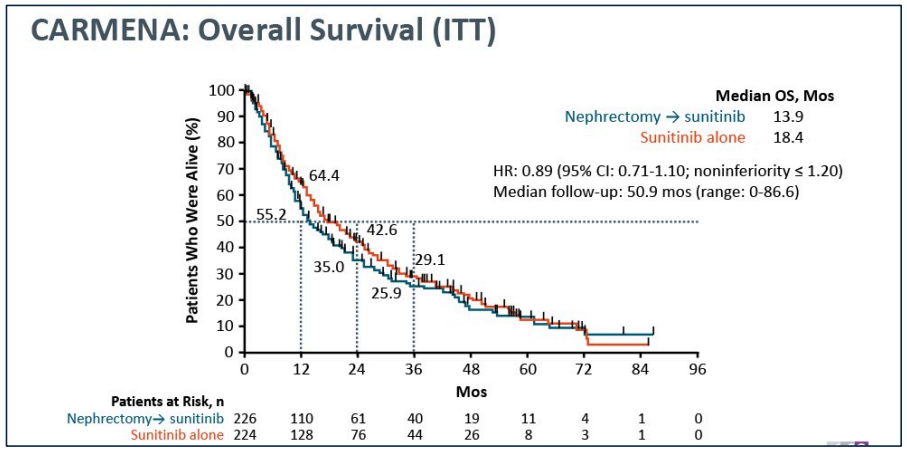

- Non-Inferiority; prospective
- 1:1 mccRCC for nephrectomy to undergo nephrectomy and then receive sunitinib vs to receive sunitinib alone.
- In the intention-to-treat population, patients in the sunitinib-alone group had a longer median overall survival than those in the nephrectomy–sunitinib group 18.4 months vs 13.9 months
- In the nephrectomy–sunitinib group, 16 patients (7.1%) did not undergo nephrectomy and 40 (17.7%) never received sunitinib
- In the sunitinib-alone group, 11 patients (4.9%) never received sunitinib and 38 (17.0%) underwent subsequent nephrectomy

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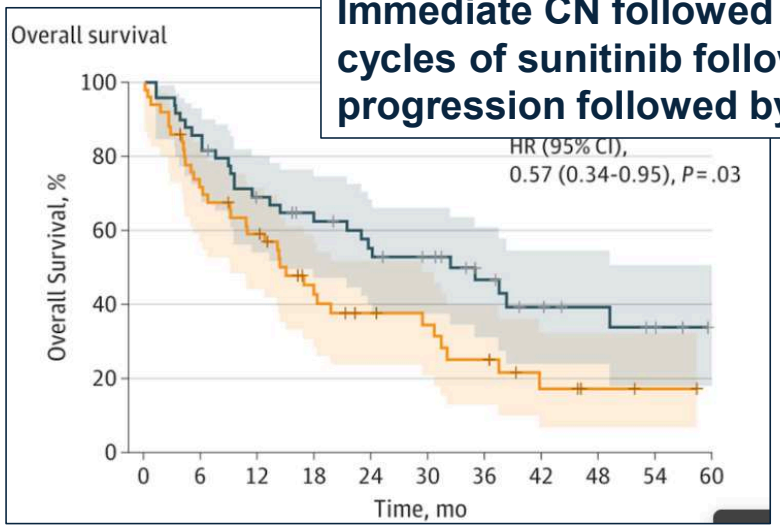
JAMA Oncology | Original Investigation

Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib
The SURTIME Randomized Clinical Trial

Axel Bex, MD, PhD; Peter Mulders, MD, PhD; Michael Jewett, MD; John Wagstaff, MD; Johannes V. van Thienen, MD, PhD; Christian U. Blank, MD, PhD; Roland van Velthoven, MD, PhD; Maria del Pilar Laguna, MD, PhD; Lori Wood, MD, PhD; Harm H. E. van Melick, MD, PhD; Maureen J. Aarts, MD, PhD; J. B. Lattouf, MD; Thomas Powles, MD; Igle Jan de Jong, MD, PhD; Sylvie Rottey, MD, PhD; Bertrand Tombal, MD, PhD; Sandrine Marreaud, MD; Sandra Collette, MSC; Laurence Collette, PhD; John Haanen, MD

JAMA Oncol. Published online December 13, 2018

Immediate CN followed by sunitinib therapy vs treatment with 3 cycles of sunitinib followed by CN in the absence of progression followed by sunitinib therapy.



…entical
…ratio of
deferred vs immediate CN was 0.57

- In the deferred CN arm, 48 of 49 patients (98%) received sunitinib vs 40 of 50 (80%) in the immediate arm.
- Systemic progression before planned CN in the deferred CN arm resulted in a per-protocol recommendation against nephrectomy in 14 patients (29%) – selects for patients who may benefit from 2nd line systemic therapy

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Metastatic Disease: Cytoreductive Nephrectomy

- 2nd Step: Should we remove the kidney/primary tumor?
  - Prior to TKI era: Very common (SOC) to undergo cytoreductive nephrectomy.
  - Then came CARMENA and SURTIME

Answer: Not necessarily, especially for patients who are IMDC poor risk or who have high risk tumors. May prevent future systemic therapy or earlier 2nd line systemic therapy.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Kidney Cancer

NCCN Guidelines Index
Table of Contents
Discussion

GENERAL PRINCIPLES OF MANAGEMENT FOR RENAL CELL CARCINOMA

- Nephron-sparing surgery (partial nephrectomy) is recommended in select patients, such as:
  - Patients with unilateral stage I–III tumors, where technically feasible
  - Patients with uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer
  - Patients at relative risk for developing progressive chronic kidney disease due to young age or medical risk factors (ie, hypertension, diabetes, nephrolithiasis)

- Open, laparoscopic, or robotic surgical techniques may be used to perform radical and partial nephrectomies.

- Regional lymph node dissection is optional but should be considered for patients with resectable adenopathy on preoperative imaging or palpable/visible adenopathy at time of surgery.

- If adrenal gland is uninvolved, adrenalectomy may be omitted.

- Special teams or referral to high-volume centers may be required for extensive inferior vena cava involvement.

- Thermal ablation (eg, cryosurgery, radiofrequency ablation, microwave ablation) is an option for the management of clinical stage T1 renal lesions.
  - Thermal ablation is suitable for renal masses ≤3 cm.
  - Thermal ablation is an option for clinical T1b masses in select patients not eligible for surgery.
  - Biopsy of lesions is recommended to be done prior to or at time of ablation.
  - Ablative techniques may require retreatment to achieve the same local oncologic outcomes as conventional surgery.[1,2]

- SBRT is considered an ablative therapy and may be considered for non-optimal surgical candidates with stage I (category 2B), II, or III (both category 3) kidney cancer (KID-1).

- Active surveillance is an option for the initial management of clinical stage T1 renal lesions, for example:
  - It is an option for renal masses <2 cm given the high rates of benign tumors and low metastatic potential of these masses.
  - Active surveillance of patients with T1a tumors (≤4 cm) that have a predominantly cystic component is recommended.
  - It is an option for patients with clinical stage T1 masses and significant competing risks of death or morbidity from intervention.
  - Active surveillance entails serial abdominal imaging with timely intervention should the mass demonstrate changes (eg, increasing tumor size, growth rate, infiltrative pattern) indicative of increasing metastatic potential.
  - Active surveillance should include periodic metastatic survey including blood work and chest imaging, particularly if the mass demonstrates growth.

- Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have:
  - Excellent performance status (ECOG PS <2)
  - No brain metastasis

- Patients either with large-volume distant metastases or tumors with large sarcomatoid burdens should receive systemic therapy prior to cytoreductive nephrectomy.

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Metastatic Disease

- ✓ • Risk Stratified
- ✓ • Consider cytoreductive nephrectomy
  - Step 3: Do we need to start systemic therapy immediately?

Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial

Brian I Rini, Tanya B Dorff, Paul Elson, Cristina Suarez Rodriguez, Dale Shepard, Laura Wood, Jordi Humbert, Linda Pyle, Yu-Ning Wong, James H Finke, Patricia A Rayman, James M G Larkin, Jorge A Garcia, Elizabeth R Plimack

Active Surveillance of Metastatic Renal Cell Carcinoma: Results From a Prospective Observational Study (MaRCC)

Michael R. Harrison, MD [1]; Brian A. Costello, MD[2]; Nrupen A. Bhavsar, PhD[1]; Ulka Vaishampayan, MD[3]; Sumanta K. Pal, MD [4]; Yousef Zakharia, MD[5]; Heather S. L. Jim, PhD [6]; Mayer N. Fishman, MD[6]; Ana M. Molina, MD[7]; Christos E. Kyriakopoulos, MD[8]; Che-Kai Tsao, MD[9]; Leonard J. Appleman, MD[10]; Benjamin A. Gartrell, MD[11,12]; Arif Hussain, MD[13]; Walter M. Stadler, MD [14]; Neeraj Agarwal, MD[15]; Russell K. Pachynski, MD[16]; Thomas E. Hutson, DO[17]; Hans J. Hammers, MD[18]; Christopher W. Ryan, MD[19]; Brant A. Inman, MD [1]; Jack Mardekian, PhD[20]; Azah Borham, PharmD[20]; and Daniel J. George, MD[1]

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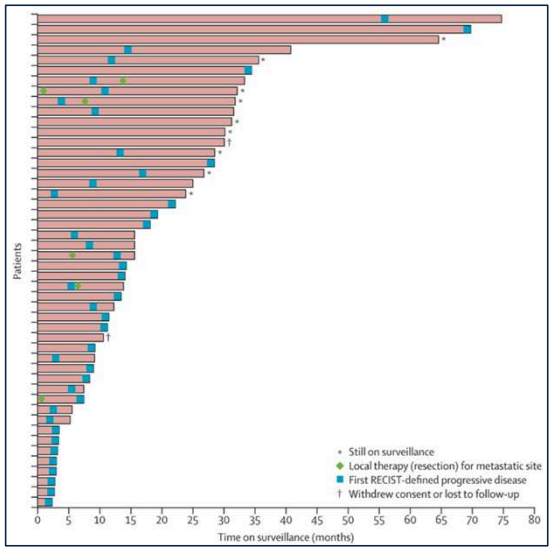
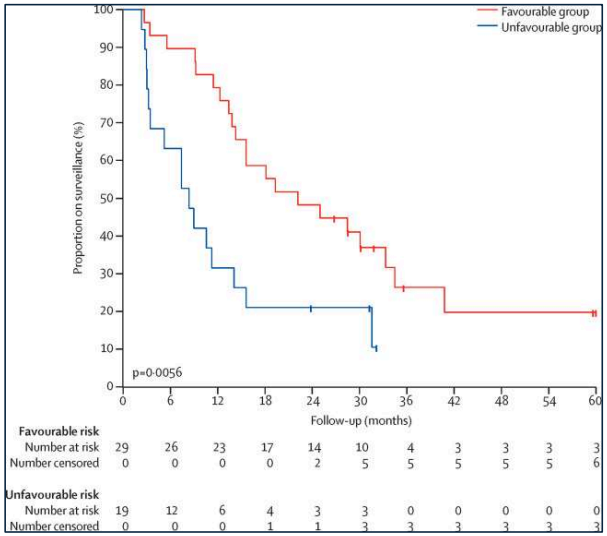
Metastatic Disease

- ✓ • Risk Stratified
- ✓ • Consider cytoreductive nephrectomy
  - • Step 3: Do we need to start systemic therapy immediately?





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Cytokine Era: ~1982 to 2005

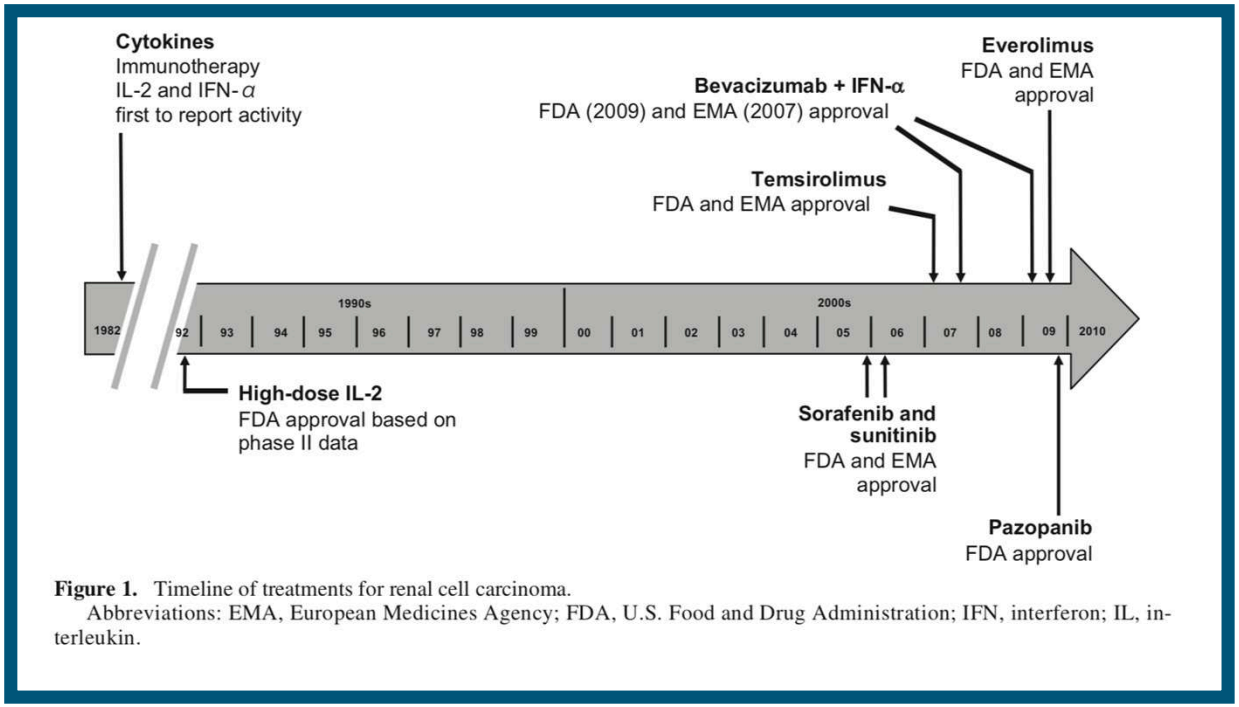

Figure 1. Timeline of treatments for renal cell carcinoma.
Abbreviations: EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; IFN, interferon; IL, interleukin.

Oncologist 2011, 16, (supp 2): 1-3

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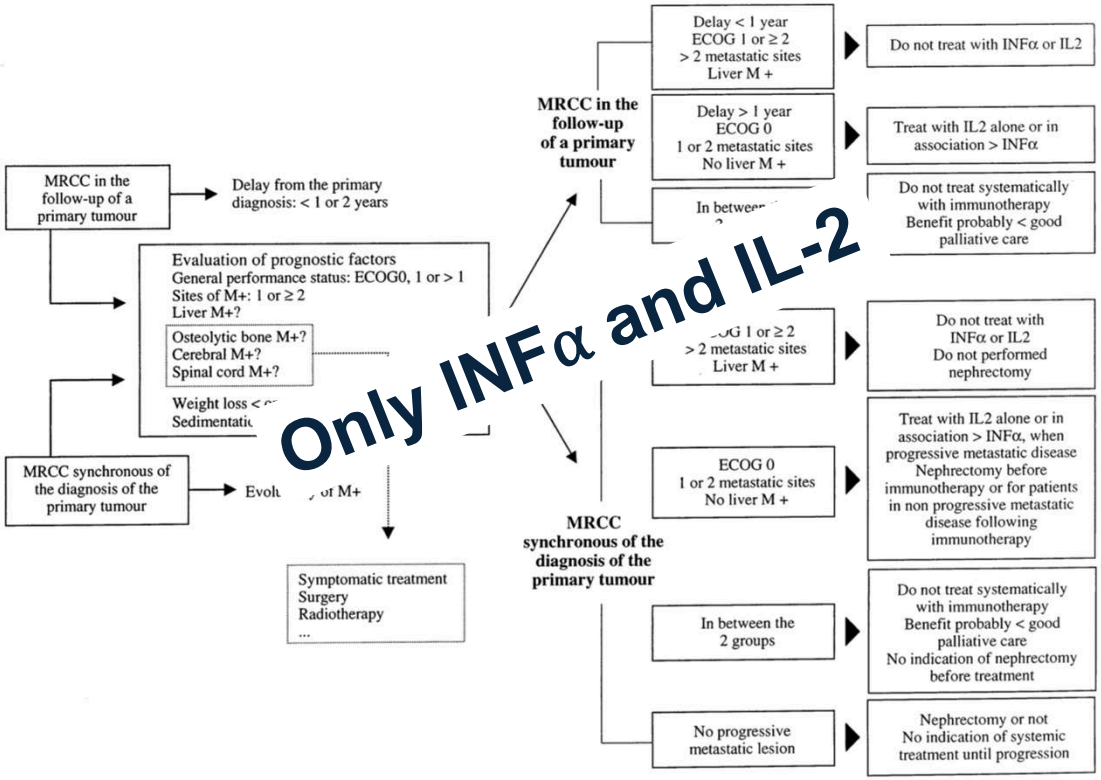
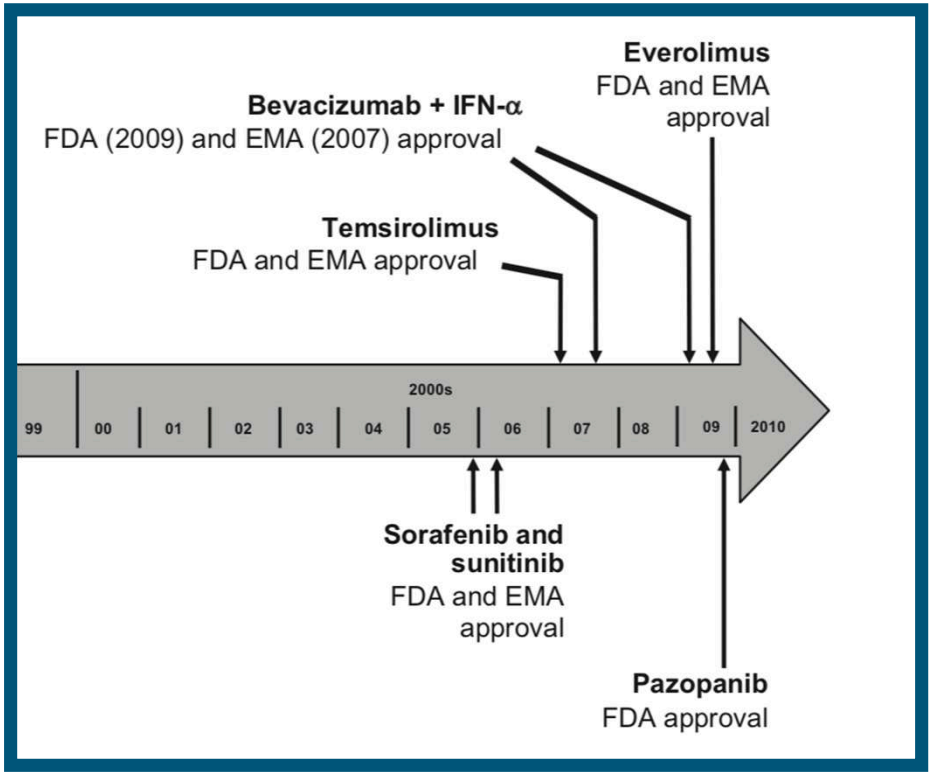
M1 Treatment Guidelines ~2000



A. Ravaud et al *Crit. Rev. Oncol. Hematol.*, vol. 31, no. 1, pp. 77–87, Jun. 1999.

Targeted Therapy Era 2005-2015



Oncologist 2011, 16, (supp 2): 1-3

Role of VHL Gene in RCC

Inactivation of the VHL tumor-suppressor protein

Accumulation of HIF transcription factor

Overexpression of a number of genes, including VEGF

VHL = von Hippel Lindau; HIF = hypoxia-inducible factor; RCC = renal cell cancer; VEGF = vascular endothelial growth factor

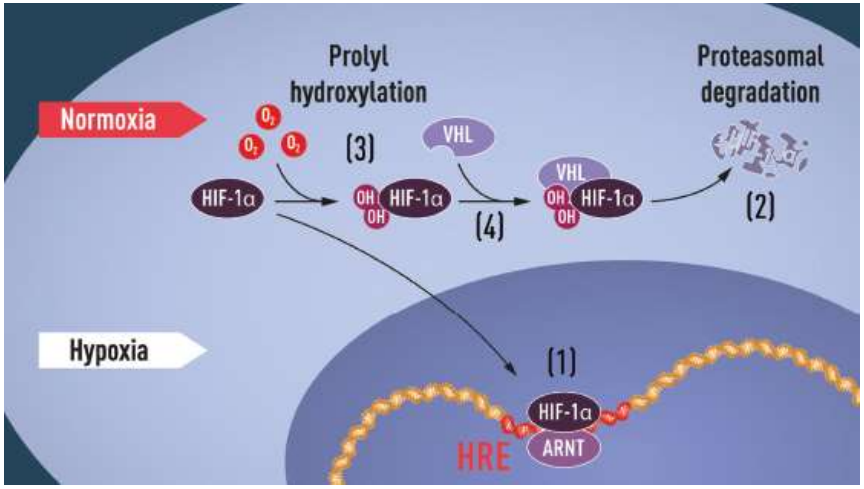
von Hippel-Lindau (*VHL*) tumor suppressor gene

- RCC tumorigenesis is dependent on mutation to the *VHL* tumor suppressor gene, present in more than 90% of patients with clear-cell RCC

VHL encodes for the ligase that targets HIF for destruction in normoxia

↓

Mutated *VHL* leads to aberrant accumulation of HIF1/2α, which acts as a TF for EPO, VEGF, and drivers of angiogenesis



Cavallo Jo. **Using the Nobel Prize to Champion Curiosity-Driven Research in Cancer.** *ASCO Post.* 2019

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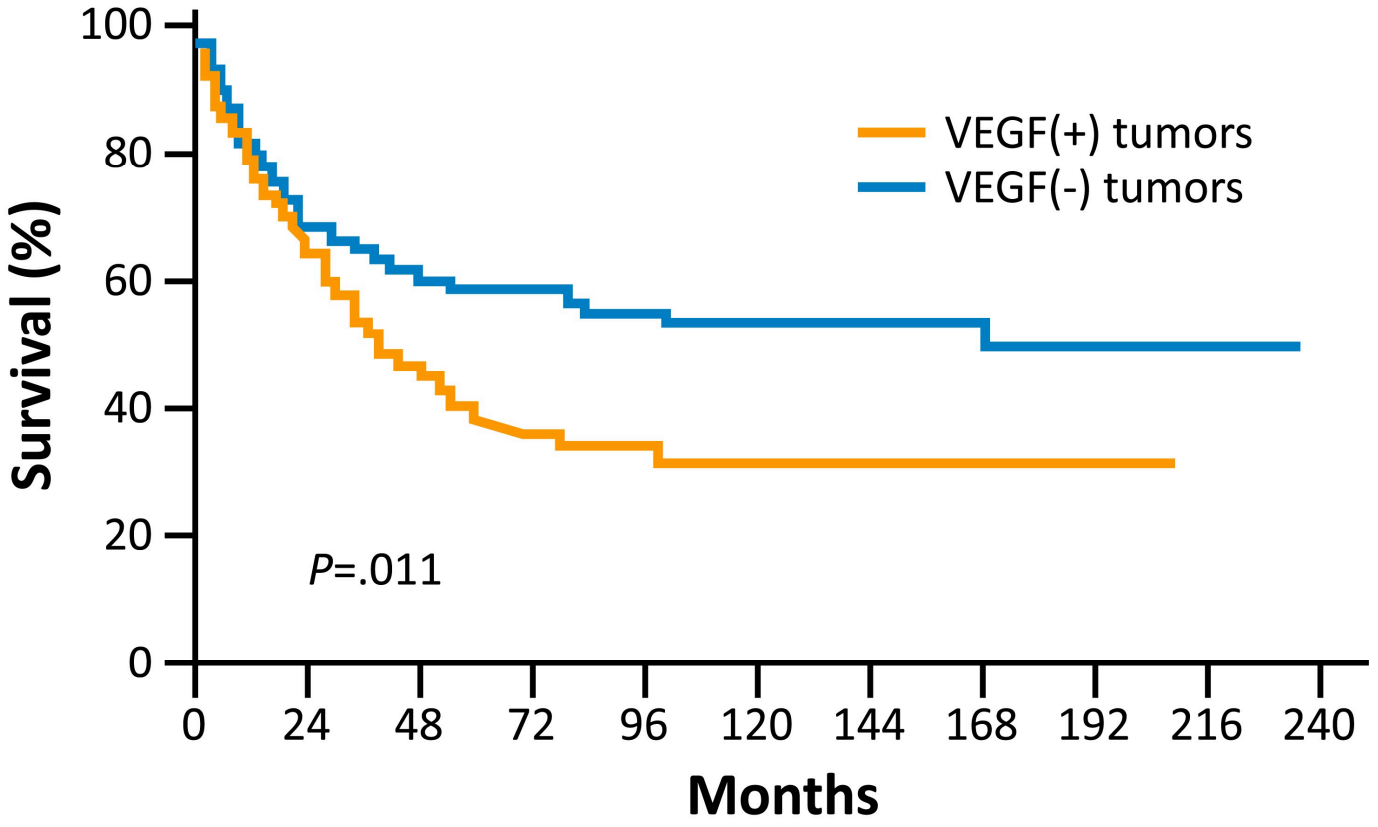
VEGF Correlated With Poorer Overall Survival



Jacobsen J, et al. *BJU Int.* 2004;93:297-302.

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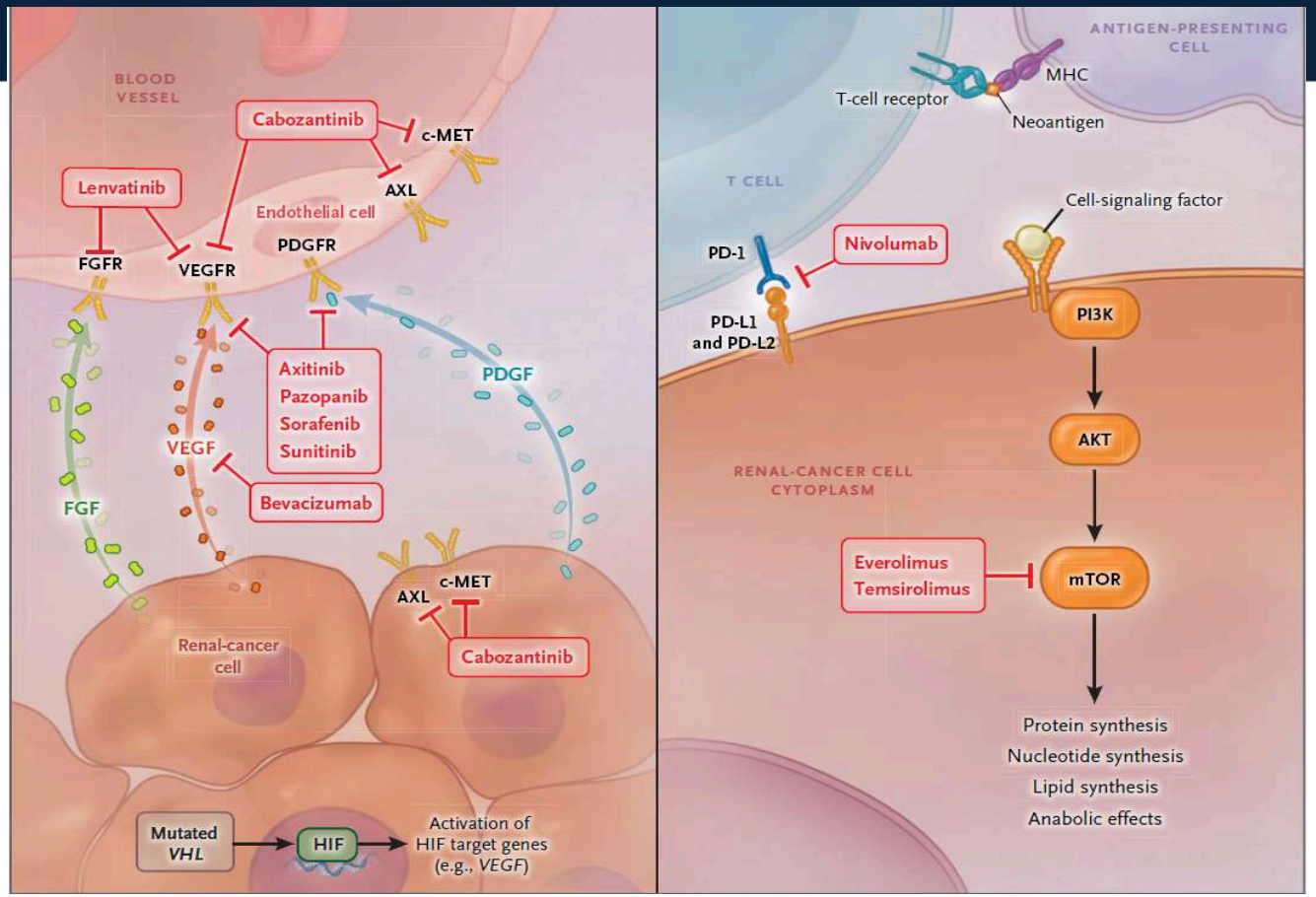
Mechanism of Action of RCC Treatments



Choueiri TK, Motzer RJ. *NEJM*. 2017;376:354-366.

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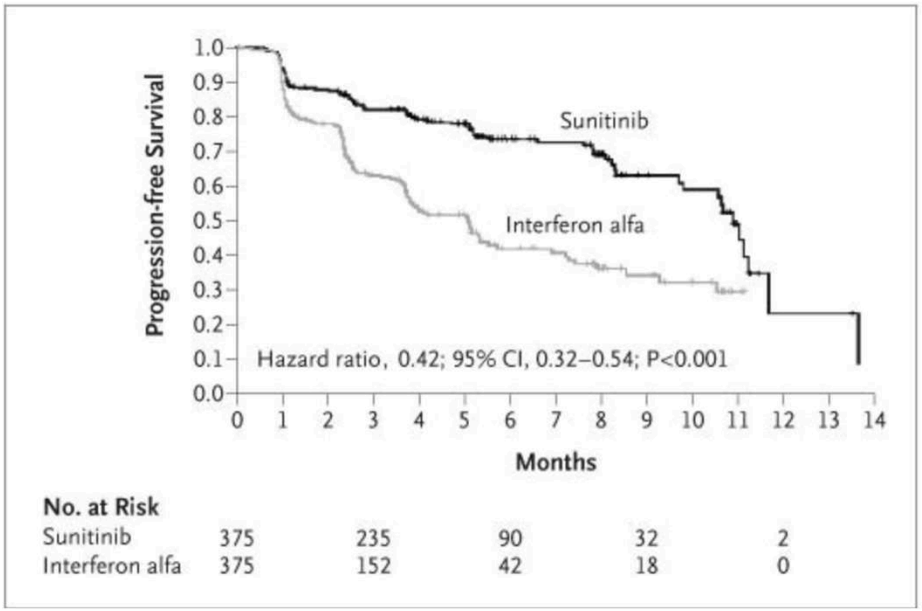
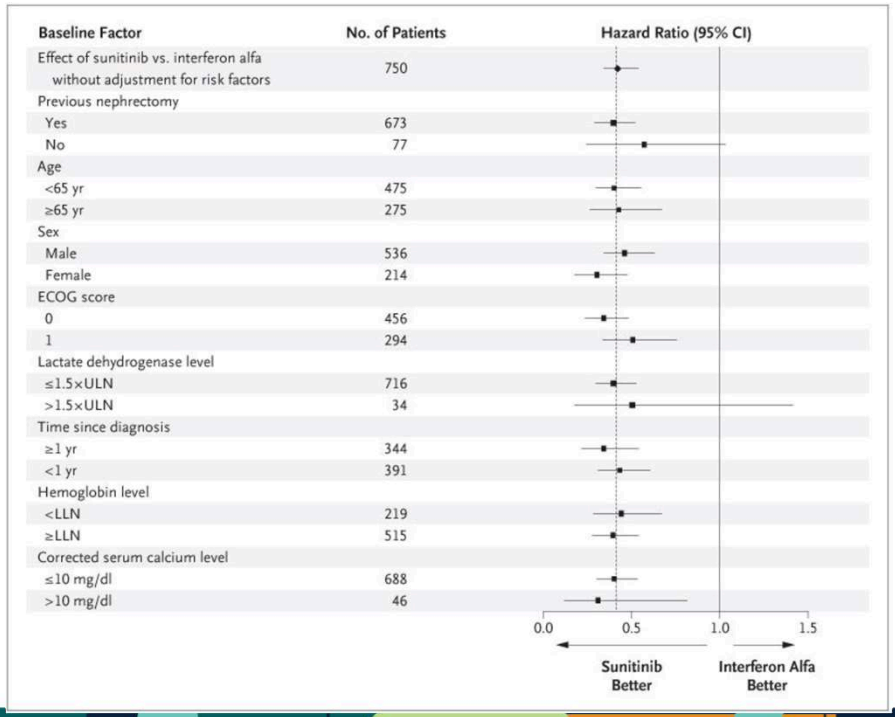
ORIGINAL ARTICLE

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., Pharm.D., Piotr Tomczak, M.D., M. Dror Michaelson, M.D., Ph.D., Ronald M. Bukowski, M.D., Olivier Rixe, M.D., Ph.D., Stéphane Oudard, M.D., Ph.D., Sylvie Negrier, M.D., Ph.D., Cezary Szczylik, M.D., Ph.D., Sindy T. Kim, B.S., Isan Chen, M.D., Paul W. Bycott, Dr.P.H., et al.





Treatment-Related Adverse Events

Event	Sunitinib (%)		IFN-α (%)	
	All grade	Grade 3/4	All grade	Grade 3/4
Fatigue	51	7	51	11/<1*
Diarrhea				
Nausea				
Stomatitis				
Hypertension				
Hand-foot syndrome				
Ejection fraction decline				
Pyrexia				
Chills				
Myalgia	5	<1	16	<1
Flu-like symptoms	1	0	8	<1

Motzer, NEJM 2007

* Greater frequency, P <0.05

ORIGINAL ARTICLE

Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma

Bernard Escudier, M.D., Tim Eisen, M.D., Walter M. Stadler, M.D., Cezary Szczylik, M.D., Stéphane Oudard, M.D., Michael Siebels, M.D., Sylvie Negrier, M.D., Christine Chevreau, M.D., Ewa Solska, M.D., Apurva A. Desai, M.D., Frédéric Rolland, M.D., Tomasz Demkow, M.D., et al., for the TARGET Study Group*

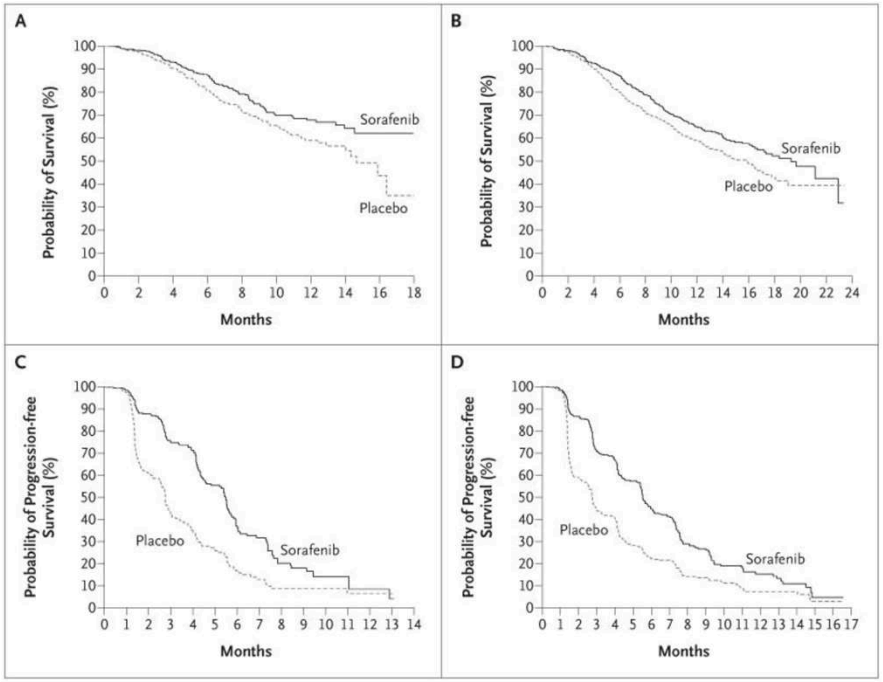


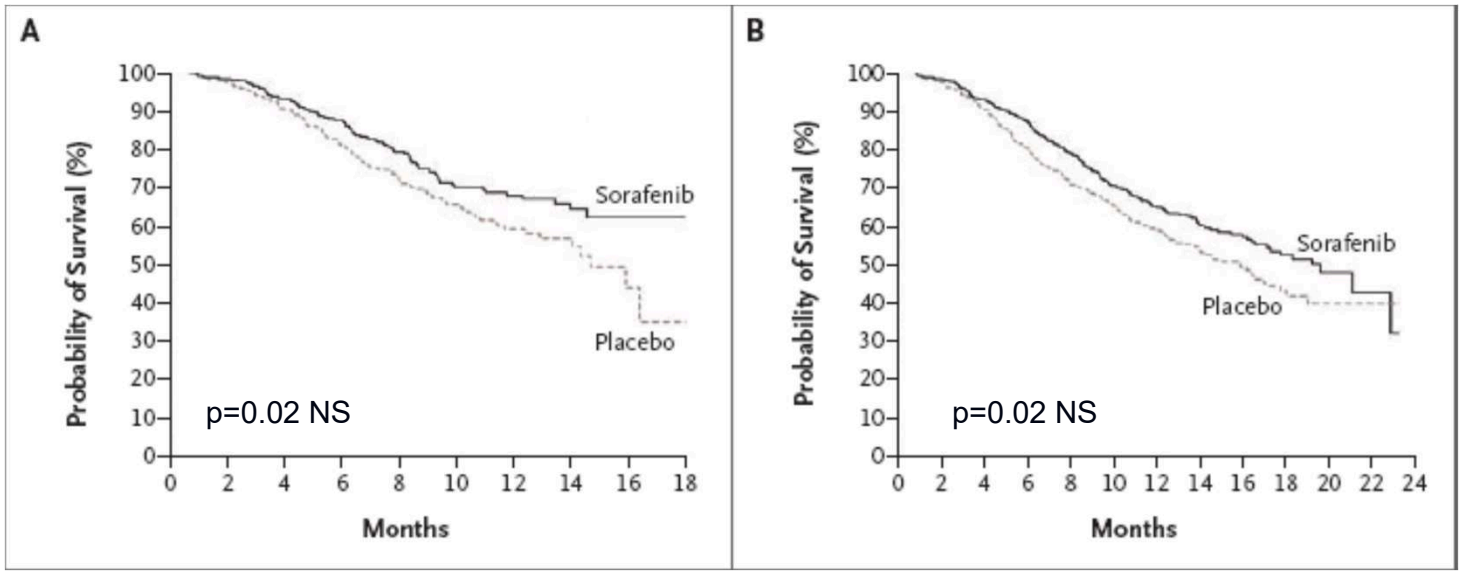
Table 2. Best Response Rates.*

Response	Sorafenib (N=451)		Placebo (N=452)	
	no. of patients	*% (95% CI)*	*no. of patients*	*% (95% CI)†*
Complete response	1	<1 (0–1)	0	0 (0–1)
Partial response	43	10 (7–13)	8	2 (1–4)
Stable disease†	333	74 (70–78)	239	53 (48–58)
Progressive disease	56	12 (10–16)	167	37 (33–42)
Not evaluated	18	4 (2–6)	38	8 (6–11)
Disease control rate‡	279	62 (57–66)	167	37 (33–42)

Escudier, NEJM 2007

Sorafenib

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 11, 2007 VOL. 356 NO. 2



6 months later
After crossover

Escudier B et al.

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Advent of Targeted Therapy Era

Table 1 – Medical treatment in advanced renal cell carcinoma phase II/phase III trials with anti-angiogenics, mTOR (mammalian target of rapamycin) inhibitors or EGFR (epidermal growth factor receptor) tyrosine kinase inhibitor

Author	Trial design	Treatment	Patients *n*	Line of treatment	OR (%)	PFS (m	OS (m
Motzer [22,23]	Phase II	Sunitinib	63	≥First			16.4
			106	≥Fi			NR
Motzer [24]	Randomised phase III	Sunitinib vs	451			11*	NR
		INF-α	4			5	–
Yang [29]	Randomised phase II	Bevacizumab HD/LD			10/0	>4*/<4	–
		vs placebo			0	<4	–
Bukowski [31]	Randomised phase II	Bevacizumab/		First	13	8.5	NR
		vs Bev	51		14	9.9	20
Escudier [30]	Randomised phase III		327	First	31*	10,2*	NR
			322		13	5,4	19.8
Escudier [32]	Randomised		451	Second	2	5.5*	NR
		placebo	452		0	2.8	14.7
Szczylik [34]		Sorafenib	97	First	5	5.7	–
		vs INF-α	92		9	5.6	–
Hud	ed phase III	Temsirolimus	209	First	8.6	3.7**	10.9*
		vs INF-α	207		4.8	1.9	7.3
		vs INF-α/temsirolimus	210		8.1	3.7*	8.4
	Phase II	Everolimus	41	≥First	32	>11.2	>24.2
avaud [40]	Randomised	Lapatinib	209	Second	1.4	3.7	11.4
	Phase III	vs hormonal therapy	207		0.5	3.7	10.5

OR: objective response rate; PFS: progression-free survival rate; OS: Overall survival rate; HD (high dose): 10 mg/kg; LD (low dose): 3 mg/kg. NR: Not remarkable.
*$p < 0.001$; **$p < 0.0001$.

Targeted Therapy Agents Randomized Against IFN-α

Ravaud, H. *European Urology*, vol. 54, no. 2, pp. 315–325, Aug. 2008.

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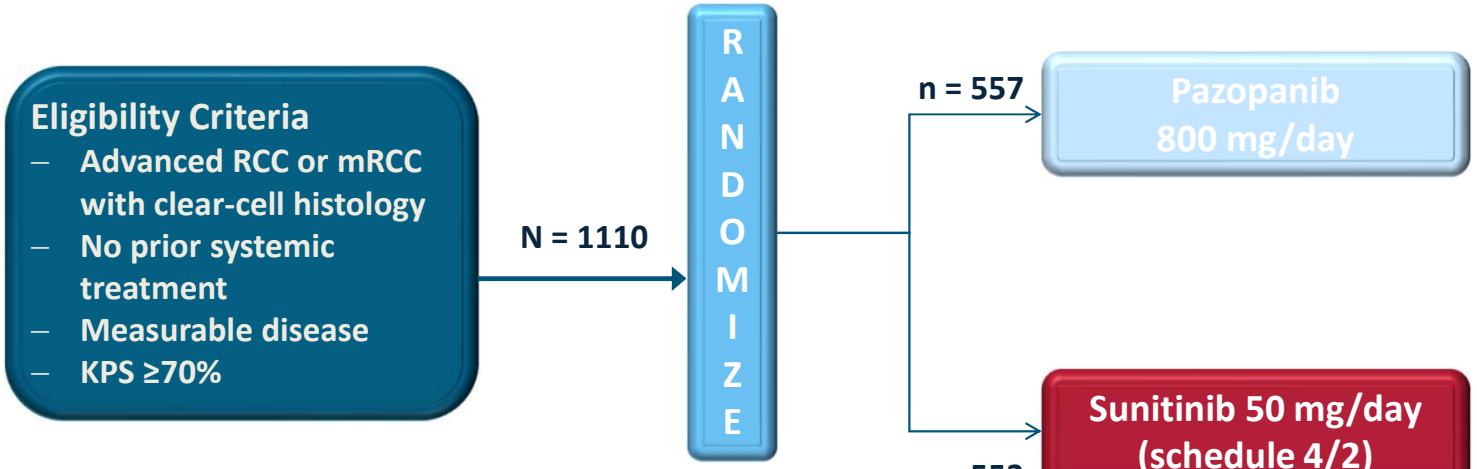
Phase III COMPARZ Trial: First-line Pazopanib vs Sunitinib

Non-inferiority Study



Primary end point: PFS
Secondary end points: OS, ORR, PRO, safety and QoL

Motzer RJ, et al. *N Engl J Med*. 2013;369:722-31.

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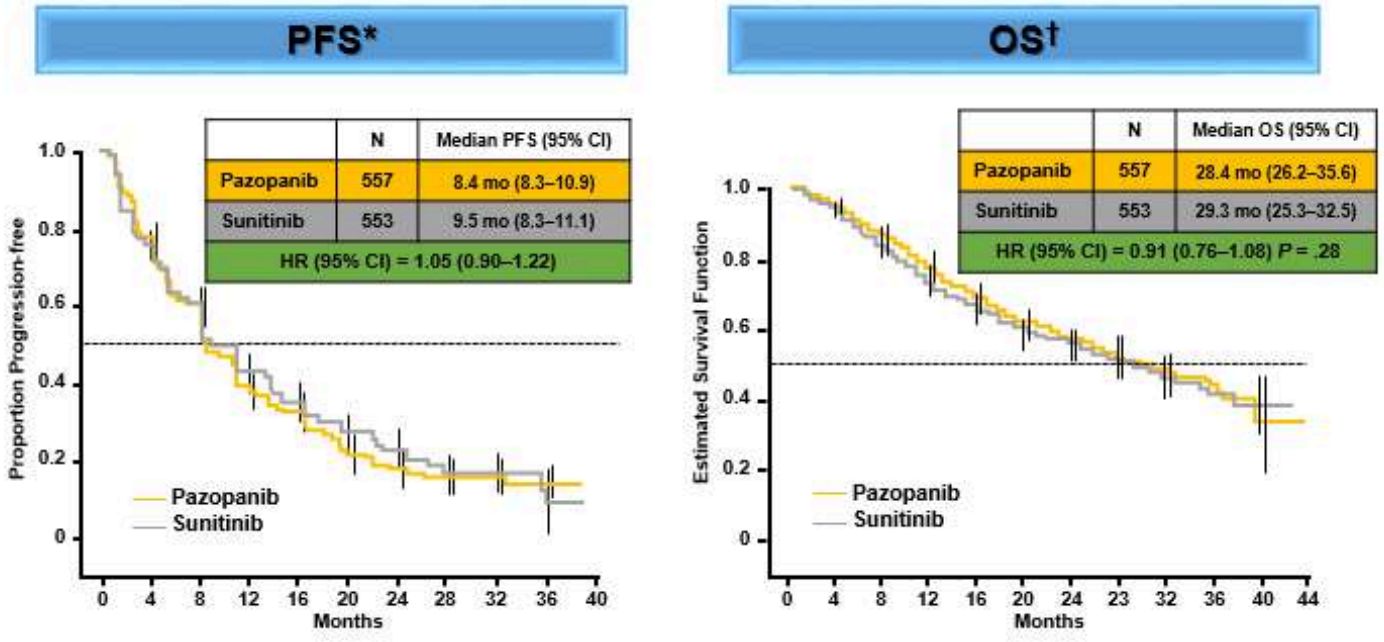
COMPARZ: Efficacy of Pazopanib is Non-inferior to Sunitinib



Motzer RJ, et al. *N Engl J Med*. 2013;369:722-31.

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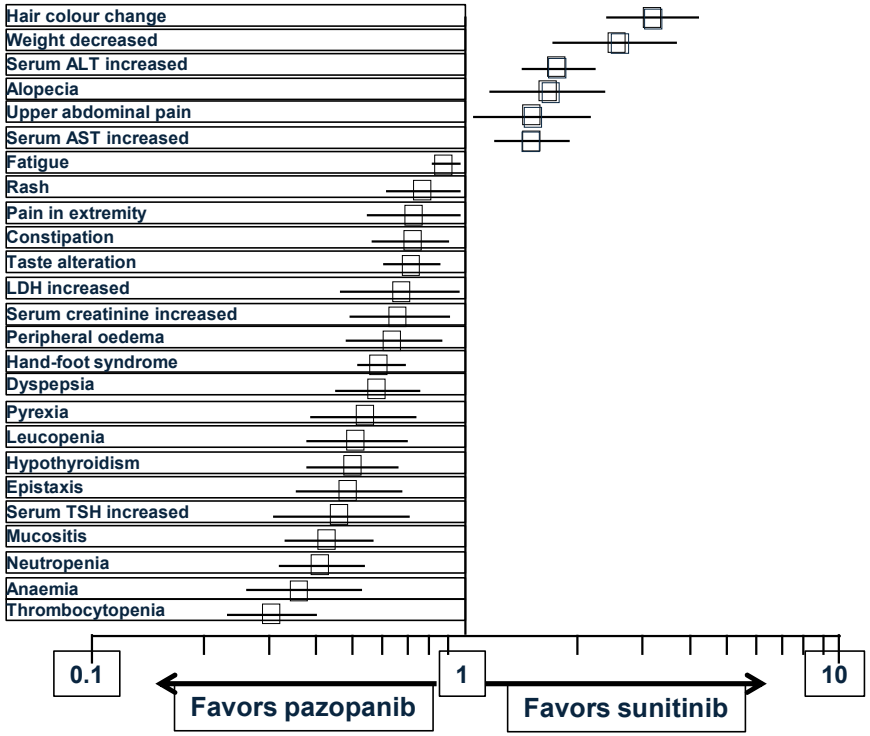
COMPARZ: Relative Risk of AEs

AE occurrence ≥ 10% in either arm; 95% CI for RR does not cross 1



Motzer RJ, et al. *N Engl J Med*. 2013;369:722-31.

Table 1. Drugs Approved by the FDA for Renal Cell Carcinoma

Drug	Labeled indication
Axitinib	Advanced renal cell cancer after failure of one prior systemic therapy
Bevacizumab	Metastatic renal cell cancer
Everolimus	Advanced renal cell cancer in treatment failure with sorafenib or sunitinib
Pazopanib	Advanced renal cell cancer
Sorafenib	Advanced renal cell cancer
Sunitinib	Advanced renal cell cancer
Temsirolimus	Advanced renal cell cancer

Note. FDA = US Food and Drug Administration.

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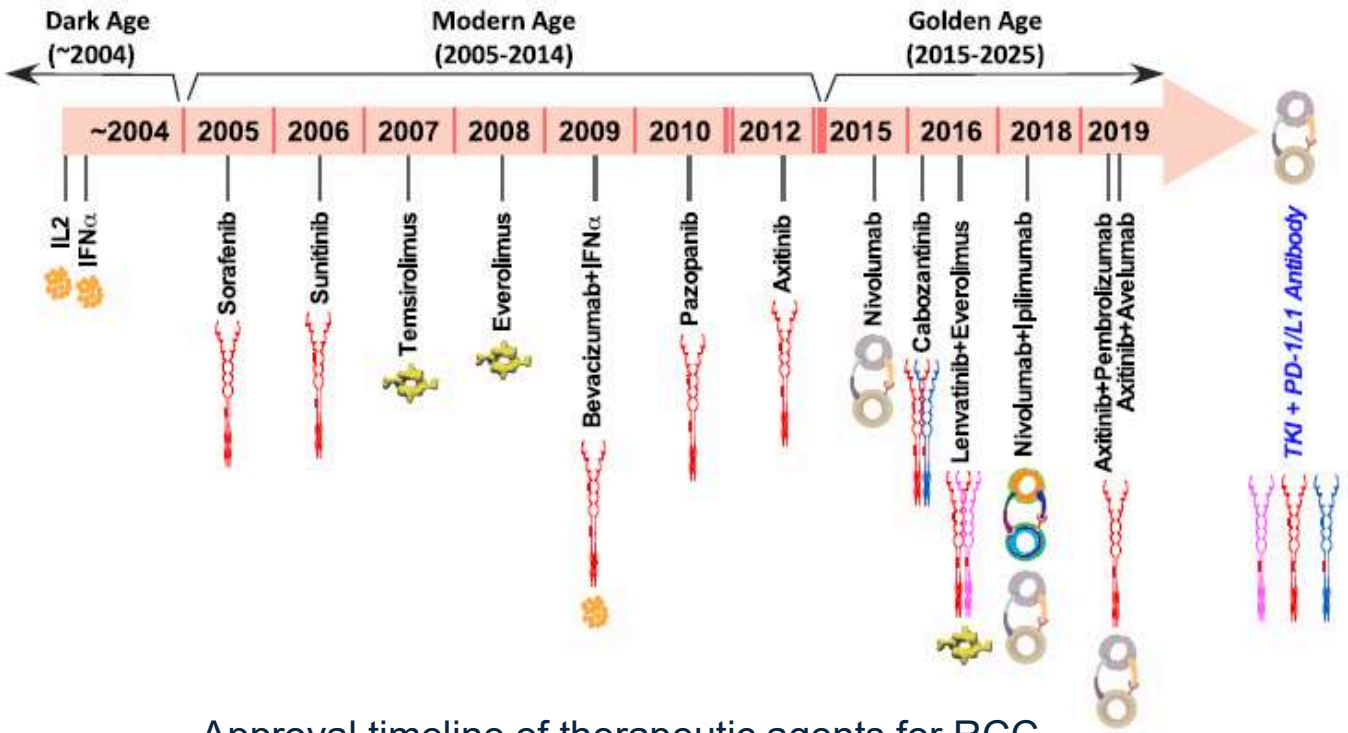
The Golden Age of mRCC Care



Approval timeline of therapeutic agents for RCC.

Huang and Hsieh, Sem Neph. Jan 2020; 28-41

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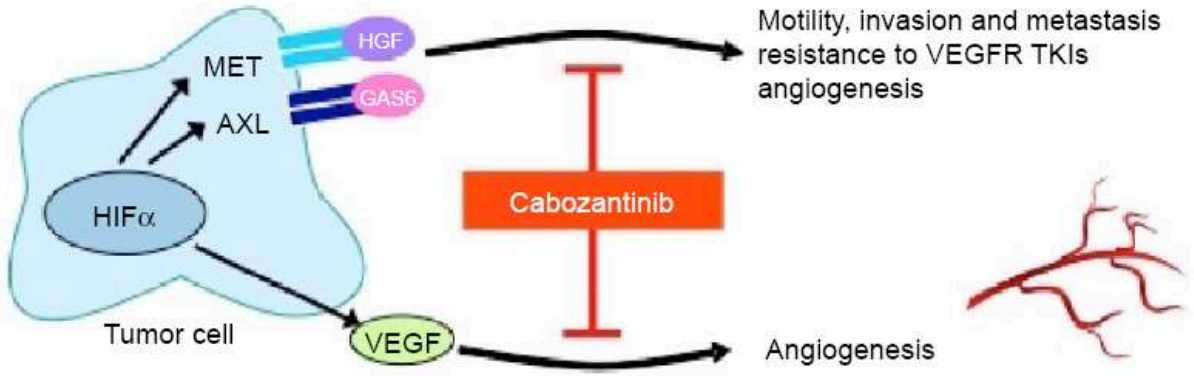
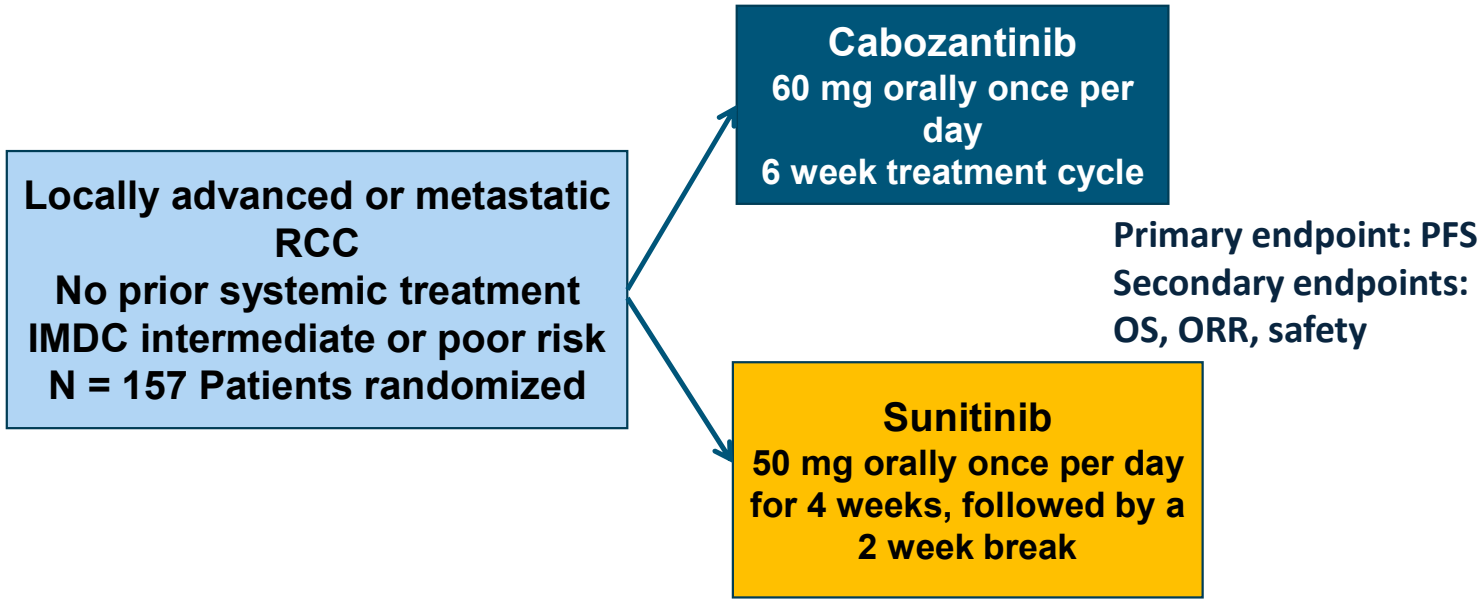
Cabozantinib – inhibitor of VEGFR, MET and AXL



- MET and AXL upregulation are associated with poor prognosis in RCC
- These targets have also been implicated in resistance to treatments with VEGFR inhibitors

Yu et al Oncotargets and Therapy 2016

CABOSUN Trial: First-Line Cabozantinib vs Sunitinib in Poor- or Intermediate-Risk Patients (Phase II)



Choueiri TK, et al. *J Clin Oncol*. http://ascopubs.org/doi/pdf/10.1200/JCO.2016.67.7398

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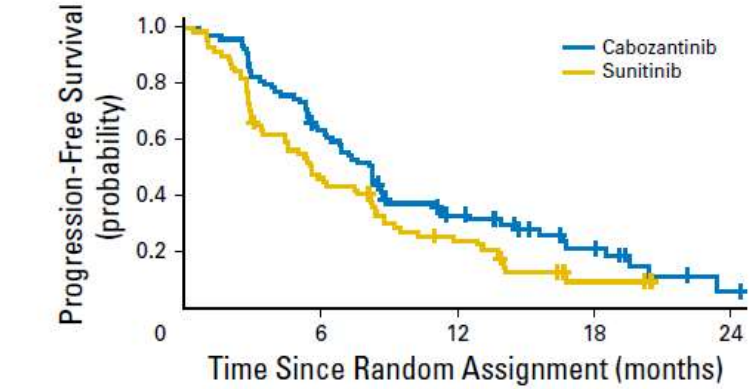
CABOSUN Trial: First-Line Cabozantinib vs Sunitinib in Poor- or Intermediate-Risk Patients



No. at risk					
Cabozantinib	79	49	22	9	1
Sunitinib	78	32	15	3	0

- Median PFS 8.2 mos vs 5.6 mos
- ORR 46% vs 18%
- Rates of G3/4 AE 67% vs 68% (similar AE = fatigue, HTN, diarrhea)
- First study to show an agent demonstrating superiority to sunitinib

Cabozantinib now approved for 1st line mRCC

Choueiri et al JCO 2017

Immunotherapy → Targeted therapy → Back to IO

Immunotherapy	Targeted Therapy	Immunotherapy
HD-IL2 IFN (plus bevacizumab)	Sunitinib Pazopanib Axitinib Sorafenib Temsirolimus (poor risk)	Many first line combos trials underway featuring PD1 and PDL1 agents…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

November 2015

- 821 patients with advanced cc RCC for which they had received previous treatment with one or two regimens of antiangiogenic therapy were randomized 1:1

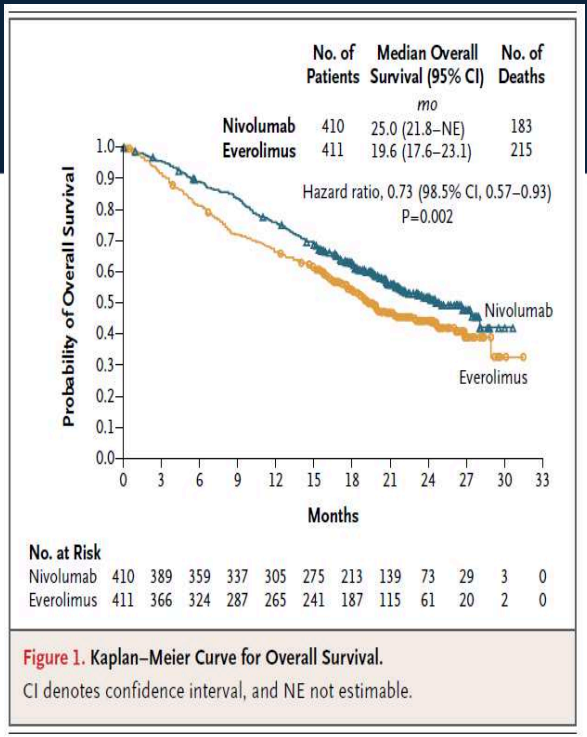


Figure 1. Kaplan–Meier Curve for Overall Survival.
CI denotes confidence interval, and NE not estimable.

- HR for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; P=0.002), which met the prespecified criterion for superiority
- Grade 3 or 4 treatment-related adverse events occurred in 19% of the patients receiving nivolumab and in 37% of the patients receiving everolimus

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ORIGINAL ARTICLE

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

Robert J. Motzer, M.D., Nizar M. Tannir, M.D., David F. McDermott, M.D., Osvaldo Arén Frontera, M.D., Bohuslav Melichar, M.D., Ph.D., Toni K. Choueiri, M.D., Elizabeth R. Plimack, M.D., Philippe Barthélémy, M.D., Ph.D., Camillo Porta, M.D., Saby George, M.D., Thomas Powles, M.D., Frede Donskov, M.D., Ph.D., et al., for the CheckMate 214 Investigators*

- CheckMate 214: Phase 3 trial compared nivolumab (anti PD-1) plus ipilimumab (anti CTLA-4) with sunitinib for previously ***untreated*** advanced ccRCC
- 1096 patients randomized 1:1 - 425 and 422, respectively, had intermediate or poor risk disease (IMDC score)
- Median follow-up of 25.2 months

NEJM April 5, 2018

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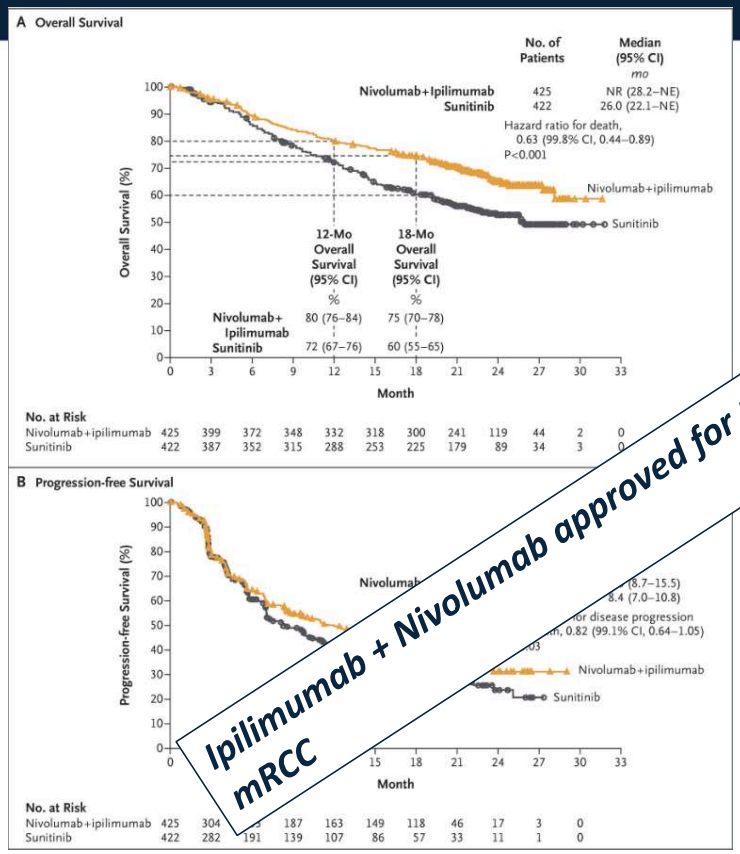


Ipilimumab + Nivolumab approved for 1st line intermediate-poor risk mRCC

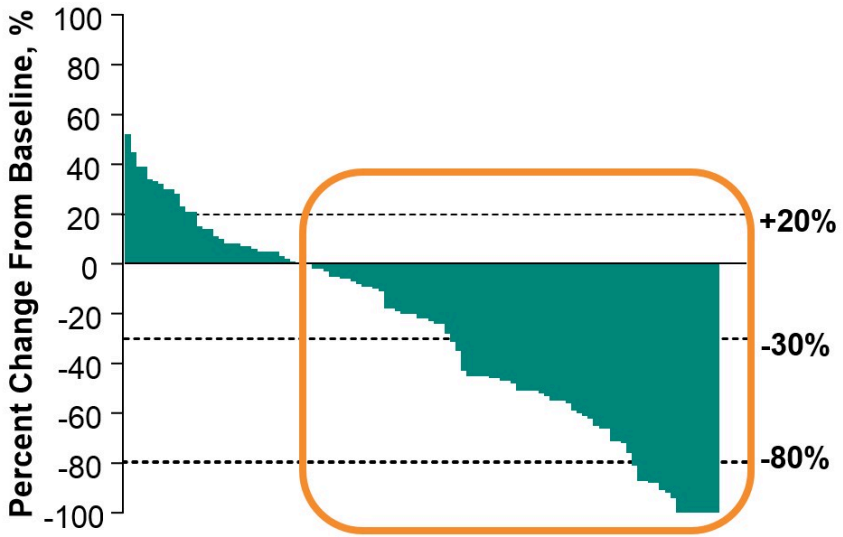
- 18-month overall survival rate was 75% (95% confidence int[illegible]l [CI], 70 to 78) with nivo/ipi a[illegible]5% CI, 55 to 65) with suni[illegible]
- [illegible]erall survival was not reached [illegible]volumab plus ipilimumab versus [illegible].0 months with sunitinib (hazard ratio for death, 0.63; P<0.001)
- Objective response rate was 42% versus 27% (P<0.001), and the **complete response rate** was 9% versus 1%
- Grade 3/4 AE occurred in 250 patients (46%) and 335 patients (63%), respectively. Treatment-related adverse events leading to discontinuation occurred in 22% and 12%.

For favorable risk, Response rate and PFS were better with sunitinib vs ipi + nivo

Outcome	N = 249[a]	
	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) ***P* < 0.0001**	

Escudier et al. ESMO 2017 (NEJM 2018)

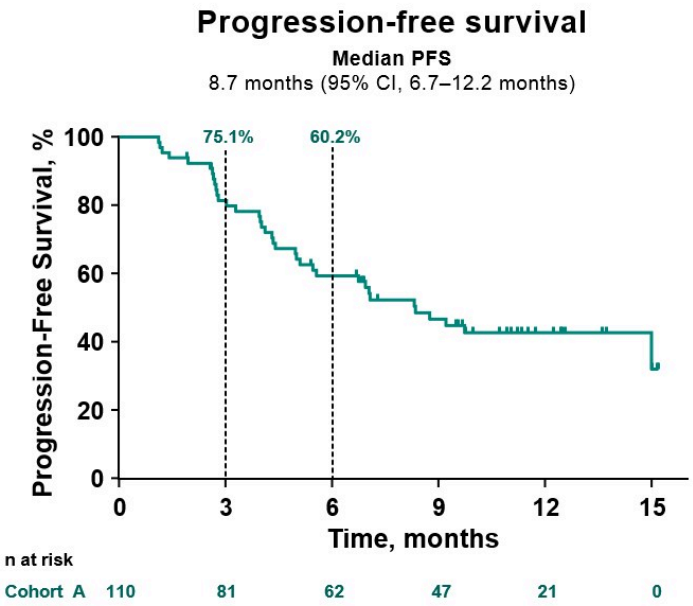
Pembrolizumab Monotherapy in Treatment-Naive Clear Cell RCC (single arm trial)

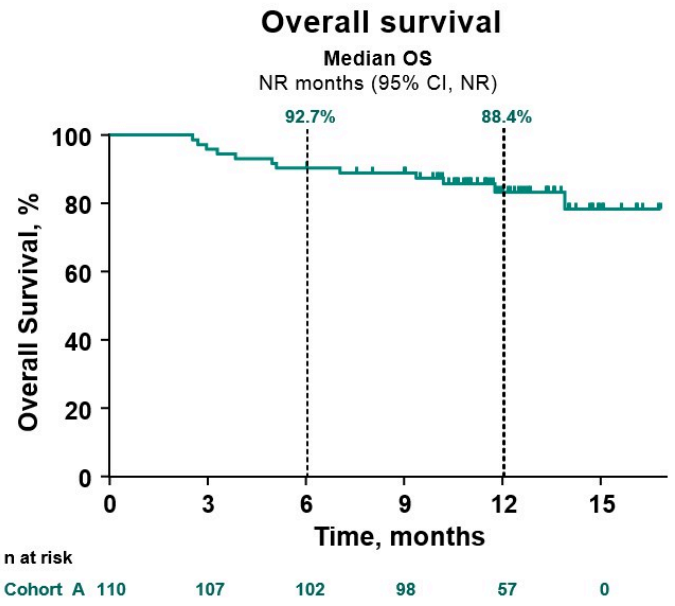


IMDC Risk	ORR n=110
Favorable (n=41)	32%
Poor/Intermediate (n=69)	42%
All Risk Groups (n=110)	38%

McDermott et al. ASCO 2018

Line Clear Cell RCC





McDermott et al. ASCO 2018

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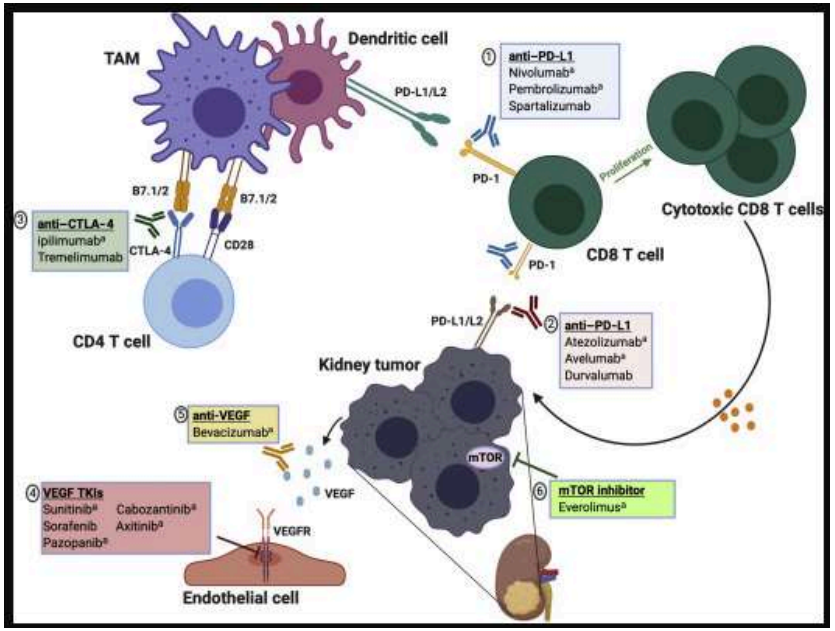
First Line Combination
VEGF Targeted Therapy + Immunotherapy



Urologic Clinics of North America
Volume 47, Issue 4, November 2020, Pages 419-431

AUA 2
APRIL 26-29
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ORIGINAL ARTICLE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

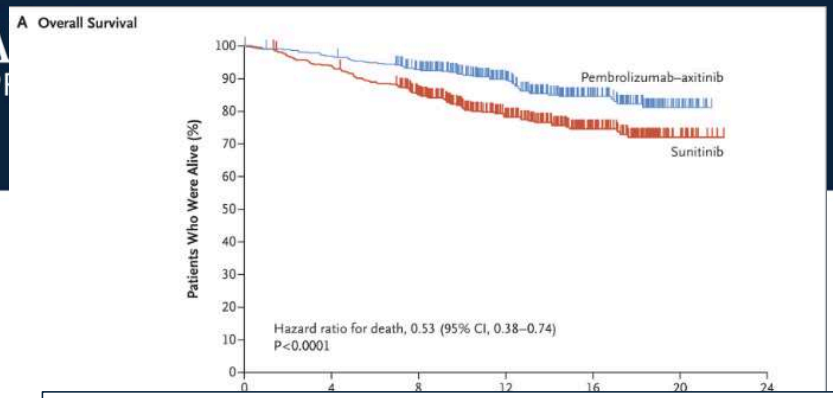
Brian I. Rini, M.D., Elizabeth R. Plimack, M.D., Viktor Stus, M.D., Ph.D., Rustem Gafanov, M.D., Robert Hawkins, M.B., B.S., Ph.D., Dmitry Nosov, M.D., D.Sci., Frédéric Pouliot, M.D., Ph.D., Boris Alekseev, M.D., Denis Soulières, M.D., Bohuslav Melichar, M.D., Ph.D., Ihor Vynnychenko, M.D., Ph.D., Anna Kryzhanivska, M.D., et al., for the KEYNOTE-426 Investigators*

- Phase 3 trial randomly assigned 861 patients with previously untreated advanced clear-cell renal-cell carcinoma to receive pembrolizumab (200 mg) intravenously once every 3 weeks plus axitinib (5 mg) orally twice daily (432 patients) or sunitinib (50 mg)

- Primary end points: OS and PFS in the intention-to-treat population.

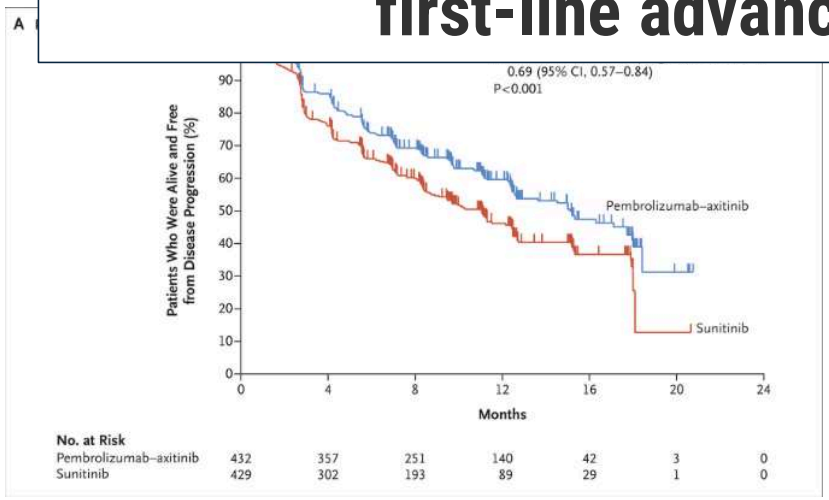
- Secondary end point was the objective response rate.

NEJM 2/21/2019



April 9, 2019: FDA approves pembrolizumab plus axitinib for first-line advanced renal cell carcinoma

- ORR 59.3% in the pembrolizumab–axitinib group and 35.7% (95% CI, 31.1 to 40.4) in the sunitinib group (P<0.001).
- The benefit of pembrolizumab plus axitinib was observed



AEs

- 51.3% of patients in the pembrolizumab–axitinib group and in 36.2% of patients in the sunitinib group
- Grade 3 in 8.4% of patients in the pembrolizumab–axitinib group and in 1.6% in the sunitinib group
- Grade 4 events occurred in 1.6% and 0%, respectively,
- Grade 5 events occurred in 0.7% and 0.2%, respectively.

NEJM 3/21/2019

AUA 202
APRIL 26-29 Las Vega

Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Robert J. Motzer, M.D., Konstantin Penkov, M.D., Ph.D., John Haanen, Ph.D., Brian Rini, M.D., Laurence Albiges, M.D., Ph.D., Matthew T. Campbell, M.D., Balaji Venugopal, M.D., Christian Kollmannsberger, M.D., Sylvie Negrier, M.D., Ph.D., Motohide Uemura, M.D., Ph.D., Jae L. Lee, M.D., Ph.D., Aleksandr Vasiliev, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Howard Gurney, M.D., Manuela Schmidinger, M.D., James Larkin, M.D., Ph.D., Michael B. Atkins, M.D., Jens Bedke, M.D., Boris Alekseev, M.D., Jing Wang, Ph.D., Mariangela Mariani, Ph.D., Paul B. Robbins, Ph.D., Aleksander Chudnovsky, M.D., Camilla Fowst, M.D., Subramanian Hariharan, M.D., Bo Huang, Ph.D., Alessandra di Pietro, M.D., Ph.D., and Toni K. Choueiri, M.D.

- This phase 3 trial (Javelin) involving previously untreated patients with advanced renal-cell carcinoma compared avelumab plus axitinib with the standard-of-care sunitinib.

- 886 patients randomized 1:1
  - 442 - Avelumab IV every 2 weeks plus axitinib orally BID
  - 444 - sunitinib

  - Primary end points: OS and PFS in PDL1(+) tumors

- Secondary end point: PFS overall (PDL1 + and -)

NEJM 3/21/2019

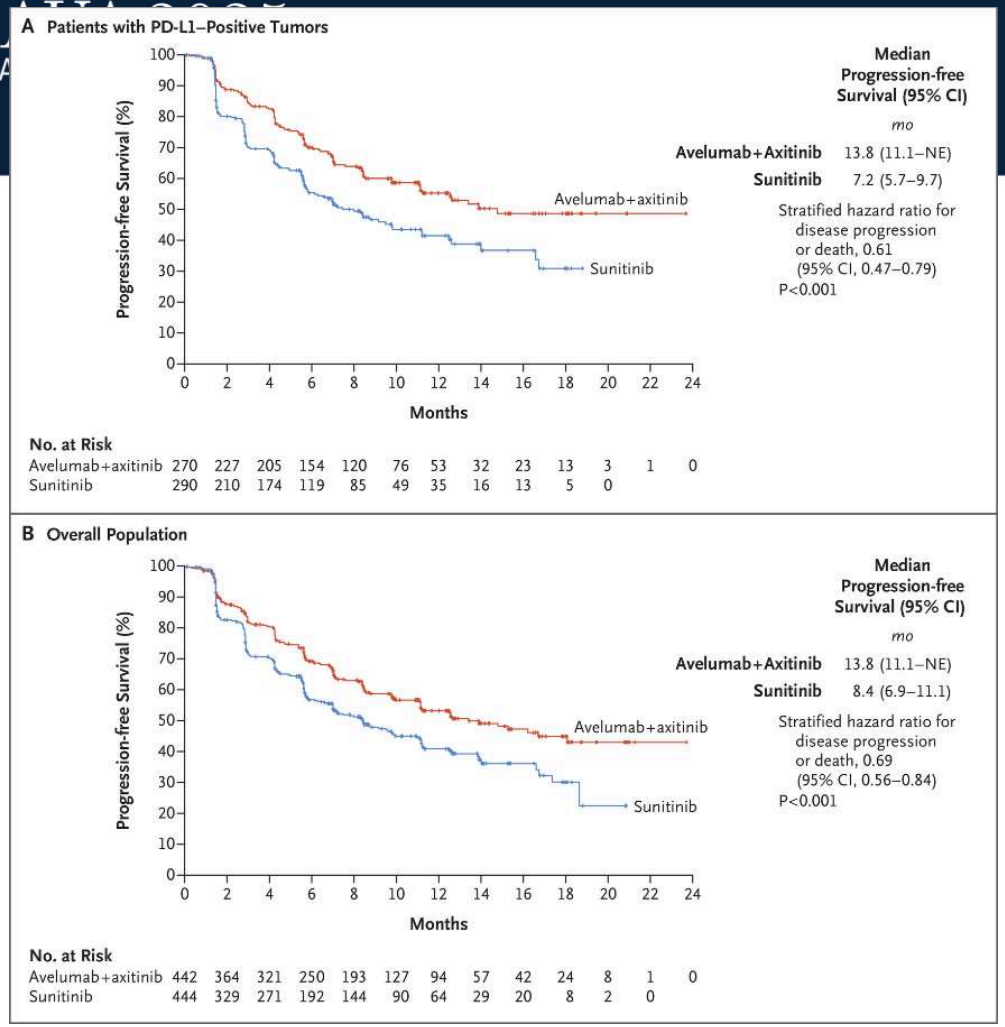


Table 2. Antitumor Activity among Patients with PD-L1–Positive Tumors and in the Overall Population.*

Variable	Patients with PD-L1–Positive Tumors		Overall Population	
	Avelumab plus Axitinib (N=270)	Sunitinib (N=290)	Avelumab plus Axitinib (N=442)	Sunitinib (N=444)
Confirmed objective response rate (95% CI) — %	55.2 (49.0–61.2)	25.5 (20.6–30.9)†	51.4 (46.6–56.1)	25.7 (21.7–30.0)‡
Confirmed best overall response — no. (%)				
Complete response	12 (4.4)	6 (2.1)	15 (3.4)	8 (1.8)
Partial response	137 (50.7)	68 (23.4)	212 (48.0)	106 (23.9)
Stable disease	72 (26.7)	125 (43.1)	131 (29.6)	202 (45.5)
Progressive disease	30 (11.1)	63 (21.7)	51 (11.5)	83 (18.7)
Could not be evaluated	12 (4.4)§	21 (7.2)¶	25 (5.7)‖	35 (7.9)**
Other††	7 (2.6)	7 (2.4)	8 (1.8)	10 (2.3)
Median time to response (range) — mo	1.6 (1.2–10.1)	3.0 (1.2–11.6)	2.6 (1.2–13.8)	3.2 (1.2–11.6)
Median duration of response (95% CI) — mo	NR (NE)	NR (10.9–NE)	NR (NE)	NR (11.2–NE)
Patients with ongoing response — no./total no. (%)	108/149 (72.5)	48/74 (64.9)	158/227 (69.6)	81/114 (71.1)

Median follow-up for OS:

- 11.6 months – A+A
- 10.7 months – S
- In the two groups, 37 patients and 44 patients had died, respectively

NEJM 3/21/2019

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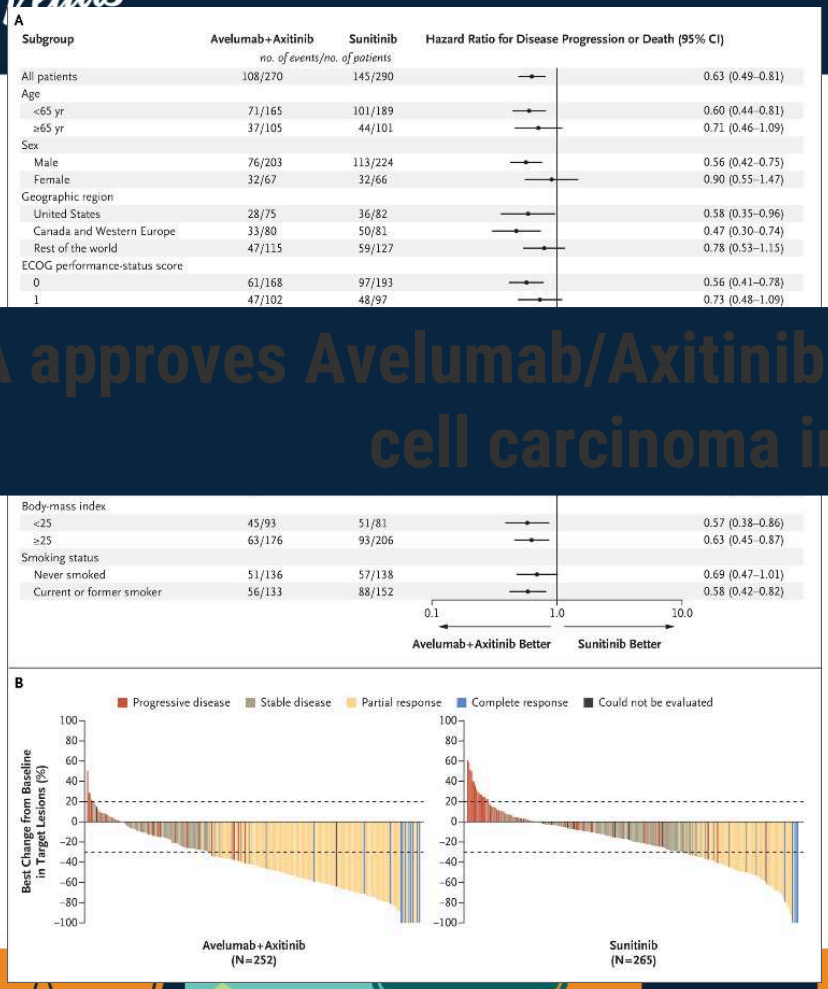


FDA approves Avelumab/Axitinib for first-line advanced renal cell carcinoma in May, 2019

AEs of any grade:

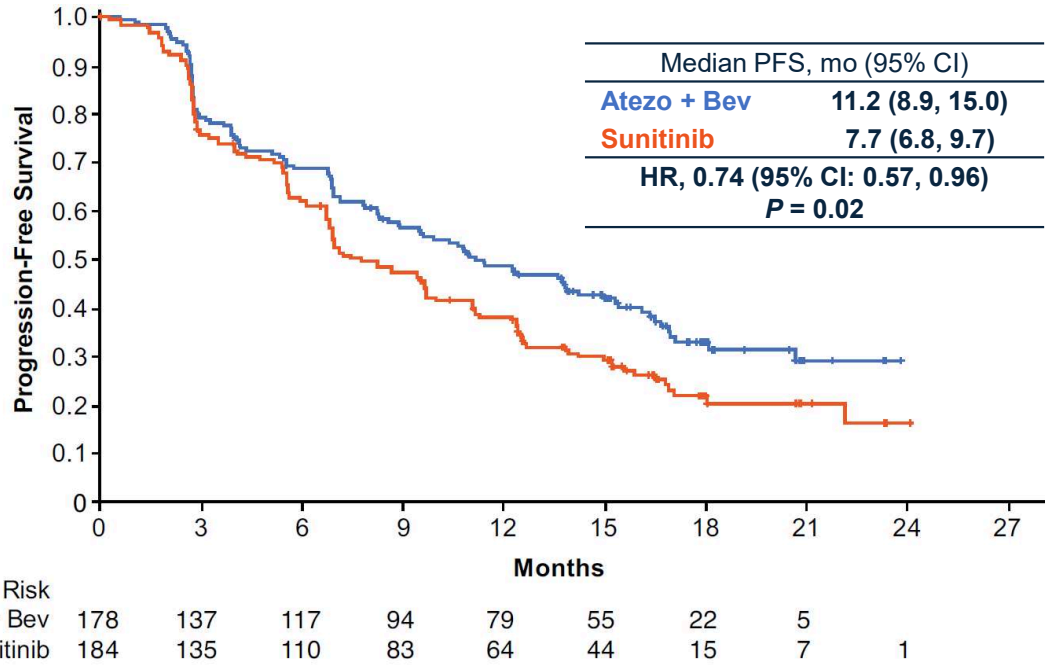
- 432 of 434 patients (99.5%) who received avelumab plus axitinib
- 436 of 439 patients (99.3%) who received

Discontinuation of drug:

- Combination - 33 patients (7.6%)
- Sunitinib - 59 patients (13.4%)

NEJM 3/21/2019

Atezolizumab/Bevacizumab vs Sunitunib



- PFS assessed by investigators.
- Minimum follow-up, 12 mo. Median of follow-up, 15 mo.

McDermott et al. GU ASCO 2018

	PD-L1+		ITT	
	Atezo + Bev n = 178	**Sunitinib n = 184**	**Atezo + Bev n = 454**	**Sunitinib n = 461[a]**
Stratified HR (95% CI)	0.68 (0.46, 1.00)		0.81 (0.63, 1.03) *P* = 0.09[d]	
Confirmed ORR, % (95% CI)	43% (35, 50)	35% (28, 42)	37% (32, 41)	33% (29, 38)
Complete response	9%	4%	5%	2%

McDermott et al. GU ASCO 2018

AUA 20
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Las Veg

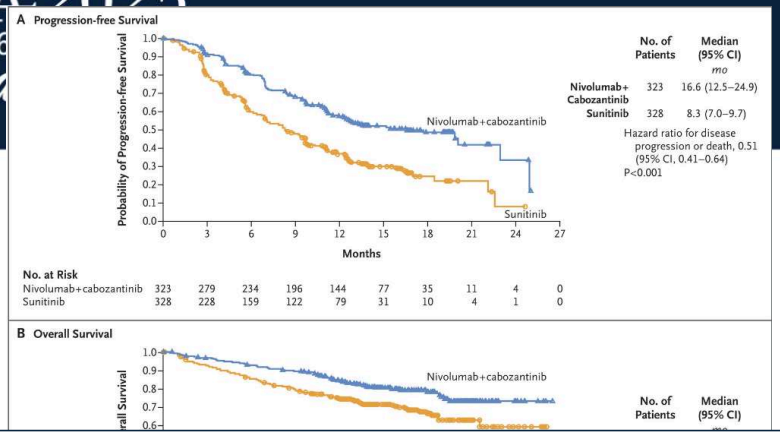
ORIGINAL ARTICLE

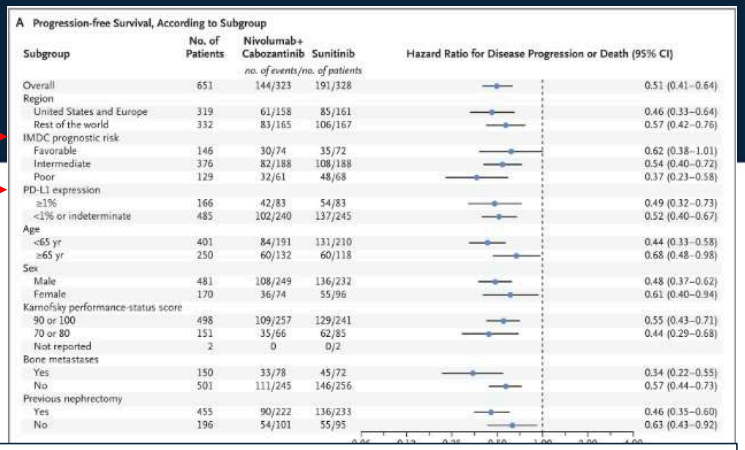
Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Toni K. Choueiri, M.D., Thomas Powles, M.D., Mauricio Burotto, M.D., Bernard Escudier, M.D., Maria T. Bourlon, M.D., Bogdan Zurawski, M.D., Ph.D., Victor M. Oyervides Juárez, M.D., James J. Hsieh, M.D., Ph.D., Umberto Basso, M.D., Amishi Y. Shah, M.D., Cristina Suárez, M.D., Ph.D., Alketa Hamzaj, M.D., et al., for the CheckMate 9ER Investigators*

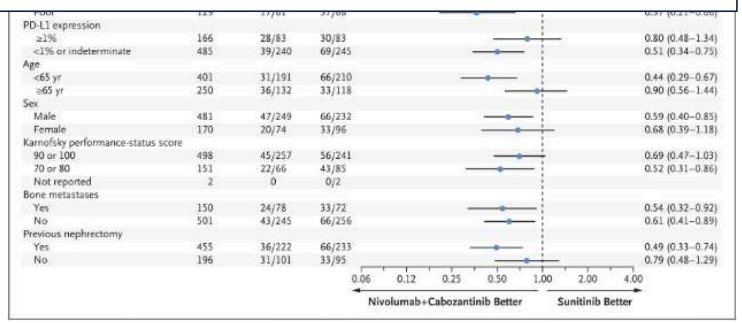
March 4, 2021
N Engl J Med 2021; 384:829-841

- Checkmate 9ER. Phase 3.
  - 651 patients with untreated ccRCC randomized 1:1
  - Nivolumab/cabozantinib (323) : Sunitinib (328)
  - Primary EP PFS
  - Secondary EP OS, OR, Safety





On January 22, 2021, the FDA approved the combination of nivolumab and cabozantinib as first-line treatment for patients with advanced RCC, across all IMDC risk groups.



- An objective response occurred in 55.7% of the patients receiving nivolumab plus cabozantinib and in 27.1% of those receiving sunitinib (P<0.001).
- Adverse events of any cause of grade 3 or higher occurred in 75.3% of the 320 patients receiving nivolumab plus cabozantinib and in 70.6% of the 320 patients receiving sunitinib.

March 4, 2021
N Engl J Med 2021; 384:829-841

AUA 2025
APRIL 26-29 Las Vegas

ORIGINAL ARTICLE

Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma

Robert Motzer, M.D., Boris Alekseev, M.D., Sun-Young Rha, M.D., Camillo Porta, M.D., Masatoshi Eto, M.D., Thomas Powles, M.D., Viktor Grünwald, M.D., Thomas E. Hutson, M.D., Evgeny Kopyltsov, M.D., María J. Méndez-Vidal, M.D., Vadim Kozlov, M.D., Anna Alyasova, M.D., et al., for the CLEAR Trial Investigators*

April 8, 2021
N Engl J Med 2021; 384:1289-1300

- Phase 3 trial randomized 1:1:1 advanced ccRCC and no previous systemic therapy
  - Lenvatinib (multi-kinase inhibitor) plus pembrolizumab
  - Lenvatinib plus everolimus (5 mg orally once daily)
  - Sunitinib

- PEP: PFS

- Secondary EP: OS and Objective Response

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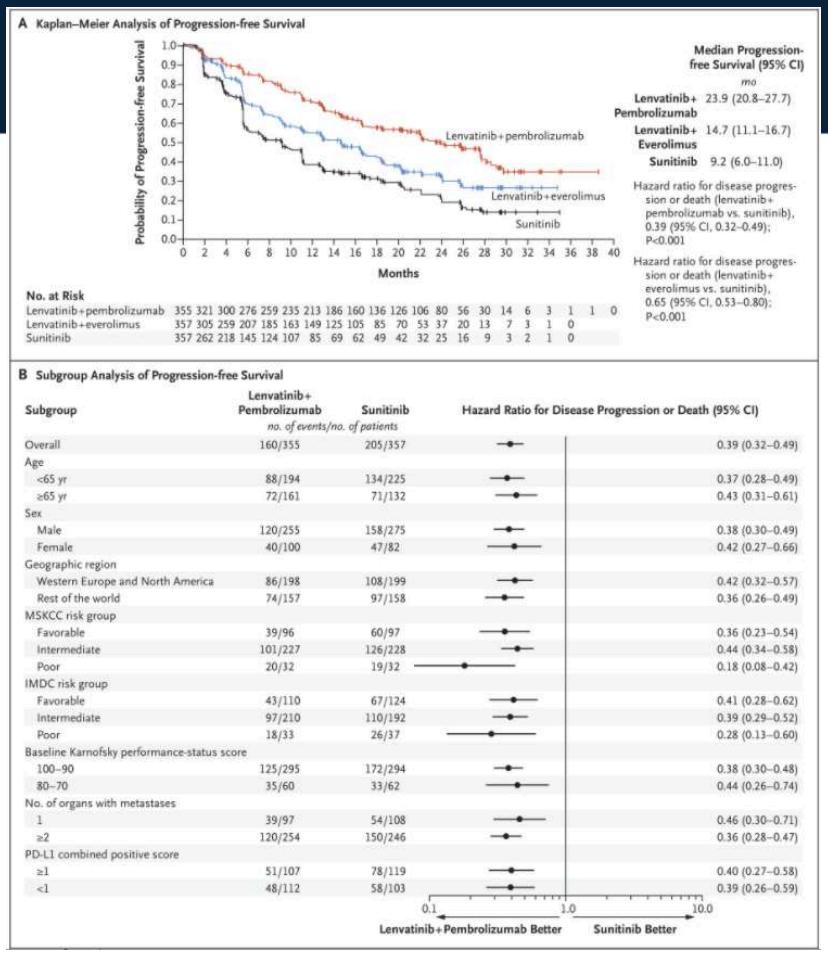
- 1069 patients underwent randomization:
  - 355 lenvatinib/pembrolizumab,
  - 357 lenvatinib/everolimus, and
  - 357 sunitinib

- PFS was significantly longer in the lenvatinib-plus-pembrolizumab group than in the sunitinib group (median, 23.9 months vs. 9.2 months); hazard ratio for disease progression or death, 0.39

- PFS was significantly longer in the lenvatinib-plus-everolimus group than in the sunitinib group 14.7 months vs. 9.2 months; HR 0.65

- Across all evaluated subgroups, including those based on IMDC risk group



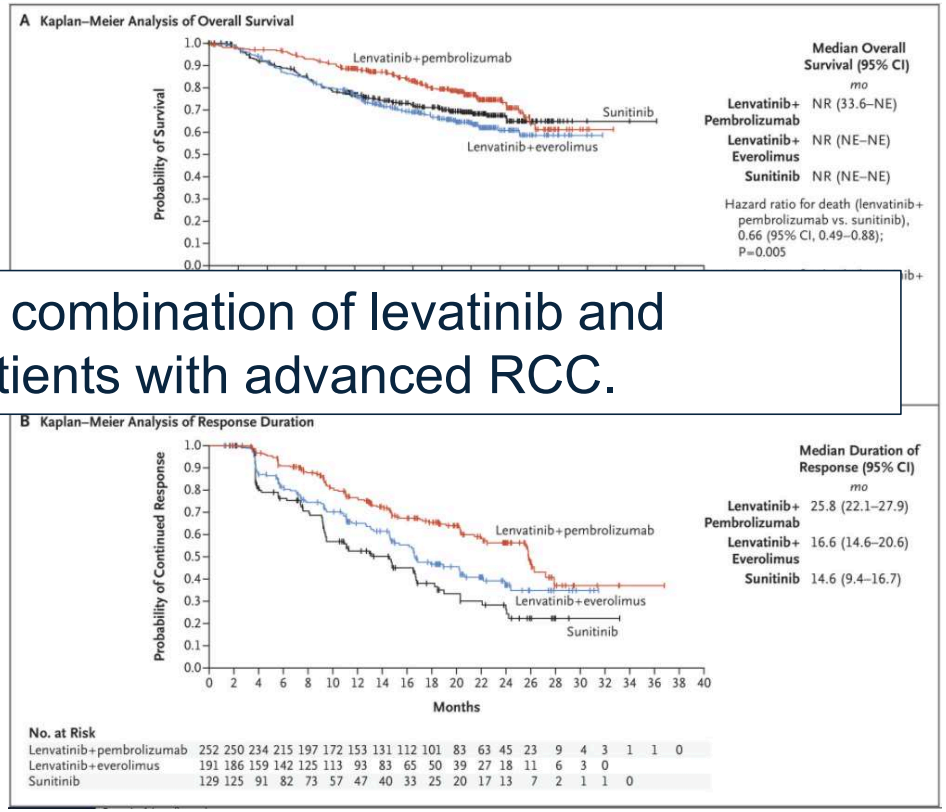
- OS: 79.2% in the lenvatinib-plus-pembrolizumab group, 66.1% in the lenvatinib-plus-everolimus group, and 70.4% in the sunitinib group were alive at 24 months

- Survival was significantly longer with lenvatinib plus

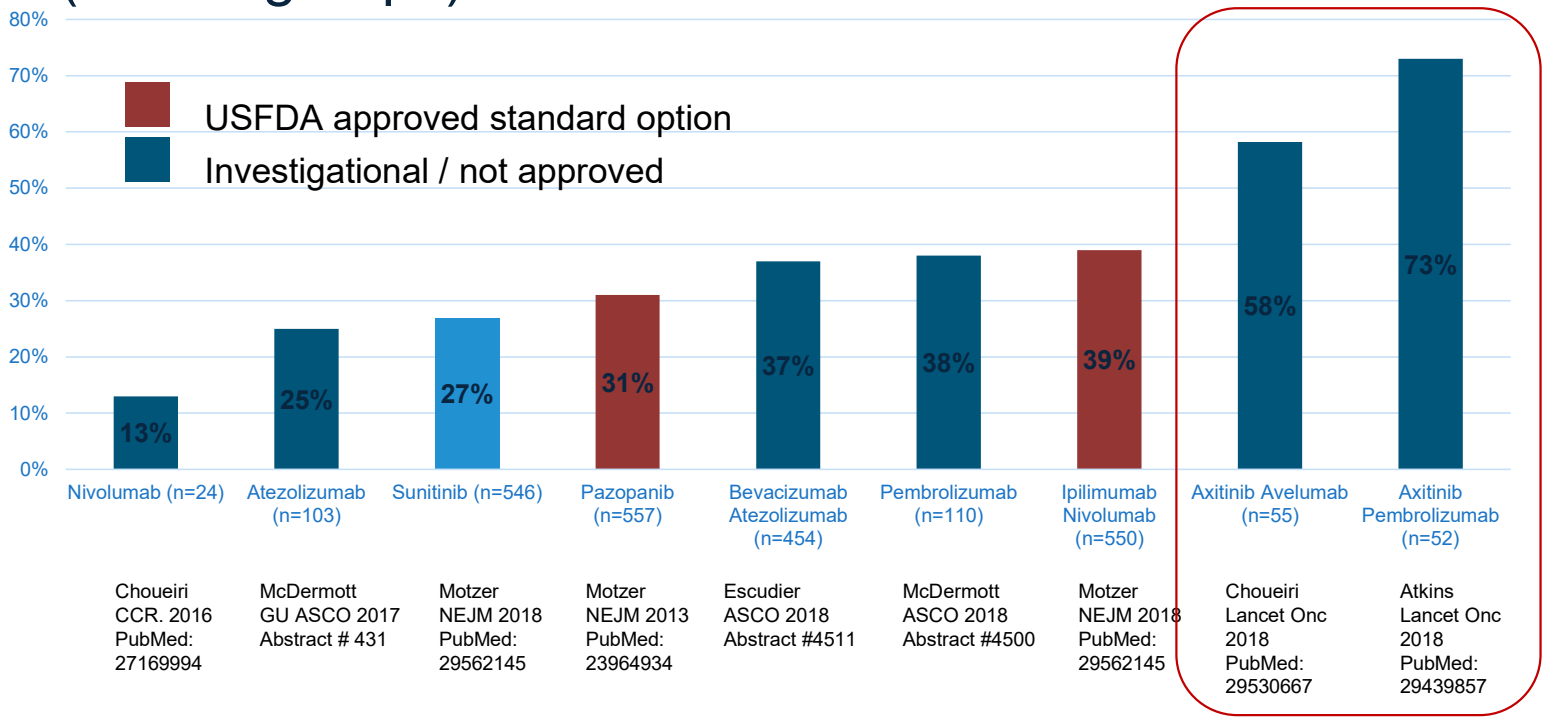
On August 11, 2021, the FDA approved the combination of levatinib and pembrolizumab as first-line treatment for patients with advanced RCC.

- Overall survival with lenvatinib plus everolimus was not significantly longer than that with sunitinib

- The HR for OS favored lenvatinib plus pembrolizumab over sunitinib in most subgroups, including patients with PD-L1–positive or –negative tumors, with an exception observed in patients with favorable risk features as defined by IMDC criteria.



Response Rates in Front Line metastatic ccRCC (all risk groups)



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PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0) OR RELAPSED DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b,c] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Ipilimumab + nivolumab[b,d]	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Pazopanib • Sunitinib	• Active surveillance[1,2,3] • Axitinib (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b,c] (category 1) • Ipilimumab + nivolumab[b,d] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B)

Footnotes:

[a] Risk Models to Direct Treatment (IMDC criteria or MSKCC Prognostic Model) (KID-E).

[b] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

[c] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

[d] Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

References:

[1] Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol 2016;17:1317-1324.

[2] Harrison MR, Costello BA, Bhavsar NA, et al. Active surveillance of metastatic renal cell carcinoma: Results from a prospective observational study (MaRCC). Cancer 2021;127:2204-2212.

[3] Bex A. Increasing the evidence for surveillance of metastatic renal cancer. Cancer 2021;127:2184-2186.

Note: All recommendations are category 2A unless otherwise indicated.

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PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV OR RELAPSED DISEASE

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)			
Immuno-oncology (IO) Therapy History Status	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
IO Therapy Naïve	• None	• Axitinib + pembrolizumab[b] • Cabozantinib • Cabozantinib + nivolumab[b,c] • Everolimus + lenvatinib • Ipilimumab + nivolumab[b,d] • Lenvatinib + pembrolizumab[b] • Nivolumab[b,c]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[f] • Belzutifan (category 2B) • Bevacizumab[g] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Belzutifan[e] • Cabozantinib • Everolimus + lenvatinib • Tivozanib[f]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b,c] • Everolimus • Ipilimumab + nivolumab[b,d] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Bevacizumab[g] (category 2B) • Axitinib + avelumab[b] (category 3)

[b] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[c] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[d] Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[e] This regimen is for patients who have received a programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).
[f] For patients who received ≥2 prior systemic therapies.
[g] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

Note: All recommendations are category 2A unless otherwise indicated.

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)

Immuno-oncology (IO) Therapy History Status	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
IO Therapy Naïve	• None	• Axitinib + pembrolizumab[b] • Cabozantinib • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + everolimus • Lenvatinib + pembrolizumab[b] • Nivolumab[b]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[g] • Belzutifan (category 2B) • Bevacizumab[h] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Belzutifan[f] • Cabozantinib • Lenvatinib + everolimus • Tivozanib[g]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Everolimus • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Bevacizumab[h] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0)[h] OR RELAPSED DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[i]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Clinical trial • Cabozantinib • Cabozantinib + nivolumab[b,c] • Lenvatinib + pembrolizumab[b]	• Erlotinib + bevacizumab[g] + for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (HERED-RCC-D) • Everolimus + lenvatinib • Nivolumab[b,c] • Pembrolizumab[b] • Sunitinib	• Axitinib • Everolimus + bevacizumab[g] • Everolimus • Ipilimumab[b] + nivolumab[b,d] (category 2B)

[b] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[c] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[d] Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[g] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[h] For first-line only.
[i] For collecting duct or medullary subtypes, partial responses have been observed with cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) and other platinum-based chemotherapies currently used for urothelial carcinomas. Gemcitabine + doxorubicin can also produce responses in renal medullary carcinoma (RMC) (Wilson NR, et al. Clin Genitourin Cancer 2021;19:e401-e408). Oral targeted therapies generally do not produce responses in patients with RMC; erlotinib + bevacizumab can produce responses even in heavily pretreated patients with RMC. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred first-line therapy for RMC.

Note: All recommendations are category 2A unless otherwise indicated.

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[i]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Clinical trial • Cabozantinib	• Lenvatinib + everolimus • Nivolumab[b] • Nivolumab[b] + cabozantinib • Pembrolizumab[b] • Sunitinib	• Axitinib • Bevacizumab[h] • Bevacizumab[h] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated RCC (HERED-RCC-D) • Bevacizumab[h] + everolimus • Erlotinib • Everolimus • Nivolumab[b] + ipilimumab[b] (category 2B) • Pazopanib • Temsirolimus[e] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

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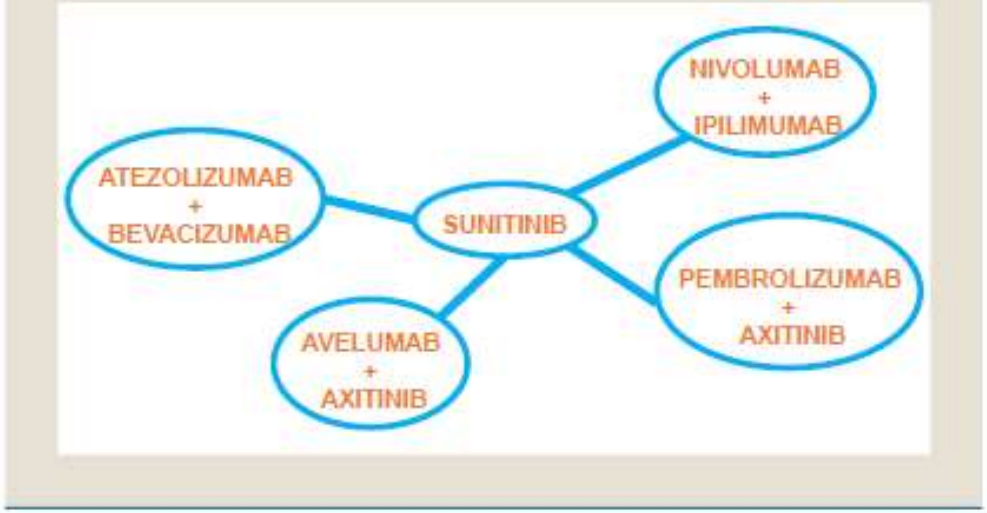
Lack of Head-to-Head Comparison

Figure 2 Network Diagram



Monteiro et al Clinical Genitourinary Cancer, 2020

Localized Disease

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Localized Disease

- Stage I-III: Quite simple → Resect the tumor!
  - Partial or complete nephrectomy, at the discretion of the surgeon
- Now question of adjuvant therapy: Its not quite simple
  - Do TKI's increase DFS in this setting?

Study	N	Intervention	Primary Endpoint	Outcome
ASSURE[35]	1943	Sorafenib or sunitinib vs placebo for one year	DFS	Non-significant; sunitinib HR 1.02, 97.5% CI 0.85–1.23, P=0.8038; sorafenib HR 0.97, 97.5% CI 0.80–1.17, P=0.718
S-TRAC[36]	615	Sunitinib vs placebo for one year	DFS	Significant; HR 0.76; 95% CI 5.8-NR; P=0.030
PROTECT[39]	1538	Pazopanib (600mg) vs placebo for one year	DFS	Non-significant; HR 0.86; 95% CI 0.70–1.06; P=0.165
ATLAS[40]	724	Axitinib vs placebo for three years	DFS	Stopped due to futility; non-significant at interim analysis; HR 0.87, 95% CI 0.66–1.15; P=0.321
SORCE[42]	1711	Sorafenib vs placebo for three years	DFS	Non-significant; HR 1.01; 95% CI 0.83–1.23; P=0.950
EVEREST[43,44]	1218	Everolimus vs placebo (nine courses of six weeks)	DFS	Results awaited

FDA →

…But not OS!

Adopted from: Tacconi EMC, Tuthill M, Protheroe A. Review of Adjuvant Therapies in Renal Cell Carcinoma: Evidence to Date. Onco Targets Ther. 2020 Nov 30;13:12301-12316.

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Adjuvant therapy in RCC

- Anti-VEGF Therapy – ASSURE (sunitinib/sorafenib), SORCE (sunitinib), ATLAS (axitinib), PROTECT (pazopanib), S-TRAC (sunitinib)
- mTOR inhibitors – EVEREST (everolimus)
- Tumor antigen antibody – ARISER (girentuximab)
- Immunotherapy – IMmotion010 (atezolizumab), PROSPER (nivolumab)

Adjuvant therapy

Trial	Phase	n	Drug	Route	Arms	Histology	Features	1° Outcome
SOURCE	III	1656	Sorafenib	PO	1-Placebo 2-Sorafenib 1 yr 3- Sorafenib 3 yrs	All Histology	SSIGN 3-11	DFS
ASSURE	III	1923	Sorafenib Sutent	PO	1-Placebo 2-Sorafenib-9 cycles 3- Sutent-9 cycles	All exept collecting duct or medullary	T1b, G3-4 T2,3,4 N+	DFS
S-TRAC	III	720	Sutent	PO	1-Placebo 2-Sutent-1 yr	Predominant clear cell	UISS High risk	DFS
ARISER	III	864	G250-Ab	IV	1- Placebo 2- G250-Ab x 24 wks	Clear Cell	T1b/2, G3-4 T3,T4 N+	DFS, OS
PROTECT	III	1500	Pazopanib	PO	1-Placebo 2- Pazopanib x 1 yr	Predominant clear cell	T2 (G3-4), T3, T4, N1	DFS
EVEREST	III	1218	Everolimus	PO	1- placebo 2- everolimus x 1 yr	All exept collecting duct or medullary	T1b, G3-4 T2,3,4 N+	DFS, OS
ATLAS	III	592	Axitinib	PO	1- placebo 2- Axitinib x 3 yr	>50%, clear cell RCC	≥T2 or N1	DFS

DFS of 6.8 years in the sunitinib arm versus 5.6 years in the placebo group

Therapy discontinuation rate of 28.1% due to toxicity in the sunitinib arm (5.6% in placebo)

OS data not mature

- Role for immune checkpoint blockade?

Study	Intervention	Sample Size	Primary EP	Results
PROSPER	Neoadjuvant + Adjuvant Nivolumab	805	RFS	Negative
IMmotion010	Adjuvant Atezolizumab	778	DFS	Negative
KEYNOTE-564	Adjuvant Pembrolizumab	950	DFS	**DFS benefit!**
CheckMate 914	Adjuvant Ipi/Nivo	1600	DFS	Negative
RAMPART	Adjuvant durvalumab +/- tremelimumab	1750	DFS + OS	??

Adopted from: Tacconi EMC, Tuthill M, Protheroe A. Review of Adju... Therapies in Renal Cell Carcin... Evidence to Date ... Targets Ther. 2020 Nov 30;13:12301-12316.

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ORIGINAL ARTICLE

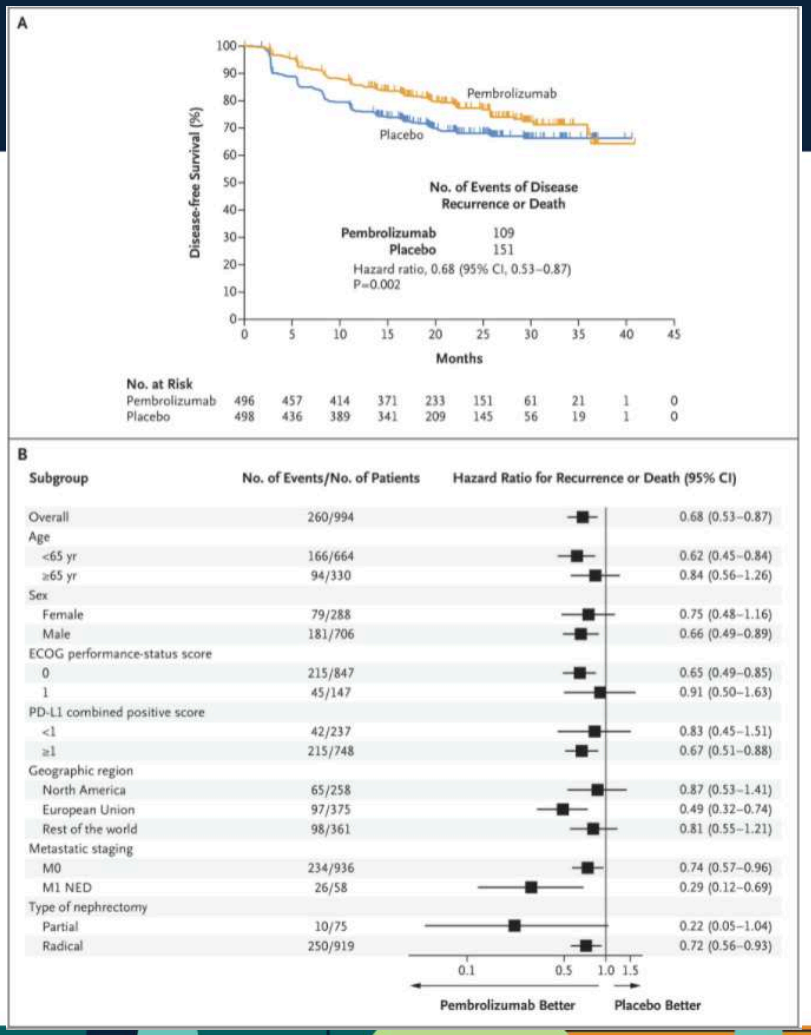
Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma

Toni K. Choueiri, M.D., Piotr Tomczak, M.D., Ph.D., Se Hoon Park, M.D., Balaji Venugopal, M.D., Thomas Ferguson, M.D., Yen-Hwa Chang, M.D., Ph.D., Jaroslav Hajek, M.U.Dr., Stefan N. Symeonides, M.D., Ph.D., Jae Lyun Lee, M.D., Ph.D., Naveed Sarwar, M.D., Ph.D., Antoine Thiery-Vuillemin, M.D., Ph.D., Marine Gross-Goupil, M.D., Ph.D., et al., for the KEYNOTE-564 Investigators*

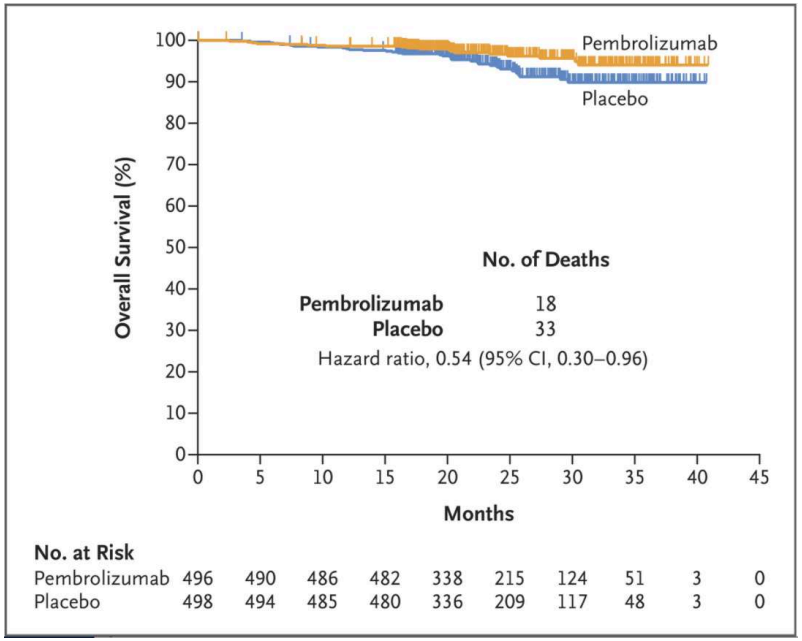
2021 Aug 19;385(8):683-694

- Double-blind, phase 3 trial
- In a 1:1 ratio, patients with ccRCC who were at high risk for recurrence after nephrectomy, to receive either adjuvant pembrolizumab or placebo IV once every 3 weeks for up to 17 cycles
  - pT2 with nuclear grade 4 or sarcomatoid differentiation
  - pT3 or higher
  - LN+
  - M1 with NED (complete metastatectomy)
- PEP: Disease-free survival.
- Secondary EP: Overall survival and Safety

- 994 patients in intention-to-treat population - adjuvant pembrolizumab (496 patients) or placebo (498 patients)
- Pembro group, 61.1% of the patients completed the full 17 cycles of trial treatment; the most common reason for discontinuation being an adverse event (in 21.3%), followed by disease recurrence (in 10.5%).
- Placebo group, 73.6% of the patients completed the full 17 cycles; with the most common reason for discontinuation being disease recurrence (in 20.4%)
- The risk of disease recurrence or death was 32% lower with adjuvant pembrolizumab therapy than with placebo



- 51 deaths occurred (18 in the pembrolizumab group and 33 in the placebo group).
- The median overall survival was not reached in either group
- 32.4% of the patients who received pembrolizumab and 17.7% of those who received placebo had an adverse event of grade 3 to 5.



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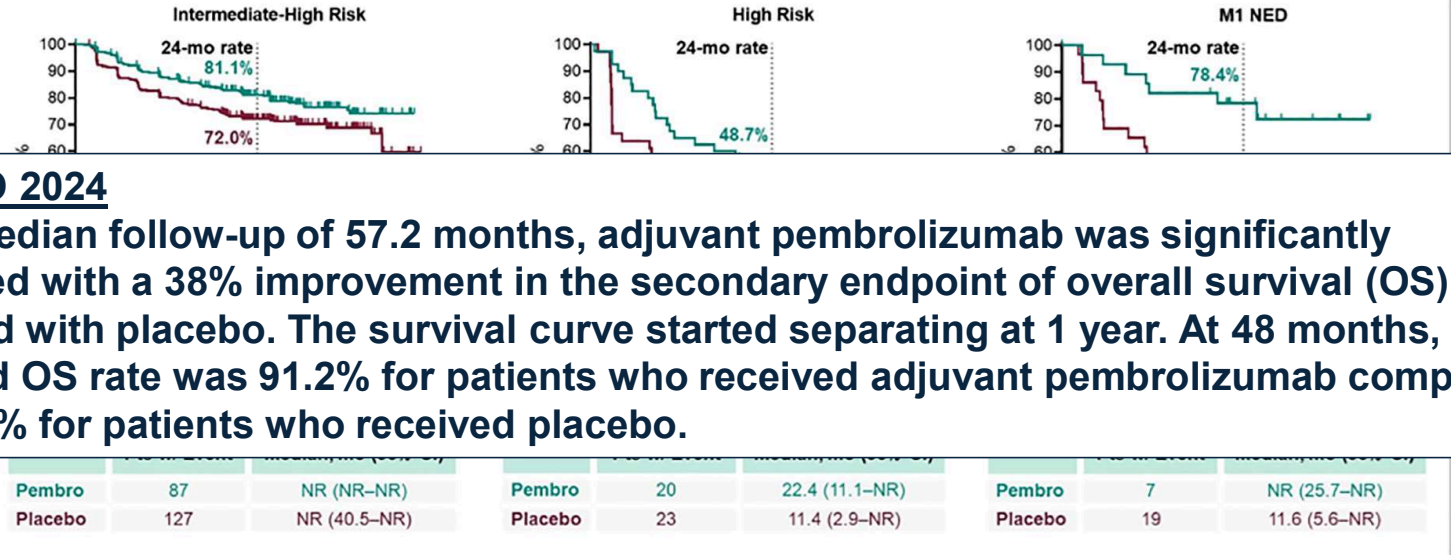
Localized disease: Adjuvant Pembrolizumab



GU ASCO 2024

Over a median follow-up of 57.2 months, adjuvant pembrolizumab was significantly associated with a 38% improvement in the secondary endpoint of overall survival (OS) compared with placebo. The survival curve started separating at 1 year. At 48 months, the estimated OS rate was 91.2% for patients who received adjuvant pembrolizumab compared with 86.0% for patients who received placebo.

Pembro	87	NR (NR–NR)
Placebo	127	NR (40.5–NR)

Pembro	20	22.4 (11.1–NR)
Placebo	23	11.4 (2.9–NR)

Pembro	7	NR (25.7–NR)
Placebo	19	11.6 (5.6–NR)

- The risk of disease recurrence or death was 32% lower with adjuvant pembrolizumab therapy than with placebo
- The median overall survival was not reached in either group

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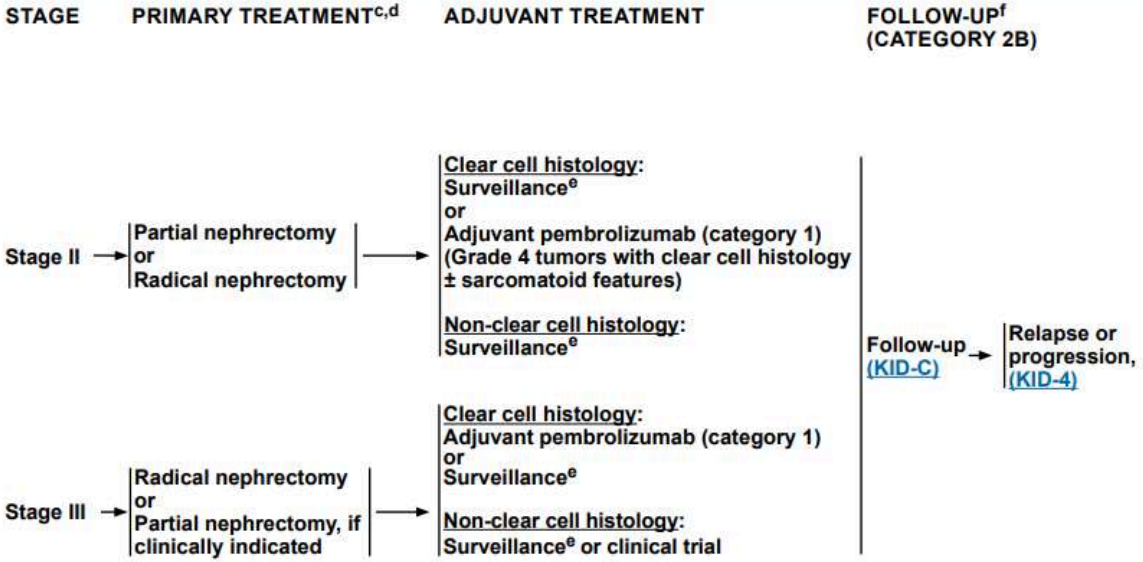

[c] General Principles of Management for Renal Cell Carcinoma (KID-A).
[d] SBRT may be considered for non-optimal surgical candidates with stage I kidney cancer (category 2B) or with stage II/III kidney cancer (both category 3). See Principles of Radiation Therapy (KID-B).
[e] Follow-up (KID-C).
[f] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

Note: All recommendations are category 2A unless otherwise indicated.

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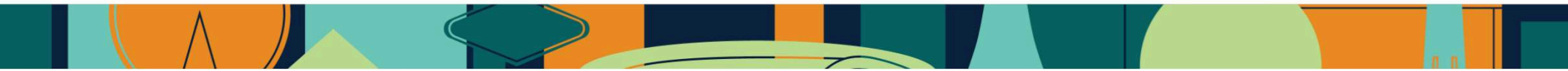
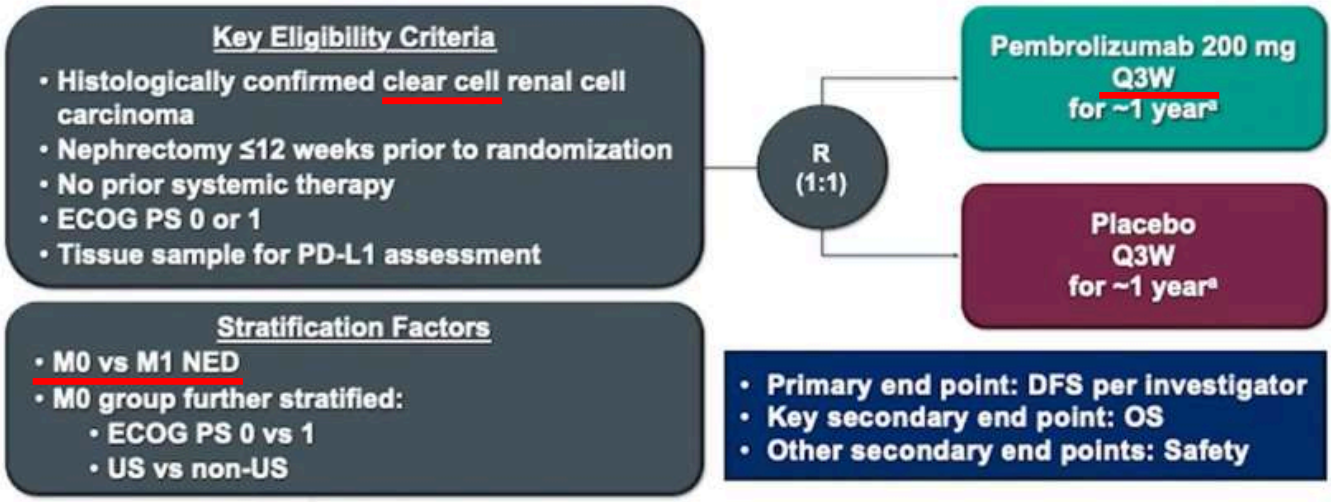
THANK YOU



Pembrolizumab

- KEYNOTE-564



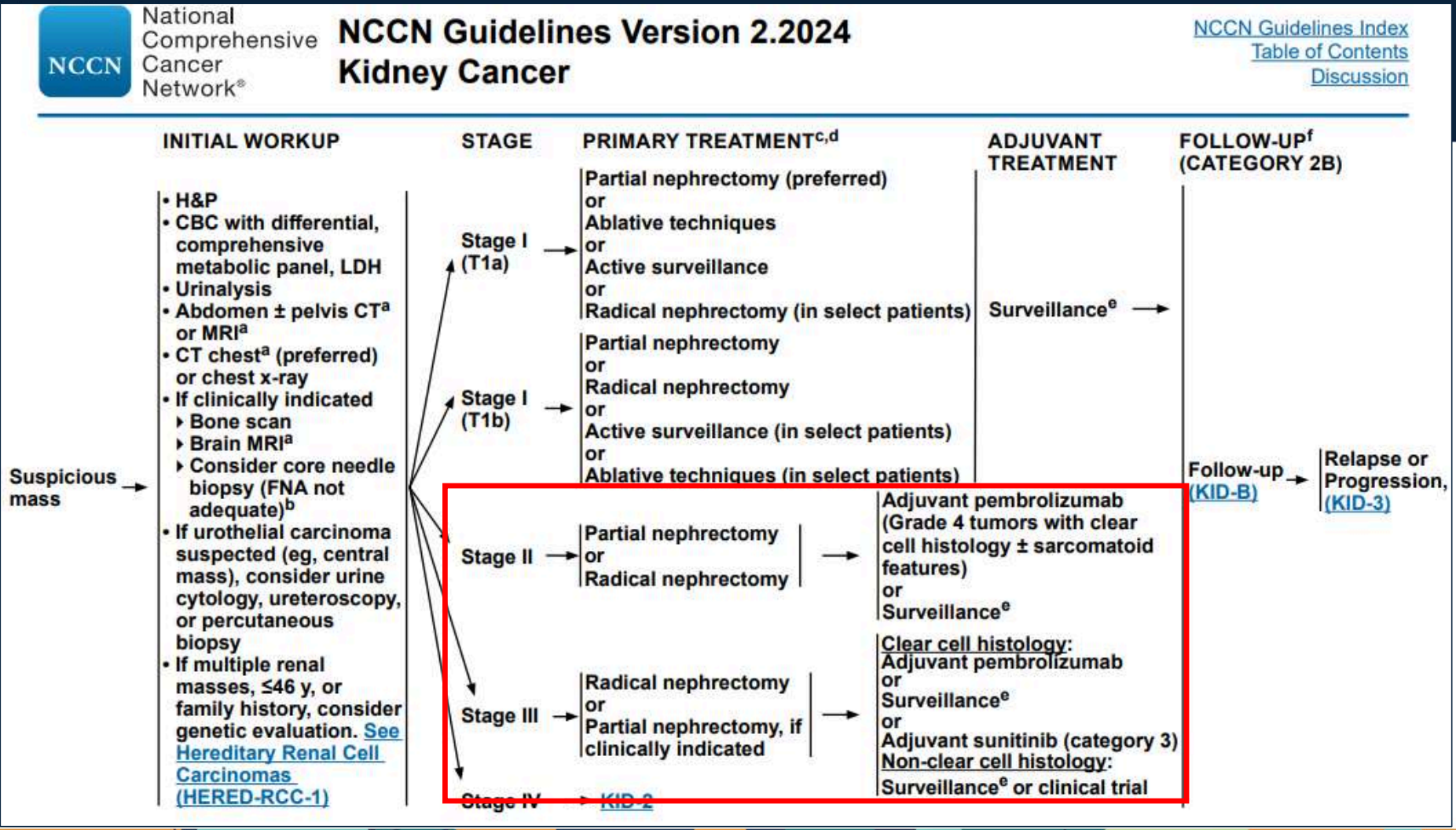
Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang YH, Hajek J, Symeonides SN, Lee JL, Sarwar N, Thiery-Vuillemin A, Gross-Goupil M, Mahave M, Haas NB, Sawrycki P, Gurney H, Chevreau C, Melichar B, Kopyltsov E, Alva A, Burke JM, Doshi G, Topart D, Oudard S, Hammers H, Kitamura H, Bedke J, Perini RF, Zhang P, Imai K, Willemann-Rogerio J, Quinn DI, Powles T; KEYNOTE-564 Investigators. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. N Engl J Med. 2021 Aug 19;385(8):683-694.

Localized Disease Summary

- KEYNOTE-564 remains the only positive trial in this space
  - Lots of uncertainty
  - FDA approved, NCCN guidelines

Intermediate-High Risk		High Risk		M1 No Evidence of Disease
pT2 Grade 4 or sarcomatoid N0 M0	pT3 Any grade N0 M0	pT4 Any grade N0 M0	Any pT Any grade N+ M0	No evidence of disease after resection of oligometastatic sites ≤1 year from nephrectomy

  - Remains a patient-centered decision. Thorough risk/benefit discussion is necessary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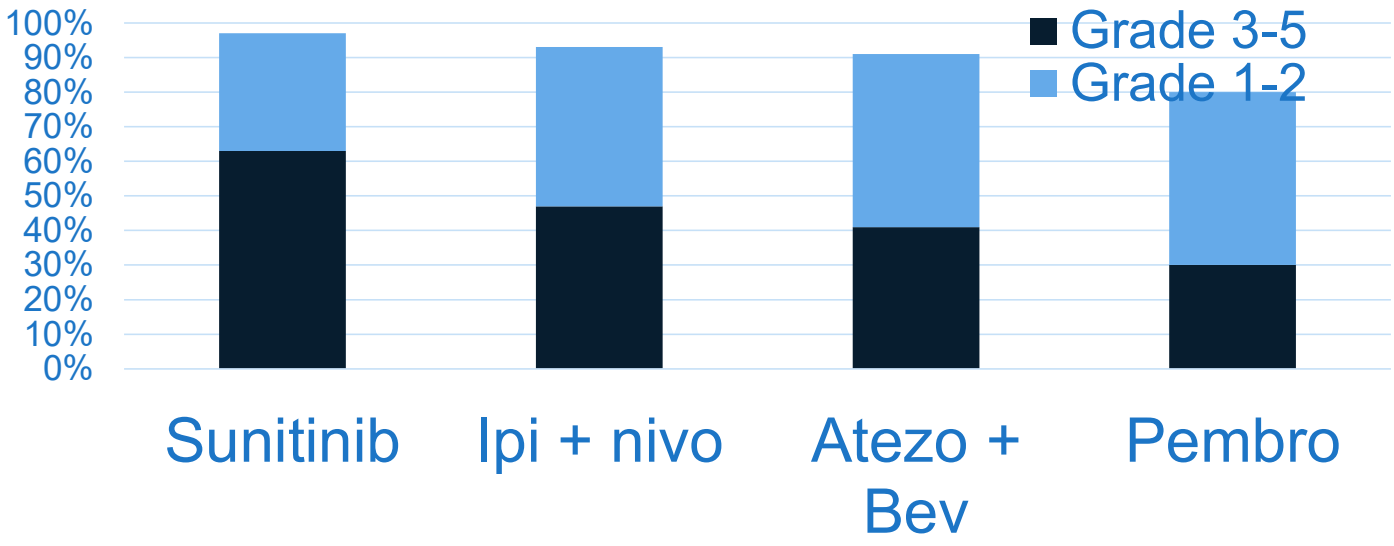
INITIAL WORKUP
STAGE
PRIMARY TREATMENT[c,d]
ADJUVANT TREATMENT
FOLLOW-UP[f] (CATEGORY 2B)
Suspicious mass
• H&P
• CBC with differential, comprehensive metabolic panel, LDH
• Urinalysis
• Abdomen ± pelvis CT[a] or MRI[a]
• CT chest[a] (preferred) or chest x-ray
• If clinically indicated
‣ Bone scan
‣ Brain MRI[a]
‣ Consider core needle biopsy (FNA not adequate)[b]
• If urothelial carcinoma suspected (eg, central mass), consider urine cytology, ureteroscopy, or percutaneous biopsy
• If multiple renal masses, ≤46 y, or family history, consider genetic evaluation. See Hereditary Renal Cell Carcinomas (HERED-RCC-1)
Stage I (T1a)
Partial nephrectomy (preferred)
or
Ablative techniques
or
Active surveillance
or
Radical nephrectomy (in select patients)
Surveillance[e]
Stage I (T1b)
Partial nephrectomy
or
Radical nephrectomy
or
Active surveillance (in select patients)
or
Ablative techniques (in select patients)
Stage II
Partial nephrectomy
or
Radical nephrectomy
Adjuvant pembrolizumab (Grade 4 tumors with clear cell histology ± sarcomatoid features)
or
Surveillance[e]
Stage III
Radical nephrectomy
or
Partial nephrectomy, if clinically indicated
Clear cell histology:
Adjuvant pembrolizumab
or
Surveillance[e]
or
Adjuvant sunitinib (category 3)
Non-clear cell histology:
Surveillance[e] or clinical trial
Stage IV
KID-2
Follow-up (KID-B)
Relapse or Progression, (KID-3)

metastatic ccRCC (All Risk)



~35% received high dose steroids

12.7% received high dose steroids

Metastatic RCC

	Preferred	Alternate	Special circumstances
Favorable IMDC risk	Pazopanib	Sunitinib	Active surveillance
Poor/intermediate IMDC risk	Ipilimumab + nivolumab	Pazopanib (Cabozantinib)	Best supportive care

Watch for:

- Potential favorable risk/benefit with single agent pembrolizumab.
  - Await OS data
- Potential for improved outcomes with VEGF / TKI combinations
  - Multiple phase III trials ongoing/completed, results awaited
- Value assessments increasingly incorporated into guideline recommendations are likely to affect combos

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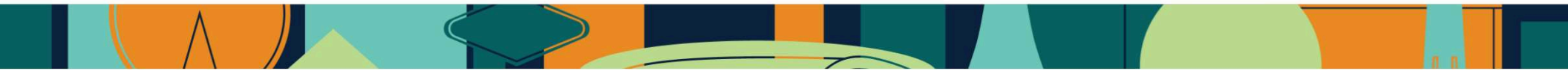
Immunotherapy in the Second Line and Beyond



Ipilimumab + Nivolumab
Nivo
Cabozantinib
Axitinib
Lenvatinib + Everolimus
Pazopanib
Sunitinib
Bevacizumab
(Sorafenib, HD IL2, Temsirolimus)

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Nivolumab vs Everolimus in RCC post TKI

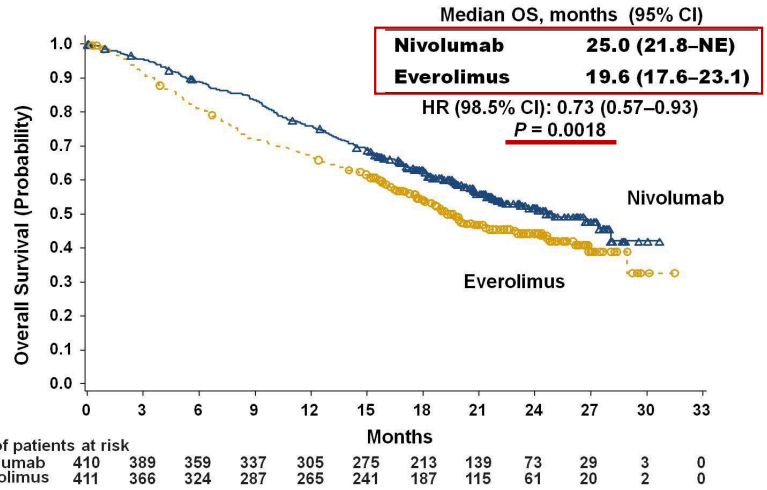
Antitumor activity

	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI)	5.98 (3.68–9.72)	
P value	<0.0001	
Best overall response, %		
Complete response	1	1
Partial response	24	5
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12
Median time to response, months (range)	3.5 (1.4–24.8)	3.7 (1.5–11.2)
Median duration of response, months (range)*	12.0 (0–27.6)	12.0 (0–22.2)
Ongoing response, n/N (%)	49/103 (48)	10/22 (45)

*For patients without progression or death, duration of response is defined as the time from the first response (CR/PR) date to the date of censoring.

13

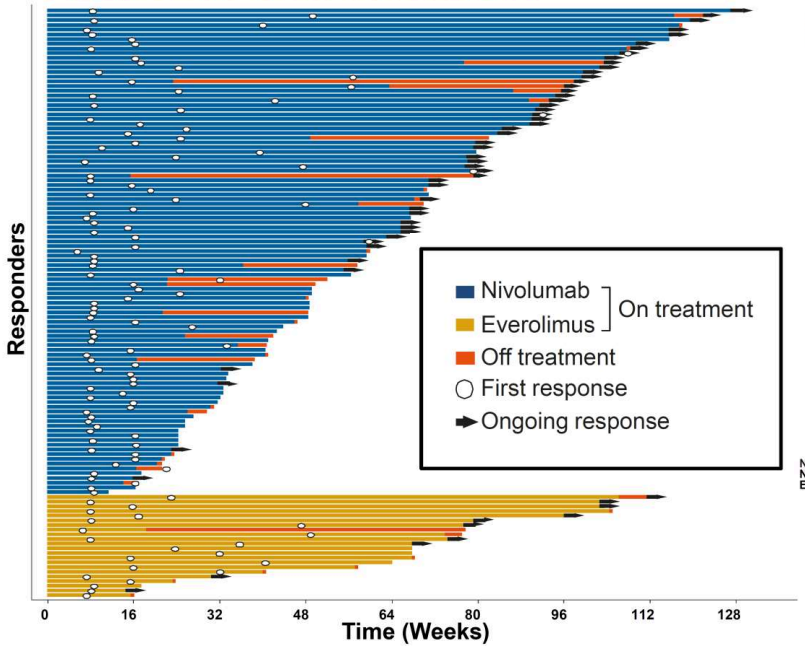
Overall survival



Presented by Sharma et al at the European Cancer Congress, Vienna, 26 September 2015

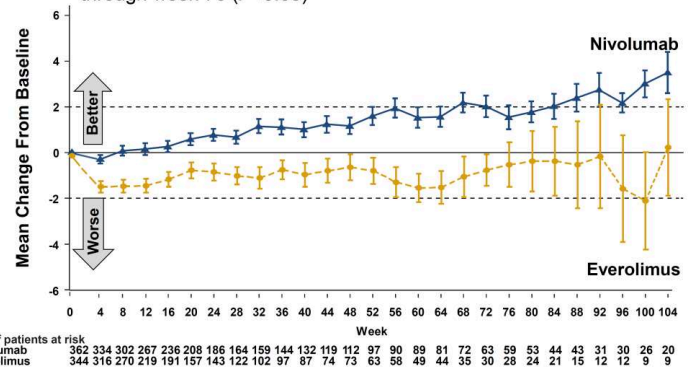
Quality of Response and QOL

Response characteristics



Change from baseline in quality of life scores on FKSI-DRS

- Mean change from baseline in the nivolumab group increased over time and differed significantly from the everolimus group at each assessment through week 76 ($P<0.05$)

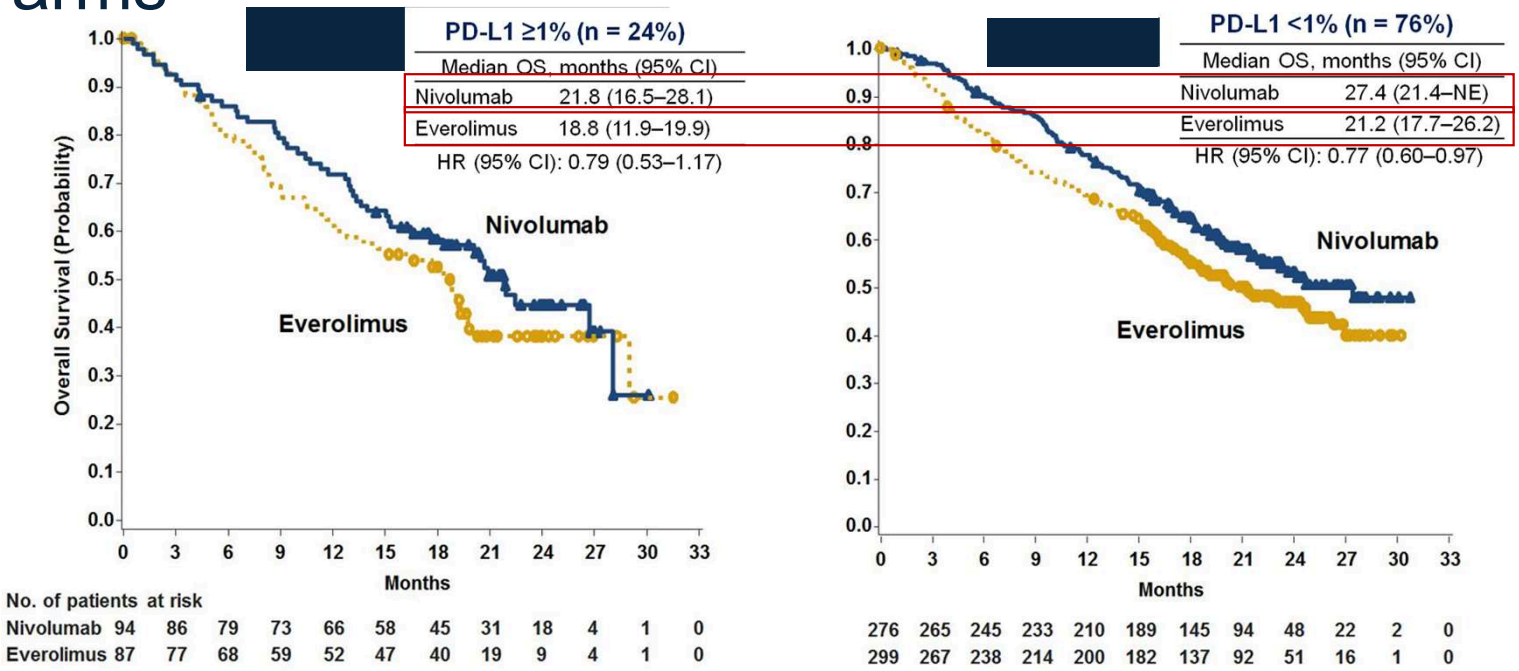


No. of patients at risk

Nivolumab	362	334	302	267	236	208	186	164	159	144	132	119	112	97	90	89	81	72	63	59	53	44	43	31	30	26	20
Everolimus	344	316	270	219	191	157	143	122	102	97	87	74	73	63	58	49	44	35	30	28	24	21	15	12	12	9	9

Questionnaire completion rate: ≥80% during the first year of follow-up.

but was a negative prognostic marker in both arms



ccRCC (IO in red)

Indolent (good risk)	Very aggressive (Poor Risk)	Intermediate/ Poor Risk	Pt who started with TKI	Pt who started with TKI → nivo
Observation	Cabozantinib	Ipi + Nivo	Pazopanib	Pazopanib
Pazopanib	Ipi + Nivo	Pazopanib	Ipi + Nivo	Nivolumab
Axitinib	Lenvatinib Everolimus	Cabozantinib	Cabozantinib	If good response to nivo add ipi at PD
Cabozantinib	?	Lenvatinib Everolimus	Lenvatinib Everolimus	Cabozantinib
Nivolumab → add ipi if PD				Lenvatinib Everolimus
Lenvatinib Everolimus				

Pivotal Phase III Trials in ccRCC post TKI

	RECORD-1[1]	AXIS[2]	METEOR[3]	CHECKMATE 025[4]	LEN EVE[5]
	Everolimus vs placebo	Axitinib vs sorafenib	Cabozantinib vs everolimus	Nivolumab vs everolimus	Lenvatinib + Everolimus vs everolimus*
Patients, n	416	389	658	821	154
Risk group, %					
Good	29	Not stated	46	36	23
Intermediate	56		42	49	36
Poor	14		13	15	40
Prior drug	VEGF	Sunitinib	VEGF	VEGF	VEGF
Line of therapy	2nd or beyond	2nd	2nd or beyond	2nd or 3rd	2nd
Overall Response Rate %	1 vs 0	19 vs 9	21 vs 5	25 vs 5	43 vs 3
Median OS, months	14.8 vs 14.4	15.2 vs 16.5	Not yet reported	25 vs 19.6	25 vs 15

1. Motzer, R.J. et all Lancet 372, 449-56 (2008).
2. Rini, B.I. et al. Lancet 378, 1931-9 (2011).
3. Choueiri, T.K. et al. N Engl J Med (2015).
4. Motzer, R.J. et al. N Engl J Med (2015).
5. Motzer, R.J. et al. Lancet (2015).

ASSUF
(May 2(

Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial

Naomi B Haas, Judith Manola, Robert G Uzzo, Keith T Flaherty, Christopher G Wood, Christopher Kane, Michael Jewett, Janice P Dutcher, Michael B Atkins, Michael Pins, George Wilding, David Cella, Lynne Wagner, Surena Matin, Timothy M Kuzel, Wade J Sexton, Yu-Ning Wong, Toni K Choueiri, Roberto Pili, Igor Puzanov, Manish Kohli, Walter Stadler, Michael Carducci, Robert Coomes, Robert S DiPaola*

Lancet 2016; 387: 2008–16
Published Online March 8, 2016
http://dx.doi.org/10.1016/S0140-6736(16)00559-6
This online publication has been corrected. The corrected version first appeared at thelancet.com on May 12, 2016

Summary

Background Renal-cell carcinoma is highly vascular, and proliferates primarily through dysregulation of the vascular endothelial growth factor (VEGF) pathway. We tested sunitinib and sorafenib, two oral anti-angiogenic agents that are effective in advanced renal-cell carcinoma, in patients with resected local disease at high risk for recurrence.

Methods In this double-blind, placebo-controlled, randomised, phase 3 trial, we enrolled patients at 226 study centres in the USA and Canada. Eligible patients had pathological stage high-grade T1b or greater with completely resected non-metastatic renal-cell carcinoma and adequate cardiac, renal, and hepatic function. Patients were stratified by recurrence risk, histology, Eastern Cooperative Oncology Group (ECOG) performance status, and surgical approach,

in DFS or OS for adjuvant sunitinib or sorafenib compared with placebo

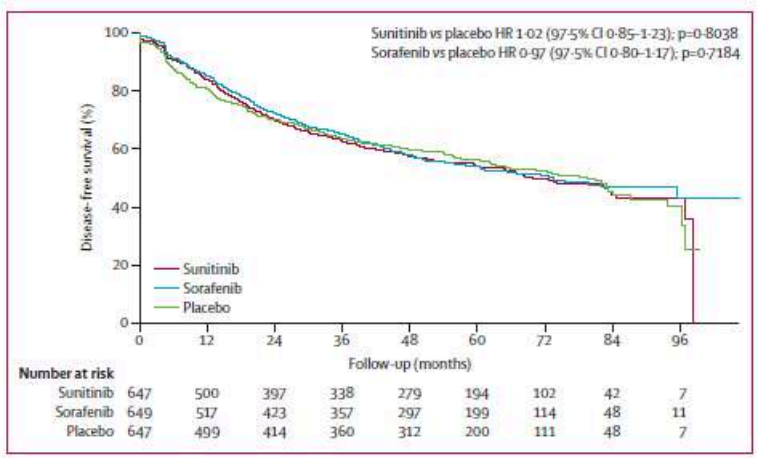


Figure 2: Disease-free survival
HR=hazard ratio.

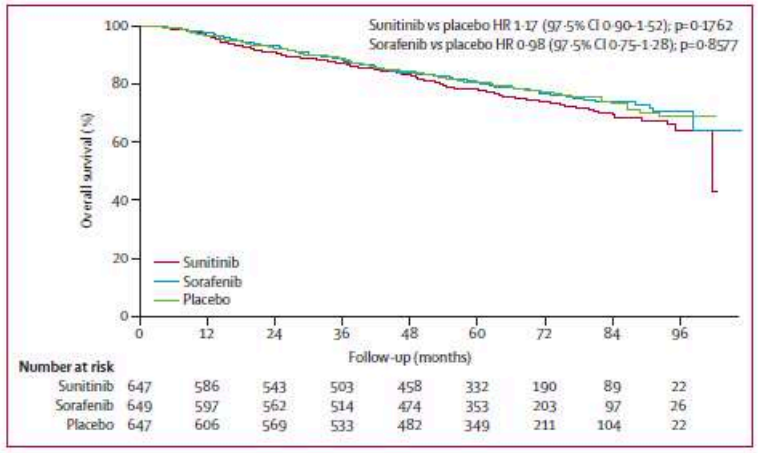


Figure 3: Overall survival
HR=hazard ratio.

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(Oct 20

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy

A. Ravaud, R.J. Motzer, H.S. Pandha, D.J. George, A.J. Pantuck, A. Patel, Y.-H. Chang, B. Escudier, F. Donskov, A. Magheli, G. Carteni, B. Laguerre, P. Tomczak, J. Breza, P. Gerletti, M. Lechuga, X. Lin, J.-F. Martini, K. Ramaswamy, M. Casey, M. Staehler, and J.-J. Patard, for the S-TRAC Investigators*

ABSTRACT

BACKGROUND

Sunitinib, a vascular endothelial growth factor pathway inhibitor, is an effective treatment for metastatic renal-cell carcinoma. We sought to determine the efficacy and safety of sunitinib in patients with locoregional renal-cell carcinoma at high risk for tumor recurrence after nephrectomy.

METHODS

In this randomized, double-blind, phase 3 trial, we assigned 615 patients with locoregional, high-risk clear-cell renal-cell carcinoma to receive either sunitinib (50 mg per day) or placebo on a 4-weeks-on, 2-weeks-off schedule for 1 year or until disease recurrence, unacceptable toxicity, or consent withdrawal. The primary end point was disease-free survival, according to blinded independent central review. Secondary end points included investigator-assessed disease-free survival, overall survival, and safety.

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estigators in the
reatment for Pa-
currence of Renal
ng Nephrectomy
ed in the Supple-
able at NEJM.org.

ard contributed

RCC

- DFS of 6.8 years in the sunitinib arm versus 5.6 years in the placebo group
- This trial focused on high risk ccRCC (high risk defined by UISS – includes grade, stage, PS)

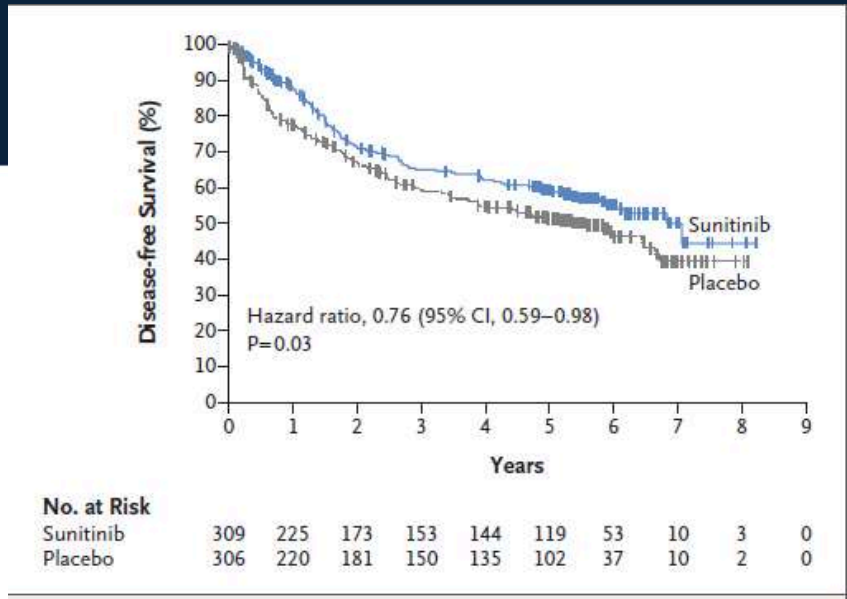

Figure 2. Disease-free Survival.

The median duration of disease-free survival according to independent central review was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group. At the time of data cutoff, an event of disease recurrence, a second cancer, or death had occurred in 113 of 309 patients (36.6%) in the sunitinib group and in 144 of 306 patients (47.1%) in the placebo group.

- Therapy discontinuation rate of 28.1% due to toxicity in the sunitinib arm (5.6% in placebo)
- G3 or higher AE were noted in 63.4% of the sunitinib group and 21.7% of the placebo group
- Patients receiving sunitinib had significantly lower scores on QOL surveys taken as part of the trial
- OS data not mature

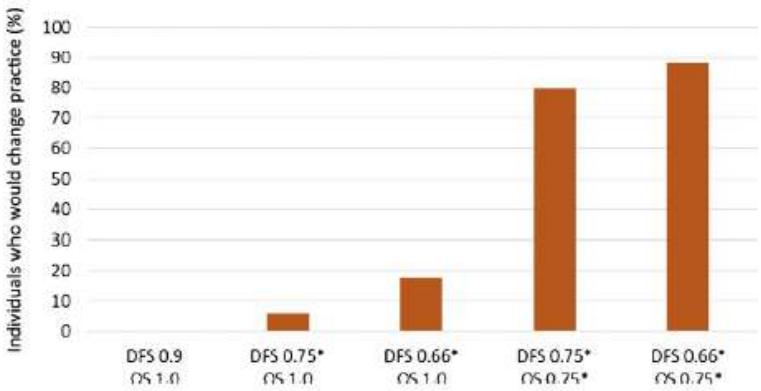

Fig. 2 – Members were asked which results from S-TRAC would change their standard practice in the context of the data available in ASSURE and toxicity profiles consistent with those seen for sunitinib. * Statistically significant. DFS = disease-free survival; OS = overall survival.

Bex et al Eur Urol May 2017

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Adjuvant therapy in RCC

Protocol	Type	Phase	Subjects	Agent	Comparison	Eligibility	Histology	1° Endpoint
EA8143 (PROSPER)	Neo/ Adjuvant	III	766	Nivolimab	Upfront Surgery	T2+ or N+ M0	Clear cell 90% Other subtypes (15%)	RFS
IMMOTION010	Adjuvant	III	664	Atezolizumab	IV Placebo	T2G4, T3aG3/4, T3b/T4, N+ M1 resected NED (met)	Clear Cell Sarcomatoid Features	DFS
KEYNOTE-564	Adjuvant	III	950	Pembrolizumab	IV Placebo	T2G4, T3/4Gany, N1 M1 resected NED (syn)	Clear Cell +/- Sarcomatoid Features	DFS
CheckMate 914	Adjuvant	III	800	Nivolimab + Ipilimumab	IV Placebo	T2G3/4, T3/4Gany, N1	Clear Cell +/- Sarcomatoid Features	DFS

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ORIGINAL ARTICLE

Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma

Toni K. Choueiri, M.D., Piotr Tomczak, M.D., Ph.D., Se Hoon Park, M.D., Balaji Venugopal, M.D., Thomas Ferguson, M.D., Yen-Hwa Chang, M.D., Ph.D., Jaroslav Hajek, M.U.Dr., Stefan N. Symeonides, M.D., Ph.D., Jae Lyun Lee, M.D., Ph.D., Naveed Sarwar, M.D., Ph.D., Antoine Thiery-Vuillemin, M.D., Ph.D., Marine Gross-Goupil, M.D., Ph.D., et al., for the KEYNOTE-564 Investigators*

2021 Aug 19;385(8):683-694

- Double-blind, phase 3 trial
- In a 1:1 ratio, patients with ccRCC who were at high risk for recurrence after nephrectomy, to receive either adjuvant pembrolizumab or placebo IV once every 3 weeks for up to 17 cycles
  - pT2 with nuclear grade 4 or sarcomatoid differentiation
  - pT3 or higher
  - LN+
  - M1 with NED (complete metastatectomy)
- PEP: Disease-free survival.
- Secondary EP: Overall survival and Safety

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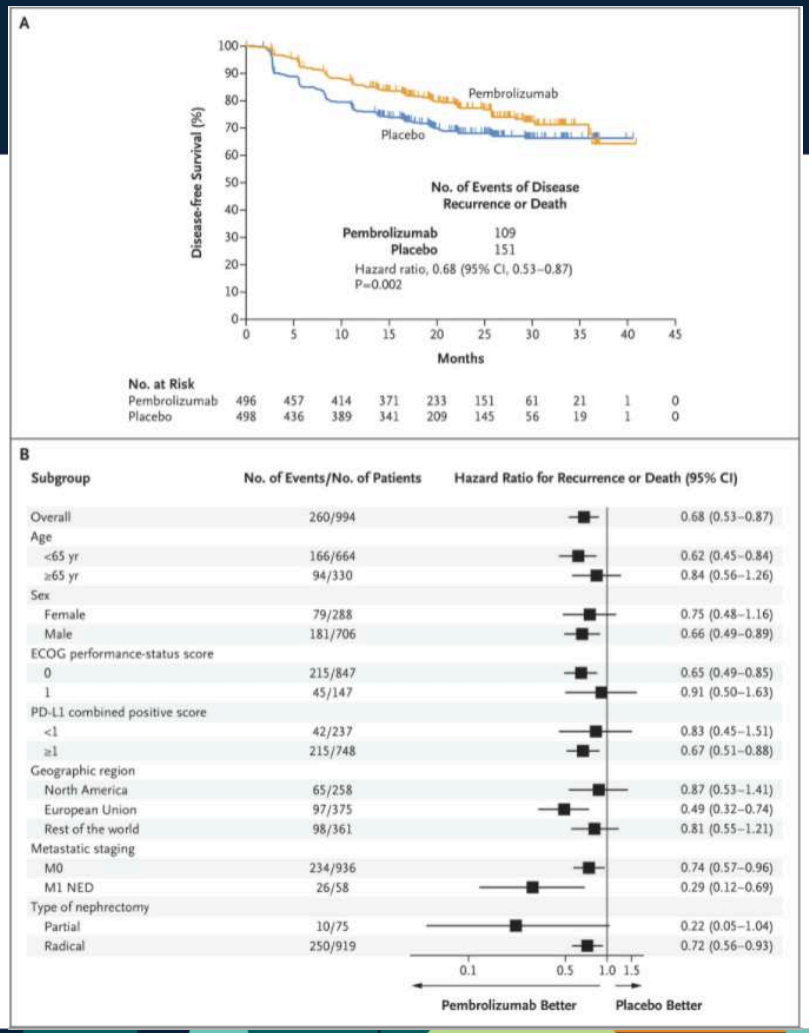
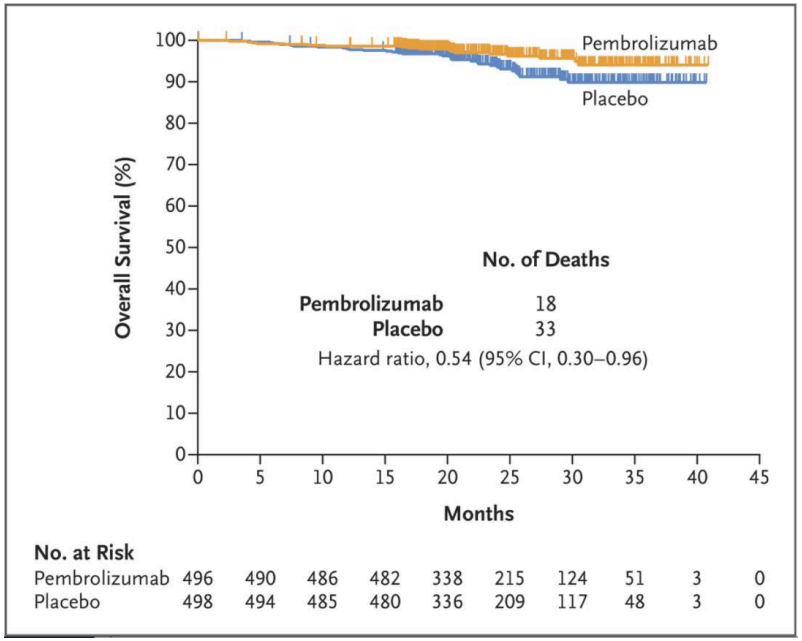
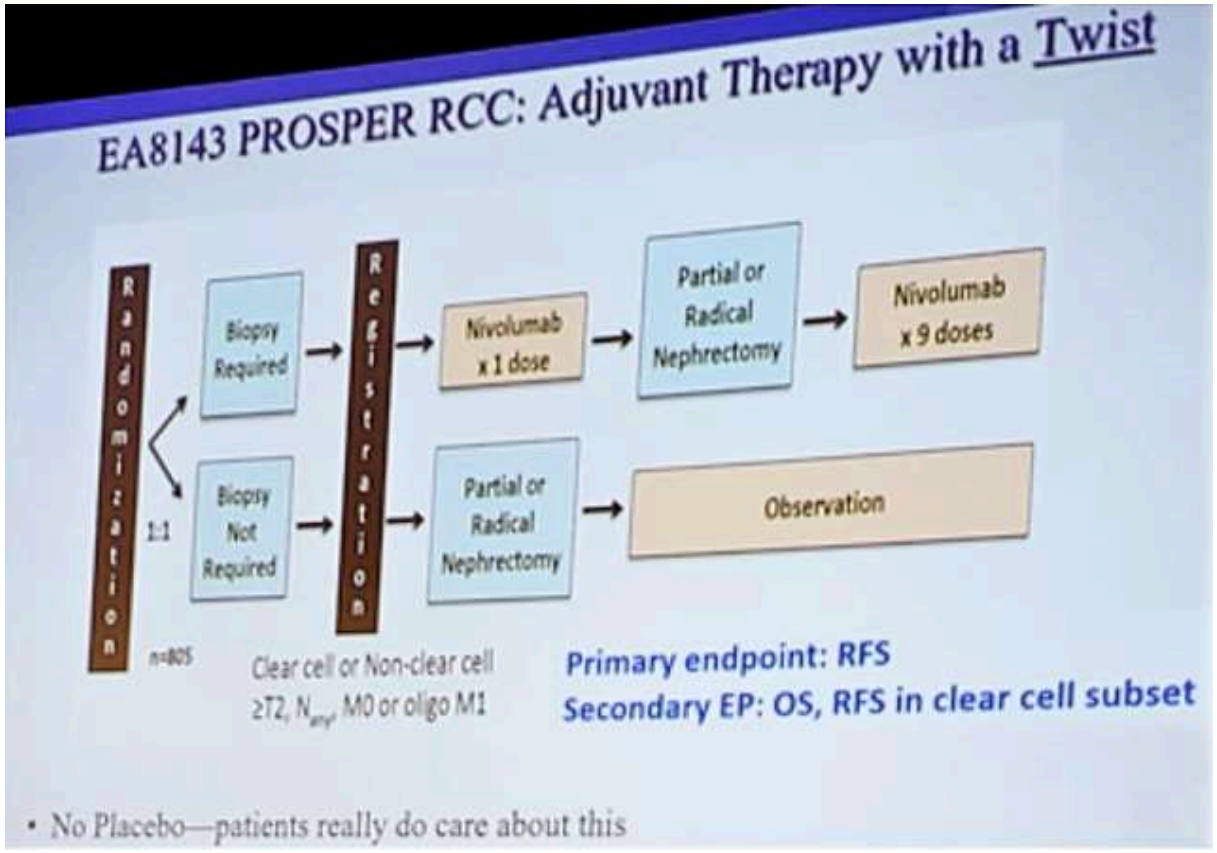
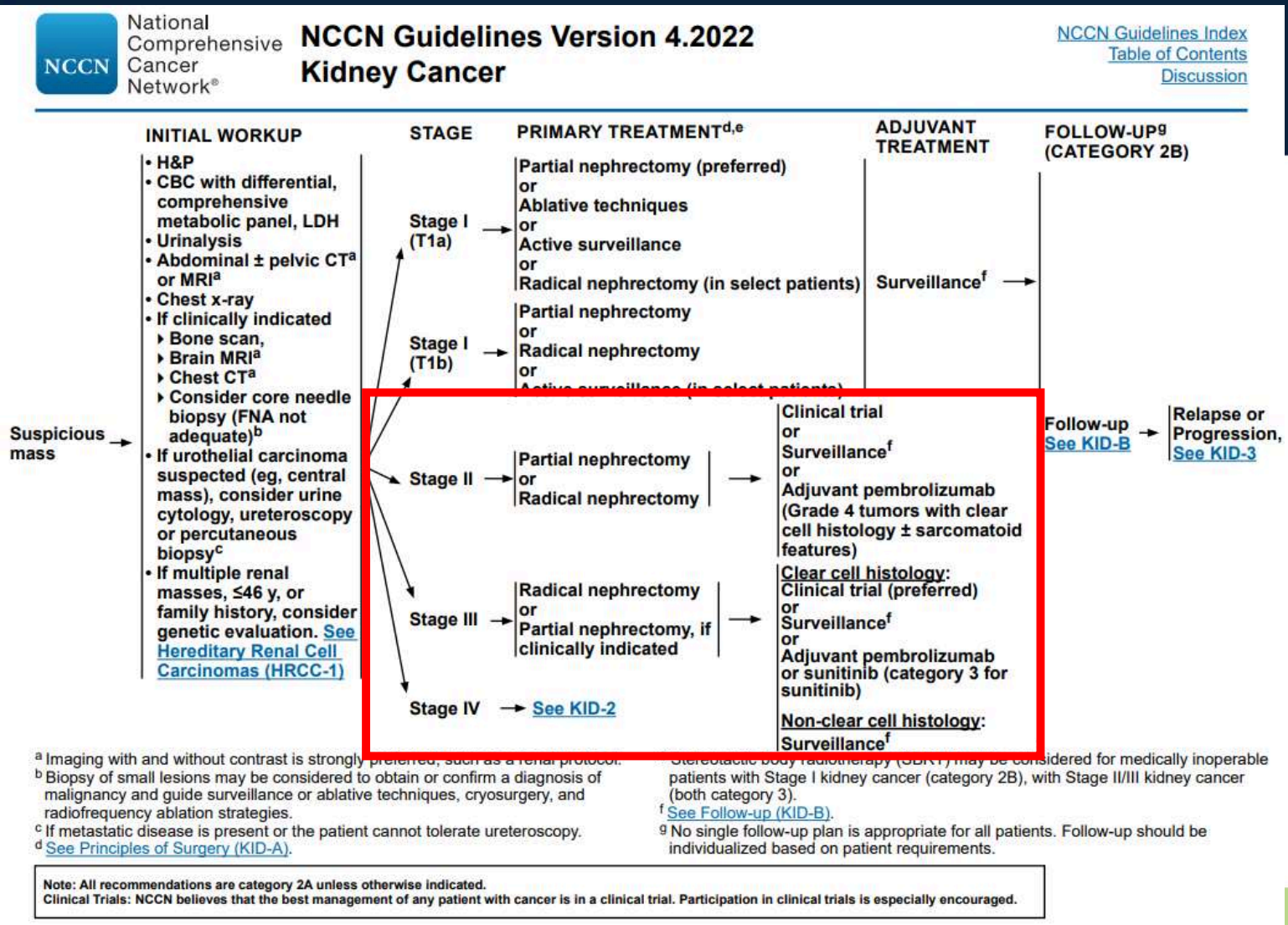
- 994 patients in intention-to-treat population - adjuvant pembrolizumab (496 patients) or placebo (498 patients)
- Pembro group, 61.1% of the patients completed the full 17 cycles of trial treatment; the most common reason for discontinuation being an adverse event (in 21.3%), followed by disease recurrence (in 10.5%).
- Placebo group, 73.6% of the patients completed the full 17 cycles; with the most common reason for discontinuation being disease recurrence (in 20.4%)
- The risk of disease recurrence or death was 32% lower with adjuvant pembrolizumab therapy than with placebo



- 51 deaths occurred (18 in the pembrolizumab group and 33 in the placebo group).
- The median overall survival was not reached in either group
- 32.4% of the patients who received pembrolizumab and 17.7% of those who received placebo had an adverse event of grade 3 to 5.




EA8143 PROSPER RCC: Adjuvant Therapy with a Twist
Randomization
1:1
Biopsy Required
Biopsy Not Required
Registration
Nivolumab x 1 dose
Partial or Radical Nephrectomy
Nivolumab x 9 doses
Partial or Radical Nephrectomy
Observation
n=805
Clear cell or Non-clear cell
≥T2, N$_{any}$, M0 or oligo M1
Primary endpoint: RFS
Secondary EP: OS, RFS in clear cell subset
• No Placebo—patients really do care about this


National Comprehensive Cancer Network®
NCCN Guidelines Version 4.2022
Kidney Cancer
NCCN Guidelines Index
Table of Contents
Discussion
INITIAL WORKUP
• H&P
• CBC with differential, comprehensive metabolic panel, LDH
• Urinalysis
• Abdominal ± pelvic CT[a] or MRI[a]
• Chest x-ray
• If clinically indicated
▸ Bone scan,
▸ Brain MRI[a]
▸ Chest CT[a]
▸ Consider core needle biopsy (FNA not adequate)[b]
• If urothelial carcinoma suspected (eg, central mass), consider urine cytology, ureteroscopy or percutaneous biopsy[c]
• If multiple renal masses, ≤46 y, or family history, consider genetic evaluation. See Hereditary Renal Cell Carcinomas (HRCC-1)
Suspicious mass
STAGE
PRIMARY TREATMENT[d,e]
ADJUVANT TREATMENT
FOLLOW-UP[g] (CATEGORY 2B)
Stage I (T1a)
Partial nephrectomy (preferred)
or
Ablative techniques
or
Active surveillance
or
Radical nephrectomy (in select patients)
Surveillance[f]
Stage I (T1b)
Partial nephrectomy
or
Radical nephrectomy
or
Stage II
Partial nephrectomy
or
Radical nephrectomy
Clinical trial
or
Surveillance[f]
or
Adjuvant pembrolizumab (Grade 4 tumors with clear cell histology ± sarcomatoid features)
Stage III
Radical nephrectomy
or
Partial nephrectomy, if clinically indicated
Clear cell histology:
Clinical trial (preferred)
or
Surveillance[f]
or
Adjuvant pembrolizumab or sunitinib (category 3 for sunitinib)
Non-clear cell histology:
Surveillance[f]
Stage IV
See KID-2
Follow-up
See KID-B
Relapse or Progression,
See KID-3
[a] Imaging with and without contrast is strongly preferred, such as a renal protocol.
[b] Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance or ablative techniques, cryosurgery, and radiofrequency ablation strategies.
[c] If metastatic disease is present or the patient cannot tolerate ureteroscopy.
[d] See Principles of Surgery (KID-A).
Stereotactic body radiotherapy (SBRT) may be considered for medically inoperable patients with Stage I kidney cancer (category 2B), with Stage II/III kidney cancer (both category 3).
[f] See Follow-up (KID-B).
[g] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Metastatic Disease – Cytoreductive Nephrectomy

- Removing kidney in the face of metastatic disease
- Traditional dogma for patients who will tolerate operation
- Spontaneous metastases regression after nephrectomy
- Bulky tumors thought to inhibit natural immune anti-tumor action
- Ex-vivo data suggested large primary tumors inhibited T-Cell Function
- Systemic immune agents (such as cytokines) made no effect on primary renal tumors although affecting metastases
- These rationales were inhibited by risk of morbidity and mortality and inability of large portion of patients to get nephrectomy

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EORTC 30947

ARTICLES

Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial

G H J Mickisch, A Garin, H van Poppel, L de Prijck, R Sylvester, and members of the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group

Summary

Background Surgery is the main treatment for localised renal cell carcinoma, but use of radical nephrectomy for metastatic disease is highly controversial. We aimed to establish whether radical nephrectomy done before interferon-alfa-based immunotherapy improved time to progression and overall survival (primary endpoints) compared with interferon alfa alone.

Methods We included 85 patients from June, 1995, to July, 1998: two (one per group) were ineligible. 42 of the 83 participants were randomly assigned combined treatment (study group) and 43 immunotherapy alone (controls). All patients had metastatic renal-cell carcinoma that had been histologically confirmed and was progressive at entry. In study patients, surgery was done within 4 weeks of randomisation, and immunotherapy (5×10^6 IU/m^2 subcutaneously three times

Introduction

At diagnosis, about 20% of patients with renal-cell carcinoma have disseminated disease, and another 25% have locally advanced disease. About a third of patients with tumour of the kidney at diagnosis will develop metastatic disease postoperatively. Thus, some 50% of all patients with renal-cell carcinoma will eventually present with disease that requires complex treatment decisions.[1] Radical nephrectomy is the preferred treatment in organ-confined stages of disease.[2] However, because curative surgery is almost impossible in disseminated disease, the benefits of surgery to a patient with metastatic renal-cell carcinoma have been disputed. With arrival of modern immunotherapies, albeit of restricted efficacy, we need to critically reassess surgical treatment of metastatic renal-cell carcinoma.[3,4]

The effect of nephrectomy before immunotherapy in patients with renal-cell carcinoma has not been measured.

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SWOG 8949

The New England
Journal of Medicine

VOLUME 345 · DECEMBER 6, 2001 · NUMBER 23

NEPHRECTOMY FOLLOWED BY INTERFERON ALFA-2b COMPARED WITH INTERFERON ALFA-2b ALONE FOR METASTATIC RENAL-CELL CANCER

ROBERT C. FLANIGAN, M.D., SYDNEY E. SALMON, M.D., BRENT A. BLUMENSTEIN, PH.D., SCOTT T. BEARMAN, M.D., VIVEK ROY, M.D., PATRICK C. MCGRATH, M.D., JOHN R. CATON, JR., M.D., NIKHIL MUNSHI, M.D., AND E. DAVID CRAWFORD, M.D.

ABSTRACT

Background The value of nephrectomy in metastatic renal-cell cancer has long been debated. Several nonrandomized studies suggest a higher rate of response to systemic therapy and longer survival in patients who have undergone nephrectomy.

Methods We randomly assigned patients with metastatic renal-cell cancer who were acceptable candidates for nephrectomy to undergo radical nephrectomy followed by therapy with interferon alfa-2b or to receive interferon alfa-2b therapy alone. The primary end point was survival, and the secondary end point

There are indications that patients with metastatic renal-cell cancer who are treated with interferon alfa or other cytokines have improved outcomes if they first undergo nephrectomy.[1-3] Patients who undergo nephrectomy followed by immunotherapy with interleukin-2, with or without tumor-infiltrating lymphocytes, also survive longer than historical controls.[4-11] However, none of the reports were studies based on prospective, controlled trials.

In 1989, the Southwest Oncology Group (SWOG) initiated a study to determine whether nephrectomy

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0022-5347/04/1713-1071/0
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Vol. 171, 1071–1076, March 2004
Printed in U.S.A.
DOI: 10.1097/01.ju.0000110610.61545.ae

CYTOREDUCTIVE NEPHRECTOMY IN PATIENTS WITH METASTATIC RENAL CANCER: A COMBINED ANALYSIS

ROBERT C. FLANIGAN,* G. MICKISCH, RICHARD SYLVESTER, CATHY TANGEN,†
H. VAN POPPEL AND E. DAVID CRAWFORD

From the Southwest Oncology Group and European Organization for the Research and Treatment of Cancer Genitourinary Group, Loyola University Medical Center (RCF), Maywood, Illinois, Centrum Fuer Operative Urologie (GM), Bremen, Germany, European Organization for the Research and Treatment of Cancer Data Center (RS), Brussels and UZ Gasthuisberg (HVP), Leuven, Belgium, Southwest Oncology Group Statistical Center (CT), Seattle, Washington, and University of Colorado Medical Center (EDC), Denver, Colorado

Flanigan et al. SWOG & EORTC, *J Urology 2004; 171: 1071-6.*

OVERALL SURVIVAL

Median survival:

- Nx+IFN: 13.6 mo
- IFN only: 7.8 months

1 year survival

- Nx+IFN: 51.9%
- IFN only: 37.1%

*intention to treat analysis

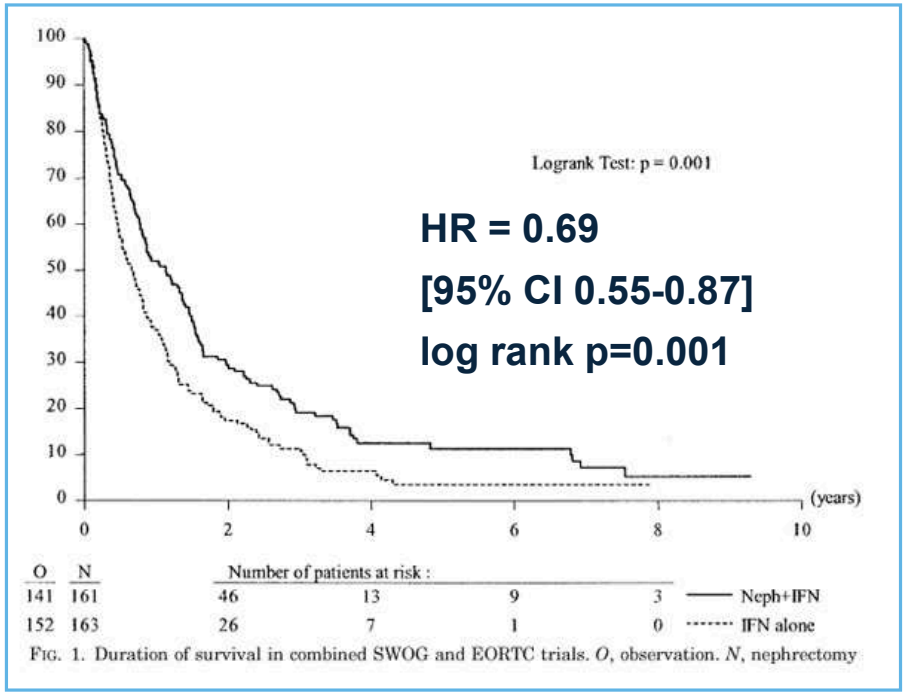


FIG. 1. Duration of survival in combined SWOG and EORTC trials. *O*, observation. *N*, nephrectomy

Cytoreductive Nephrectomy In Patients with Metastatic Renal Cancer:A Combined Analysis

Flanigan et al. SWOG & EORTC, *J Urology 2004; 171*[redacted]*71-6.*

CONCLUSIONS:

- Cytoreductive nephrectomy offers s[redacted]l advantage (31% decrease death rate, 5.8 m[redacted]advantage)
- Highest benefit in pts with p[redacted]mance status 0
- Minimal surgical compl[redacted]ons; only 5.6% did not proceed on to IFN t[redacted]ment after nephrectomy

CRITICISM[redacted]

- Mo[redacted]benefit
- Lon[redacted] accrual period: 7 years for 246 pts with 80 institutions

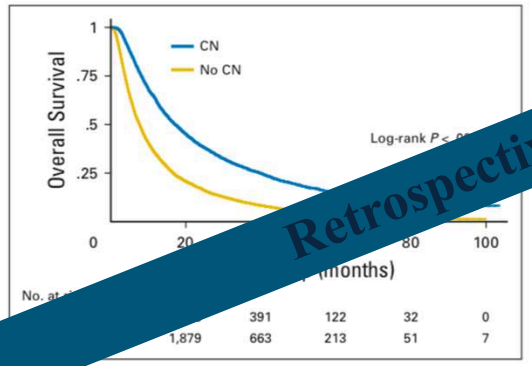
VOLUME 34 · NUMBER 27 · SEPTEMBER 20, 2016
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Survival Analyses of Patients With Metastatic Renal Cancer Treated With Targeted Therapy With or Without Cytoreductive Nephrectomy: A National Cancer Data Base Study

Nawar Hanna, Maxine Sun, Christian P. Meyer, Paul L. Nguyen, Sumanta K. Pal, Steven L. Chang, Guillermo de Velasco, Quoc-Dien Trinh, and Toni K. Choueiri

See accompanying editorial on page 3235

Retrospective comparisons



Kaplan-Meier survival analyses of patients with metastatic renal cell carcinoma treated with targeted therapy stratified according to cytoreductive nephrectomy (CN) status (yes or no), National Cancer Data Base, 2006 to 2012. Data were restricted to 12,995 patients with no missing information on vital status or follow-up time.

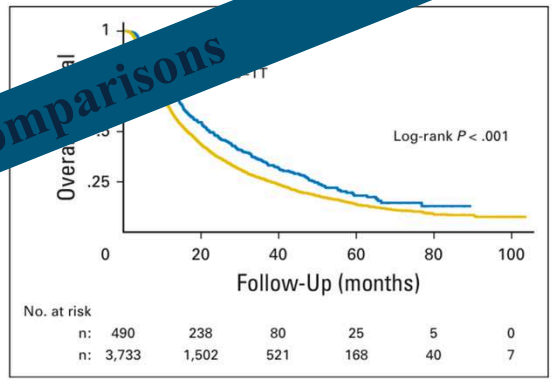


Fig 3. Kaplan-Meier survival analyses of patients with metastatic renal cell carcinoma treated with cytoreductive nephrectomy and targeted therapy (TT) stratified according to timing of surgery (before or after systemic therapy), National Cancer Data Base, 2006 to 2012. Data were restricted to 4,223 patients with available information on timing of surgery and targeted therapy.

Cytoreductive Nephrectomy in The Wrong Patient

- Surgery in poor candidates may worsen outcome
- May limit receipt of systemic therapy (~50% of high risk patients)

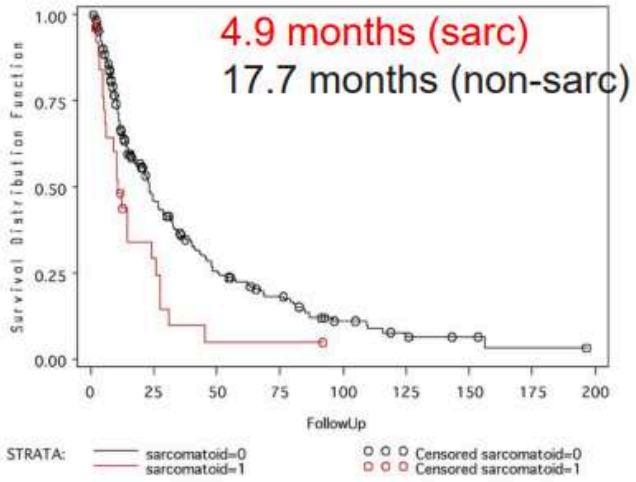


Figure 3. Kaplan-Meier analysis of overall survival (months) of sarcomatoid and nonsarcomatoid groups able to proceed to systemic therapy.

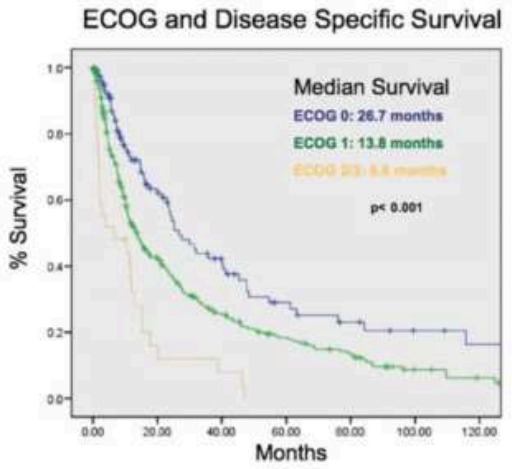


FIGURE 1. This chart illustrates disease-specific survival for patients with renal cell carcinoma who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, and 2.

Phase 2 Trials (Sutent/Pazopanib): Lessons Learned

Series		Powles 2011	Powles 2016
Agent		Sutent	Pazopanib
subjects		66	104
Treatment		12-16 weeks	10-12 weeks
Washout		28 days	2 days
IMDC Group	Intermediate	45 (68%)	83 (82%)
	Poor	21 (32%)	18 (18%)
Nephrectomy		47 (71%)	63 (61%)
Poor Risk Proceeding to Surgery		9 (43%)	8 (44%)
Survival (OS)	Overall	15.2 months	22.7 months
	Poor Risk	9.0 months	5.7 months

Avoid immediate surgery in Poor Risk Progressors with OS < 4 months (HR 4.5 Death)

AUA 2025
APRIL 26-29 Las Vegas

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 2, 2018 VOL. 379 NO. 5

CARMENA

Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

A. Méjean, A. Ravaud, S. Thezenas, S. Colas, J.-B. Beauval, K. Bensalah, L. Geoffrois, A. Thiery-Vuillemin, L. Cormier, H. Lang, L. Guy, G. Gravis, F. Rolland, C. Linassier, E. Lechevallier, C. Beisland, M. Aitchison, S. Oudard, J.-J. Patard, C. Theodore, C. Chevreau, B. Laguerre, J. Hubert, M. Gross-Goupil, J.-C. Bernhard, L. Albiges, M.-O. Timsit, T. Lebret, and B. Escudier

- Non-Inferiority; prospective
- 1:1 mccRCC for nephrectomy to undergo nephrectomy and then receive sunitinib vs to receive sunitinib alone.
- In the intention-to-treat population, patients in the sunitinib-alone group had a longer median overall survival than those in the nephrectomy–sunitinib group 18.4 months vs 13.9 months
- In the nephrectomy–sunitinib group, 16 patients (7.1%) did not undergo nephrectomy and 40 (17.7%) never received sunitinib
- In the sunitinib-alone group, 11 patients (4.9%) never received sunitinib and 38 (17.0%) underwent subsequent nephrectomy

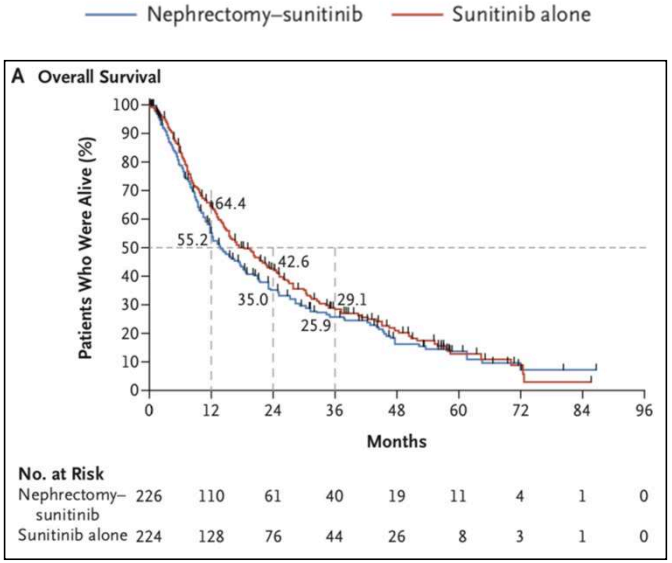


Table 2. Tumor Response Outcomes.*

Response	Nephrectomy–Sunitinib (N=186)	Sunitinib Alone (N=213)
Best overall response — no./total no. (%)		
Complete response	1/178 (0.6)	0/208
Partial response	50/178 (28.1)	62/208 (29.8)
Stable disease	64/178 (36.0)	97/208 (46.6)
Progression of disease	49/178 (27.5)	40/208 (19.2)
Could not be evaluated	14/178 (7.9)	9/208 (4.3)
Objective response rate — % (95% CI)†	27.4 (21.1–34.4)	29.1 (23.1–35.7)
Disease control rate — % (95% CI)‡	61.8 (54.4–68.8)	74.6 (68.2–80.3)
Clinical benefit — no. (%)§	68 (36.6)	102 (47.9)

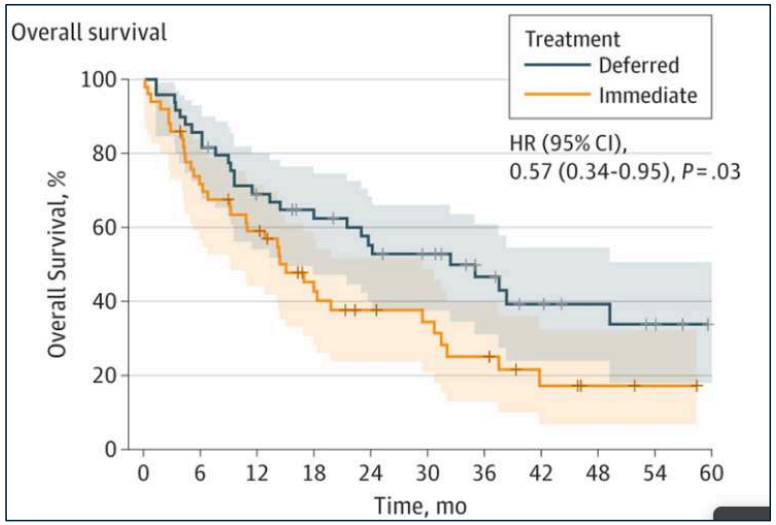
AUA 2025
APRIL 26-29 Las Vegas

JAMA Oncology | Original Investigation

Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib
The SURTIME Randomized Clinical Trial

Axel Bex, MD, PhD; Peter Mulders, MD, PhD; Michael Jewett, MD; John Wagstaff, MD; Johannes V. van Thienen, MD, PhD; Christian U. Blank, MD, PhD; Roland van Velthoven, MD, PhD; Maria del Pilar Laguna, MD, PhD; Lori Wood, MD, PhD; Harm H. E. van Melick, MD, PhD; Maureen J. Aarts, MD, PhD; J. B. Lattouf, MD; Thomas Powles, MD; Igle Jan de Jong, MD, PhD; Sylvie Rottey, MD, PhD; Bertrand Tombal, MD, PhD; Sandrine Marreaud, MD; Sandra Collette, MSC; Laurence Collette, PhD; John Haanen, MD

JAMA Oncol. Published online December 13, 2018



- Rate of surgical complications identical
- The intention-to-treat OS hazard ratio of deferred vs immediate CN was 0.57
- In the deferred CN arm, 48 of 49 patients (98%) received sunitinib vs 40 of 50 (80%) in the immediate arm.
- Systemic progression before planned CN in the deferred CN arm resulted in a per-protocol recommendation against nephrectomy in 14 patients (29%) – selects for patients who may benefit from 2nd line systemic therapy

1. C

2. N

3. N

4. C ed by CN.

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Kidney Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SURGERY

- Nephron-sparing surgery (partial nephrectomy) is appropriate in selected patients, for example:
  - Unilateral stage I–III tumors where technically feasible
  - Uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer
  - Patients at relative risk for developing progressive chronic kidney disease due to young age or medical risk factors (ie, hypertension, diabetes, nephrolithiasis)
- Open, laparoscopic, or robotic surgical techniques may be used to perform radical and partial nephrectomies.
- Regional lymph node dissection is optional but is recommended for patients with resectable adenopathy on preoperative imaging or palpable/visible adenopathy at time of surgery.
- If adrenal gland is uninvolved, adrenalectomy may be omitted.
- Special teams or referral to high-volume centers may be required for extensive inferior vena cava involvement.
- Thermal ablation (eg, cryosurgery, radiofrequency ablation) is an option for the management of patients with clinical stage T1 renal lesions.
  - Thermal ablation is an option for masses <3 cm, but may also be an option for larger masses in select patients. Ablation in masses >3 cm is associated with higher rates of local recurrence/persistence and complications.
  - Biopsy of small lesions confirms a diagnosis of malignancy for surveillance, cryosurgery, and radiofrequency ablation strategies.
  - Ablative techniques are associated with a higher local recurrence rate than conventional surgery and may require multiple treatments to achieve the same local oncologic outcomes.[a,b]
- Active surveillance is an option for the initial management of patients with clinical stage T1 renal lesions, for example:
  - Patients with small renal masses <2 cm given the high rates of benign tumors and low metastatic potential of these masses.
  - Active surveillance of patients with T1a tumors (≤4 cm) that have a predominantly cystic component is recommended.
  - Patients with clinical stage T1 masses and significant competing risks of death or morbidity from intervention.
  - Active surveillance entails serial abdominal imaging with timely intervention should the mass demonstrate changes (eg, increasing tumor size, growth rate, infiltrative pattern) indicative of increasing metastatic potential.
  - Active surveillance should include periodic metastatic survey including blood work and chest imaging, particularly if the mass demonstrates growth.
- Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have:
  - Excellent performance status (ECOG PS <2)
  - No brain metastasis

- Follow up – according to NCCN Guidelines
  - Scans
  - Labs

AUA 2026 Washington, DC MAY 15-18

Bladder Cancer

Edouard Trabulsi, MD, MBA, FACS
Professor and Chair of Urology
Jefferson Einstein Philadelphia Hospital
Philadelphia, PA

Disclosures:

Edouard J. Trabulsi, MD, MBA, FACS

Consultant for Veracyte, Johnson & Johnson

DSMB for CG Oncology and Protara

Slide contributions from Jean Hoffman-Censits, MD

Bladder Cancer

Bladder Cancer - Outline

- Incidence
- Stage and Grade
- Diagnosis and Procedure
- Treatment of Non-Muscle Invasive Bladder Cancer (NMIBC)
- Treatment of Muscle Invasive Bladder Cancer
- Treatment of Metastatic Bladder Cancer
- Upper Tract Urothelial Carcinoma

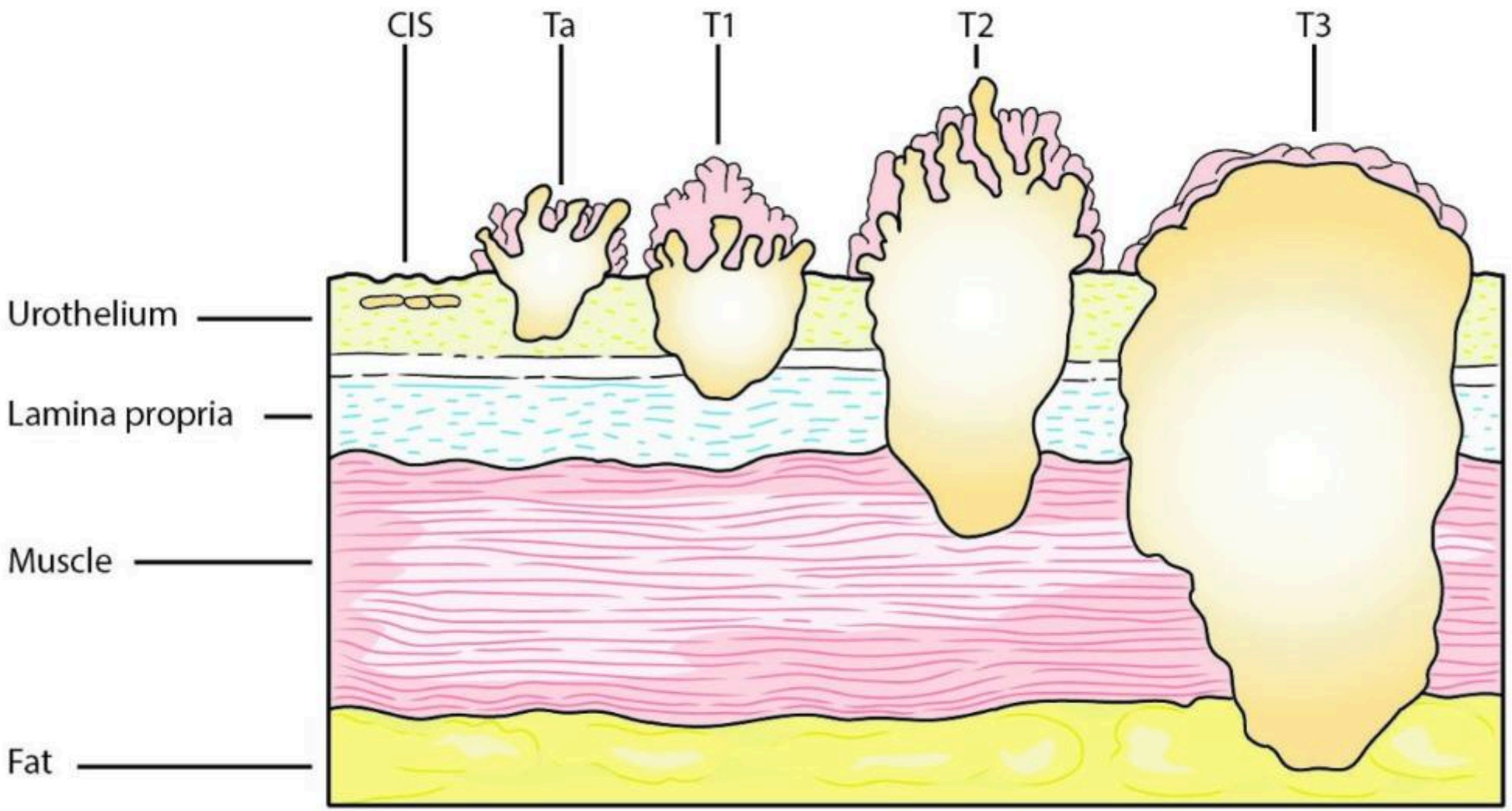
Bladder Cancer

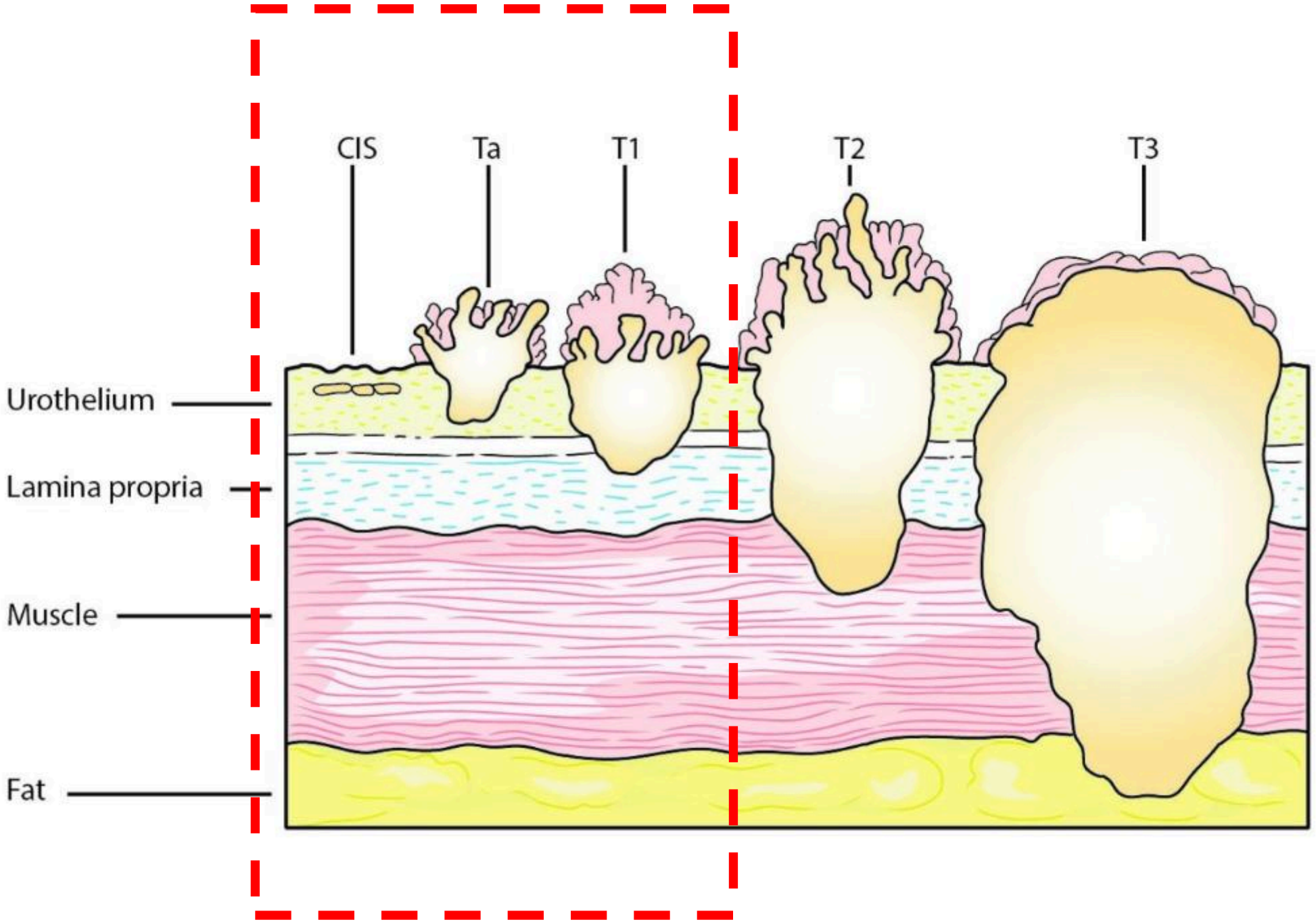
- Introduction
  - More than 84,000 new cases/year (US)
    - >17,000 deaths/year
  - Bladder cancer is the 5th most common malignancy among men (10th leading cause of cancer death)
  - Prevalence ~10X incidence (>750,000 US)
    - At presentation
      - 75% are superficial
      - 20% are invasive
      - 5% are metastatic
  - Average age of onset: 68 years
  - ~ 9000 radical cystectomies US/year

Defining Bladder Urothelial Cancer

- Low Risk Non-Muscle Invasive Bladder Cancer: superficial, noninvasive, less aggressive (often papillary), Ta
- High Risk Non-Muscle Invasive Bladder Cancer (HR NMIBC): within the superficial or lamina propria layers (HG Ta, HG T1), or carcinoma in-situ (CIS)
- Muscle-Invasive Bladder Cancer (MIBC): invasion through the superficial and lamina propria layers, into the bladder muscle

Superficial (Non-Muscle Invasive) Bladder Cancer


CIS
Ta
T1
T2
T3
Urothelium
Lamina propria
Muscle
Fat


CIS
Ta
T1
T2
T3
Urothelium
Lamina propria
Muscle
Fat

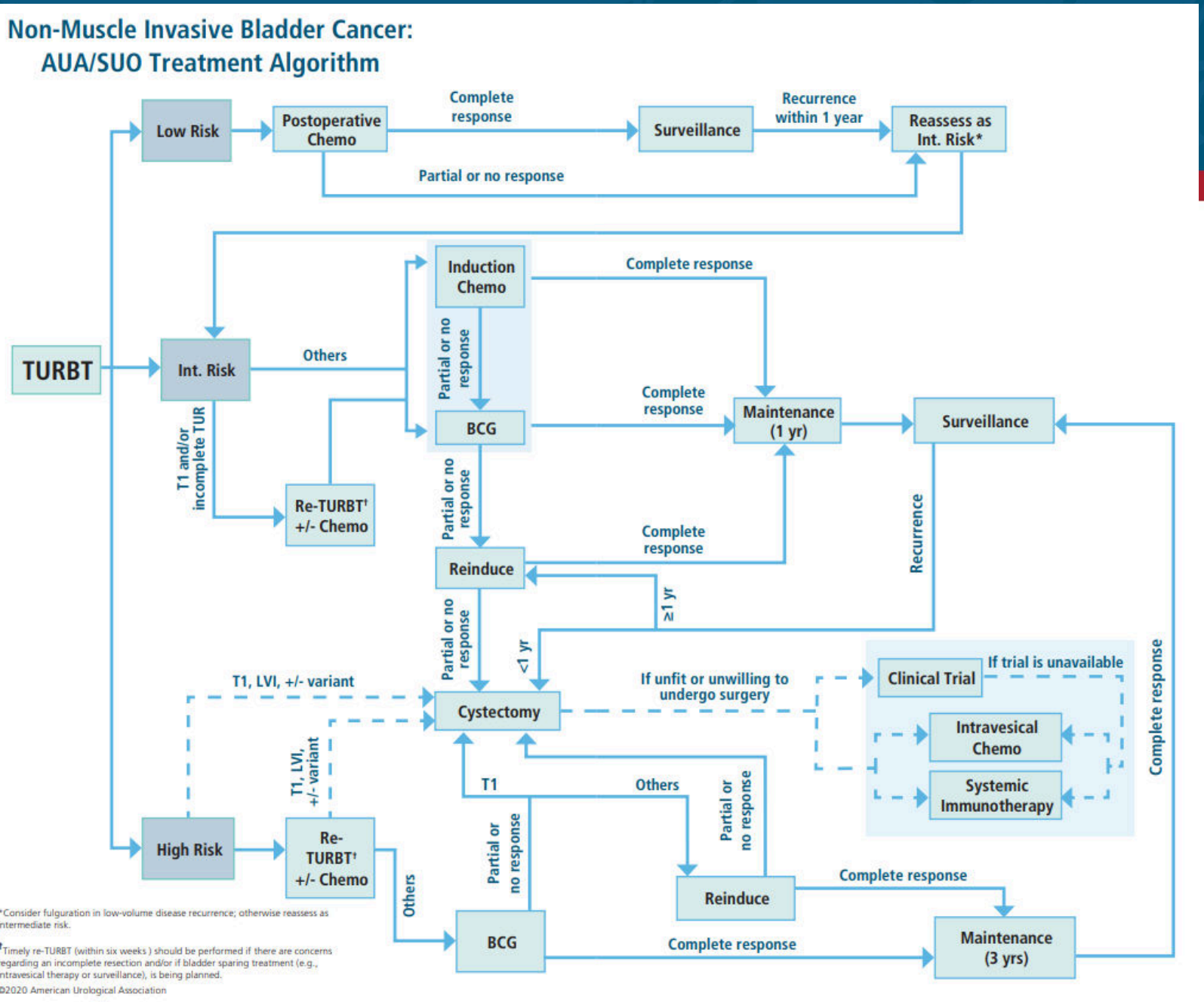
NMIBC Risk Stratification

- Tumor Size
- Tumor Grade (low or high grade)
- Focality (solitary or multifocal)
- T Stage (Ta, T1 or CIS)
- Recurrence

AUA Risk Stratification for Non–Muscle-Invasive Bladder Cancer*

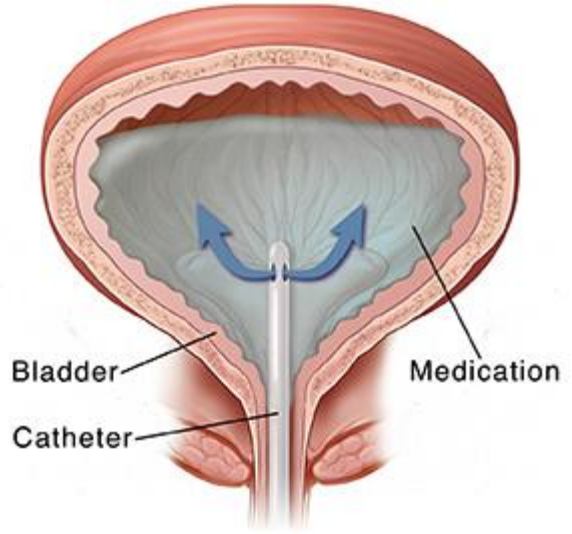
Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• Low grade urothelial carcinoma ▸ T1 or ▸ >3 cm or ▸ Multifocal or ▸ Recurrence within 1 year • High grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• High grade urothelial carcinoma ▸ CIS or ▸ T1 or ▸ >3 cm or ▸ Multifocal • Very high risk features (any): ▸ BCG unresponsive[l] ▸ Certain histopathologic subtypes[m] ▸ Lymphovascular invasion ▸ Prostatic urethral invasion

NMIBC Management by Risk Stratification



Intravesical Therapy

- Induction Intravesical Therapy (office)
  - Immunotherapy
    - BCG – full dose or reduced dose
    - Nadofaragene firadenovec
    - Nogapendekin alfa inbakicept-pmln + BCG
  - Chemotherapy
    - Gemcitabine +/- Docetaxel
    - Gemcitabine Intravesical drug-releasing system (iDRS)
    - Mitomycin
    - Valrubicin (historical)



May 8, 2018

Effect of Intravesical Instillation of Gemcitabine vs Saline Immediately Following Resection of Suspected Low-Grade Non-Muscle-Invasive Bladder Cancer on Tumor Recurrence

SWOG S0337 Randomized Clinical Trial

Edward M. Messing, MD[1]; Catherine M. Tangen, DrPH[2,3]; Seth P. Lerner, MD[4]; et al

» Author Affiliations | Article Information

JAMA. 2018;319(18):1880-1888. doi:10.1001/jama.2018.4657

Postop Intravesical Chemo

Table 2. Primary and Secondary Analysis Comparisons by Treatment Group

Outcomes and Populations	Gemcitabine Group		Saline Group		Hazard Ratio (95% CI)[c]	*P* Value by 1-Sided Log-Rank Test
	No. With Outcome/ Total No.[a]	4-y Recurrence Rate, % (95% CI)[b]	No. With Outcome/ Total No.[a]	4-y Recurrence Rate, % (95% CI)[b]		
Primary Outcome and Primary Population						
Recurrence among all randomized, eligible patients (intention-to-treat population)	67/201	35 (29-42)	91/205	47 (41-54)	0.66 (0.48-0.90)	<.001[d]
Secondary Populations						
Recurrence among all patients who received instillation and had low-grade non-muscle-invasive disease	34/102	34 (26-44)	59/113	54 (45-65)	0.53 (0.35-0.81)	.001[d]
Recurrence among all patients who received instillation and had high-grade non-muscle-invasive disease	17/44	40 (27-58)	19/42	45 (32-63)	0.84 (0.45-1.60)	.38[d]
Secondary Outcomes						
Muscle invasion in intention-to-treat population	5/201		10/205		0.51 (0.17-1.49)	.11
Death due to any cause in intention-to-treat population	17/201		25/205		0.68 (0.37-1.27)	.12

[a] Only a first recurrence for a given patient was counted; number of recurrences represents the number of individuals with a first recurrence.

[b] Four-year event rates were estimated from cumulative incidence curves in which either cystectomy or death prior to recurrence was managed as a competing risk.

[c] Hazard ratios are adjusted for stratification factors as covariates except for time to muscle-invasive disease and survival, which had no adjustment because of low event rates.

[d] Stratified by primary vs recurrent tumor and 1 vs 2 or more tumors.

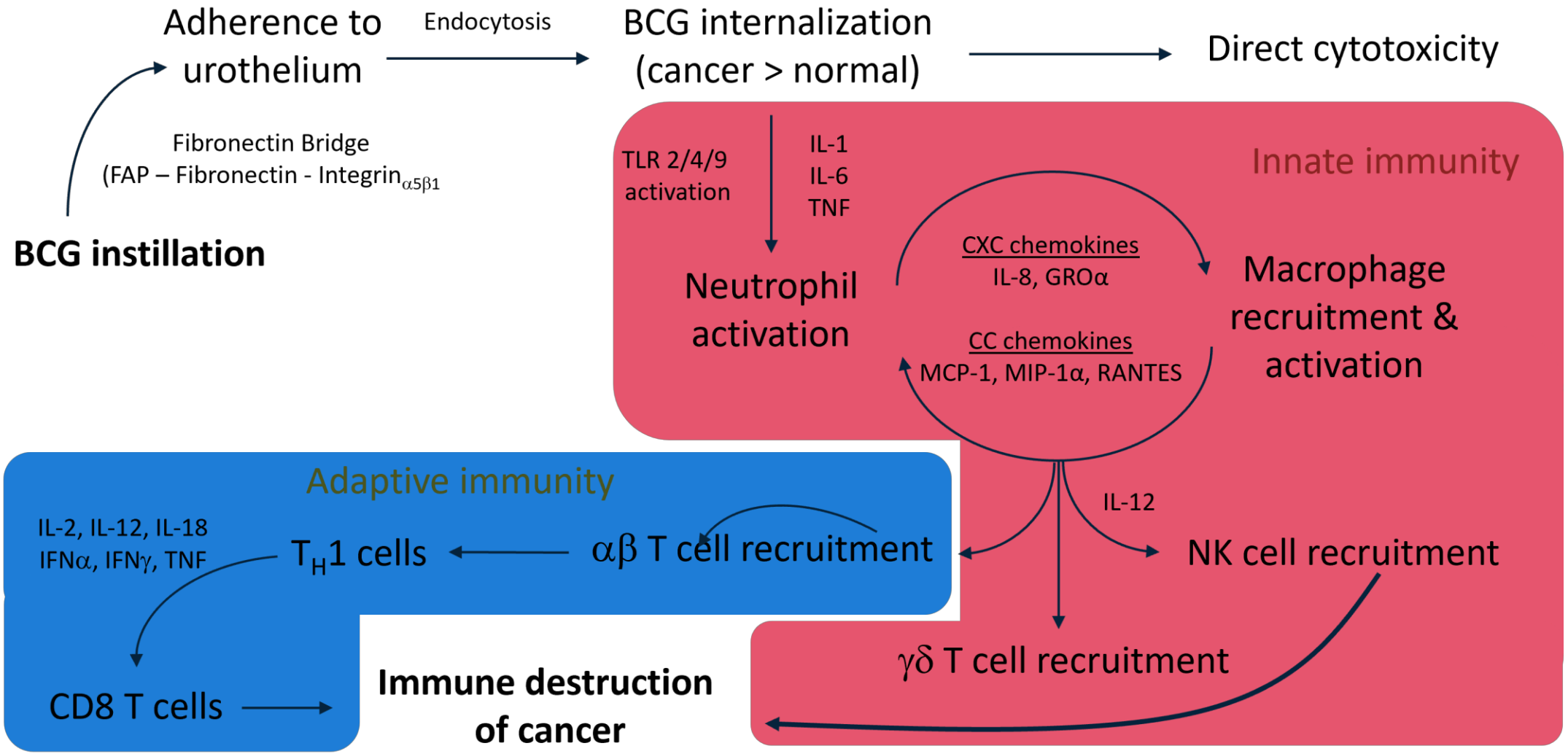
Among patients with suspected low-grade non–muscle-invasive urothelial cancer, immediate postresection intravesical instillation of gemcitabine, compared with instillation of saline, significantly reduced the risk of recurrence over a median of 4.0 years.

BCG: the gold standard

- Non-specific immune adjuvant
- Inflammatory host response; release of cytokines
- Benefits
  - Reduces recurrences (~30%)
  - Reduces progressions (~25%, only if maintenance)
- Risks
  - Mild: fever, irritative LUTS
  - Severe: BCG cystitis, Reiter's syndrome, BCGosis
- Maintenance is key to efficacy

Meta-analyses: Sylvester et al. J Urol 2002

How BCG works: Mechanisms of Action



Bacillus Calmette-Guerin Immunotherapy

- Induction Treatment – 1 treatment/week x 6 weeks
  - Instilled via catheter
  - Held in bladder x 2 hours
  - Patient voids and places bleach in toilet x 15 minutes
  - Barrier contraception
  - Common Side Effects:
    - Urgency and frequency
    - Dysuria
    - Mild flu-like symptoms
- Maintenance Treatment -1 treatment/week x 3 weeks

  *May use reduced dose in patients who do not tolerate well or with short supplies

BCG: reduced dose and maintenance

- EORTC 30962 randomizing intermediate and high risk NMIBC to 4 groups – reduced dose vs full, and maintenance duration (1 year vs 3 years)

- Comparing reduced dose (1/3D) BCG vs full dose BCG (FD) for intermediate and high risk
  - Reduced dose was not inferior to FD with median FU of 7.1 yrs
  - Intermediate-risk patients should be treated with FD for 1 yr.
  - High-risk patients: 3 years of FD reduces recurrences vs 1 yr FD but not progressions or deaths.
  - The benefit of the two additional years of maintenance should be weighed against its added costs and inconvenience.

EORTC 30962: Oddens et al. Eur Urol. 2013 Mar;63(3):462-72.

BCG Shortage – AUA Statement 2020

1. BCG should not be used for patients with low-risk disease.
2. Intravesical chemotherapy should be used as the first-line option for patients with intermediate-risk NMIBC. Patients with recurrent/multifocal low-grade Ta lesions who require intravesical therapy should receive intravesical chemotherapy such as mitomycin, gemcitabine, epirubicin or docetaxel instead of BCG.
3. If BCG would be administered as second-line therapy for patients with intermediate-risk NMIBC, an alternative intravesical chemotherapy should be used rather than BCG in the setting of this BCG shortage.
4. For patients with high-risk NMIBC, high-grade T1 and CIS patients receiving induction therapy, they should be prioritized for use of full-strength BCG. If not available, these patients and other high-risk patients should be given a reduced 1/2 to 1/3 dose, if feasible.
5. If supply exists for maintenance therapy for patients with NMIBC, every attempt should be made to use 1/3 dose BCG and limit dose to one year.
6. In the event of BCG supply shortage, maintenance therapy should not be given and BCG-naïve patients with high-risk disease should be prioritized for induction BCG.
7. If BCG is not available, a preferable alternative to BCG is mitomycin (induction and monthly maintenance up to one year). Other options such as gemcitabine, epirubicin, docetaxel, valrubicin or sequential gemcitabine/docetaxel or gemcitabine/mitomycin may also be considered with an induction and possible maintenance regimen.
8. Patients with high-risk features (i.e., high-grade T1 with additional risk factors such as concomitant carcinoma in situ, lymphovascular invasion, prostatic urethral involvement or variant histology) who are not willing to take any potential oncologic risks with alternative intravesical agents, should be offered initial radical cystectomy, if they are surgical candidates.

https://www.auanet.org/bcg-shortage-notice

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https://www.auanet.org/bcg-shortage-notice

Recurrences after BCG: Defining Failures

- Definition schema for failures after ***adequate*** BCG:
  - 2 induction BCG courses or induction plus maintenance (at least 5/6 induction and 2/3 maintenance or 2/6 of 2nd induction) (7 doses minimum)
- BCG ***Intolerant***: recurrent/persistent NMIBC in pts unable to complete adequate BCG
- BCG ***Unresponsive***:
  - CIS recurrence (+/- papillary) within 12 mos
  - High grade papillary recurrence (Ta/T1) within 6 mos
  - Persistent T1 disease at first post-treatment assessment at 3 months
- BCG ***Exposed***: any high risk recurrence after 12 months

Kamat A, et al JCO 34:16, 2016

Options for Recurrence After BCG

BCG unresponsive, relapsing, or exposed patients (or intolerant):

- Radical cystectomy with urinary diversion

- Salvage intravesical therapy:
  - Intravesical chemotherapy
    - Gemcitabine + docetaxel
    - Gemcitabine intravesical releasing device
- Novel immune modulators
  - Nadofaragene firadenovec
  - Nogapendekin alfa inbakicept-pmln + BCG

- Clinical trial based therapy

- Systemic immune check point inhibitor therapy

Salvage Strategies for Recurrent NMIBC

- FDA Guidance document in 2018 opened door to innovation
- Incorporates BCG unresponsive definition
- Mandates CR endpoint for CIS with or without papillary disease
- Allows single arm trial design (compared with historical controls)
- Allows CR endpoint of negative cystoscopy and cytology with for-cause biopsies as needed
  - High risk disease at 3 months (persistent CIS or HGT1 with or without CIS) should be considered a failure and removal from study, with cystectomy if appropriate
  - Recent approved therapies have CIS +/- papillary disease on-label

Options for Recurrence After BCG

BCG unresponsive NMIBC, CIS +/- Ta/T1 papillary		
Preferred • Cystectomy[V] • Clinical trial	Other recommended • Gemcitabine intravesical system • Intravesical multi-agent chemotherapy[S] • Nadofaragene firadenovec-vncg • Nogapendekin alfa inbakicept-pmln + BCG	Useful in certain circumstances[W] • Pembrolizumab • Intravesical single-agent chemotherapy[S] (category 2B)
BCG unresponsive NMIBC, Ta/T1 papillary only without CIS		
Preferred • Cystectomy[V] • Clinical trial	Other recommended • Gemcitabine intravesical system • Intravesical multi-agent chemotherapy[S] • Nadofaragene firadenovec-vncg • Nogapendekin alfa inbakicept-pmln + BCG • Intravesical single-agent chemotherapy[S] (category 2B)	Useful in certain circumstances • Pembrolizumab (category 2B)
BCG exposed high-risk NMIBC		
Preferred • Repeat BCG induction (particularly if initial BCG course inadequate)[S] • Clinical trial	Other recommended • Intravesical multi-agent chemotherapy[S] • Intravesical single agent chemotherapy[S]	Useful in certain circumstances • Cystectomy

Immune Checkpoint Inhibition for High Risk NMIBC

Pembrolizumab: anti PD1 antibody

- Jan 2020: approved for high risk BCG unresponsive non-muscle invasive CIS +/- papillary disease

- Based on Keynote-057 trial of 148 pts
  - CR rate = 41%
  - Median duration of response = 16 months

Nadofaragene firadenovec (Astiladrin™)

- Replication-deficient recombinant adenovirus
- Gene therapy: delivers human interferon alfa-2b cDNA into the bladder epithelium
- Indicated for BCG unresponsive HG NMIBC
  - CIS ± Ta/T1 Disease
- Single intravesical 75 mL dose (3×10^{11} viral particles per mL)
  - Repeat dosing at 3, 6, and 9 months
- Approved Dec 2022

Nadofaragene firadenovec (Astiladrin™)

The Lancet. Oncology
Author Manuscript HHS Public Access

Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial

Stephen A Boorjian, Mehrdad Alemozaffar, [...], and Colin P N Dinney

Lancet Oncol. 2021 January ; 22(1): 107–117.

Efficacy Analysis

Assessment Period	CIS ± Ta/T1 Disease (n=103) CR (% [n])
Month 3	53.4% (55)
Month 6	40.8% (42)
Month 9	35.0% (36)
Month 12	24.3% (25)

151 patients

Nogapendekin-α inbakicept pmln + BCG (Anktiva™)

- IL-15RαFc superagonist (N-803) given together with BCG
- N-803 is a high affinity IL-15 immunostimulatory fusion protein:
  - promotes proliferation and activation of natural killer (NK) cells and CD8+ T cells
  - Doesn’t upregulate T reg cells (suppressive)
- Quilt 3.032 trial for BCG unresponsive CIS +/- papillary disease
  - 83 patients enrolled to cohort A (CIS +/- pap)
  - CR rate: 71% (13/58 responders required a re-induction).
    - 55% CR at 3 months
    - 56% CR at 6 months
    - 45% CR at 12 months
  - The median duration of response (DOR) in complete responders was 26.6 months.
  - The 24-month progression-free, overall, and disease-specific survival rates were 85%, 94%, and 100% respectively.
- FDA approved April 2024

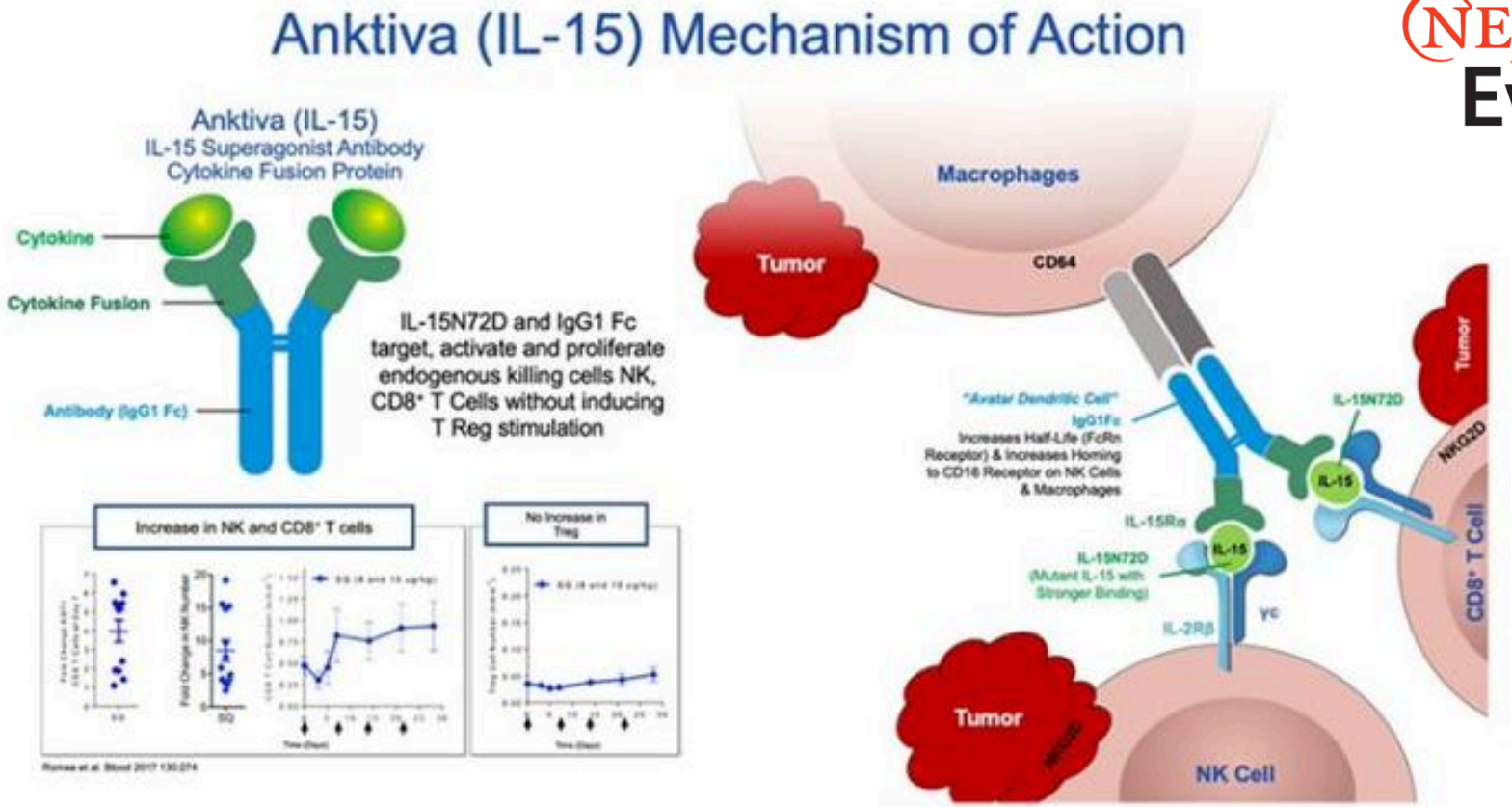
AUA 2026
Washington, DC
MAY 15-18

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

NEJM Evidence

Published November 10, 2022
NEJM Evid 2022; 2 (1)



ANKTIVA (N803) comprises mutated (N72D) human IL-15 bound to the IL15Rα fused with a human IgG1 Fc.

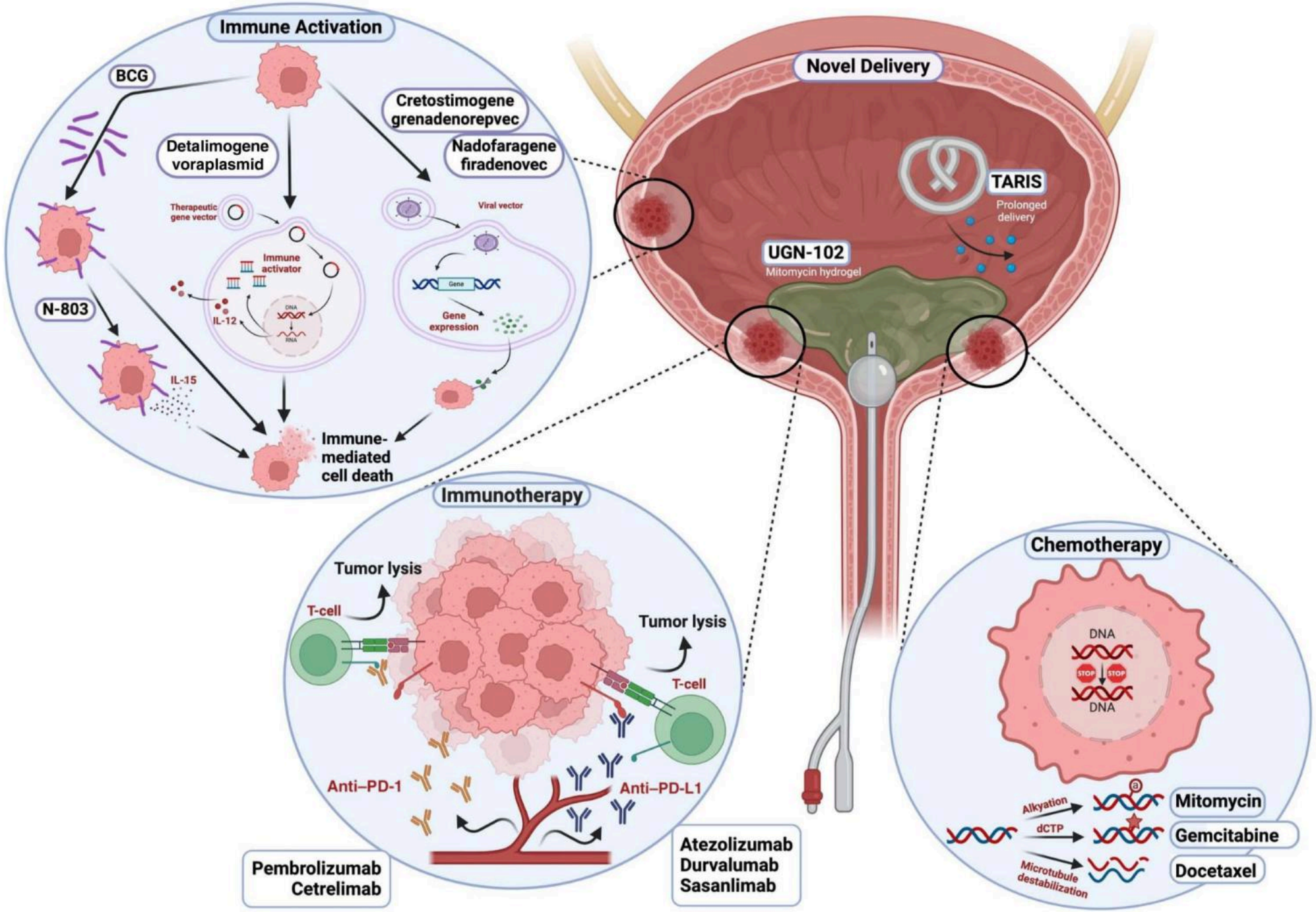
Gemcitabine intravesical system (Inlexzo™)

- Novel drug elution device with microfluidic pore
- Implanted intravesically through catheter (3 week dwell time)
- Gradual continuous elution of gemcitabine into bladder
- SunRIse 1 trial:
  - 82% complete response at 3 months
  - 51% maintained CR at 12 months
- Treatment course:
  - q3 weeks for 6 months (initial treatment)
  - Maintenance: 3 week device every 3 months for 18 months
  - (14 devices over 2 years)

- Approved Sept 2025

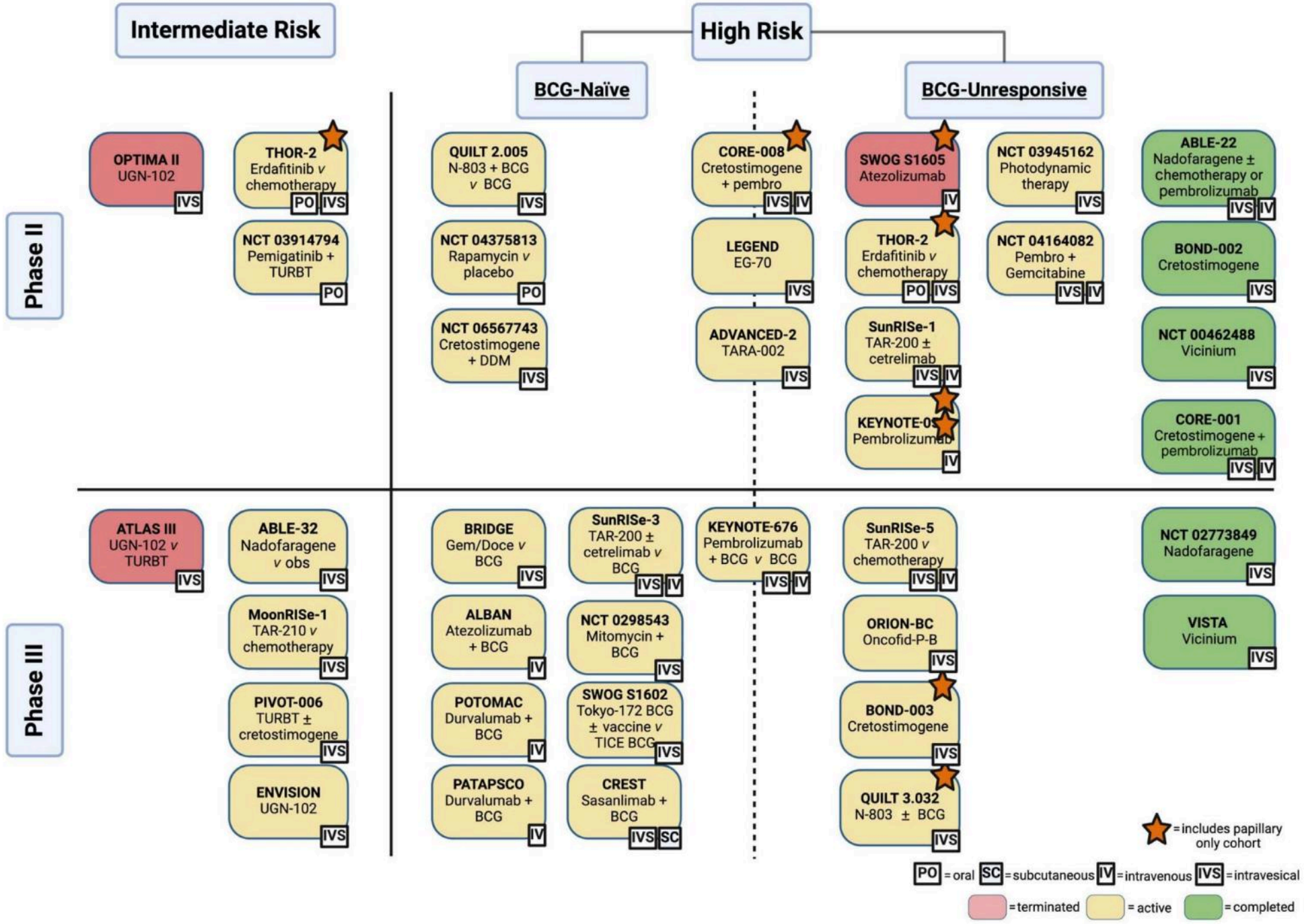
AUA-202
Washington,

New Agents on the Horizon



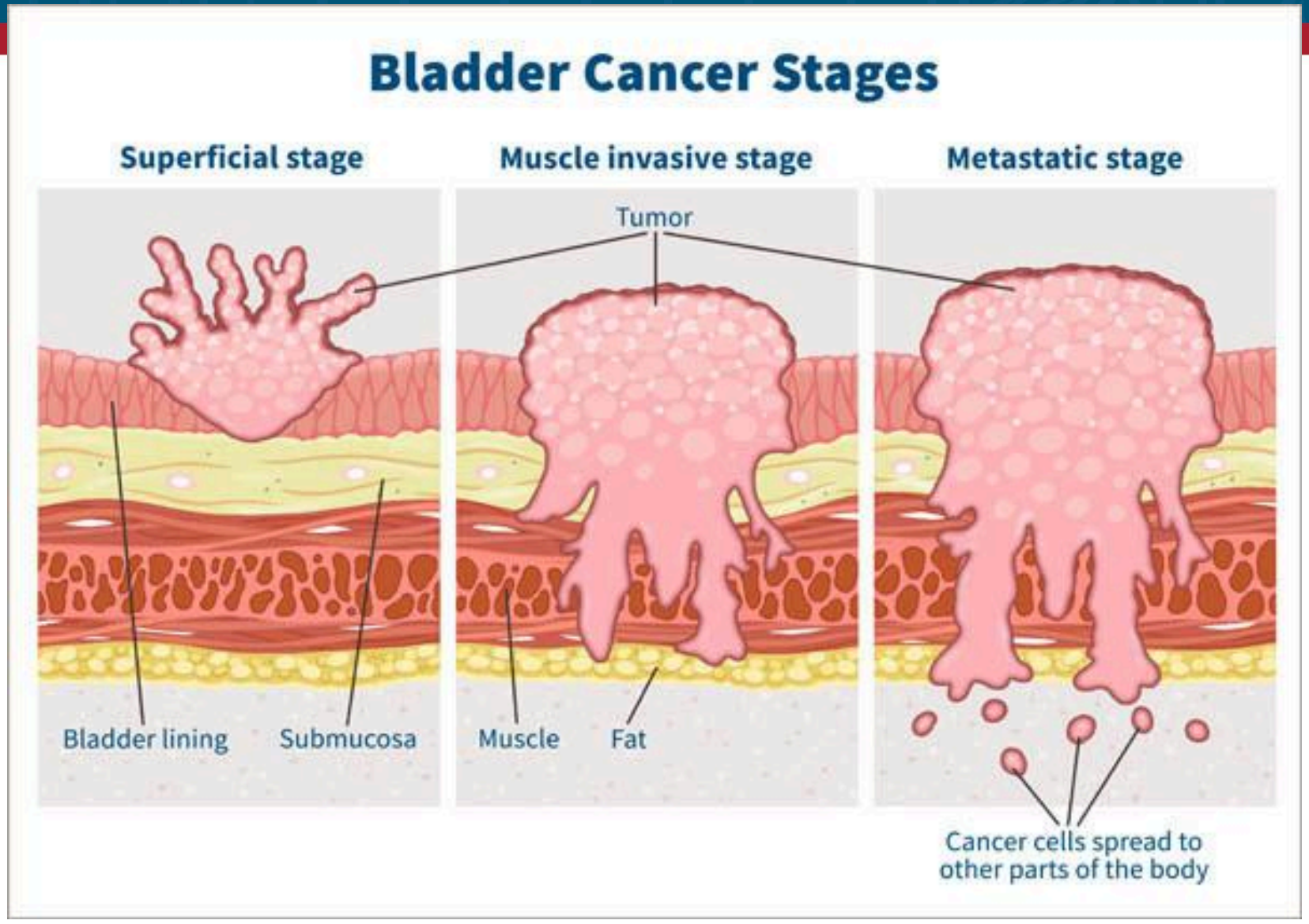
Filon M, and Schmidt B, American Society of Clinical Oncology Educational Book
Volume 45, Number 2

New Agents on the Horizon



Filon M, and Schmidt B, American Society of Clinical Oncology Educational Book
Volume 45, Number 2

Muscle Invasive Bladder Cancer



Muscle Invasive Bladder Cancer

- Stage cT2, cT3+
  - Identified on TURBT –muscle present and involved on pathologic diagnosis
  - Rule out metastatic disease with CT or MRI a/p, chest imaging, bone scan
  - Requires cystectomy in patients with few comorbidities or able to undergo invasive procedure
  - Consider chemotherapy/radiation in patients who are not good surgical candidates

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer

H. Barton Grossman, M.D., Ronald B. Natale, M.D., Catherine M. Tangen, Dr.P.H., V.O. Speights, D.O., Nicholas J. Vogelzang, M.D., Donald L. Trump, M.D., Ralph W. deVere White, M.D., Michael F. Sarosdy, M.D., David P. Wood, Jr., M.D., Derek Raghavan, M.D., Ph.D., and E. David Crawford, M.D.

N ENGL J MED 349;9 WWW.NEJM.ORG AUGUST 28, 2003

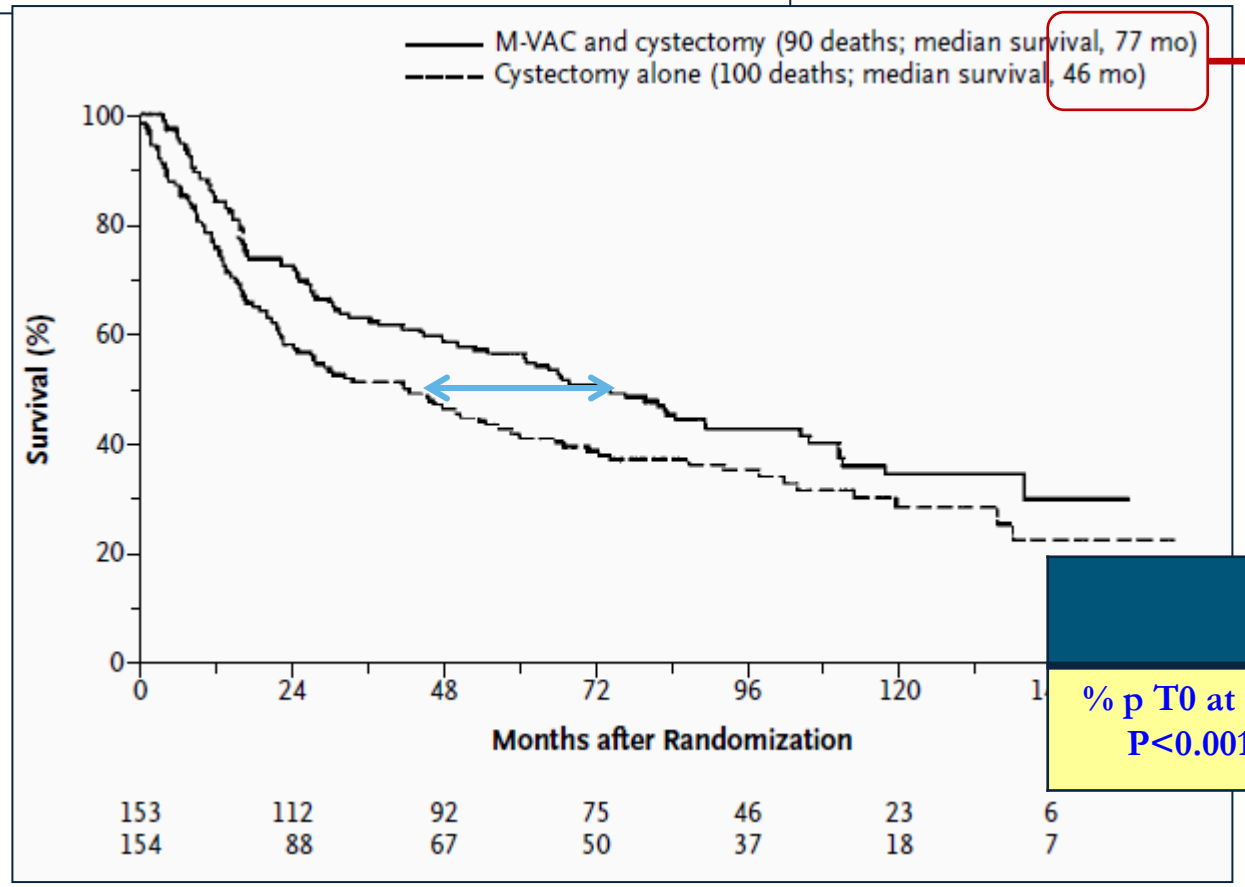
Neoadjuvant Chemotherapy: standard of care for MIBC

3 cycles standard MVAC → Cystectomy

Vs.

Cystectomy alone

SWOG-8710



2.6 year Overall Survival Benefit

	Cystectomy	MVAC + Cystectomy
% p T0 at RC P<0.001	15	38

Grossman et al, NEJM, 2003

Phase III Studies of Neoadjuvant CISPLATIN Based Chemotherapy for Invasive Bladder Cancer

Citation	Patients	Agents	Outcome	Note
J Urology 1996 Malmstrom	N=325 T1G3 or T2-T4N0	Cisplatin Doxorubicin Q 21 days	5 year OS 59 vs 51% 5 year CSS 64 vs 54%	15% difference in OS in T3 and T4 patients P=0.03
NEJM 2003 Grossman	N=317 T2-T4a N0	Methotrexate Cisplatin Vinblastine Doxorubicin Multidose Q 28 days	Median Survival 77 vs 46 months P=0.05	ypT0 predicted for better outcome 38 vs 15% P<0.001
J Clin Oncology 2011 Updated survival Medical Research Council ABC working group	N=917 T2-T4a N0	Methotrexate Cisplatin Vinblastine Multidose Q 21 days	Following cystectomy and / or radiation 10 year overall survival 36 vs 30% P=0.037	
Eur Urology 2005 ABC Meta Analysis	N=3005 11 prospective studies			OS benefit of platinum combo chemotherapy (HR = 0.86, 95% CI 0.77–0.95, p = 0.003)

AUA-20
Washingto

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Accelerated Methotrexate, Vinblastine, Doxorubicin, and Cisplatin Is Safe, Effective, and Efficient Neoadjuvant Treatment for Muscle-Invasive Bladder Cancer: Results of a Multicenter Phase II Study With Molecular Correlates of Response and Toxicity

Elizabeth R. Plimack, Jean H. Hoffman-Censits, Rosalia Viterbo, Edouard J. Trabulsi, Eric A. Ross, Richard E. Greenberg, David Y.T. Chen, Costas D. Lallas, Yu-Ning Wong, Jianqing Lin, Alexander Kutikov, Efrat Dotan, Timothy A. Brennan, Norma Palma, Essel Dulaimi, Reza Mehrazin, Stephen A. Boorjian, William Kevin Kelly, Robert G. Uzzo, and Gary R. Hudes

FOX CHASE CANCER CENTER
TEMPLE HEALTH

Jefferson®

Published Ahead of Print on May 12, 2014 as 10.1200/JCO.2013.53.2465

Timing of Chemotherapy

Neoadjuvant

OR

Adjuvant

Neoadjuvant

Timing

of

Chemotherapy

?

OR

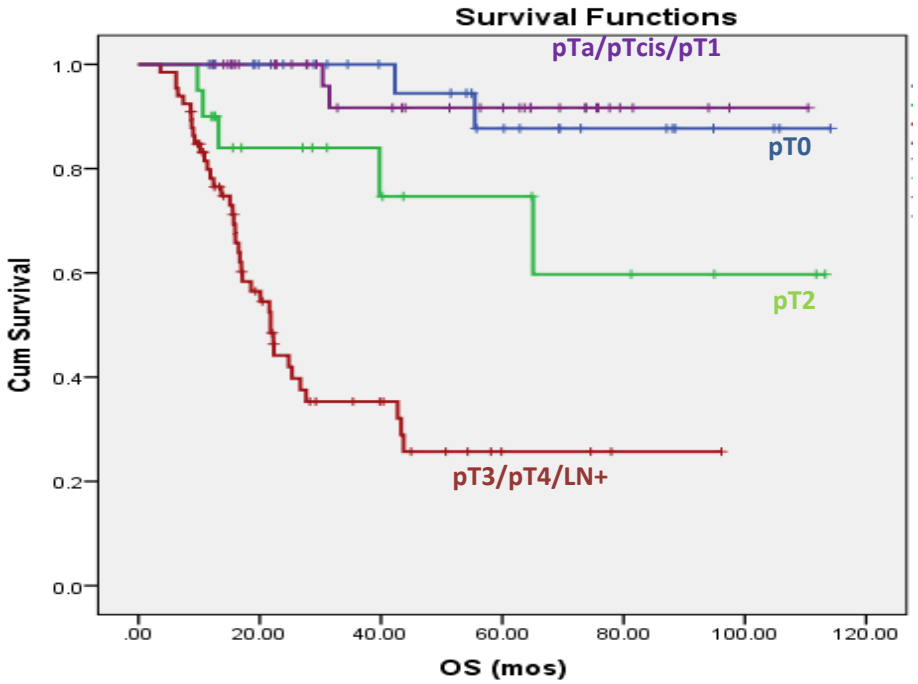
Adjuvant

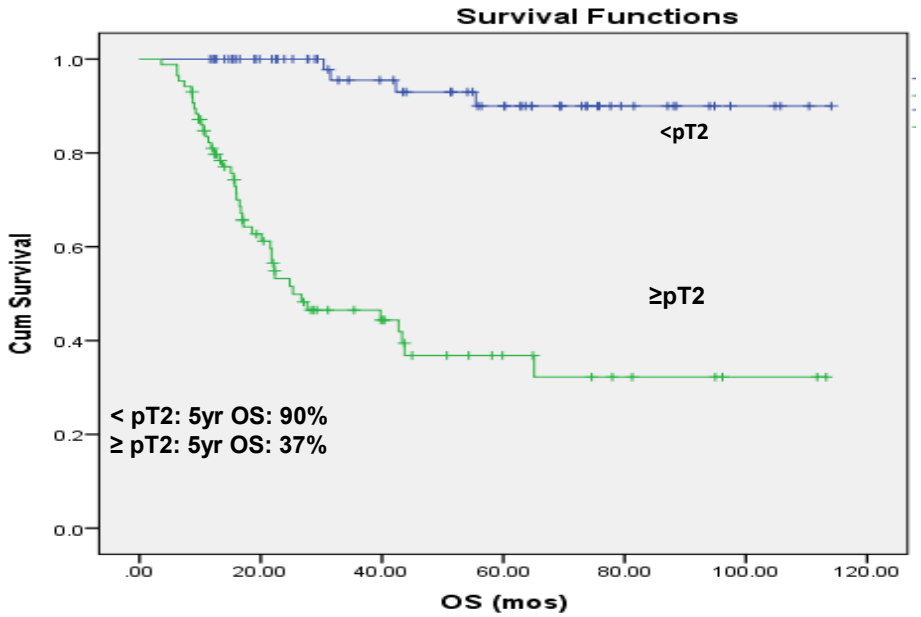
Adjuvant Chemotherapy

- Advantages of adjuvant vs neoadjuvant therapy:
  - Local treatment not delayed
  - More accurate patient selection

- However:
  - 30% of postop become unfit for chemo
  - Lack of level 1 evidence/EBM

Pathologic Down-Staging: Associated with Improved Cure Rates





c/o D. Bajorin/J. Rosenberg

20-40% of patients achieve a pathologic response
Can we do better?

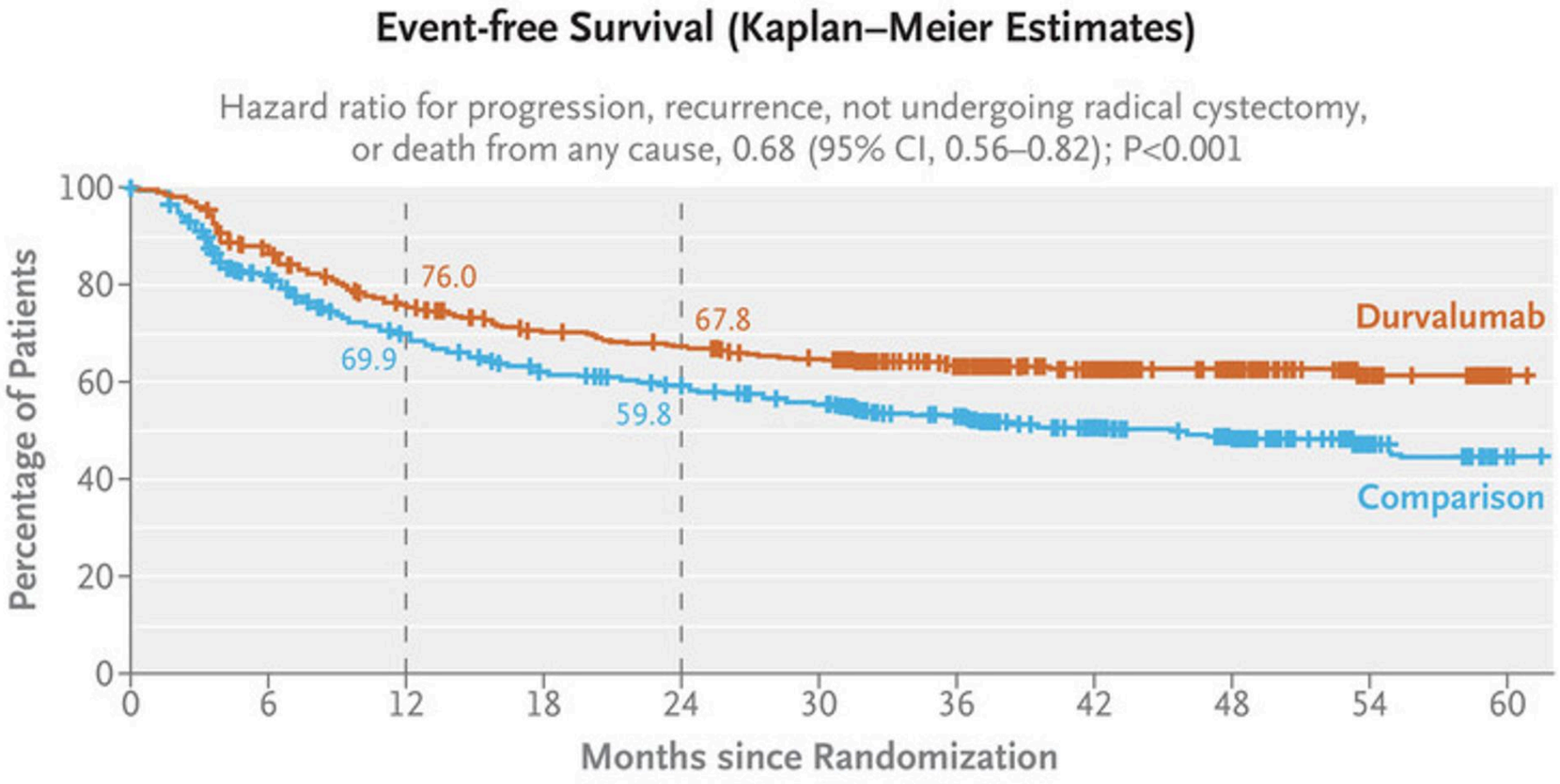
Perioperative Sandwich Therapy

NIAGARA Trial of perioperative Durvalumab with Neoadjuvant Gemcitabine/cisplatin

- Phase 3 randomized trial for pts w/MIBC scheduled for radical cystectomy (1066 patients)
- 1:1 Randomization to standard neoadjuvant GC x 4 cycles vs durvalumab + GC x 4 cycles followed by adjuvant durvalumab x 8 cycles postop
- Primary endpoint = event free survival
    - Overall survival secondary endpoint
- Periop sandwich (neoadjGC-Durva with adjuvant durva):
    - significantly improved EFS
    - Improved pathological CR rate (37% vs 27%)

Perioperative Sandwich Therapy

NIAGARA Trial of perioperative Durvalumab with Neoadjuvant Gemcitabine/cisplatin



Neoadjuvant Enfortumab-Pembro (EVP): A New Paradigm?

Enfortumab-vedotin (EV):

- Antibody drug conjugate directed against nectin-4
- Nectin-4 overexpressed in a variety of solid tumors

EV combined with pembrolizumab being studied in a variety of settings for UC

- Neoadjuvant in platinum ineligible cystectomy pts
- Neoadjuvant vs cisplatin combo chemo prior to cystectomy
- Definitive therapy with RT for bladder preservation
- First-line locally advanced/metastatic UC

Neoadjuvant Enfortumab-Pembro (EVP): A New Paradigm?

- EV 303: Neoadj EVP and postop pembro after cystectomy vs cystectomy alone (platinum ineligible patients):
  - Significantly higher path CR rate (57%)
  - Significant improvement in EFS and OS compared with cystectomy alone (75% vs 39% and 80% and 63%)
  - ***New paradigm for cisplatin ineligible neoadjuvant therapy***

Neoadjuvant Enfortumab-Pembro (EVP): A New Paradigm?

- EV 304: Neoadj EVP and postop pembro after cystectomy vs neoadjuvant cisplatin/gemcitabine
  - Significantly higher path CR rate (56% vs 33%)
  - Median EFS and OS not reached but trending towards significant improvement compared with neoadjuvant GC arm
  - ***New paradigm for cisplatin eligible neoadjuvant therapy??***
    - ***Priority review status by FDA***

Adjuvant Therapy After Extirpative Surgery

- Patients with residual invasive disease after cystectomy at high risk for recurrence and death

- Patients with residual invasive disease despite previous cisplatin chemo at highest risk
  - After neoadj chemo: path pT2+ or node positive

  - No neoadj chemo: pT3/4 or node positive

Adjuvant Therapy After Extirpative Surgery

ADJUVANT TREATMENT

NCCN Guidelines Version 1.2026

Following cystectomy →

- If Cisplatin/Gemcitabine + Durvalumab given preoperatively, then Durvalumab should be used postoperatively[bb]
- If Enfortumab vedotin-ejfv + Pembrolizumab given preoperatively, then Enfortumab vedotin-ejfv + Pembrolizumab should be used postoperatively[bb]
- Based on pathologic risk,[ii]
  - If no Cisplatin neoadjuvant treatment given and pT3, pT4a, or pN+
    - ◊ Adjuvant Cisplatin-based chemotherapy should be discussed (preferred)[bb]

    or
    - ◊ Consider adjuvant Nivolumab (category 1)[jj] or Pembrolizumab[bb,jj]

    or
  - If Cisplatin neoadjuvant chemotherapy given and ypT2–ypT4a or ypN+, Nivolumab (category 1) (preferred),[jj] or Pembrolizumab[bb,jj]

    or
  - Consider adjuvant RT in selected patients (pT3–4, positive nodes/margins at the time of surgery)[ee] (category 2B)

NCCN Guidelines Version 1.2026
Bladder Cancer

PRINCIPLES OF SYSTEMIC THERAPY[a]

Neoadjuvant Chemotherapy
Preferred • DDMVAC (dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin) with growth factor support for 3–6 cycles[1,2] **Useful in certain circumstances** • Cisplatin/Gemcitabine for 4 cycles[3,4]

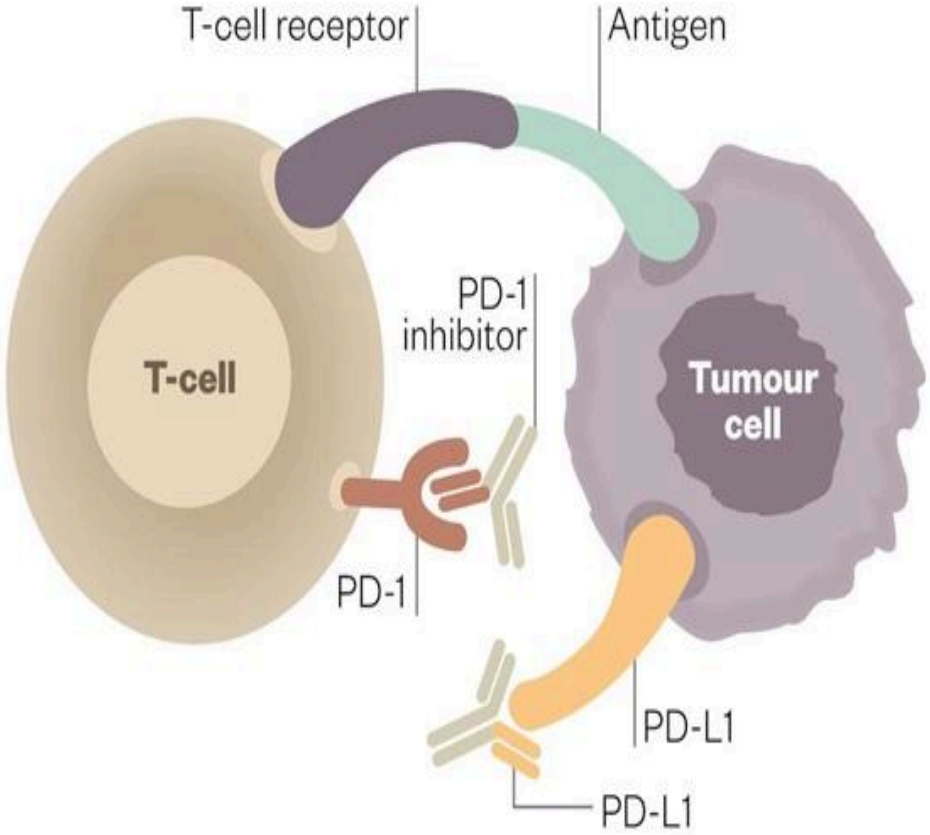
Perioperative/Sandwich Therapy
Preferred • Cisplatin/Gemcitabine + Durvalumab for 4 cycles prior to cystectomy, then Durvalumab for 8 cycles after cystectomy[5] (for bladder cancer only) (category 1) • Enfortumab vedotin-ejfv + Pembrolizumab for 3 cycles prior to cystectomy, then Enfortumab vedotin-ejfv (6 cycles) + Pembrolizumab (14 cycles) after cystectomy (for cisplatin-ineligible bladder cancer only)[b,6]

Adjuvant Therapy	
No previous platinum-based neoadjuvant therapy (pT3, pT4a, pN+)	**Previous platinum-based neoadjuvant therapy (ypT2–ypT4a or ypN+)**
Preferred • DDMVAC with growth factor support for 3–6 cycles[1,2] **Other recommended** • Nivolumab (category 1)[7] • Cisplatin/Gemcitabine for 4 cycles[3,4] • Pembrolizumab[8]	**Preferred** • Nivolumab[7] (category 1) **Other recommended** • Pembrolizumab[8]

Metastatic Urothelial Carcinoma

Immunotherapy

PD-L1 Inhibition

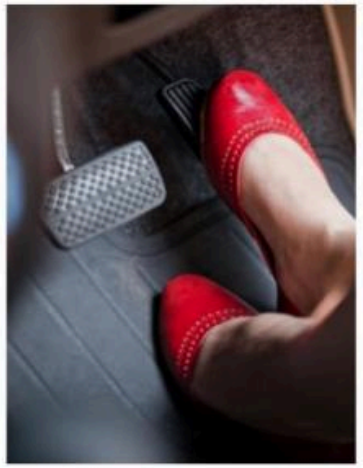


T Cell tolerance

"Driving" an Immune Response

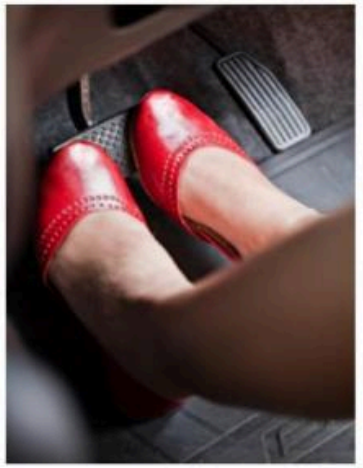
TCR: antigen-MHC

Signal 1



CD28: B7

Signal 2

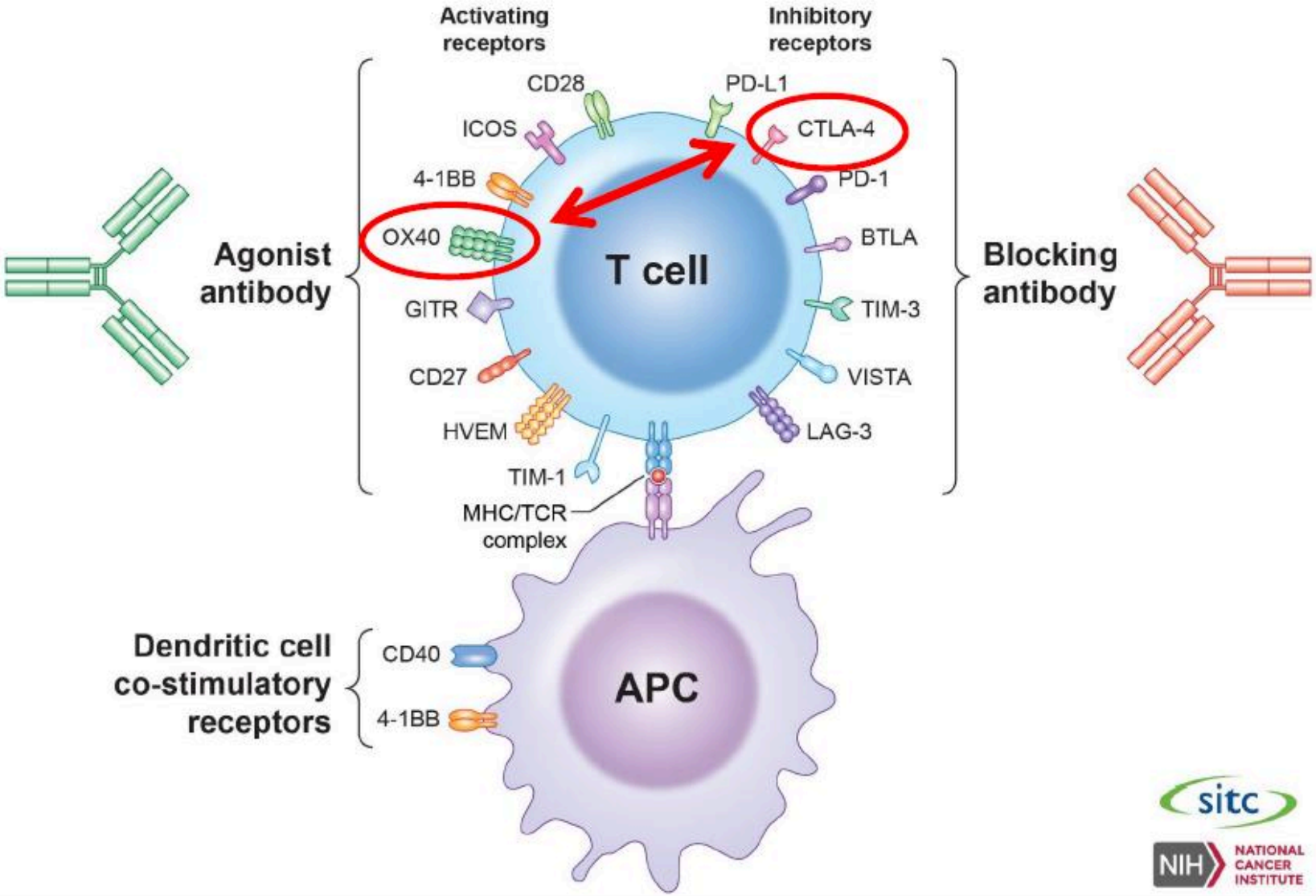


CTLA4: B7
PD-1: PD-L1

Blockade of Signal 2

EARLE A. CHILES RESEARCH INSTITUTE

Regulation of T cell activation



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NIH NATIONAL CANCER INSTITUTE

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,13] • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,13] • Nivolumab, gemcitabine, and cisplatin followed by nivolumab maintenance therapy[14] • Pembrolizumab and enfortumab vedotin-ejfv[15]
Cisplatin ineligible	**Preferred regimens** • Gemcitabine and carboplatin[16] followed by avelumab maintenance therapy (category 1)[a,13] • Pembrolizumab and enfortumab vedotin-ejfv[17] **Other recommended regimens** • Gemcitabine[18] • Gemcitabine and paclitaxel[19] • Atezolizumab[20] (only for patients whose tumors express PD-L1[b]) (category 2B) **Useful under certain circumstances** • Ifosfamide, doxorubicin, and gemcitabine[21] (for patients with good kidney function and good performance status) • Pembrolizumab[22] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Atezolizumab[20] (only for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Gemcitabine and cis[illegible]in[4] (category 1) follo[illegible]d by avelumab maintenance therapy (category 1)[a,13] • DDMVAC with gro[illegible] support (cat[illegible][2,8] followed by avelumab maintenance therapy (category 1)[a,13] • Nivolumab, gem[illegible]cisplatin[illegible]nivolumab maintenance therapy[14] • Pembrolizumab[illegible]
Cisplatin ineligible	**Preferred regimens** • Gemcitabine and carb[illegible]elumab maintenance therapy (category 1)[a,13] • Pembrolizumab and enfo[illegible]v[17] **Other recommended [illegible]** • Gemcitabine[18] • Gemcitabine an[illegible] • Atezolizumab[20] (c[illegible]ents whos[illegible]xpress PD-L1[b]) (category 2B) **Useful under certain ci[illegible]umstances** • Ifosfamide, doxorubicin, and gemcitabine[21] (for patients with good kidney function and good performance status) • Pembrolizumab[22] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Atezolizumab[20] (only for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

NCCN Guidelines Version 1.2026
Bladder Cancer

PRINCIPLES OF SYSTEMIC THERAPY[a]

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)		
Preferred	**Other recommended**	**Useful in certain circumstances**
• Enfortumab vedotin-ejfv[13,14] + Pembrolizumab (category 1)	• Cisplatin/Gemcitabine[4] (category 1) followed by Avelumab maintenance therapy (category 1)[c,15] • Cisplatin/Gemcitabine + Nivolumab (category 1) followed by Nivolumab maintenance therapy[16] (category 1) • DDMVAC with growth factor support[2,11] (category 1) followed by Avelumab maintenance therapy (category 1)[c,15]	• Carboplatin/Gemcitabine[17] followed by Avelumab maintenance therapy (category 1)[c,15] • Pembrolizumab (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)[18] • Atezolizumab[19] (only for patients whose tumors express PD-L1[d] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

NCCN Guidelines Version 1.2026
Bladder Cancer

PRINCIPLES OF SYSTEMIC THERAPY[a]

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)		
Preferred • Enfortumab vedotin-ejfv[13,14] + Pembrolizumab (category 1)	**Other recommended** • Cisplatin/Gemcitabine[4] (category 1) followed by Avelumab maintenance therapy (category 1)[c,15] • Cisplatin/Gemcitabine + Nivolumab (category 1) followed by Nivolumab maintenance therapy[16] (category 1) • DDMVAC with growth factor support[2,11] (category 1) followed by Avelumab maintenance therapy (category 1)[c,15]	**Useful in certain circumstances** • Carboplatin/Gemcitabine[17] followed by Avelumab maintenance therapy (category 1)[c,15] • Pembrolizumab (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)[18] • Atezolizumab[19] (only for patients whose tumors express PD-L1[d] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 7, 2024 VOL. 390 NO. 10

Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

T. Powles, B.P. Valderrama, S. Gupta, J. Bedke, E. Kikuchi, J. Hoffman-Censits, G. Iyer, C. Vulsteke, S.H. Park, S.J. Shin, D. Castellano, G. Fornarini, J.-R. Li, M. Gümüş, N. Mar, Y. Loriot, A. Fléchon, I. Duran, A. Drakaki, S. Narayanan, X. Yu, S. Gorla, B. Homet Moreno, and M.S. van der Heijden, for the EV-302 Trial Investigators*

EV 302 Trial: enfortumab/pembro 1st line

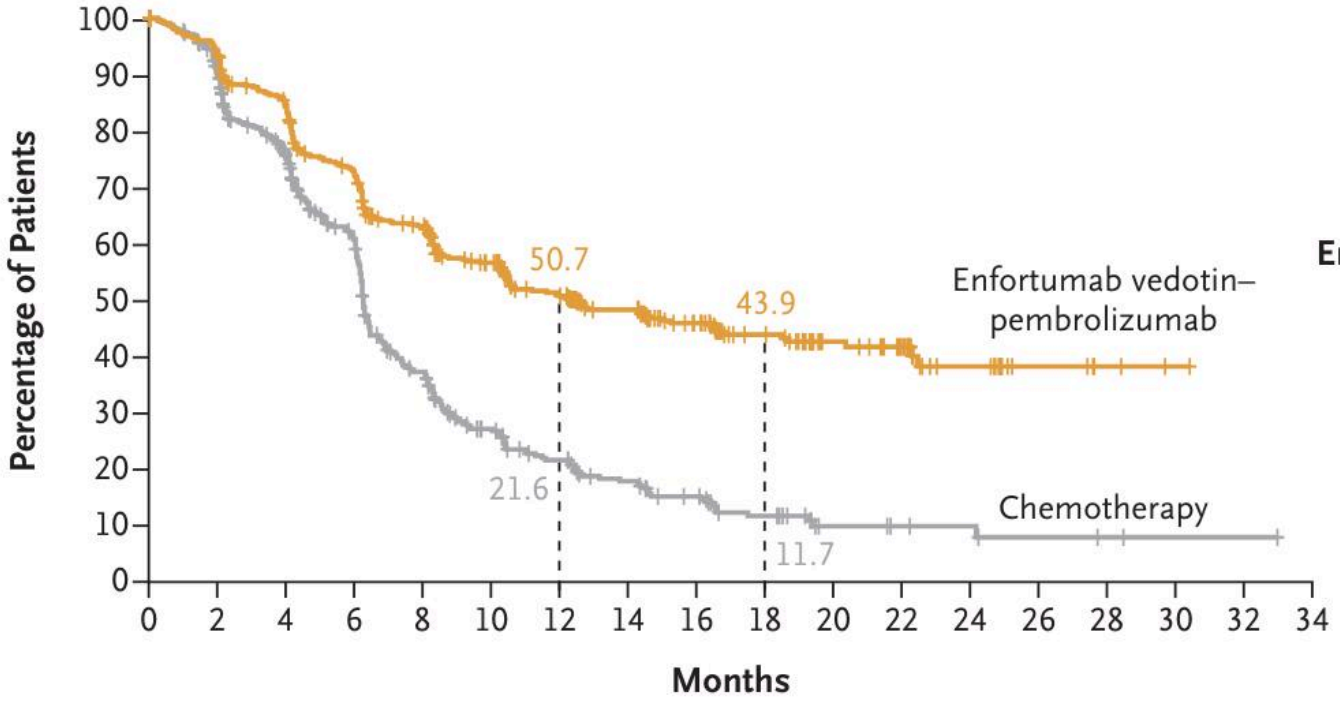
- Antibody drug conjugate directed against nectin-4
- Nectin-4 overexpressed in a variety of solid tumors

EV 302 Trial: enfortumab/pembro 1st line

- Phase III trial for advanced urothelial ca (first line)
- Two arm superiority study:
  - Gemcitabine +cisplatin (or carbo for cis-ineligible (6 cycles)
  - Enfortumab + pembrolizumab
- Total of 888 pts (1:1 randomization)
- Primary endpoint = PFS
- Significant improvement in PFS and OS with enfortumab/pembro
  - Median PFS 12.5 months vs. 6.3 months; HR 0.45; P<0.001
  - Median OS 31.5 months vs. 16.1 months; HR 0.47; P<0.001

N Engl J Med. 2024 Mar 7;390(10):875-888.

A Progression-free Survival



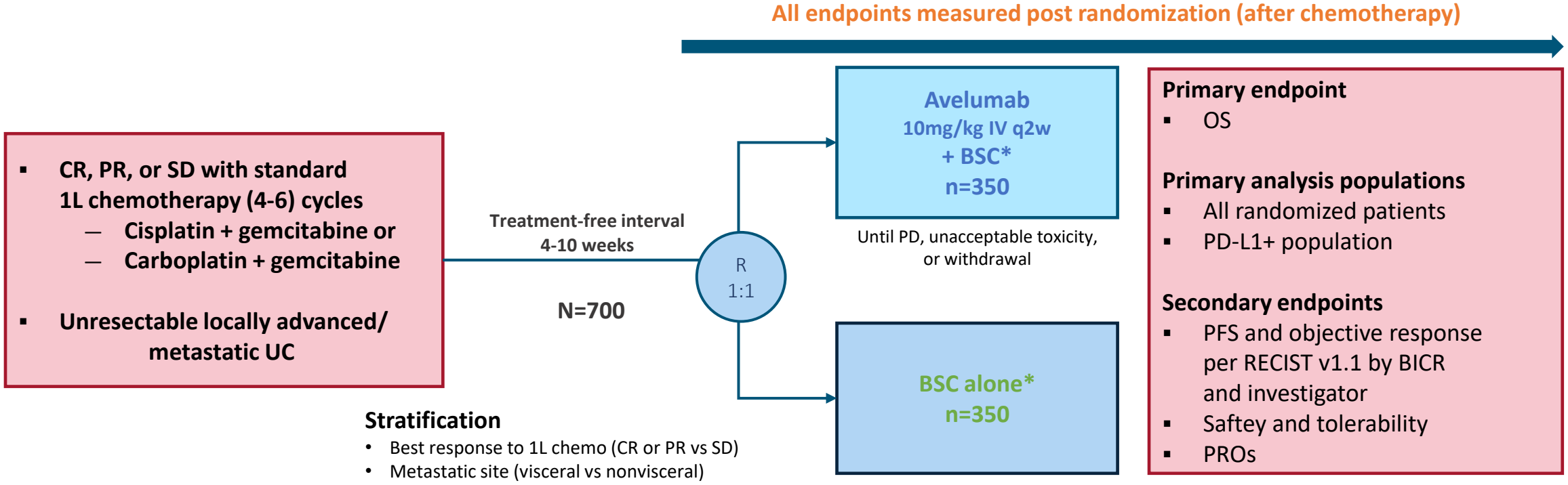
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Enfortumab Vedotin–Pembrolizumab	223/442	12.5 (10.4–16.6)
Chemotherapy	307/444	6.3 (6.2–6.5)

Hazard ratio, 0.45 (95% CI, 0.38–0.54)
Two-sided P<0.001

No. at Risk

Enfortumab vedotin–pembrolizumab	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1	
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

JAVELIN Bladder 100: Phase 3 Study of First-Line Maintenance With Avelumab

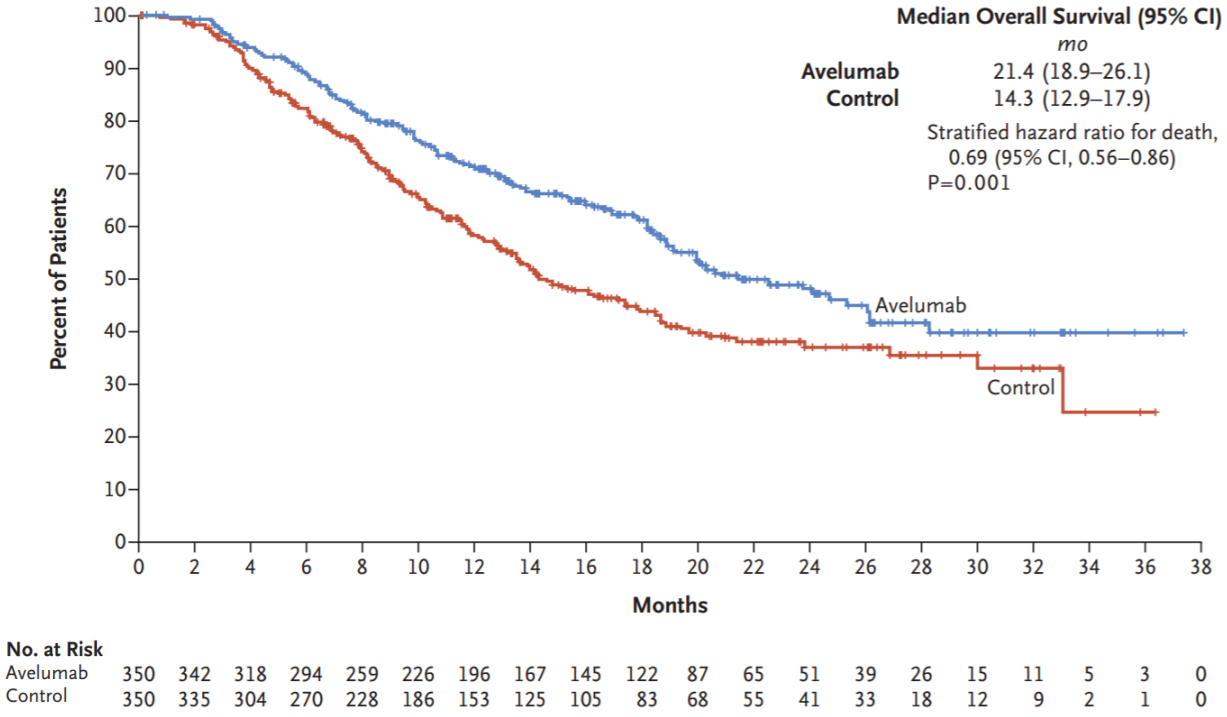


- PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells, or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was ≥1% or 1%, respectively, using the SP263 assay; 358 patients (51%) had a PD–L1+ tumor

Powles T, et al. *N Engl J Med*. 2020;383(13):1218-1230.

JAVELIN Bladder 100: Overall Survival

OS in the Overall Population



- **Median OS in the PD-L1+ population[1]**
  - Avelumab: NE (20.3 mo-NE)
  - Control: 17.1 mo (13.5-23.7)
    - HR: 0.56 (95% CI 0.40-0.79), P<0.001
- No treatment-by-subgroup interactions were observed (age, ECOG PS, PD-L1 status, site of baseline metastasis, etc)[2]
- Avelumab + BSC prolonged OS and PFS vs BSC alone irrespective of duration or cycles of 1L chemotherapy[3]

1. Powles T, et al. *N Engl J Med*. 2020;383(13):1218-1230. 2. Grivas P, et al. ESMO 2020. Abstract 704MO.
3. Loriot Y, et al. ASCO GU 2021. Abstract 438.

Checkmate 901: GC + Nivolumab

- Phase III trial for advanced urothelial ca (first line)
- Two arm study:
  - Gemcitabine/cisplatin (6 cycles) with concurrent nivo followed by nivo maintenance
  - Gemcitabine/cisplatin (6 cycles) alone
- Total of 608 pts (304 each arm)
- Primary endpoint = overall survival
- Significant improvement in OS, PFS and ORR with GC/nivo
  - median OS 21.7 months vs 18.9 months; HR 0.78; P = 0.02

N Engl J Med. 2023 Nov 9;389(19):1778-1789.

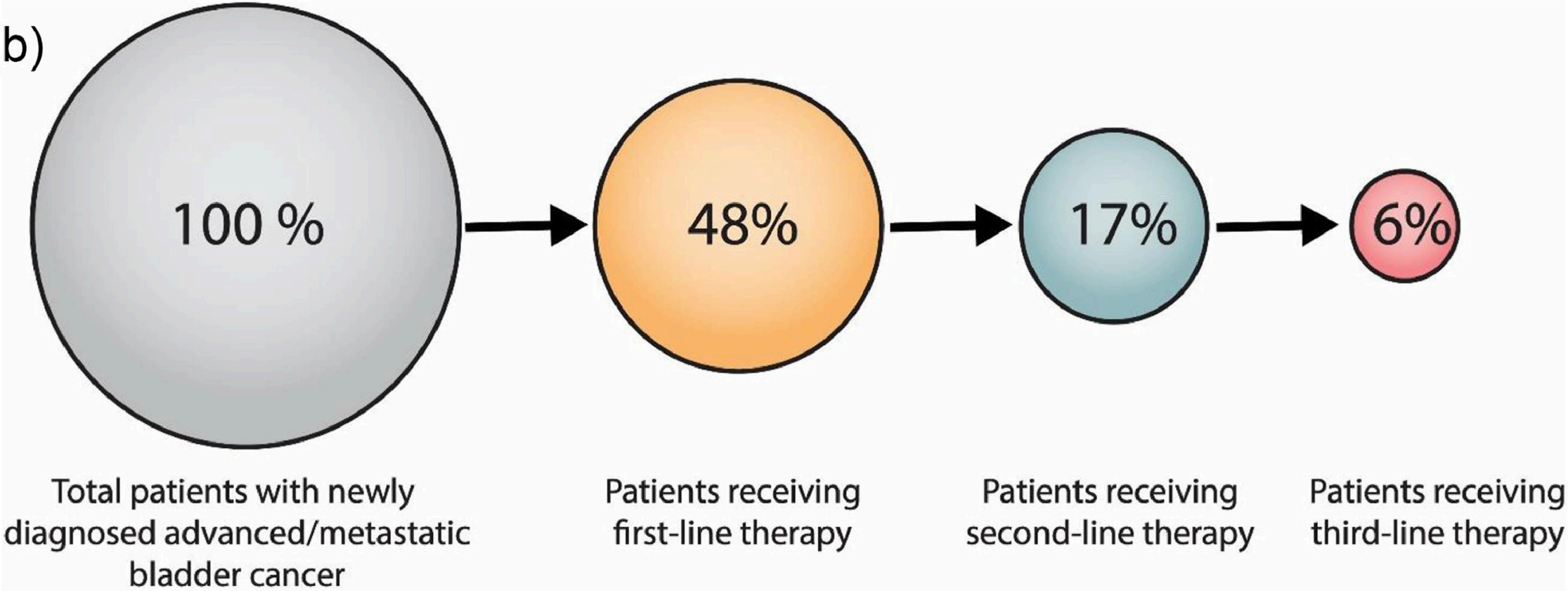
2nd /3rd Line and Beyond – After Chemo/ICI

Biomarker driven therapy

- **Erdafitinib (Balversa™)**:
  - Oral FGFR inhibitor
  - Approved for 2nd /3rd line met UC with FGFR 2 & 3 alterations
    - ORR 32%, PR 30% and CR 2.3%
    - FGFR alterations present in approx 20 % of patients

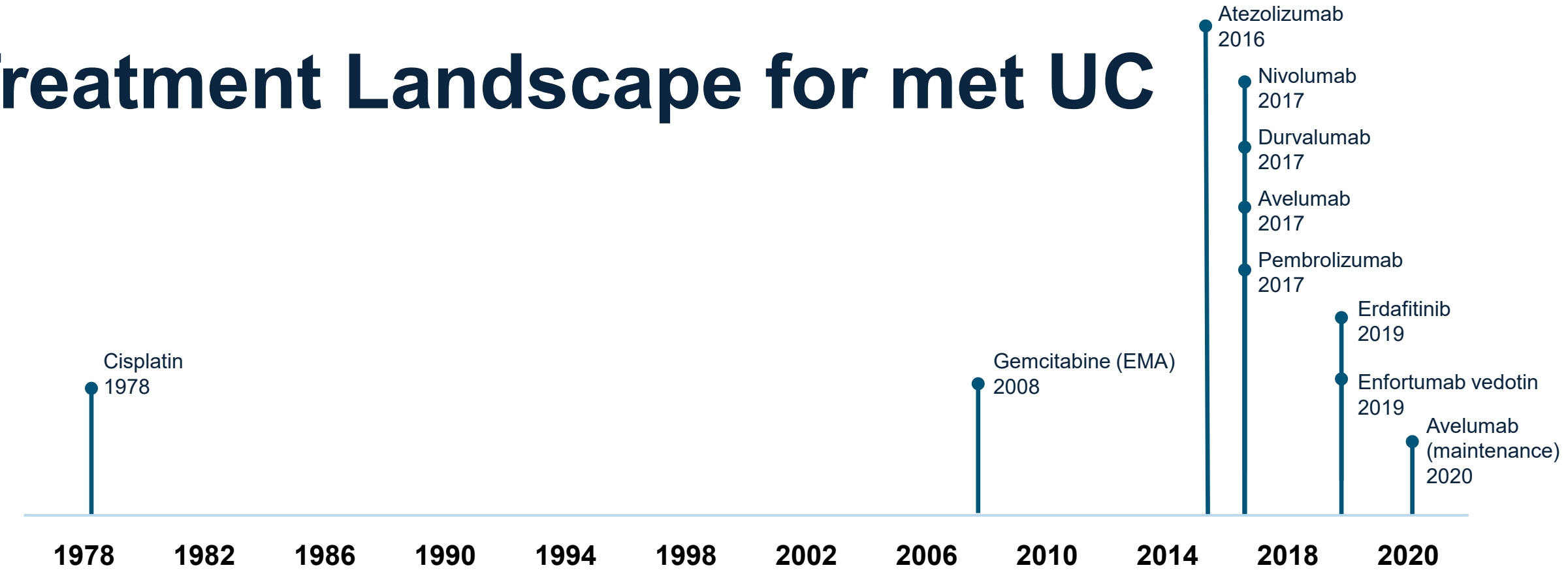
- **Trastuzumab deruxtecan (EnHerTu™)**:
  - Antibody-drug conjugate targeting HER2 (Human Epidermal growth factor Receptor 2)
  - Tumor agnostic FDA approval = any tumor with HER2
  - UC expression of HER 2: 7%-35%
  - ORR for UC: 51%

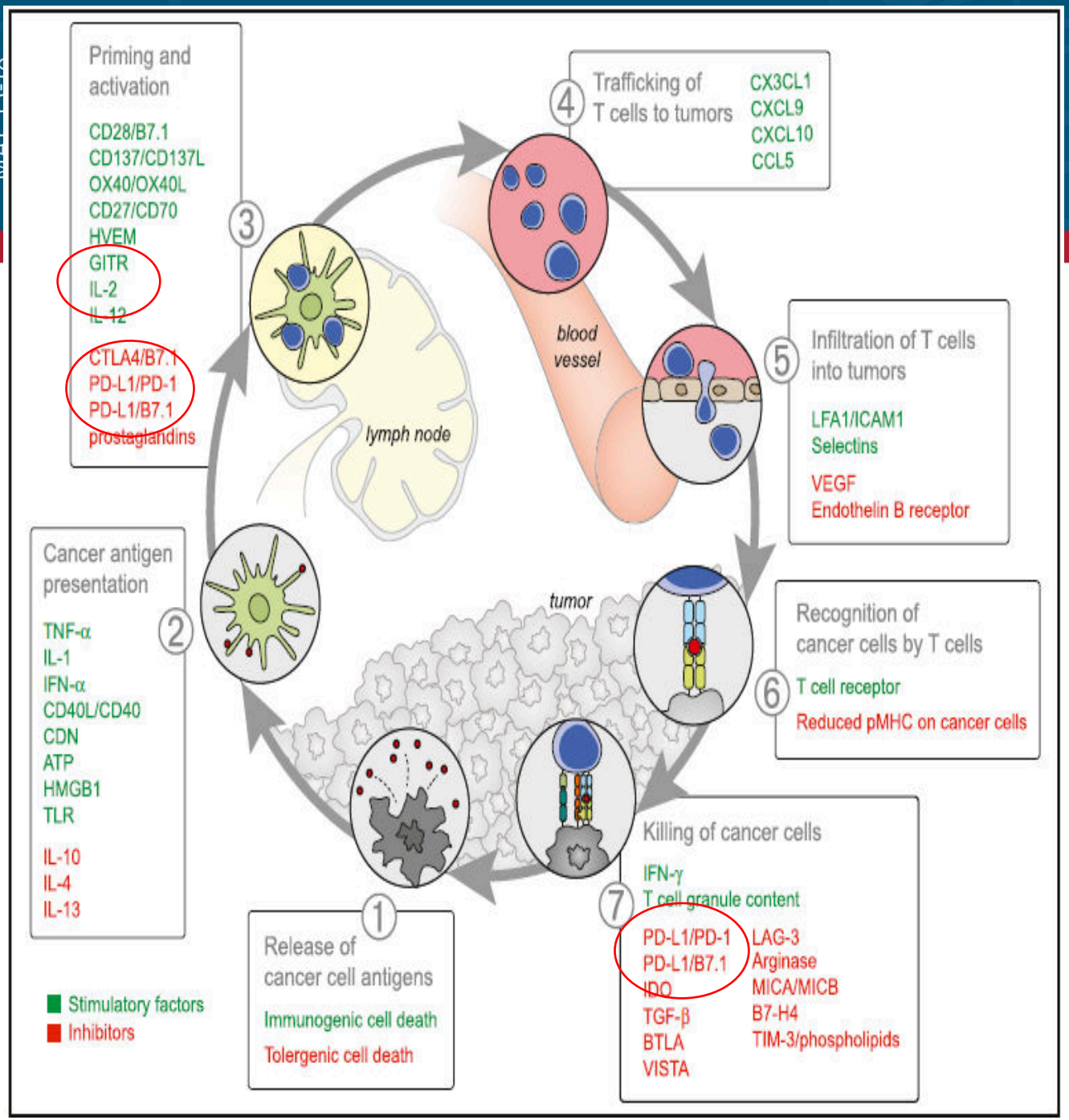
Utilization of Systemic Therapy for Advanced Urothelial Carcinoma



- Swami U, et al. *Cancer Treat Res Commun*. 2021;27:100325.

Treatment Landscape for met UC




Priming and activation
CD28/B7.1
CD137/CD137L
OX40/OX40L
CD27/CD70
HVEM
GITR
IL-2
IL-12
CTLA4/B7.1
PD-L1/PD-1
PD-L1/B7.1
prostaglandins
3
lymph node
4
Trafficking of T cells to tumors
CX3CL1
CXCL9
CXCL10
CCL5
blood vessel
5
Infiltration of T cells into tumors
LFA1/ICAM1
Selectins
VEGF
Endothelin B receptor
Cancer antigen presentation
TNF-α
IL-1
IFN-α
CD40L/CD40
CDN
ATP
HMGB1
TLR
IL-10
IL-4
IL-13
2
tumor
6
Recognition of cancer cells by T cells
T cell receptor
Reduced pMHC on cancer cells
1
Release of cancer cell antigens
Immunogenic cell death
Tolergenic cell death
7
Killing of cancer cells
IFN-γ
T cell granule content
PD-L1/PD-1
PD-L1/B7.1
IDO
TGF-β
BTLA
VISTA
LAG-3
Arginase
MICA/MICB
B7-H4
TIM-3/phospholipids
Stimulatory factors
Inhibitors

Upper Tract UC

- Very uncommon malignancy
- Most systemic therapies and relative efficacies are extrapolated from the bladder cancer literature.
- Neoadjuvant ddMVAC (Hoffman-Censits, et al, ECOG-ACRIN 8141)
  - 14% pCR, 60% <=pT1
- Adjuvant GC/Gca (POUT Trial): significantly improved DFS
- Current trial in accrual:
  - ECOG-ACRIN 8192: Randomizing neoadjuvant ddMVAC +/- durvalumab

Thank you!