AUA 2026 MAY 15-18 Washington, DC

M1 CRPC: PARP Inhibitors, Microsatellite Instability and Precision Medicine

Kristen R. Scarpato MD
Vanderbilt University Medical Center

1

AUA 2026 MAY 15-18 Washington, DC

Disclosures

- CxBladder
- Photocure
- Urogen

2

AUA2026 Washington, DC MAY 15-18

Outline

- Genetic Testing
  - What and why?
  - Somatic vs. Germline
  - Logistics
- PARP Inhibitors
  - What are they?
  - Which patients
    - Data: monotherapy and combination therapy
  - FDA approvals
- Microsatellite Instability

3

Precision Medicine

Genomic profiling of patient tumors

Individualized treatments

4

AUA 2026 Washington, DC MAY 15-18

Genetic Testing

Germline (inherited)

- Inherited cancer risk
- Buccal or blood
- Cancer screening and prevention, genetic testing in close relatives, informing treatment and clinical trials

Somatic (acquired)

- Genomic tumor sequencing
- Tissue or liquid biopsy
- Extensive testing for tumor specific mutations
- Direct targeted therapies, clinical trial eligibility

5

AUA 2026 Washington, DC MAY 15-18

Genetic Testing

Germline (inherited)

- Regional or metastatic
- High risk or very high risk
- FHx of high-risk germline mutation
- A positive FHx of cancer
- Intraductal, cribriform

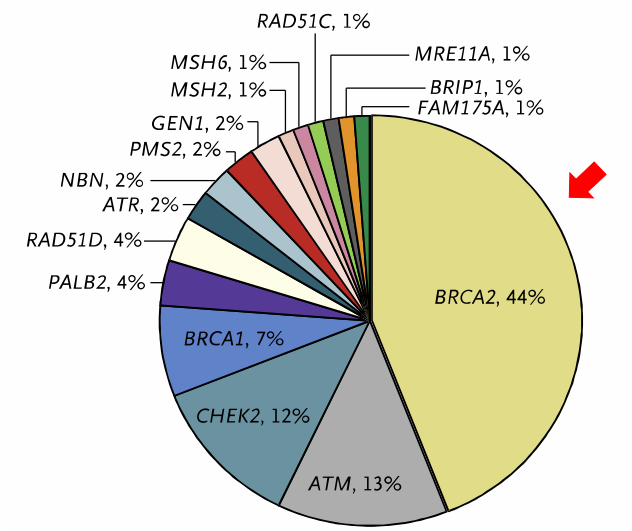
Somatic (acquired)

- Metastatic
- Regional (consider)

BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, HOXB13

6

DNA Repair Gene Alterations are common in Metastatic Pca (Germline)



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, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

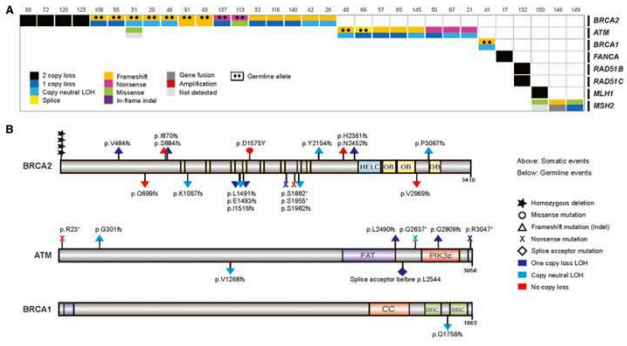
- 692 men with metastatic PCA
- Sequenced their genome
- 84 germline DNA-repair gene mutations
- **82 men (11.8%)**
- Mutations were found in 16 genes

7

AUA 2026 Washington, DC MAY 15-18

DNA Repair Gene Alterations are common in Metastatic Pca (Somatic)

- Of mCRPCs, 23% harbor DNA repair alterations
- **The frequency of DNA repair alterations increases with disease progression (metastatic vs. local)**



Cell 2015;161:1215-1228

8

AUA 2026 Washington, DC MAY 15-18

Genetic Testing: What do patients want to know?

- What are possible results?
  - Pathogenic, likely pathogenic, uncertain, negative
- Genetic counseling
- How much does it cost?
- Will I be discriminated against?

9

9

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

INITIAL PROSTATE CANCER DIAGNOSIS[a,b,c] | **WORKUP**

Clinically localized prostate cancer (Any T, N0, M0 or Any T, NX, MX)

- Perform physical exam
- Perform digital rectal examination (DRE) to confirm clinical stage
- Perform and/or collect prostate-specific antigen (PSA) and calculate PSA density
- Obtain and review diagnostic prostate biopsies
- Estimate life expectancy (Principles of Life Expectancy Estimation [PROS-A])
- Inquire about known high-risk germline mutations and family history[d]
  - Perform somatic and/or germline testing as appropriate[d]
- Assess quality-of-life measures[e]

→ **See Initial Risk Stratification and Staging Workup for Clinically Localized Disease (PROS-2)**

Regional prostate cancer (Any T, N1, M0)

Metastatic prostate cancer (Any T, Any N, M1)

- Perform physical examination
- Perform bone and soft tissue imaging for staging[f]
- Perform DRE to confirm clinical stage
- Perform and/or collect PSA and calculate PSA doubling time (PSADT)
- Estimate life expectancy (Principles of Life Expectancy Estimation [PROS-A])
- Inquire about known high-risk germline mutations and family history[d]
  - Perform somatic and/or germline testing as appropriate[d]
- Assess quality-of-life measures[e]

→ **Regional Prostate Cancer (PROS-8)**

→ **See Workup and Treatment of M1 Castration-Sensitive Prostate Cancer (PROS-13)**

10

10

Updates to Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline (2023)

UPDATE UNDERWAY

28. In p... hould offer germline (if not already performed) and so... DNA repair deficiency, microsatellite instability (MSI) sta... tential mutations that may inform prognosis an... ial targeted therapies. (Clinical Principle)

DDR Mutations ~ 12% mPCA
Portends poor prognosis → worse cancer specific survival

Mutations in HRR genes in ~ 30% of screened mCRPC in PROFOUND

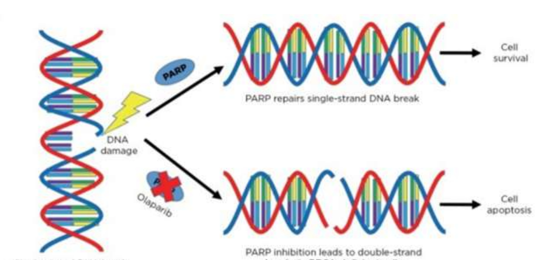
J Urol 2023;209:1082

11

AUA2026 Washington, DC MAY 15-18

PARP Inhibitors – Mechanism of Action

- poly-ADP ribose polymerase (PARP) repairs DNA damage
- PARPi are oral agents that block the repair mechanisms
- In the setting of certain mutations → "***Synthetic lethality***"
  - Block the dependent path
  - Cancer cell death



Eur Urol Oncol. 2020:S2588-9311

12

AUA2026 Washington, DC MAY 15-18

PARP Inhibitors – Single Agent

- Single agent – two FDA approved agents
  - Olaparib (PROFOUND)
  - Rucaparib (TRITON)

35. Clinicians should offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy. Platinum-based chemotherapy may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor. (*Moderate Recommendation; Evidence Level: Grade C*)

J Urol 2023;209:1082

13

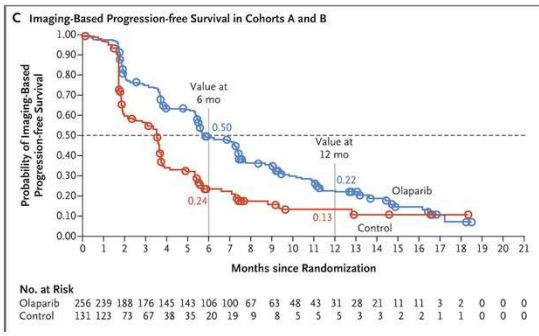
AUA2026 Washington, DC MAY 15-18

PROfound: Olaparib for mCRPC

- Patients with mCRPC who had disease progression with enzalutamide or abiraterone
- All patients had a qualifying alteration in prespecified genes
- Cohort A – BRCA1, BRCA2, ATM
- Cohort B – 12 other prespecified mutations
- Randomized 2:1 to olaparib or physician's choice

14

PROfound

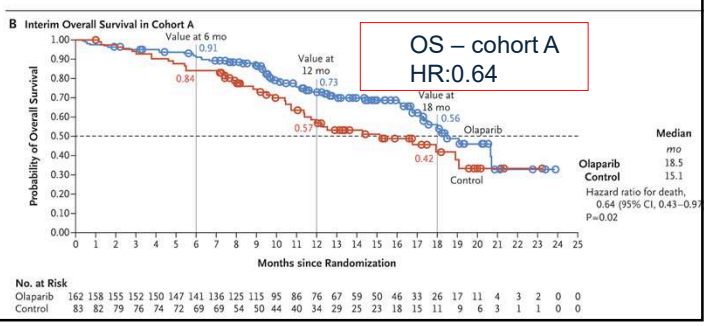


rPFS – overall cohort
HR: 0.49

	Median (mo)
Olaparib	5.8
Control	3.5

Hazard ratio for progression or death, 0.49 (95% CI, 0.38–0.63)
P<0.001

mPFS ~3.5 mos when switching ARPI



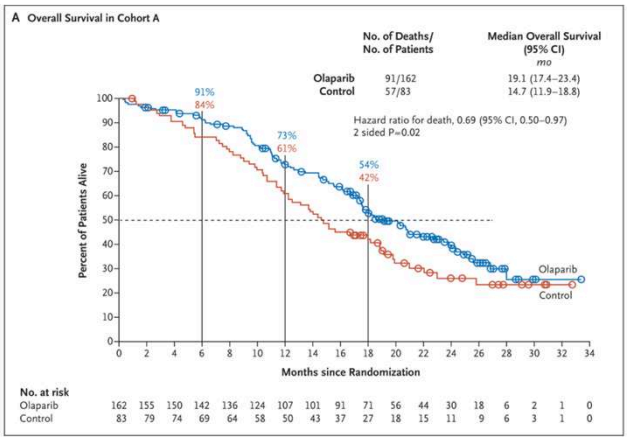
OS – cohort A
HR:0.64

N Engl J Med 2020 28;382(22):2091-2102

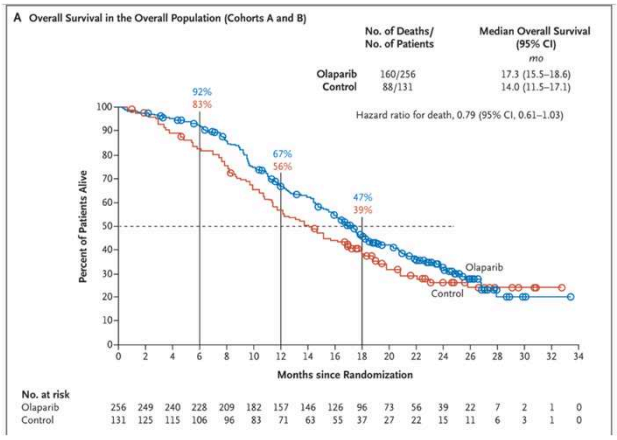
15

PROfound OS

FDA Approved May 2020



COHORT A
HR: 0.69
CI: 0.50-0.97



Overall Population
HR: 0.79
CI: 0.69 – 1.03

N Engl J Med 2020 Dec 10;383(24):2345-2357

16

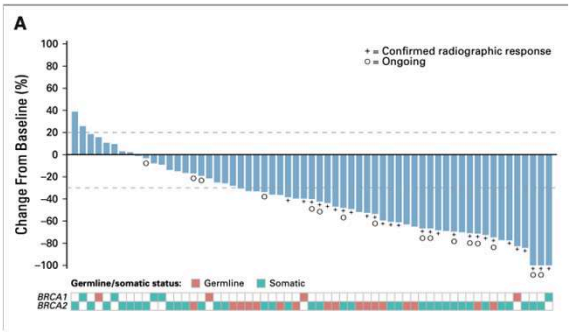
AUA 2026 Washington, DC MAY 15-18

TRITON2: Rucaparib for mCRPC

- Patients with mCRPC who had disease progression with enzalutamide or abiraterone *and* docetaxel chemotherapy
- All patients had a qualifying somatic or germline HRRm
- Given rucaparib and followed with PSA and imaging
- Treatment until radiographic progression or discontinuation

17

Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration



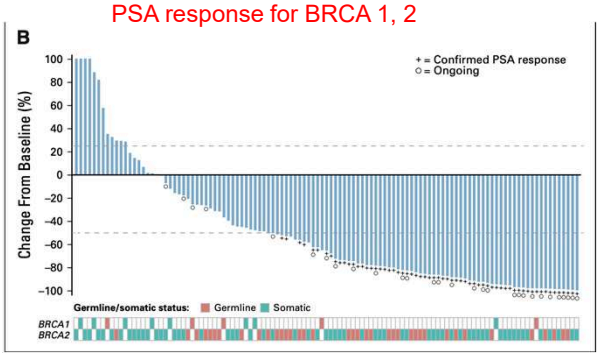
RECIST change from baseline for BRCA 1, 2

Final results of Triton 2 in Eur Urol 2023– best PFS, OS response in BRCA patients

Eur Urol. 2023;84:321-330.

Accelerated FDA Approved May 2020

PSA response for BRCA 1, 2



Abida J Clin Oncol 2020 38:3763-3772

18

AUA2026 Washington, DC MAY 15-18

TRITON3: Rucaparib for mCRPC

Chemo vs. PARP in patients with mCRPC

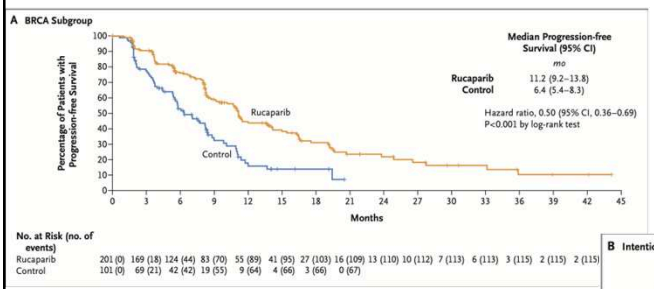
- Patients with *chemo-naïve* mCRPC who had disease progression with enzalutamide or abiraterone
- All patients had BRCA or ATM
- Stratified by PS, liver mets, BRCA1/2/ATM
- Randomized 2:1 to rucaparib or physician's choice (docetaxel or ARPI)
- Endpoints rPFS; OS, ORR; subgroup analyses

19

TRITON3

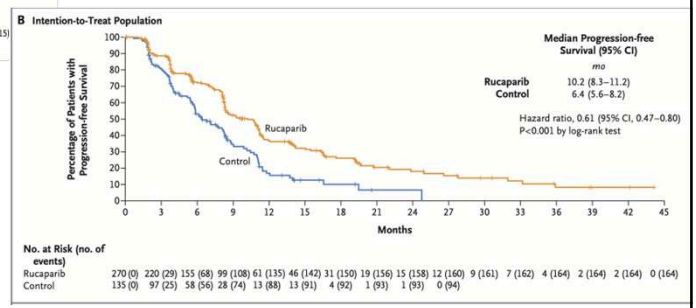
Rucaparib or Physician's Choice in Metastatic Prostate Cancer

Chemo-naïve in mCRPC
BRCA or ATM mutated
Chemo vs. PARP in patients with mCRPC



BRCA subgroup
HR 0.50 with rucaparib

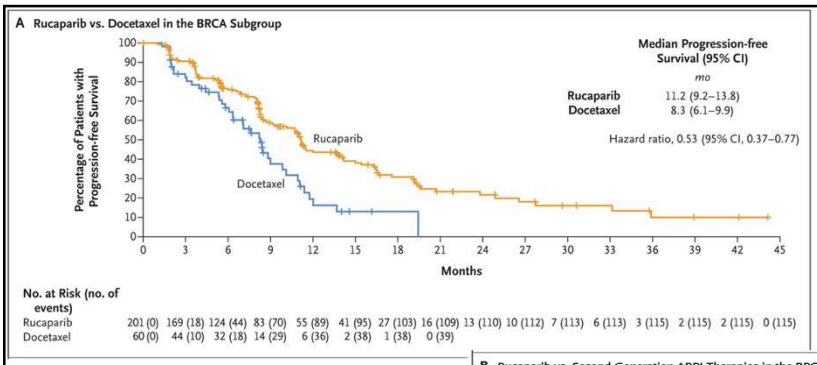
ITT Population
HR 0.61 with rucaparib



N Engl J Med 2023;388:719-32.

20

Rucaparib or Physician's Choice in Metastatic Prostate Cancer
TRITON3

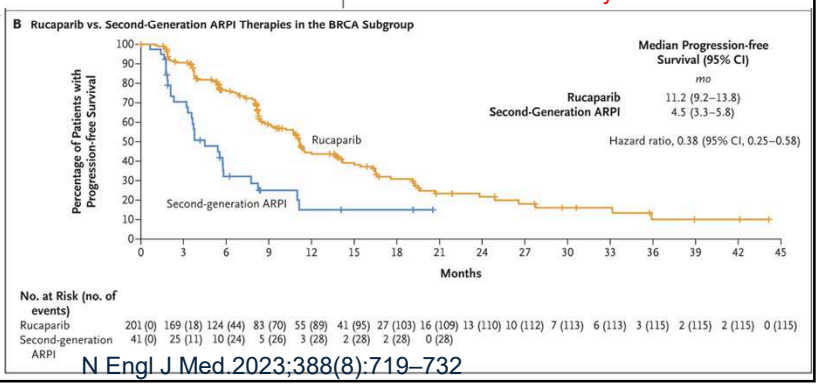


rPFS: Rucaparib superior to docetaxel by ~ 3 months

No real benefit in ATM subgroup

Updated OS in BRCA +
- ***No advantage***
- ***>50% crossover***

rPFS: Rucaparib superior to 2nd ARPI by ~ 8 months



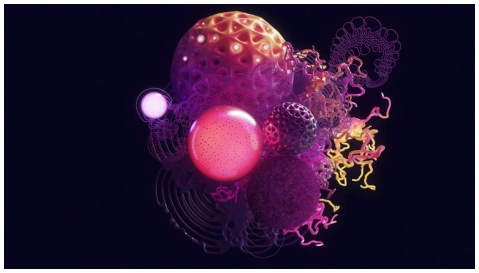
N Engl J Med 2023;388(8):719–732

21

AUA 2026 Washington, DC MAY 15-18

Rationale for combination with ARPIs

PARP inhibitors ←→ androgen pathway inhibitors



Androgen receptor signaling regulates DNA repair "BRCA-ness"

22

PARP Inhibitors – Combination therapy

- Combination with androgen receptor pathway inhibitors
  - Olaparib + abiraterone (PROpel)
  - Talazoparib + enzalutamide (TALAPRO)
  - Niraparib + abiraterone (MAGNITUDE)

First line setting

23

PROpel: Olaparib + Abiraterone for mCRPC

- mCRPC with no prior treatment enrolled *regardless* of HRR mutation status
- Prior docetaxel in castration sensitive allowed
- Randomized to olaparib + abi vs. PBO + abi
- Stratified by disease site and taxanes in mHSPC

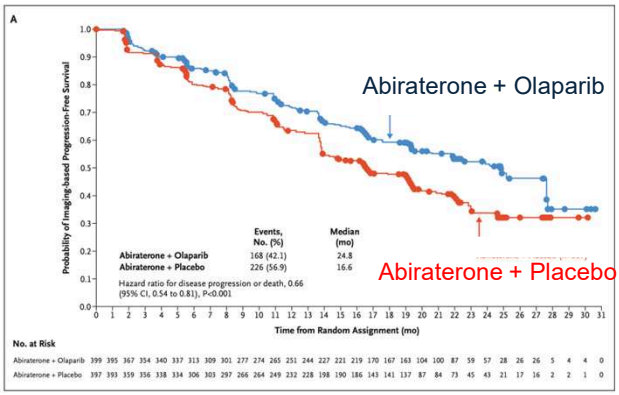
- 1º endpoint – imaging-based PFS by investigator assessment

NEJM Evid 2022;1(9)

24

AUA2026 Washington, DC MAY 15-18

PROpel: Olaparib + Abiraterone for mCRPC



Imaging-based PFS by investigator assessment
24.8 mos vs. 16.6 mos
HR 0.66

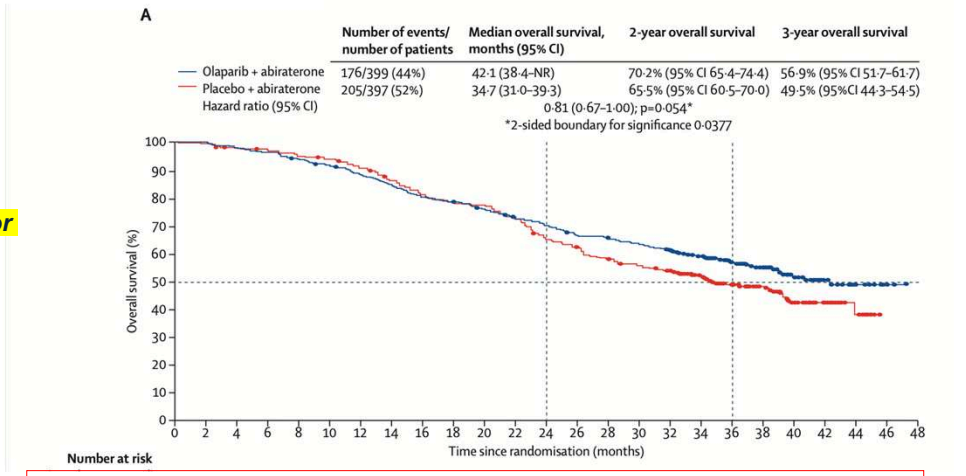
NEJM Evid 2022;1(9)

25

Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial

PROpel: Overall Survival

FDA approved May 2023 for BRCAm mCRPC



ITT population with mOS benefit of ~7 mos longer in the abiraterone + Olaparib arm
→ not statistically significantly different at final prespecified analysis

Lancet Oncol 2023;24: 1094–108

26

AUA 2026 Washington, DC MAY 15-18

TALAPRO2: Talazoparib + Enzalutamide for mCRPC

- mCRPC with no prior treatment *stratified by* HRRm status
  - Prospective assessment of HRR
- Prior docetaxel in castration sensitive allowed
- Randomized 1:1 to talazoparib + enza vs. PBO + enza
- Stratified by HRRm and taxanes or abi in mHSPC

- 1º endpoint – imaging-based PFS by investigator assessment

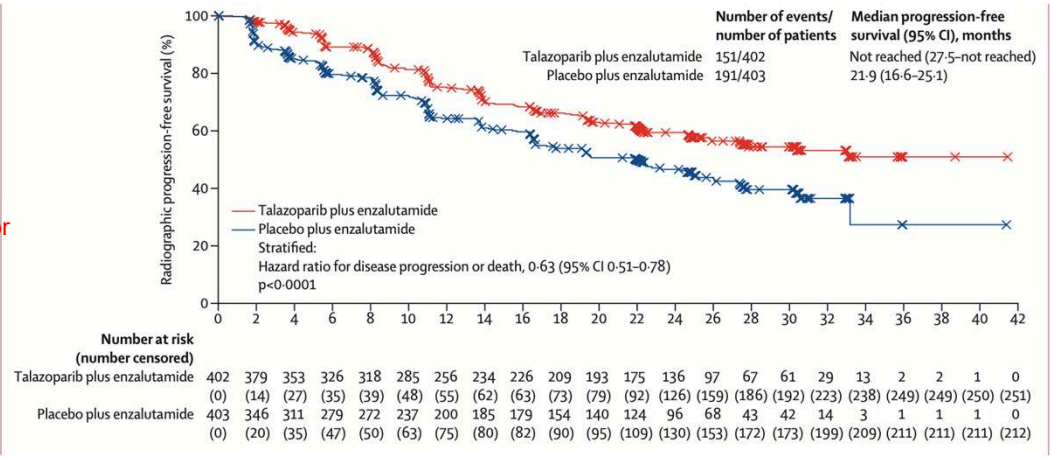
Lancet 2023; 402: 291–303

27

TALAPRO-2: Talazoparib + Enzalutamide

Radiographic Progression Free Survival

Blinded investigator assessment

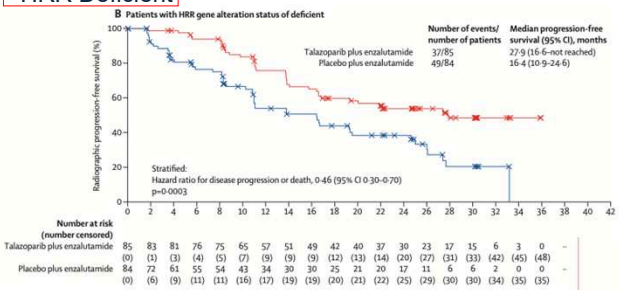


Lancet 2023; 402: 291–303

28

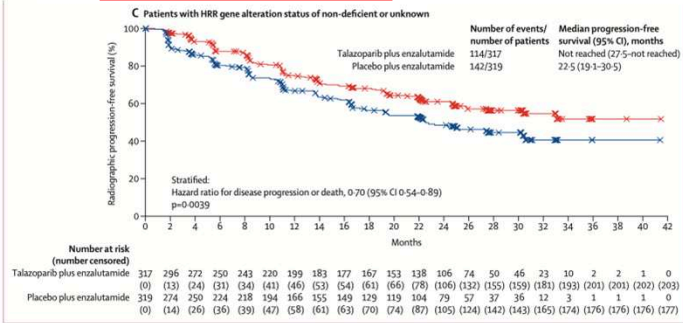
TALAPRO-2: Talazoparib + Enzalutamide

HRR Deficient



rPFS by HRR Status

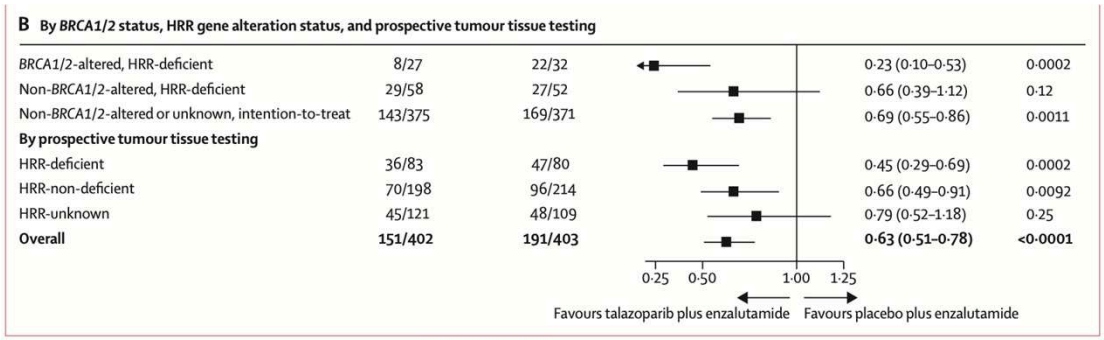
HRR Non-deficient or unk



Lancet 2023; 402: 291–303

29

TALAPRO-2: Talazoparib + Enzalutamide



Subgroup analysis by genetics

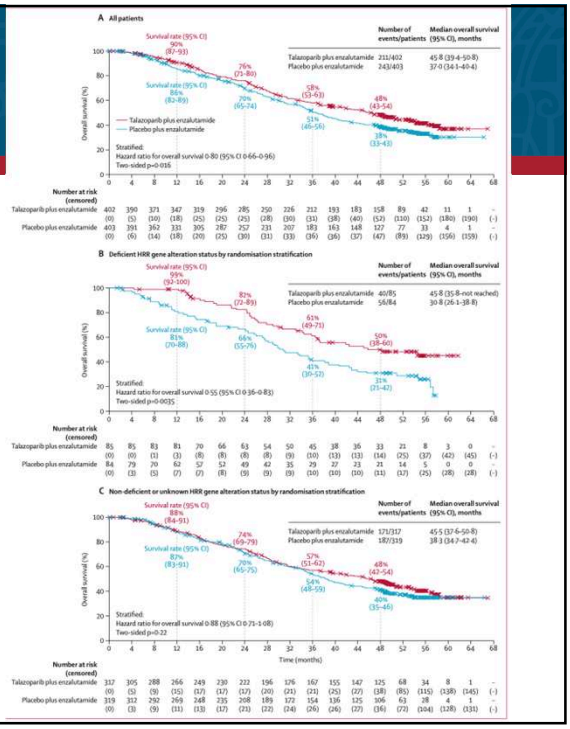
FDA approved 6/2023 for HRRm mCRPC

Lancet 2023; 402: 291–303

30

Talazoparib plus enzalutamide in men with metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial Lancet 2025; 406: 447–60

Neeraj Agarwal, Arun A Azad, Joan Carles, André P Fay, Nobuaki Matsubara, Cezary Szczylik, Ugo De Giorgi, Jae Young Joung, Peter C C Fong, Eric Voog, Robert J Jones, Neal D Shore, Fred Saad, Curtis Dunshee, Stefanie Zschäbitz, Jan Oldenburg, Xun Lin, Cynthia G Healy, Matko Kalac, Dana Kennedy, Karim Fizazi**



- ALL mCRPC PATIENTS - OS
  - **HR 0.80** (0.66-0.96), p=0.016
  - Median OS: 45.8 vs. 37.0 months
- HRR-DEFICIENCT PATIENTS- OS
  - **HR 0.55** (0.36-0.83), p=0.0035
  - Median OS: 45.8 vs. 30.8 months
- NON-DEFICIENT OR UNKNOWN PATIENTS - OS
  - **HR 0.88** (0.71-1.08), p=0.22
  - Median OS: 45.5 vs. 38.3 months

31

Talazoparib plus enzalutamide in men with HRR-deficient metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial Lancet 2025; 406: 461-74

Karim Fizazi, Arun A Azad, Nobuaki Matsubara, Joan Carles, André P Fay, Ugo De Giorgi, Jae Young Joung, Peter C C Fong, Eric Voog, Robert J Jones, Neal D Shore, Curtis Dunshee, Stefanie Zschäbitz, Jan Oldenburg, Dingwei Ye, Xun Lin, Matko Kalac, A Douglas Laird, Dana Kennedy, Neeraj Agarwal**

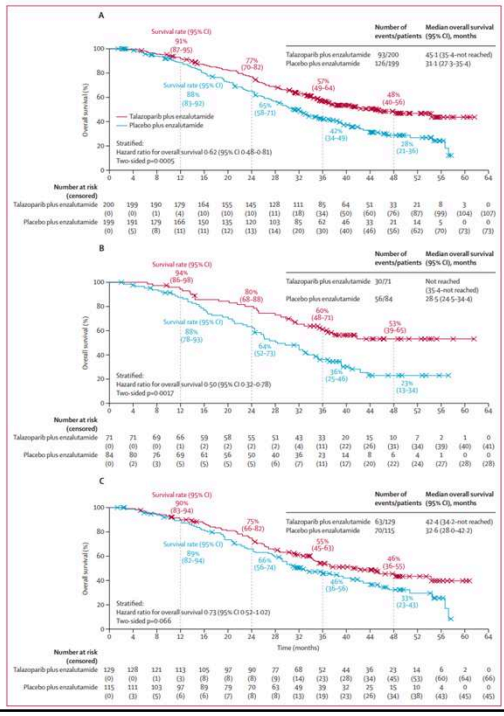


Figure 2: Overall survival
Overall survival in patients with (A) any HRR gene alteration; (B) BRCA1/2 gene alterations; and (C) non-BRCA1/2 HRR gene alterations (HRR-deficient intention-to-treat population). HRR=homologous recombination repair.

- ALL HRR-DEFICIENT - OS
  - **HR 0.62** (0.48-0.81), p=0.0005
  - Median OS: 45.1 vs. 31.1 months
- BRCA1/2 GENE ALTERATIONS - OS
  - **HR 0.50** (0.32-0.78), p=0.0017
  - Median OS: Not reached vs. 28.5 months
- NON-BRCA1/2 GENE ALTERATIONS in - OS
  - **HR 0.73** (0.52-1.02), p=0.066
  - Median OS: 42.4 vs. 32.6 months

32

AUA 2026 Washington, DC MAY 15-18

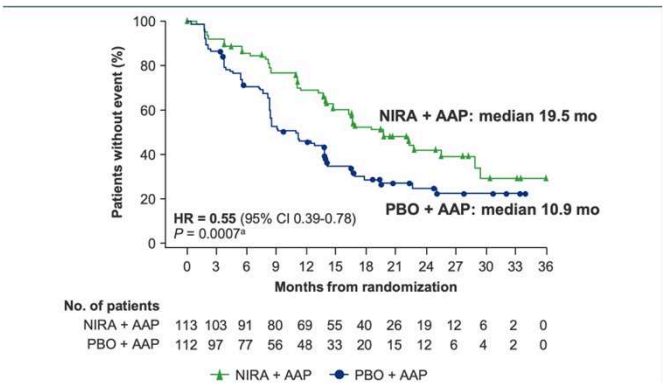
MAGNITUDE: Niraparib + Abiraterone for mCRPC

- mCRPC with no prior treatment
  - Prescreening for HRR status before randomization
  - Cohort 1: HRRm+ Cohort 2: HRRm-
- Prior docetaxel in castration sensitive, prior NHT in nmCRPC, <4mos Abi in mCRPC allowed
- Randomized 1:1 to Niraparib + abi vs. PBO + abi
- Stratified by HRRm and taxanes or abi in mHSPC
- 1º endpoint – imaging-based PFS

JCO 2023;41:3339

33

Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial☆



rPFS by central review in the BRCA subgroup

- Improved rPFS with NIRA + AAP compared with PBO + AAP in BRCA+ mCRPC
  - 16.6 mos vs 10.9 mos (HR 0.53; 95%CI 0.36-0.79; p = 0.001)
- 45% reduction in risk of progression or death and extension of the median rPFS to >1.5 years compared with PBO + AAP
- **FDA-approved August 2023 for BRCAm-mCRPC**

Ann Oncol 2023:34:772

34

Adverse Events with PARPi

- *Anemia*
- Fatigue
- Nausea/vomiting
- Anorexia
- Diarrhea
- Thrombocytopenia/neutropenia
- Cough
- Dyspnea
- VTE
- Pneumonitis
- Myelodysplasia/AML (theoretical)
- Fetal teratogenicity
- ➡ Dose interruption
- ➡ Dose reduction

35

Where has this patient been?

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2026
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[g,aa,iii,jjj]

Pre-ARPI[aa,kkk]	Post-ARPI[kkk]/Pre-Docetaxel[aa]	Post-ARPI[kkk]/Post-Docetaxel[aa]
Preferred: • Abiraterone (category 1) • Enzalutamide (category 1) **Other Recommended:** • Docetaxel[ggg] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Niraparib/abiraterone[lll] (category 1) ◊ Olaparib/abiraterone[lll] (category 1) ◊ Talazoparib/enzalutamide[lll] (category 1) ▸ *HRRm* (other than BRCA1/2) ◊ Talazoparib/enzalutamide[lll] (category 1) • Disease State-Specific Therapy ▸ Bone metastases ◊ Radium-223[mmm]/enzalutamide	**Preferred:** • Docetaxel[ggg] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Olaparib[lll] (category 1, preferred) ◊ Rucaparib[lll] (category 1, preferred) ◊ Niraparib/abiraterone[lll] (category 2B) ◊ Talazoparib/enzalutamide[lll] (category 2B) ▸ *HRRm* (other than BRCA1/2) ◊ Olaparib[lll] ◊ Talazoparib/enzalutamide[lll] (category 2B) • Disease State-Specific Therapy ▸ PSMA-positive metastases ◊ Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617)[ppp] ▸ Aggressive variant[nnn] ◊ Cabazitaxel/Carboplatin[ggg]	**Preferred:** • Cabazitaxel[ggg] (category 1) • Docetaxel rechallenge[ggg] **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Olaparib[lll] (category 1) ◊ Rucaparib[lll] ▸ *HRRm* (other than *BRCA1/2*) ◊ Olaparib[lll] ▸ Other FDA-approved agents for tissue agnostic indications[ggg] • Disease State-Specific Therapy ▸ PSMA-positive metastases ◊ Lu-177-PSMA-617[ppp] (category 1) ▸ Aggressive variant[nnn] ◊ Cabazitaxel/carboplatin[ggg] ▸ Palliation for symptomatic patients unable to tolerate other therapies ◊ Mitoxantrone[ggg]

Additional Options Irrespective of Prior ARPI or Prior Docetaxel (Useful in Certain Circumstances)

• Disease State-Specific Therapy ▸ Asymptomatic without visceral metastases ◊ Sipuleucel-T[ggg,ooo] ▸ Oligometastatic[r]/Oligoprogressive disease ◊ Metastasis-directed therapy[mmm] with metastatic castration-resistant prostate cancer (mCRPC) systemic therapy ▸ Symptomatic bone-predominant metastases ◊ Radium-223[mmm] (category 1)	• Molecular Biomarker-Directed Therapy ▸ MSI-High (MSI-H)/dMMR ◊ Pembrolizumab[ggg] (category 2B)

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

Footnotes on PROS-18A

limited or no benefit in switch to second ARPI

36

What to do

- Data to inform the optimal sequence for delivery of these agents in patients with metastatic CRPC is limited
- Choice of therapy is based largely on clinical considerations, which include patient preferences, ***prior treatment***, presence or absence of ***visceral disease***, ***symptoms***, and potential side effects.
- Patient and disease factors are key

37

Expanding Indications - Trials in Progress

- Saruparib + ARPI (PETRANHA) – mHSPC and mCRPC
- Talazoparib + enzalutamide in mHSPC (TALAPRO-3)
- Niraparib + abiraterone mHSPC (AMPLITUDE)
- Saruparib + ARPI in mHSPC (EvoPAR-Prostate01)

38

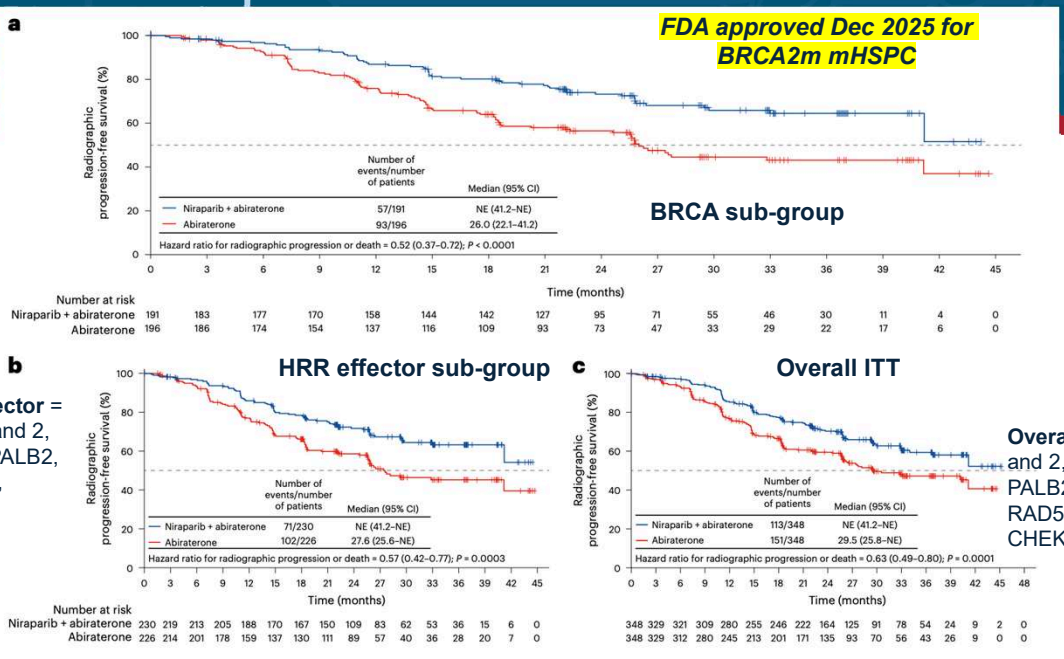
AUA2026 Washington, DC MAY 15-18

AMPLITUDE: Niraparib + Abiraterone for mHSPC

- mHSPC with no prior treatment
  - HRRm patients (somatic or germline) from AMPLITUDE, PREVALENCE, community
  - 56% BRCA1/2, 78% high volume mets, 16% prior docetaxel
- Randomized (696) 1:1 to Niraparib + abi vs. PBO + abi
- 1º endpoint – imaging-based PFS
- 2º endpoints -- OS

Nature Med 2025;31:4109

39



40

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2026
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

Table 1. PARP Inhibitors with or without ARPIs

Treatment	FDA-Approved Disease State Indication	Biomarker Pathogenic variant or mutation in gene (germline and/or somatic)	Clinical Trial
Olaparib	mCRPC that has progressed following prior treatment with enzalutamide or abiraterone.	*BRCA2, BRCA1, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L*	PROfound[1]
Rucaparib	mCRPC that has been treated with androgen receptor-directed therapy and taxane-based chemotherapy	*BRCA2, BRCA1*	TRITON2[2,3]
Olaparib/ Abiraterone	mCRPC	*BRCA2, BRCA1*	PROPel[4]
Talazoparib/ Enzalutamide	mCRPC	*BRCA2, BRCA1, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C*	TALAPRO-2[5,6]
Niraparib/ Abiraterone	mCRPC mHSPC (BRCA2m)	*BRCA2, BRCA1*	MAGNITUDE[7,8]

AMPLITUDE

41

National Comprehensive Cancer Network®

PARP Summary

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[g,aa,iii,jjj]

Pre-ARPI[aa,kkk]	Post-ARPI[kkk]/Pre-Docetaxel[aa]	Post-ARPI[kkk]/Post-Docetaxel[aa]
Preferred: • Abiraterone (category 1) • Enzalutamide (category 1) **Other Recommended:** • Docetaxel[ggg] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Niraparib/abiraterone[III] (category 1) ◊ Olaparib/abiraterone[III] (category 1) ◊ Talazoparib/enzalutamide[III] (category 1) ▸ *HRRm* (other than BRCA1/2) ◊ Talazoparib/enzalutamide[III] (category 1) • Disease State-Specific Therapy ▸ Bone metastases ◊ Radium-223[nnn]/enzalutamide	**Preferred:** • Docetaxel[ggg] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Olaparib[III] (category 1, preferred) ◊ Rucaparib[III] (category 1, preferred) ◊ Niraparib/abiraterone[III] (category 2B) ◊ Talazoparib/enzalutamide[III] (category 2B) ▸ *HRRm* (other than BRCA1/2) ◊ Olaparib[III] ◊ Talazoparib/enzalutamide[III] (category 2B) • Disease State-Specific Therapy ▸ PSMA-positive metastases ◊ Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617)[ppp] ▸ Aggressive variant[hhh] ◊ Cabazitaxel/Carboplatin[ggg]	**Preferred:** • Cabazitaxel[ggg] (category 1) • Docetaxel rechallenge[ggg] **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Olaparib[III] (category 1) ◊ Rucaparib[III] ▸ *HRRm* (other than *BRCA1/2*) ◊ Olaparib[III] ▸ Other FDA-approved agents for tissue agnostic indications[ggg] • Disease State-Specific Therapy ▸ PSMA-positive metastases ◊ Lu-177-PSMA-617[ppp] (category 1) ▸ Aggressive variant[hhh] ◊ Cabazitaxel/carboplatin[ggg] ▸ Palliation for symptomatic patients unable to tolerate other therapies ◊ Mitoxantrone[ggg]

42

AUA 2026 Washington, DC MAY 15-18

Microsatellite Instability (MSI)

- Mismatch repair (MMR)
  - Post-replicative, single-strand repair mechanism
  - Recognizes and reverses DNA base mismatches, insertions, deletions
- MSI is result of broken MMR system
  - Chemotherapy resistance
  - Immunotherapy sensitivity
- ~ 3% of patients with APC

JAMA Oncol 2019;5:471

43

AUA 2026 Washington, DC MAY 15-18

Microsatellite Instability (MSI)

- Limited evidence of activity in CRPC
- Next gen sequencing assay preferred
- FDA approved Pembrolizumab 2017
  - MSI-H or dMMR histology
  - Progressed on prior treatment
  - No alternatives

36. In patients with mismatch repair deficient or microsatellite instability-high (MSI-H) mCRPC, clinicians should offer pembrolizumab. (*Moderate Recommendation; Evidence Level: Grade C*)

Clin Ca Res 2019;25:3753
J Urol 2023;209:1082

44

AUA 2026 Washington, DC MAY 15-18

FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors

- Adult, pediatric patients
- Unresectable or metastatic
- MDI-H or dMMR solid tumors
- Progressed following prior treatment without alternative treatments
- Shared tumor biology across different tumors based on ORR
- ***First time the FDA has approved a cancer treatment for an indication based on common biomarker rather than primary site of origin***

Clin Cancer Res 2019;25:3753

45

AUA 2026 Washington, DC MAY 15-18

FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors

Table 1. MSI-H/dMMR trials

Clinical trial	Design	*N*	Testing for MSI-H/dMMR	Regimen	Prior therapy
KN-016	– Investigator initiated – Prospective, single-arm – Colorectal cancer and non-colorectal cancer cohorts	28 colorectal cancer 30 non-colorectal cancer	Local PCR or IHC	10 mg/kg every 2 weeks	– Colorectal cancer: ≥2 prior regimens – Non-colorectal cancer: ≥1 prior regimen
KN-164	– Merck initiated – Prospective, single-arm – Patients with colorectal cancer	61	Local PCR or IHC	200 mg every 3 weeks	Prior FP, oxaliplatin, and irinotecan ± anti-VEGF/EGFR biologic
KN-012	– Merck initiated – Patients retrospectively identified as MSI-H/dMMR in a multicohort trial – PD-L1–positive cancers	6[a]	Central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KN-028	– Merck initiated – Patients retrospectively identified as MSI-H/dMMR in a multicohort trial – PD-L1–positive cancers	5[a]	Central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KN-158	– Merck initiated – Prospective cohort of patients MSI-H/dMMR non-colorectal cancer or – Retrospective identification of MSI-H in patients with 1 of 10 rare tumor types	19[a]	Local PCR or IHC (central PCR for patients in rare tumor non-colorectal cancer cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		149			

Clin Cancer Res 2019;25:3753

46

AUA 2026 Washington, DC MAY 15-18

Thank you

Questions?

kristen.r.scarpato@vumc.org

47

AUA 2026 Washington, DC MAY 15-18

COMPLIMENTARY DINNER SYMPOSIUM

AUA2026 Spotlight: PARP-Inhibitor Combination Treatments for the Urologic Care Team

May 14 | 5:30-6:30 p.m. | Ballroom B

Join expert Faculty for a discussion on PARP-inhibitors in the rapidly changing metastatic prostate cancer (mPC) landscape!

48