MINNESOTA
SOCIETY OF CLINICAL ONCOLOGY

MSCO 2022 FALL CONFERENCE

Wed, September 14, 2022
5:30 PM to 8:30 PM (Central Daylight Time)

Minneapolis, MN

PARPi, PD1i, Lu-PSMA and Other New Therapies for Advanced Prostate Cancer

Emmanuel S. Antonarakis, M.D.
Clark Endowed Professor of Medicine
Division of HOT, University of Minnesota
Associate Director of Translation, Masonic Cancer Center

Disclosures

- **Consultant/advisor for:** Janssen, Astellas, Sanofi, Dendreon, Bayer, BMS, Amgen, ESSA, Constellation, Blue Earth, Exact Sciences, Invitae, Curium, Pfizer, Merck, AstraZeneca, Clovis, Eli Lilly

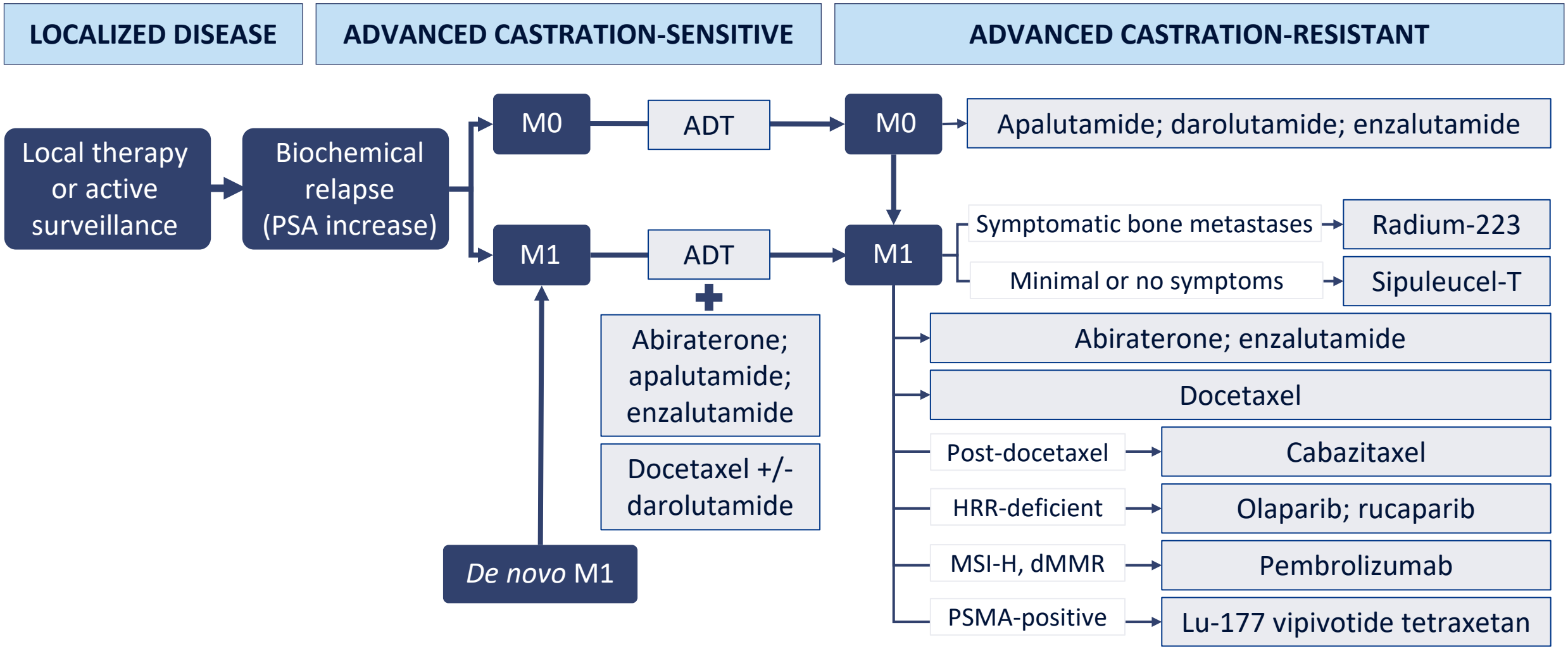
- **Grant/research support from:** Janssen, J&J, Sanofi, BMS, Pfizer, AstraZeneca, Novartis, Curium, Constellation, ESSA, Celgene, Merck, Bayer, Clovis

- **Inventions/patents:** Co-inventor of AR-V7 technology licensed to Qiagen

Outline

- Current treatment landscape for mCRPC
- PARP inhibitors for HRR-deficient PCa
- PD-1 inhibitors for MMR-deficient PCa
- PSMA-targeted therapies (Lu-PSMA)
- B7-H3–targeted therapies
- Conclusions

Treatment Landscape for Prostate Ca



PARP inhibitors for HRR-deficient mCRPC

PARP inhibitors for HRR-mutated mCRPC

OLAPARIB: In **May 2020,** based on data from the **PROfound study,** the FDA granted **full approval olaparib** for the treatment of patients with deleterious or suspected **germline or somatic HRR[a] gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone[1,b]**

[a]***BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L***.
[b]Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.

1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.

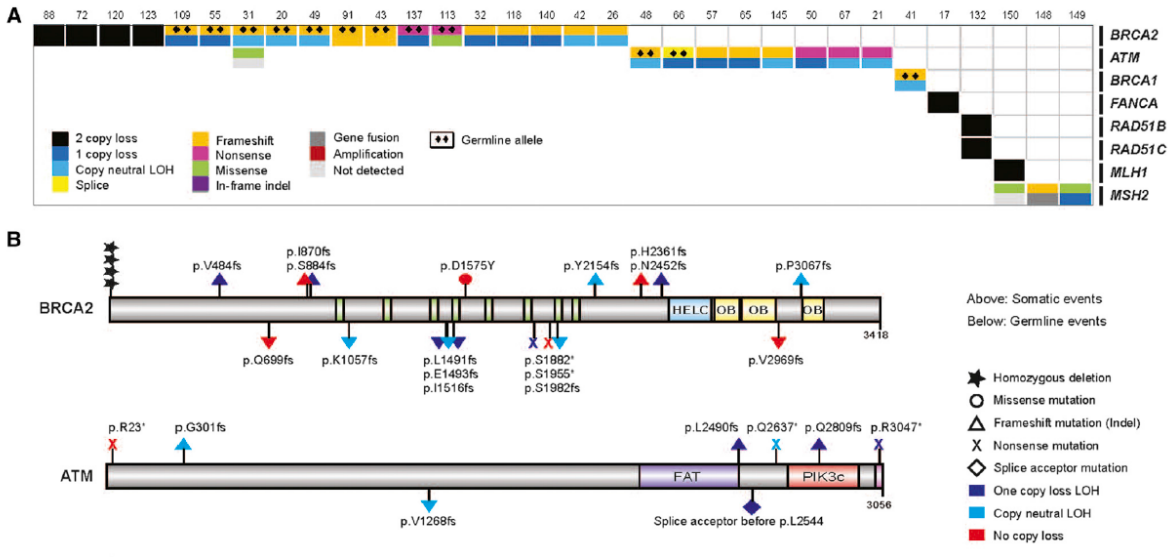
RUCAPARIB: In **May 2020,** based on data from the **TRITON2 study,** the FDA granted **accelerated approval to rucaparib** for the treatment of patients with **deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC, who have been treated with an androgen receptor-directed therapy and a taxane-based chemotherapy.[1]**

1. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate.

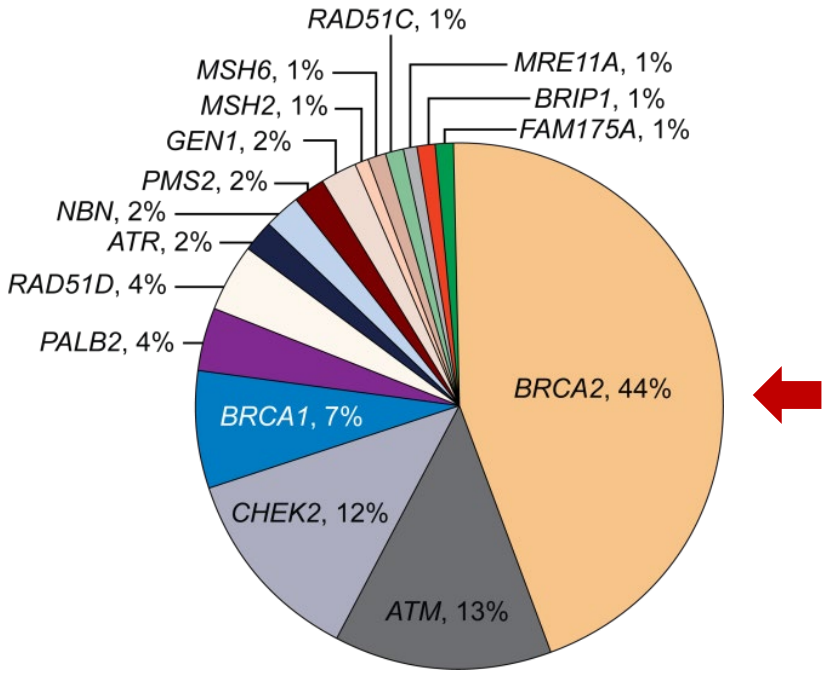
HRR Genes and Metastatic Prostate Cancer

Somatic

- **23%** of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations **increases in metastatic disease vs. localized disease**



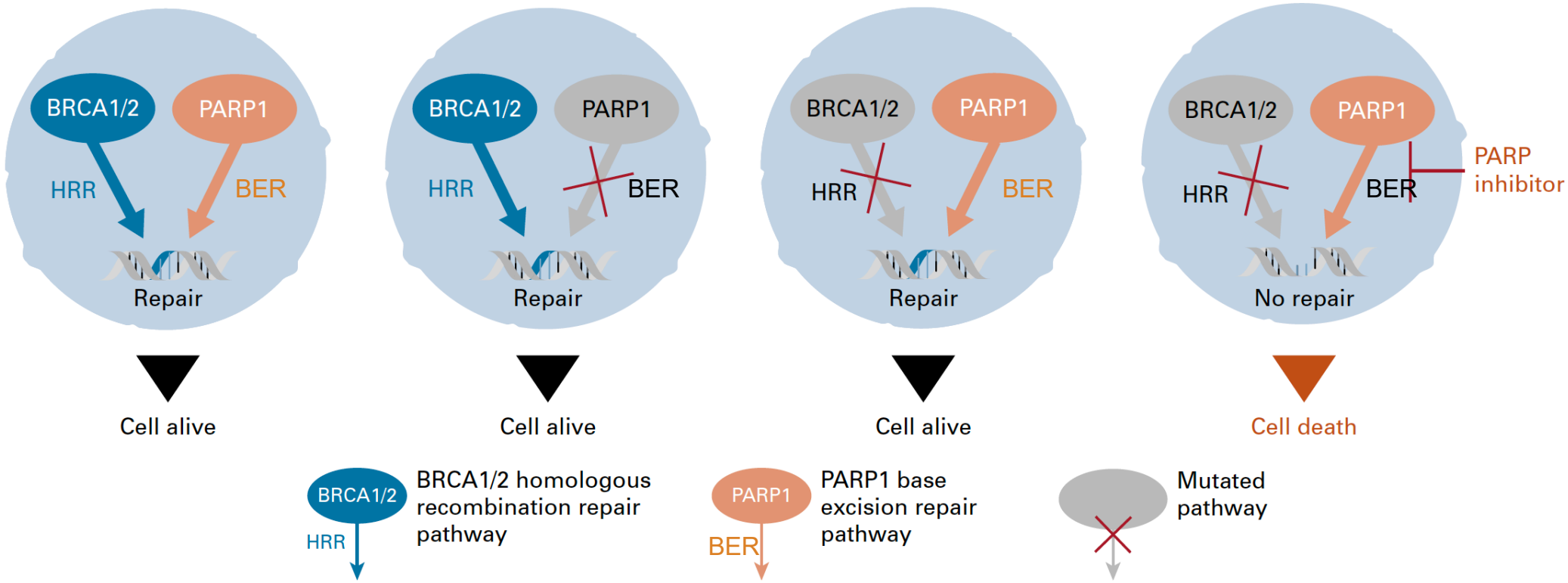
Germline



- **12%** of men with metastatic prostate cancer have a germline DNA repair defect

1. Robinson D, et al. Cell. 2015;161:1215-28. **2.** Pritchard CC, et al. N Engl J Med. 2016;375:443-53.

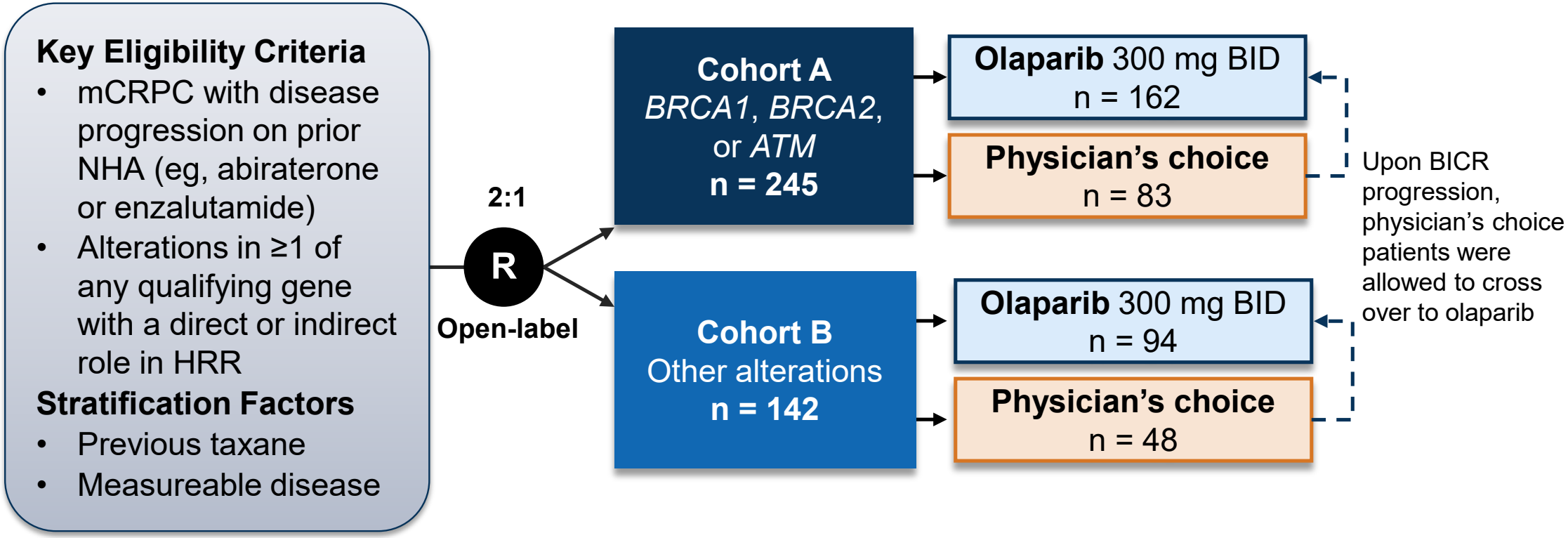
PARP Inhibition: “Synthetic Lethality”



PARP is required for single-strand break repair (e.g. via BER)

MOA – inhibiting SSB/BER is synthetic lethal with HRD

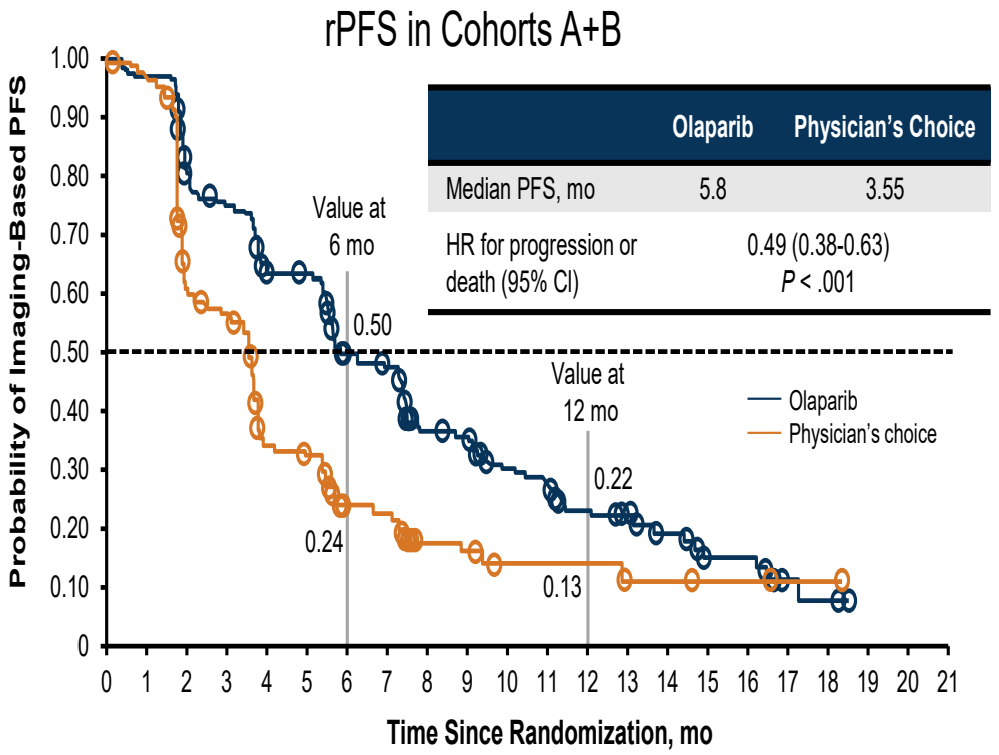
Olaparib: PROfound, Randomized Phase-3 Study



- Primary endpoint: rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)
- Key secondary endpoints: rPFS (cohorts A+B); confirmed radiographic ORR in cohort A; time to pain progression in cohort A; OS in cohort A

1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102.

PROfound: rPFS and OS in whole population (A+B)

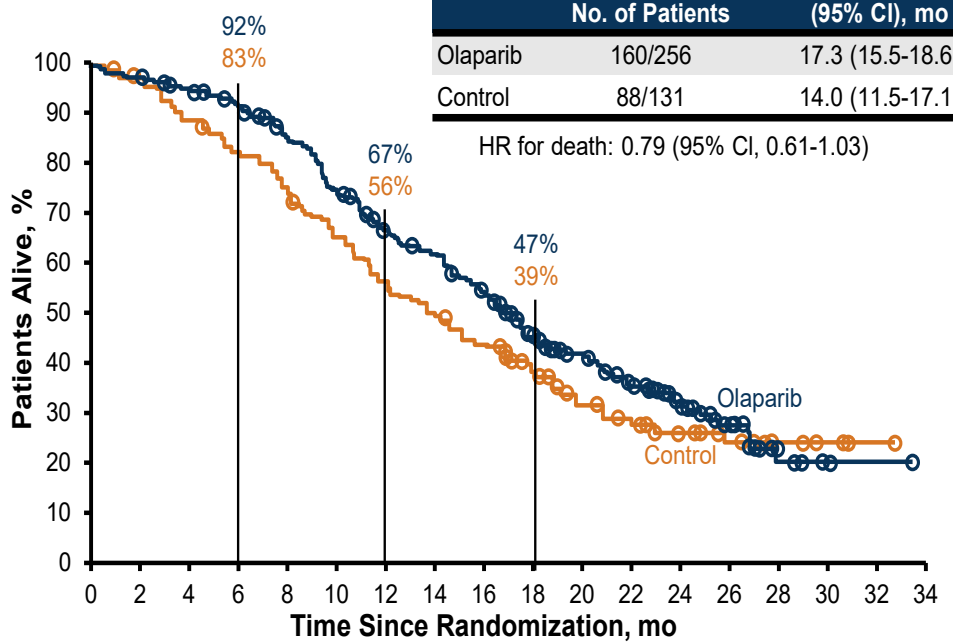


	Olaparib	Physician's Choice
Median PFS, mo	5.8	3.55
HR for progression or death (95% CI)	0.49 (0.38-0.63) *P* < .001	

No. at Risk

Olaparib	256	239	188	176	145	143	106	100	67	63	48	43	31	28	21	11	11	3	2	0	0	0
Control	131	123	73	67	38	35	20	19	9	8	5	5	5	3	3	2	2	1	1	0	0	0

OS in the Overall Population (Cohorts A + B)



	No. of Deaths/ No. of Patients	Median OS (95% CI), mo
Olaparib	160/256	17.3 (15.5-18.6)
Control	88/131	14.0 (11.5-17.1)

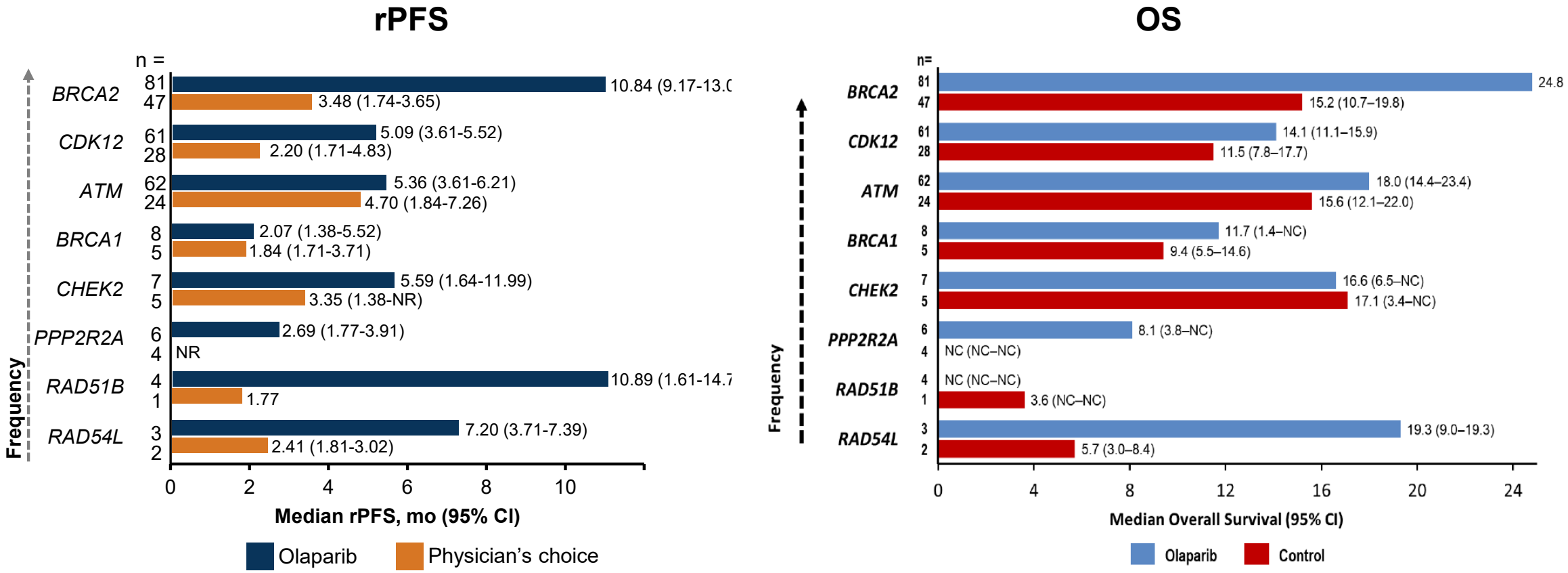
HR for death: 0.79 (95% CI, 0.61-1.03)

No. at Risk

Olaparib	256	249	240	228	209	182	157	146	126	96	73	56	39	22	7	2	1	0		
Control	131	125	115	106	96	83	71	63	55	37	27	22	15	11	6	3	1	0		

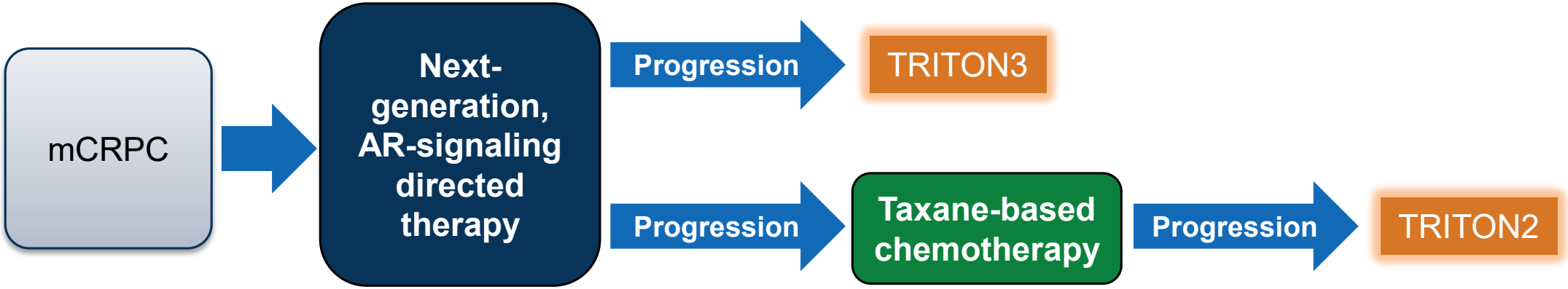
1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102. 2. Hussain M et al. *N Engl J Med*. 2020.

PROfound: Gene-by-gene, rPFS and OS analyses



1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102. 2. Hussain M et al. *N Engl J Med*. 2020.

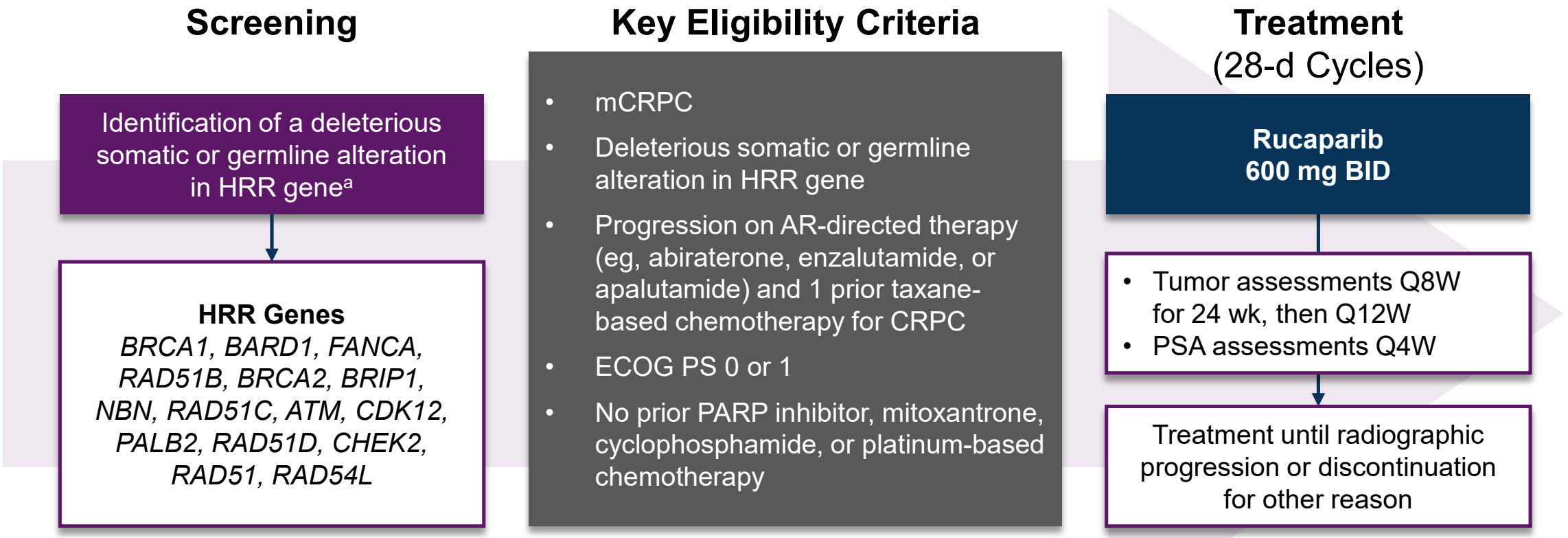
Rucaparib: TRITON2 and TRITON3 studies



HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L)*

1. Abida W et al. *Annals Onc*. 2018:29(Suppl 8):viii271-viii302.

TRITON2: Study design



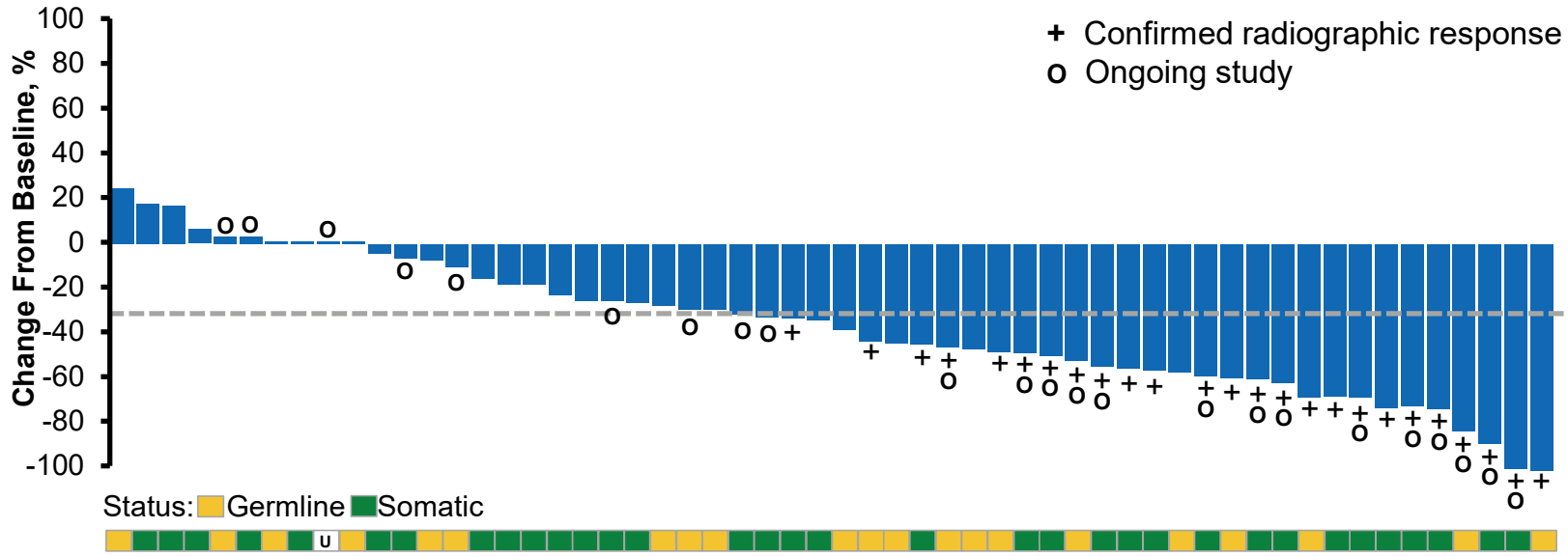
- **Primary endpoints:** **Confirmed ORR** per modified RECIST/PCWG3 by central assessment (patients with measurable disease at baseline), confirmed PSA response (≥50% decrease) rate (patients with no measurable disease at baseline)

1. Abida W et al. *Annals Onc*. 2018:29(Suppl 8):viii271-viii302.

TRITON2: Objective response rate (ORR)

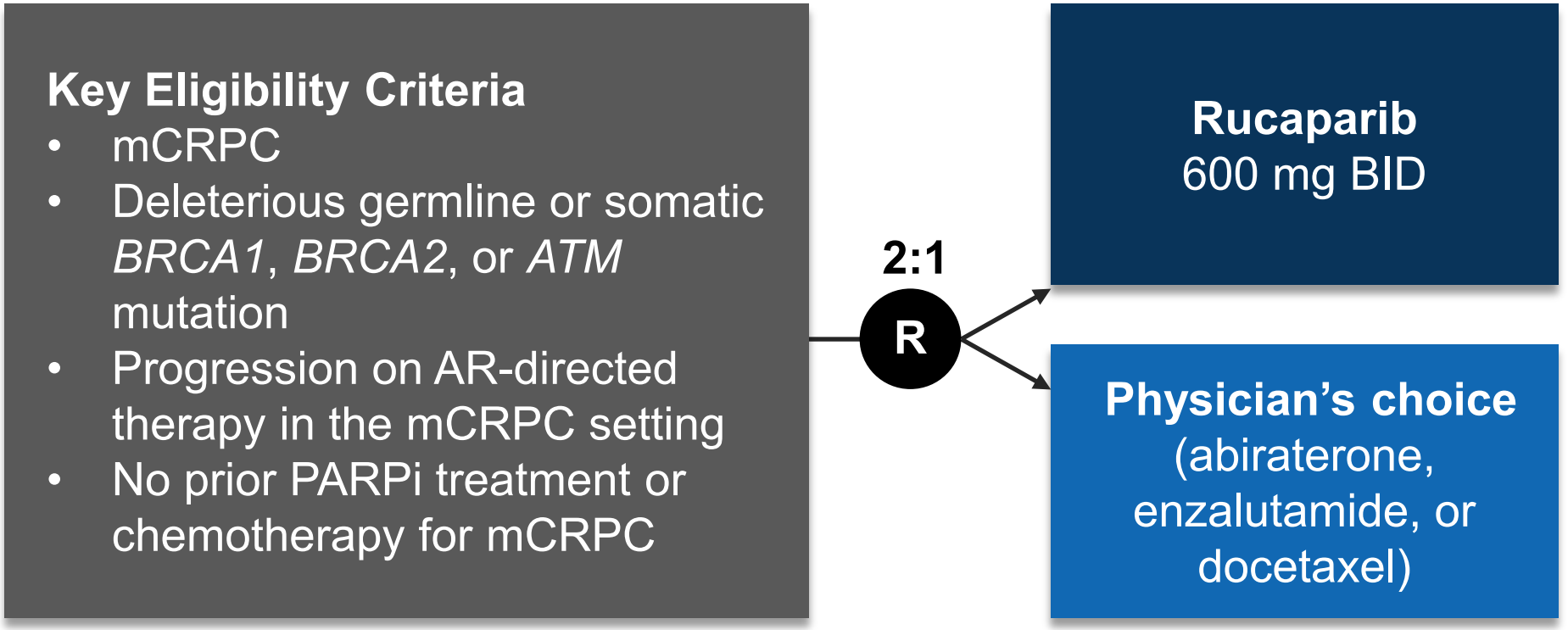
	DDR Gene				
	BRCA 1/2 (n = 57)	*ATM* (n = 21)	*CDK12* (n = 9)	*CHEK2* (n = 5)	Other (n = 13)
ORR, n (%) [95% CI]	25 (43.9) [30.7-57.6]	2 (9.5) [1.2-30.4]	0 [0.0-33.6]	0 [0.0-52.2]	5 (38.5) [13.9-68.4]
CR, n (%)	3 (5.3)	0	0	0	1 (7.7)
PR, n (%)	22 (38.6)	2 (9.5)	0	0	4 (30.8)
SD, n (%)	26 (45.6)	10 (47.6)	5 (55.6)	3 (60.0)	6 (46.2)
PD, n (%)	5 (8.8)	8 (38.1)	3 (33.3)	2 (40.0)	1 (7.7)
N/E, n (%)	1 (1.8)	1 (4.8)	1 (11.1)	0	1 (7.7)

Best Change From Baseline in Sum of Target Lesion in Patients With *BRCA 1/2* Alteration (N = 56)



1. Abida W et al. ESMO 2019. Abstract 846PD. 2. Abida W et al. *Clin Cancer Res*. 2020 Feb 21

TRITON3: Study design



- **Primary endpoint:** radiographic PFS

1. https://clinicaltrials.gov/ct2/show/NCT02975934.

Ongoing Studies of PARPi-Based Combinations

NCT03732820: Phase 3 Study of Olaparib + Abiraterone vs Abiraterone in mCRPC
(PROpel)

NCT03748641: Phase 3 Study of Niraparib + Abiraterone vs Abiraterone in mCRPC
(MAGNITUDE)

NCT03395197: Phase 3 Study of Talazoparib + Enzalutamide vs Enzalutamide in mCRPC
(TALAPRO-2)

NCT04497844: Phase 3 Study of Abiraterone ± Niraparib in HRR mHSPC
(AMPLITUDE)

NCT04455750: Phase 3 Study of Enzalutamide ± Rucaparib in mCRPC
(CASPAR)

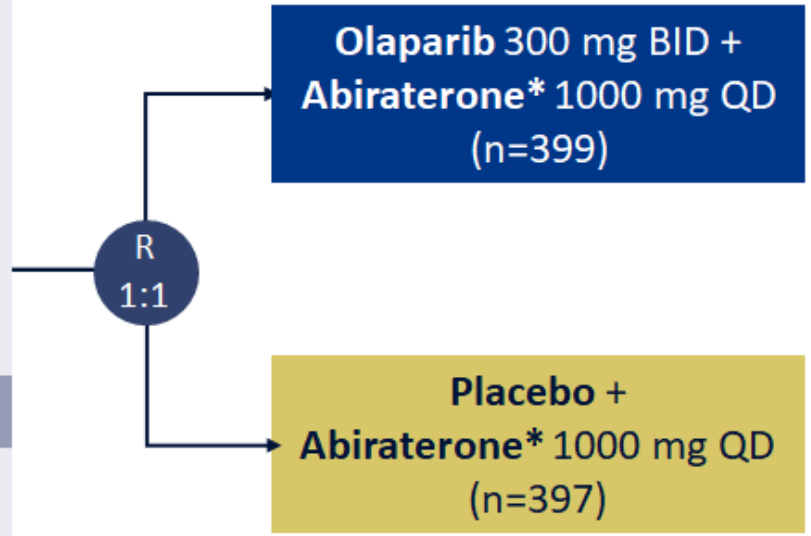
PROpel: Phase III Trial of Abiraterone +/– Olaparib

Patient population

- mCRPC
- Docetaxel for mCSPC allowed
- No prior abiraterone
- Other NHT allowed if stopped ≥12 months prior to enrollment
- Ongoing ADT
- ECOG PS 0–1

Stratification factors

- Site of distant metastases (bone only vs visceral vs other)
- Prior taxane for mCSPC



Primary endpoint

rPFS or death by investigator assessment

Key secondary endpoint

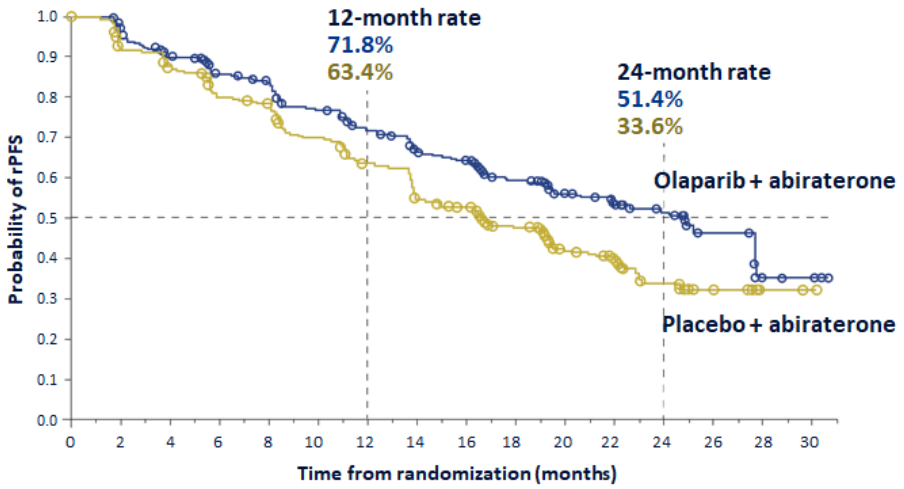
- OS

Additional endpoints

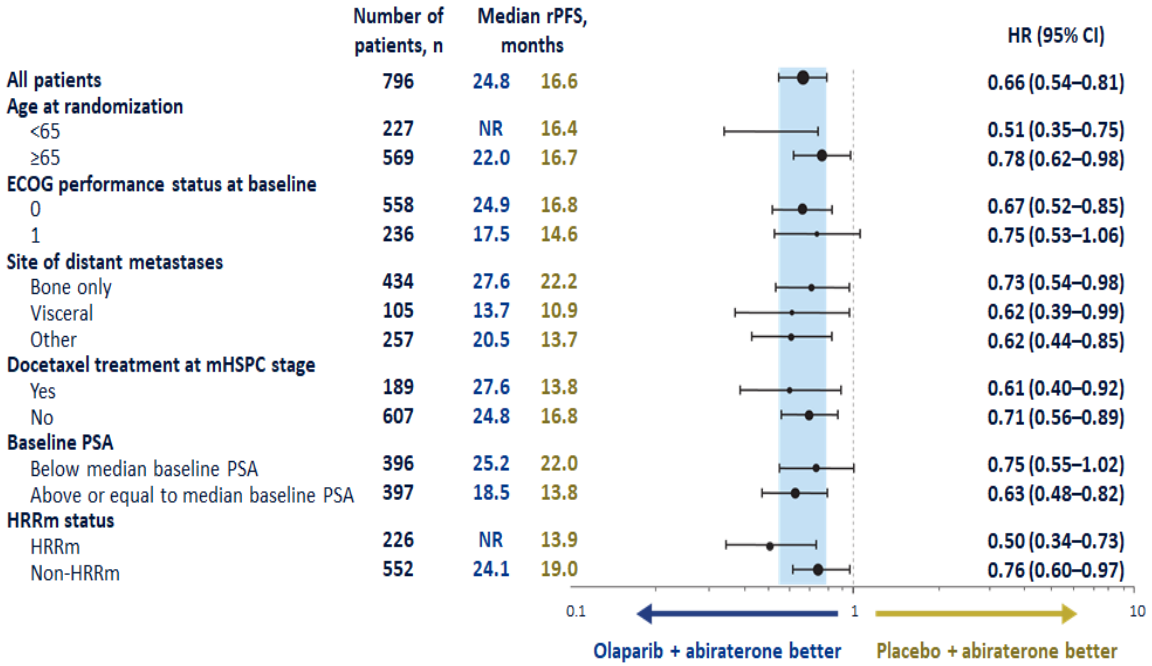
- TFST
- PFS2
- ORR
- HRR mutation prevalence (tested retrospectively)
- HRQOL
- Safety and tolerability

*Plus prednisone or prednisolone 5 mg BID

PROpel: Radiographic progression-free survival



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
rPFS by investigator assessment		
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS, months	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	
rPFS by blinded independent central review		
HR (95% CI)	0.61 (0.49–0.74); *P*<0.0001	



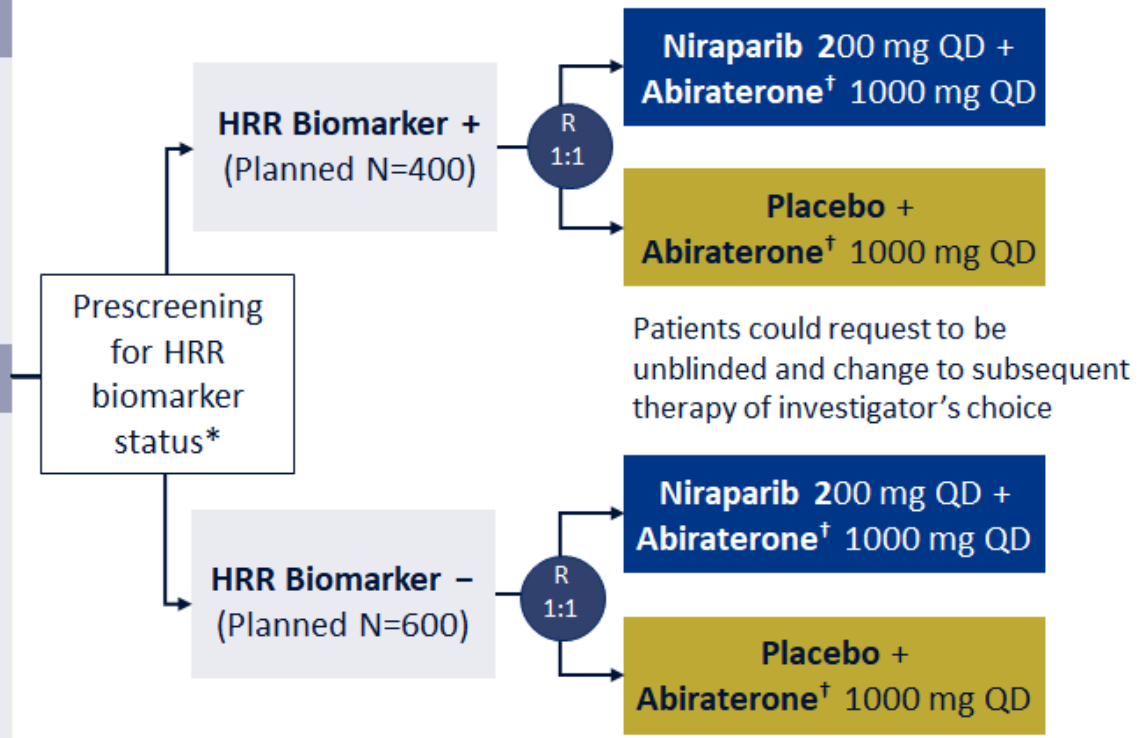
Magnitude: Phase III Trial of Abi +/– Niraparib

Patient population

- mCRPC
- ≤4 months prior abiraterone for mCRPC allowed
- ECOG PS 0–1
- BPI-SF worst pain score ≤3

Stratification factors

- Prior taxane for mCSPC
- Prior NHT for nmCRPC or mCSPC
- Prior abiraterone for mCRPC
- *BRCA1/2* vs other HRR gene alterations (HRR biomarker+ cohort only)



Patients could request to be unblinded and change to subsequent therapy of investigator's choice

Primary endpoint

rPFS by central review

Key secondary endpoints

- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

Other prespecified endpoints

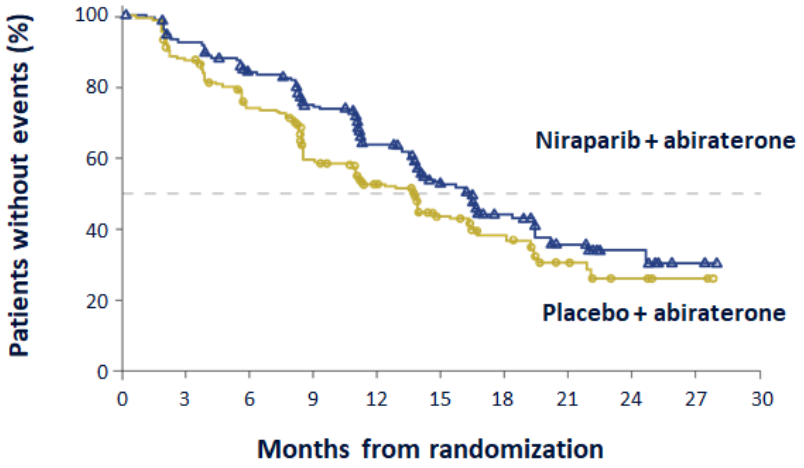
- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

*HRR gene panel: ***ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2***

†Plus prednisone 10 mg daily

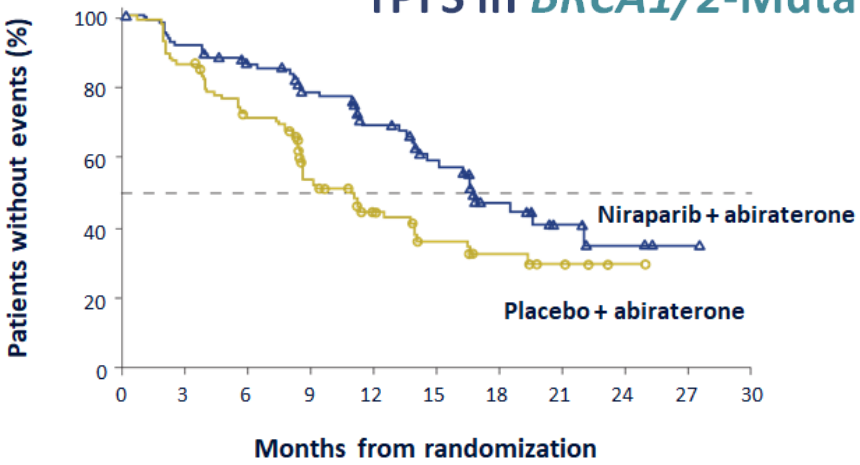
Magnitude: Radiographic progression-free survival

rPFS in All HRR BM+ Cohort



	Niraparib + abiraterone (n=212)	Placebo + abiraterone (n=211)
rPFS by central review		
Median rPFS, months	16.5	13.7
HR (95% CI)	0.73 (0.56–0.96); *P*=0.0217	
rPFS assessed by investigator		
Median rPFS, months	19.0	13.9
HR (95% CI)	0.64 (0.49–0.86); *P*=0.0022	

rPFS in *BRCA1/2*-Mutated Group



	Niraparib + abiraterone (n=113)	Placebo + abiraterone (n=112)
rPFS by central review		
Median rPFS, months	16.6	10.9
HR (95% CI)	0.53 (0.36–0.79); *P*=0.0014	
rPFS assessed by investigator		
Median rPFS, months	19.3	12.4
HR (95% CI)	0.50 (0.33–0.75); *P*=0.0006	

CASPAR: Phase III of Enza +/– Rucaparib

Arpit Rao, MD

Patient population

- mCRPC with progression per PCWG3 guidelines
- No prior treatment for CRPC
- Prior abiraterone, darolutamide, or apalutamide for nmCRPC/mHSPC allowed
- ECOG PS 0–2
- No significant uncontrolled comorbidity or medication with drug-drug interactions with either study drug

Stratification factors

- HRR status by central testing of archival tumor tissue prior to treatment

R 1:1

Rucaparib 600 mg BID + **Enzalutamide** 160 mg QD (n=492)

All patients will receive ADT (surgical or medical in 28-day cycles)

Placebo + **Enzalutamide** 160 mg QD (n=492)

Estimated primary completion: May 2023

Co-primary endpoints

- rPFS
- OS

Key secondary endpoints

- rPFS and OS in patients with or without pathogenic mutations in *BRCA1*, *BRCA2*, or *PALB2*
- Adverse events
- ORR and DOR
- PSA response rate
- QOL (FACT-P; BPI-SF; EQ-5D-5L)

Key correlative endpoint

- Concordance between tissue and plasma ctDNA-based HRR testing

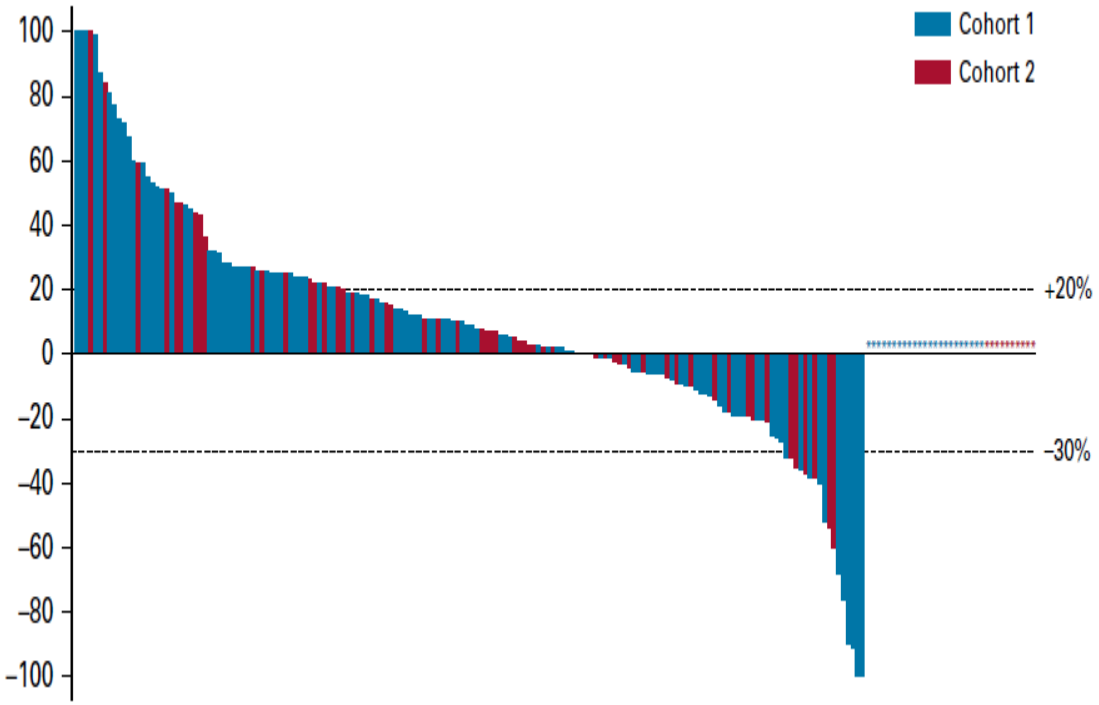
PARP Inhibitors: Conclusions

- Olaparib and Rucaparib are both FDA-approved for mCRPC
- Niraparib and Talazoparib are in development
- No PARPi-based combinations are yet FDA-approved in PCa
- PARP inhibitors:
  - ❑ Work best for *BRCA2, BRCA1* and *PALB2*
  - ❑ More limited activity in *ATM, CDK12, CHEK2*
  - ❑ Need more data for *FANCA/L, BRIP1, BARD1, NBN, RAD51/54*

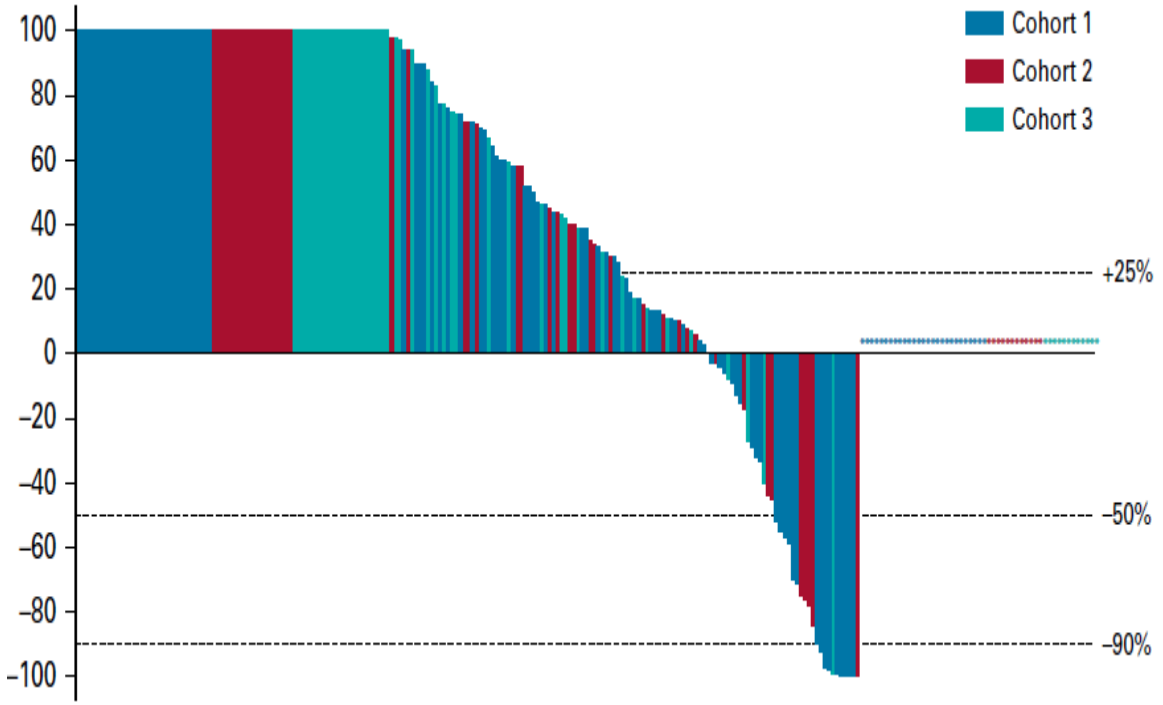
PD-1 inhibitors for MMR-deficient mCRPC

Immunotherapy for mCRPC: Anti-PD1 (KeyNote-199)

ORR: 5%



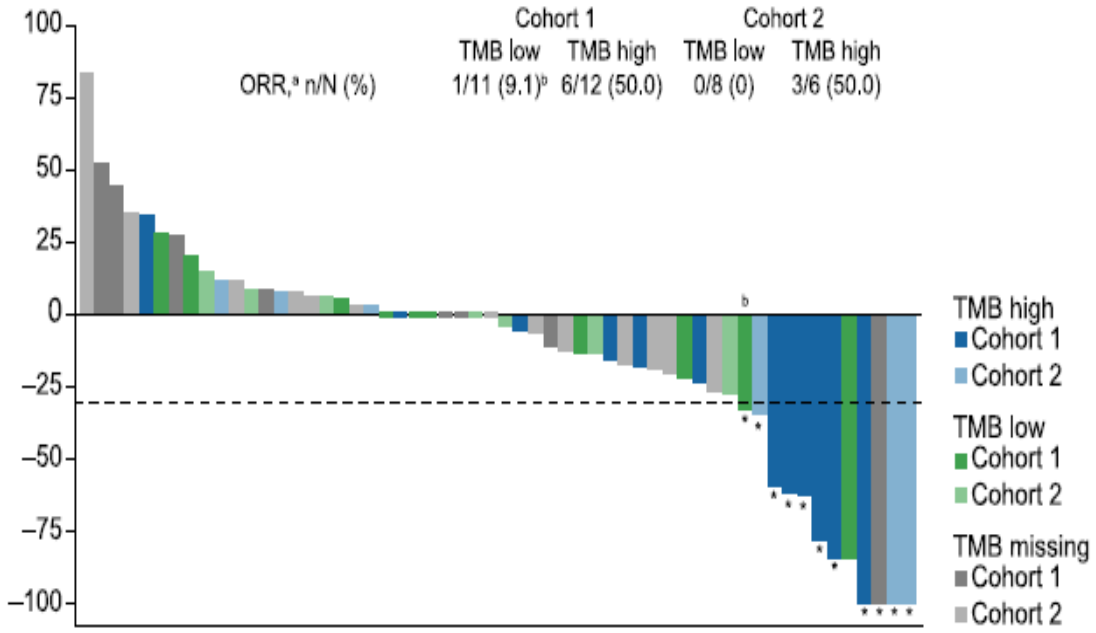
PSA_{50} Response: 7%



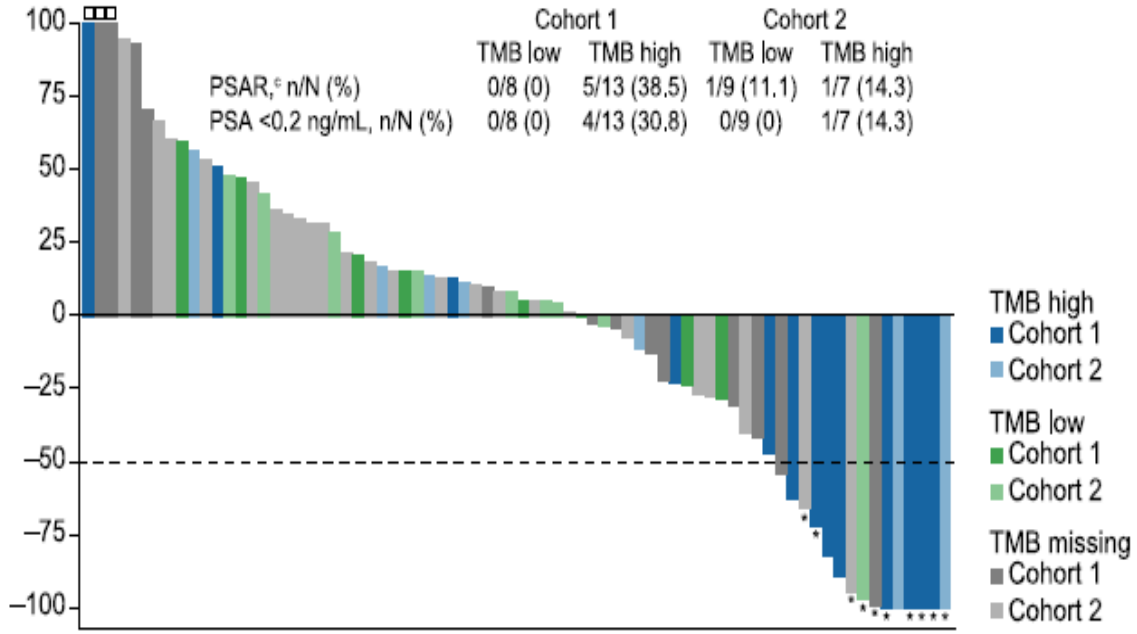
Antonarakis ES, et al. *J Clin Oncol* 2020; 38: 395-405.

Immunotherapy: Anti-PD1 + CTLA4 (CheckMate 650)

ORR: 18%



PSA_{50} Response: 14%



Sharma P, et al. *Cancer Cell* 2020; 38: 489-499.

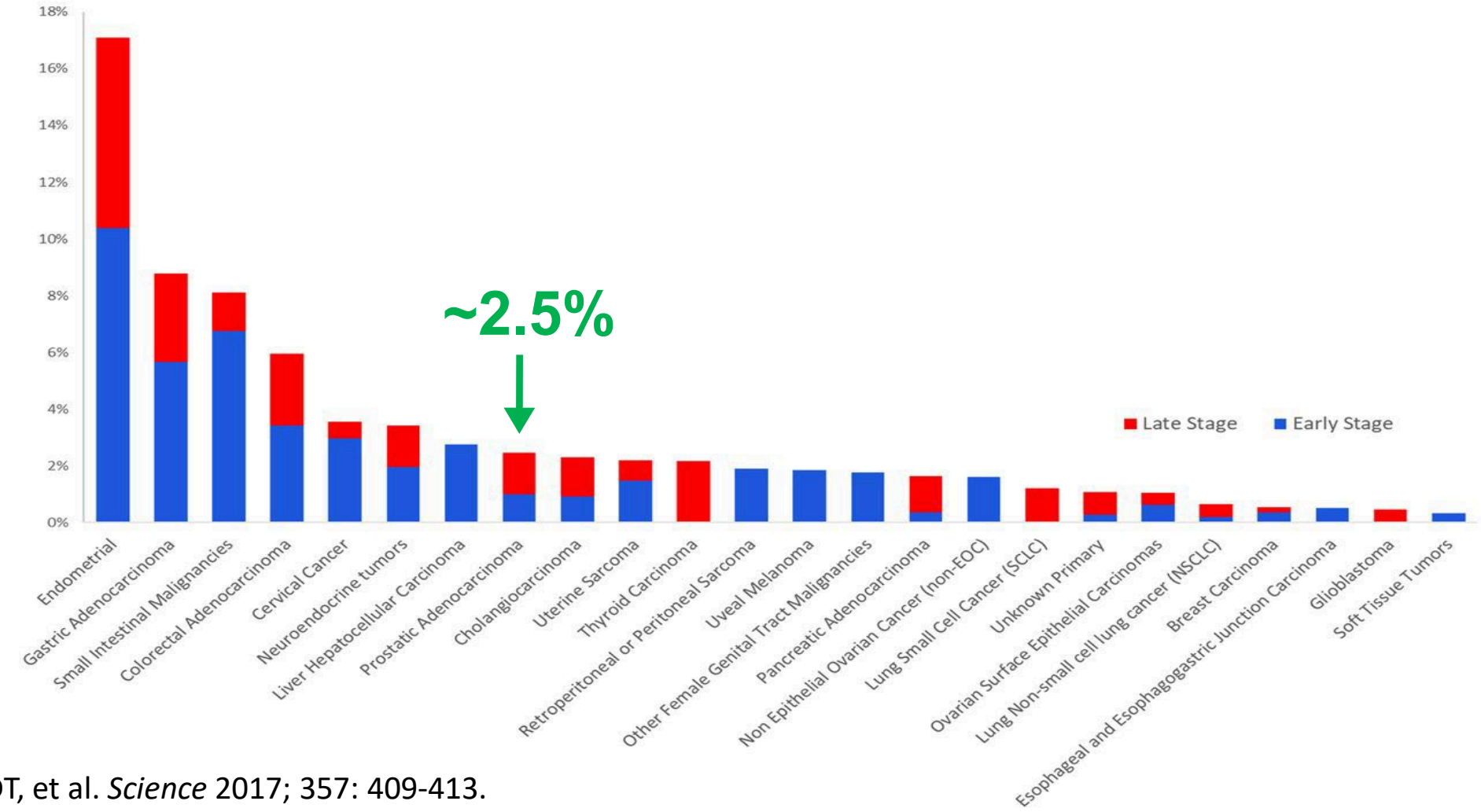
Pembrolizumab for MSI-high (dMMR) cancers

FDA Approves Merck's KEYTRUDA® (pembrolizumab) for Adult and Pediatric Patients with Unresectable or Metastatic, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient Cancer

- **Pembrolizumab for Microsatellite Instability-High (MSI-H) Cancer**
- "Treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair (MMR)-deficient:
  - Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
  - Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan"
- Dosage and administration (MSI-H cancers): **200 mg IV every 3 weeks**

FDA Package Insert, 5/23/2017

MMR-deficiency across 12 thousand cancers



Le DT, et al. *Science* 2017; 357: 409-413.

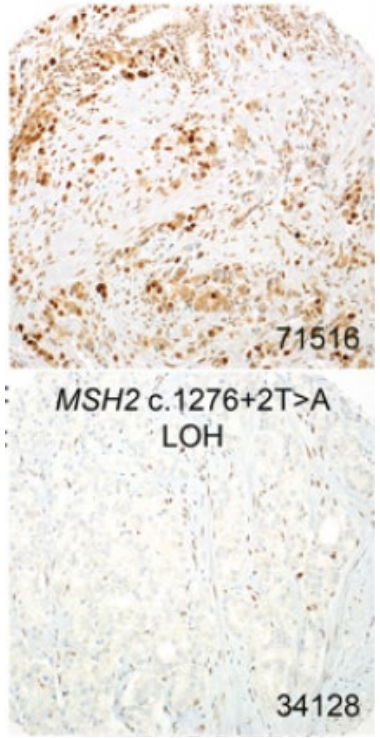
dMMR correlates with high Gleason grade

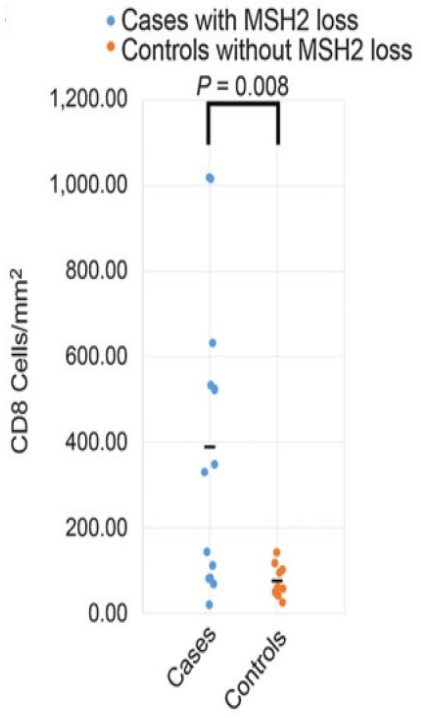
Personalized Medicine and Imaging

Clinical Cancer Research

MSH2 Loss in Primary Prostate Cancer

Liana B. Guedes[1], Emmanuel S. Antonarakis[2], Michael T. Schweizer[3], Nooshin Mirkheshti[1], Fawaz Almutairi[1], Jong Chul Park[2], Stephanie Glavaris[1], Jessica Hicks[1], Mario A. Eisenberger[2], Angelo M. De Marzo[1,2,4], Jonathan I. Epstein[1,2,4], William B. Isaacs[4], James R. Eshleman[1,2], Colin C. Pritchard[5], and Tamara L. Lotan[1,2]

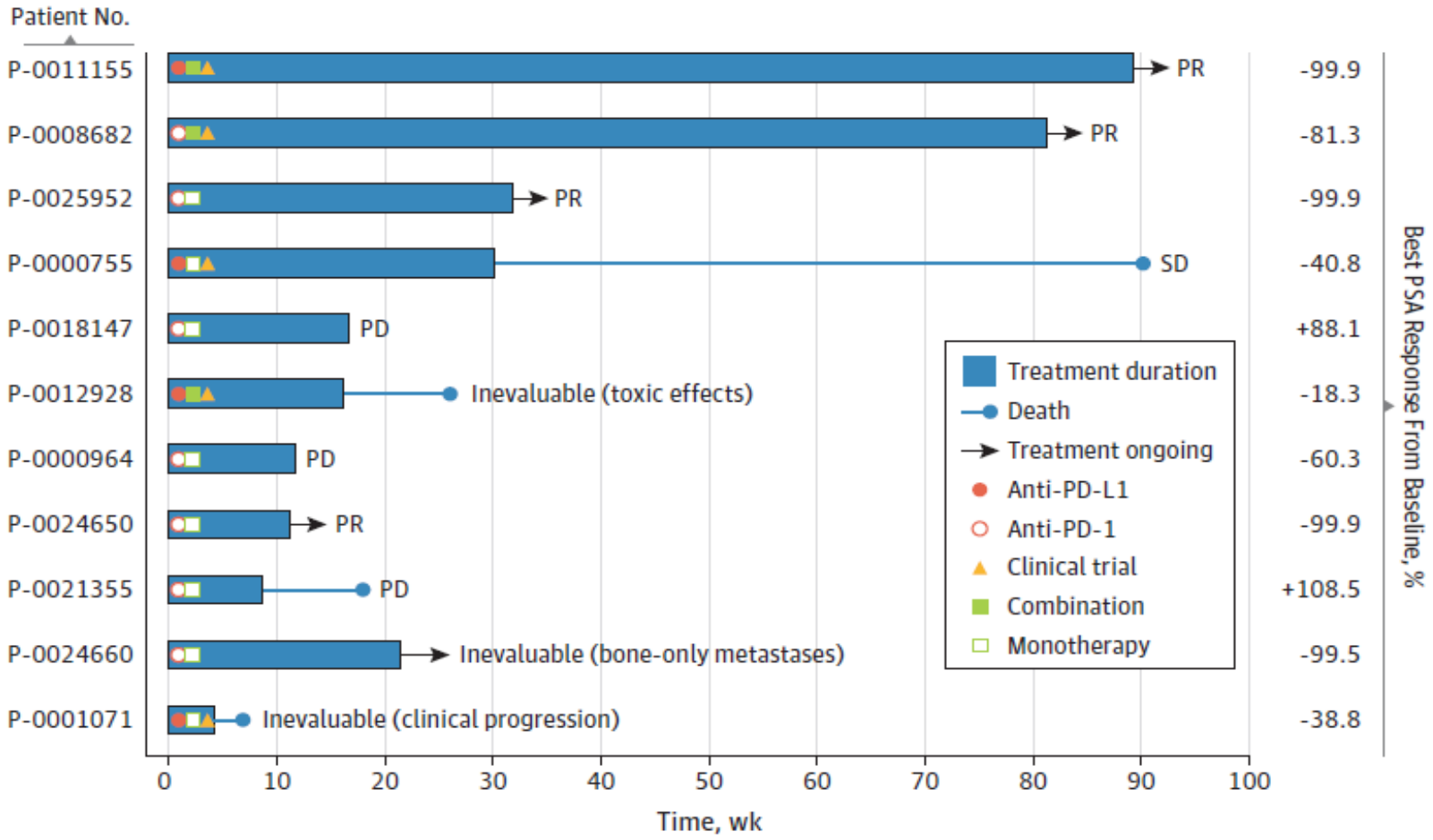




- **1.2%** (14/1176) of primary PCa had MSH2 protein loss
- Pathology and MSH2 loss:
  - Primary Gleason pattern 5 enriched for MSH2 loss: **8%** (7/91) vs. <1% (5/1042), *P*<0.0001

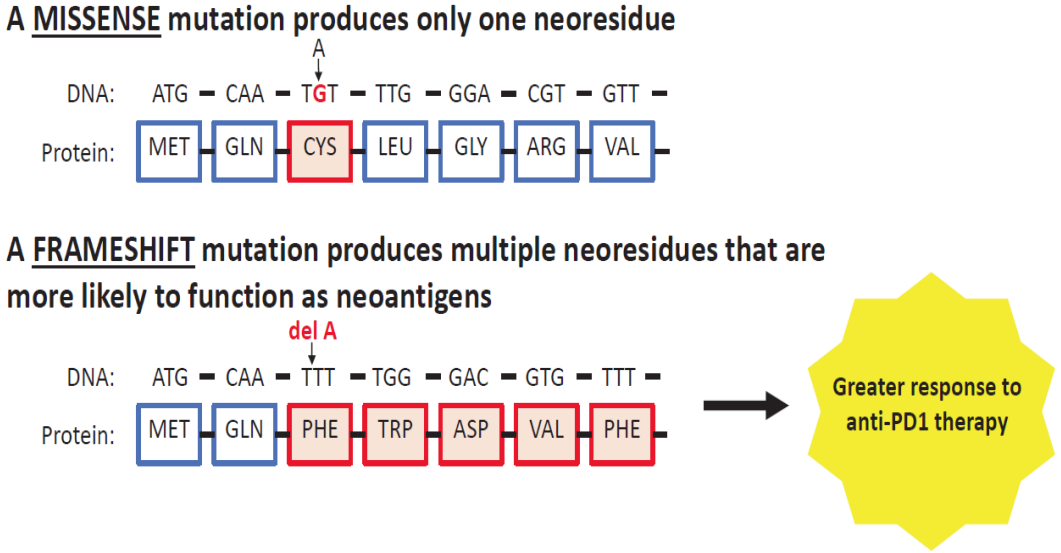
Guedes LB, Antonarakis ES, et al. *Clin Cancer Res* 2017; 23: 6863.

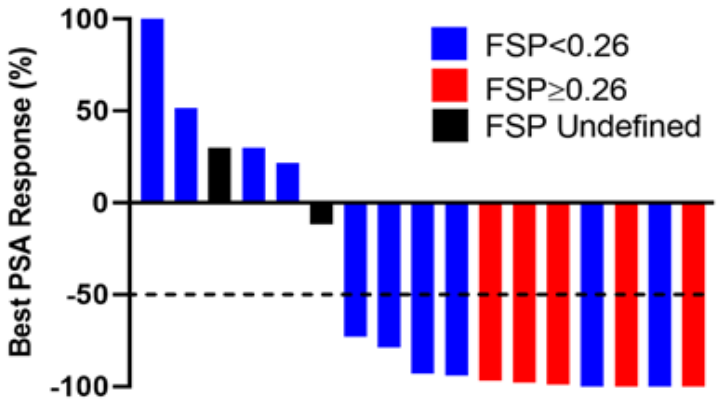
MSI-hi (dMMR) prostate cancers and anti-PD1



Abida W, et al. *JAMA Oncol* 2019; 5: 471-478.

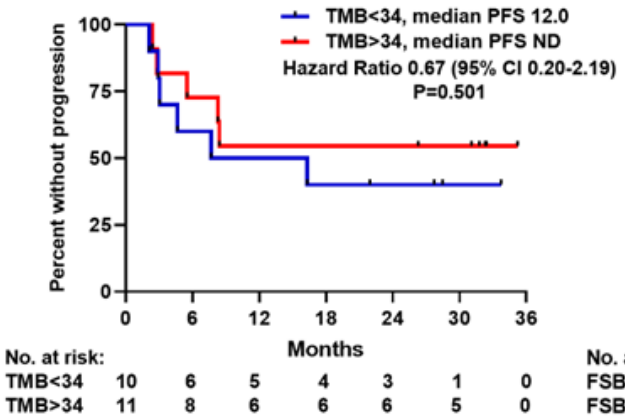
Frameshift mutations and dMMR mCRPC

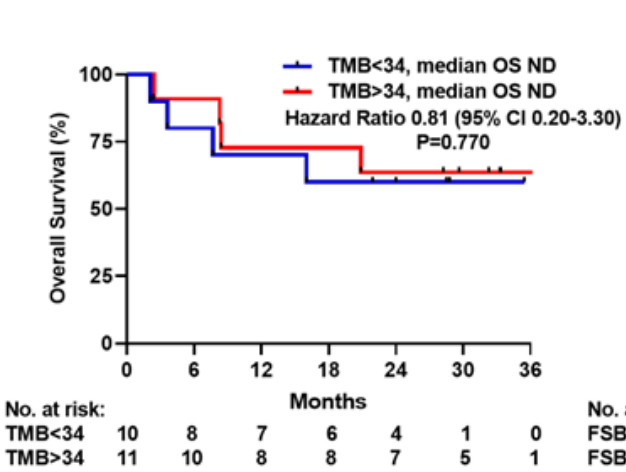




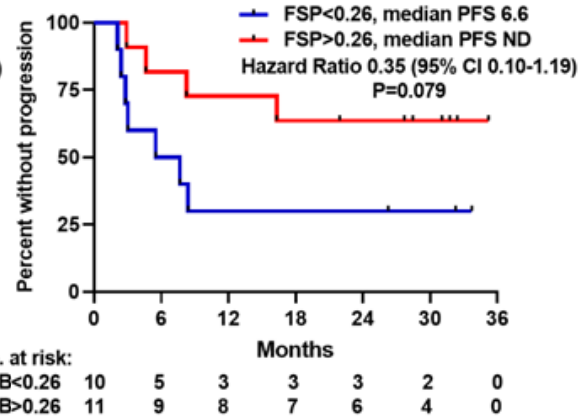
Sena LA, et al. *TheOncologist* 2021; 26: 270-278.

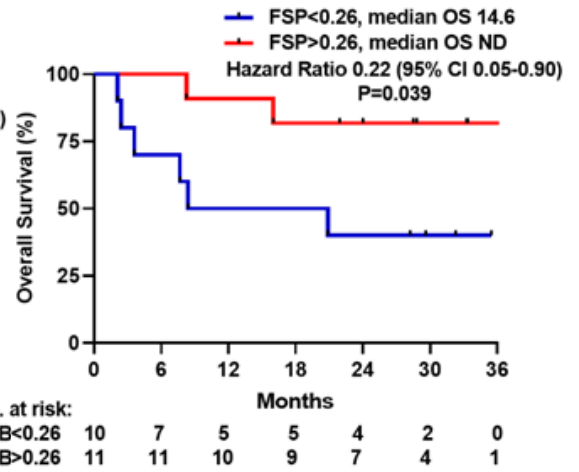
TMB



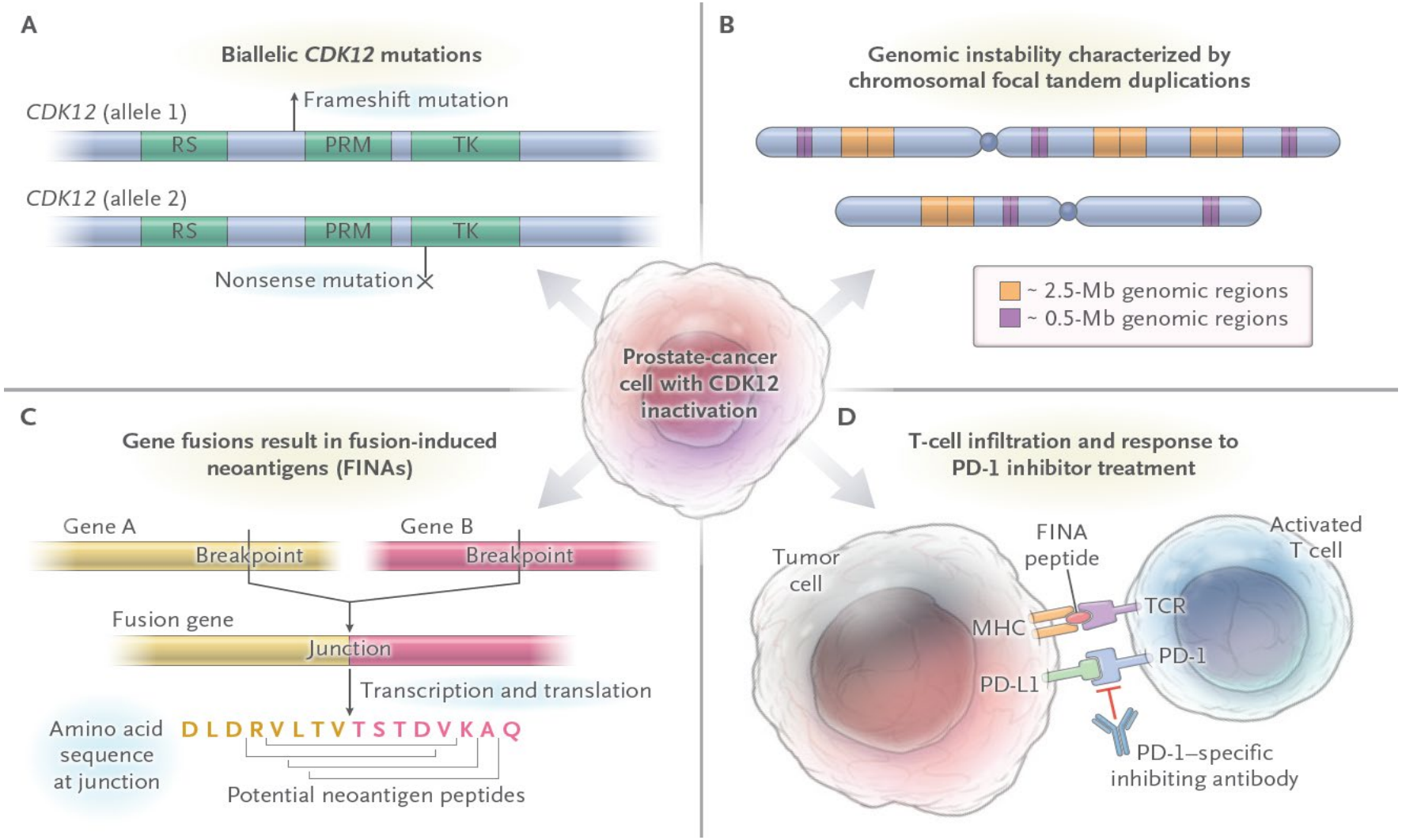


Frameshifts



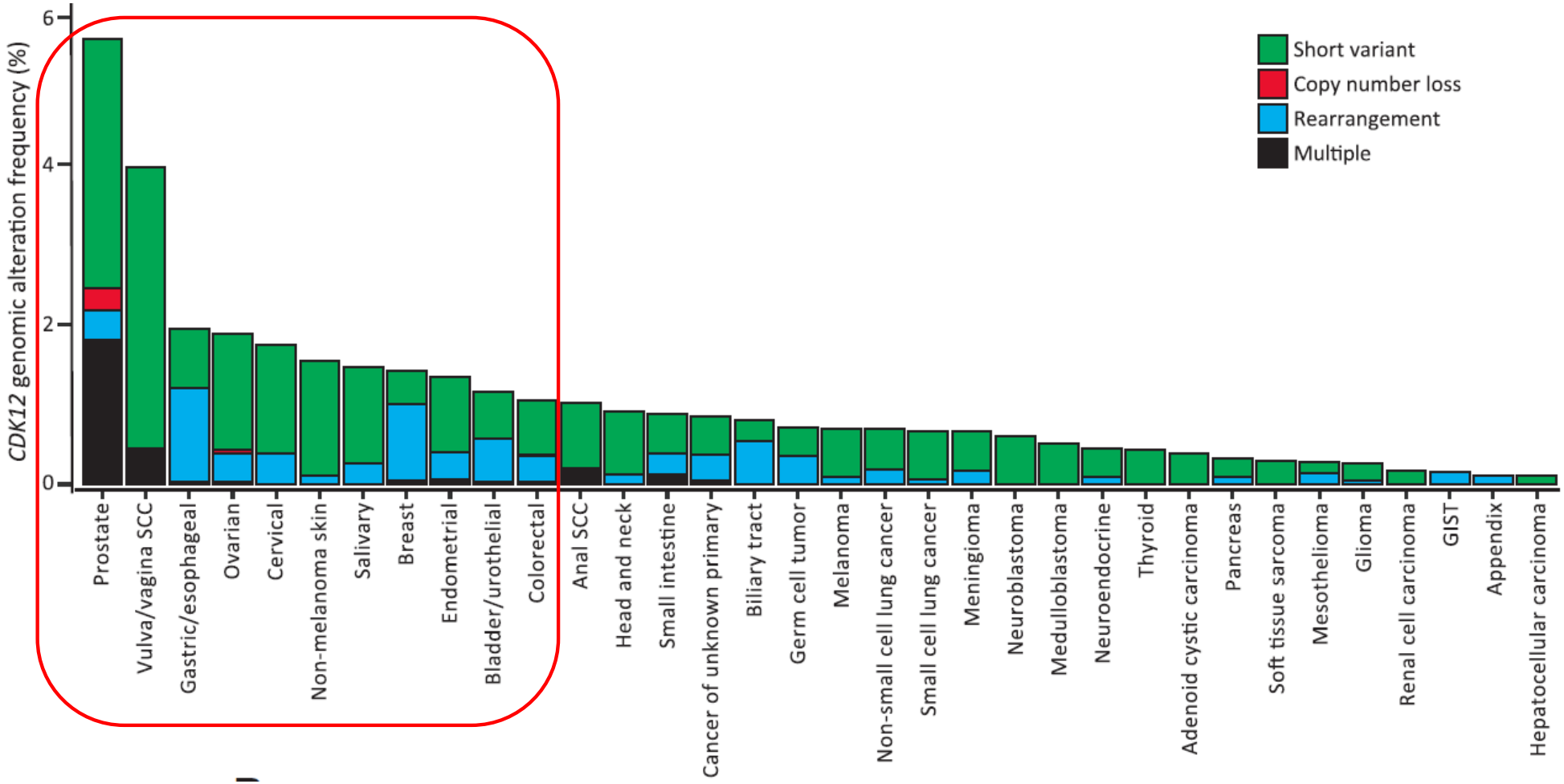


CDK12 mutations and mCRPC



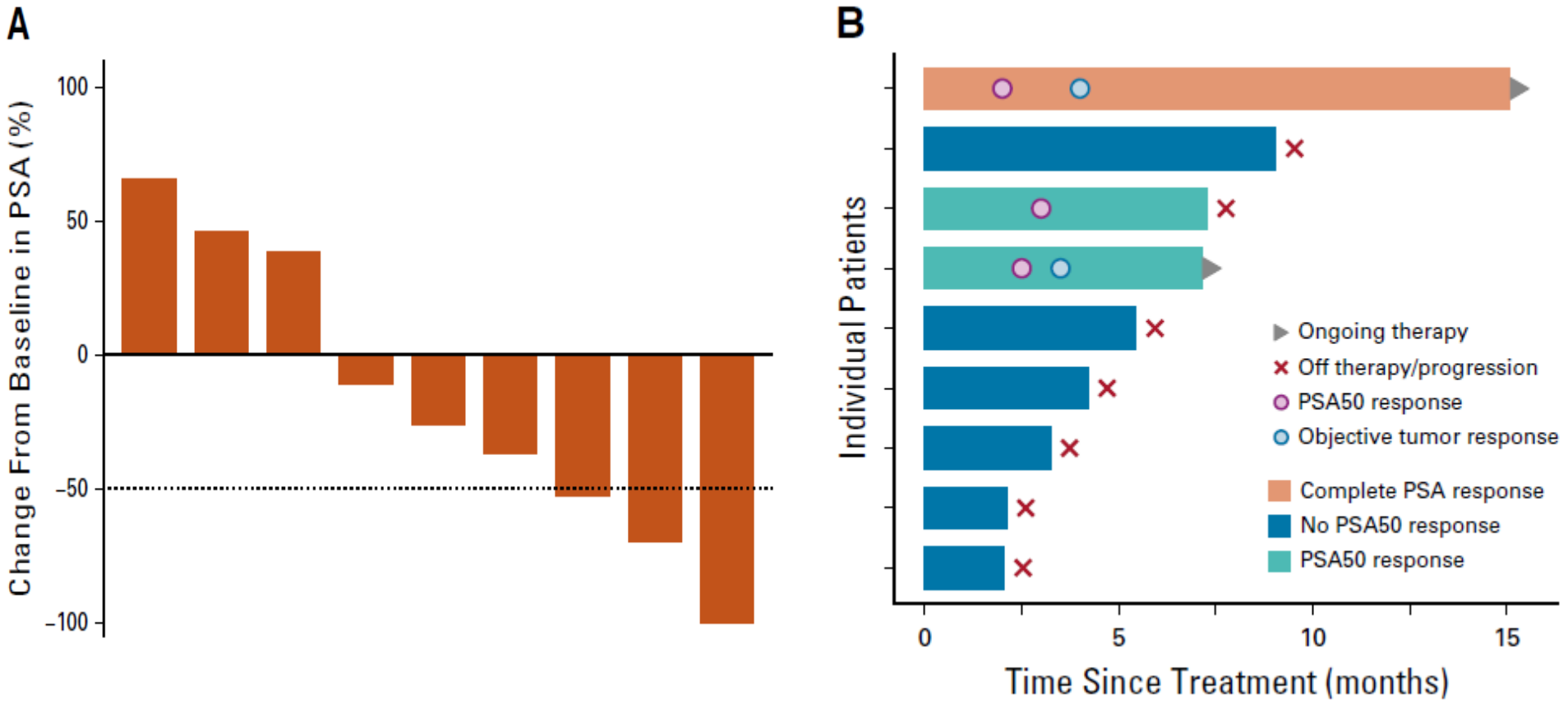
Antonarakis ES. *N Engl J Med* 2019.

CDK12 mutations across cancer types



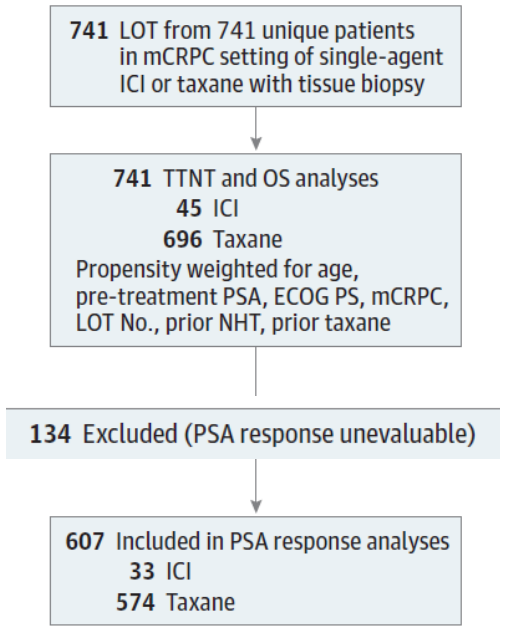
Sokol ES, et al. *TheOncologist* 2019; 24: 1526-33.

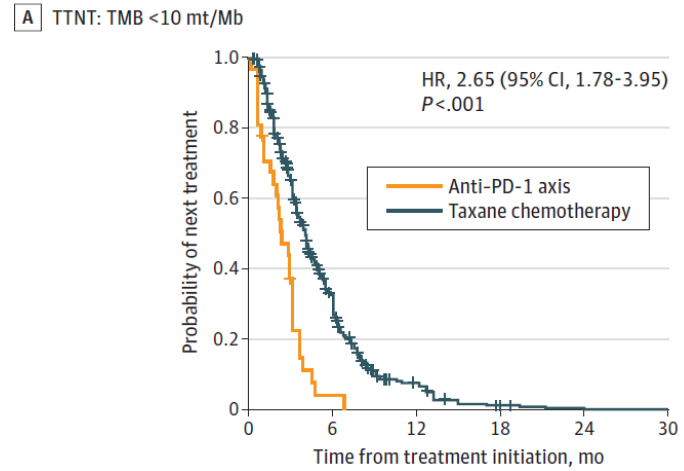
CDK12 and anti-PD1 sensitivity in mCRPC

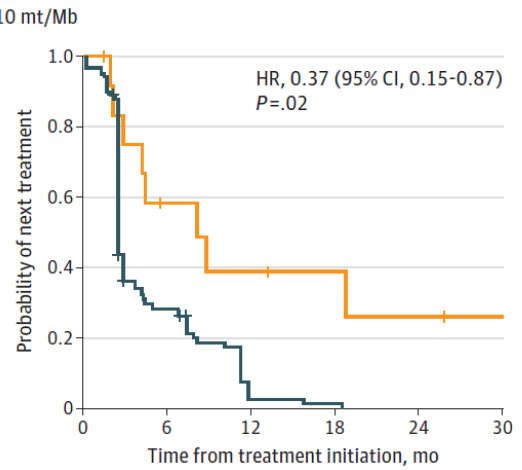


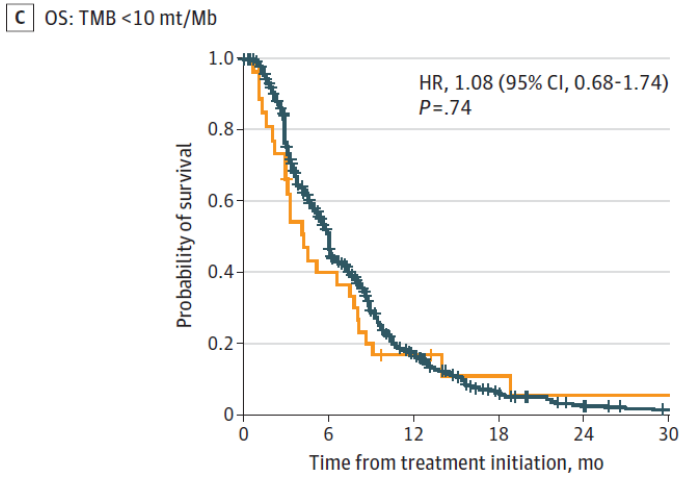
Antonarakis ES, et al. *JCO Precision Oncology 2020*; doi: 10.1200/PO.19.00399.

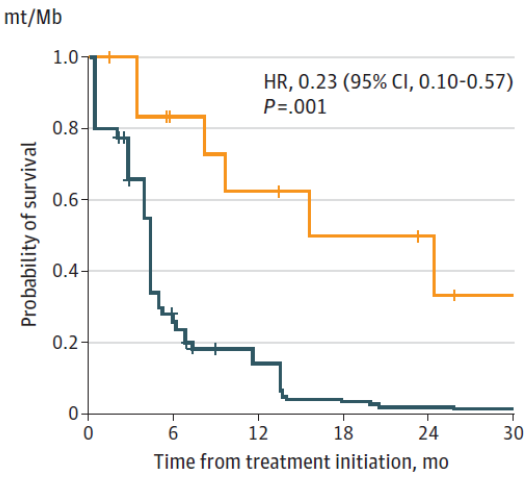
TMB ≥10 mut/Mb – Flatiron/FM database











Graf RP, et al. *JAMA Network Open* 2022; 5: e225394.

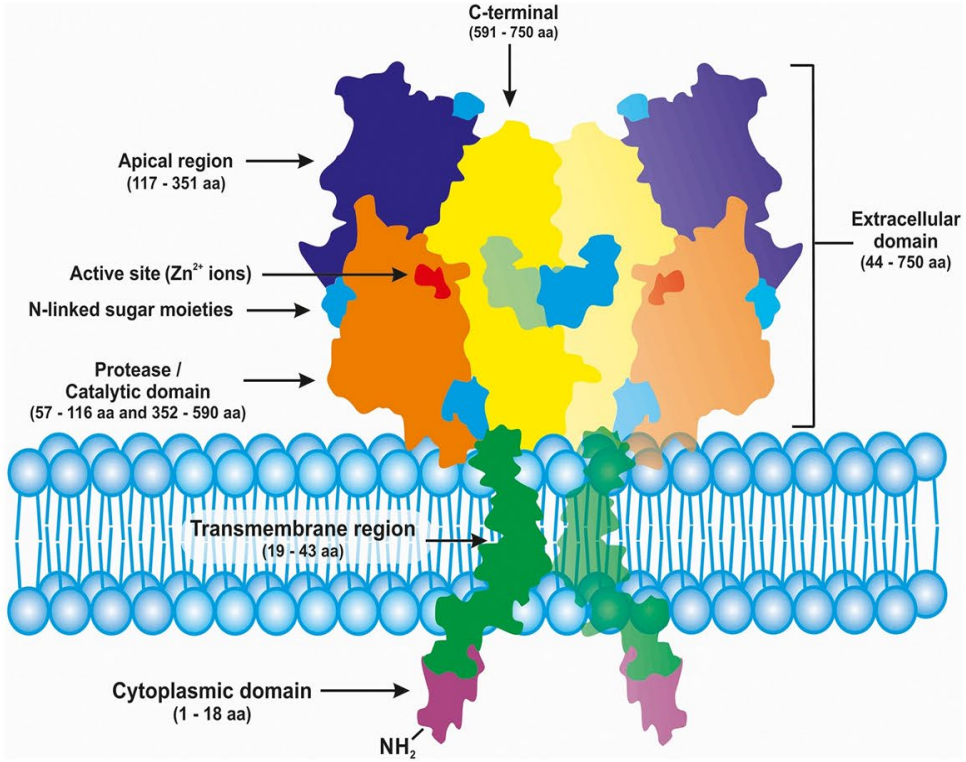
Genomic markers of ICI response in mCRPC

- dMMR / MSI-high
- TMB-high (≥10 mut/Mb)
- *CDK12* mutations
- Frameshift (fs*) mutations*?*
- Certain *TP53* mutations?
- *POLE*, *POLD1* mutations (ultra-mutated)?
- Deletion of *PD-L1* 3'-UTR?
- PD-L1 protein expression*?* NO

PSMA–Targeted Therapies

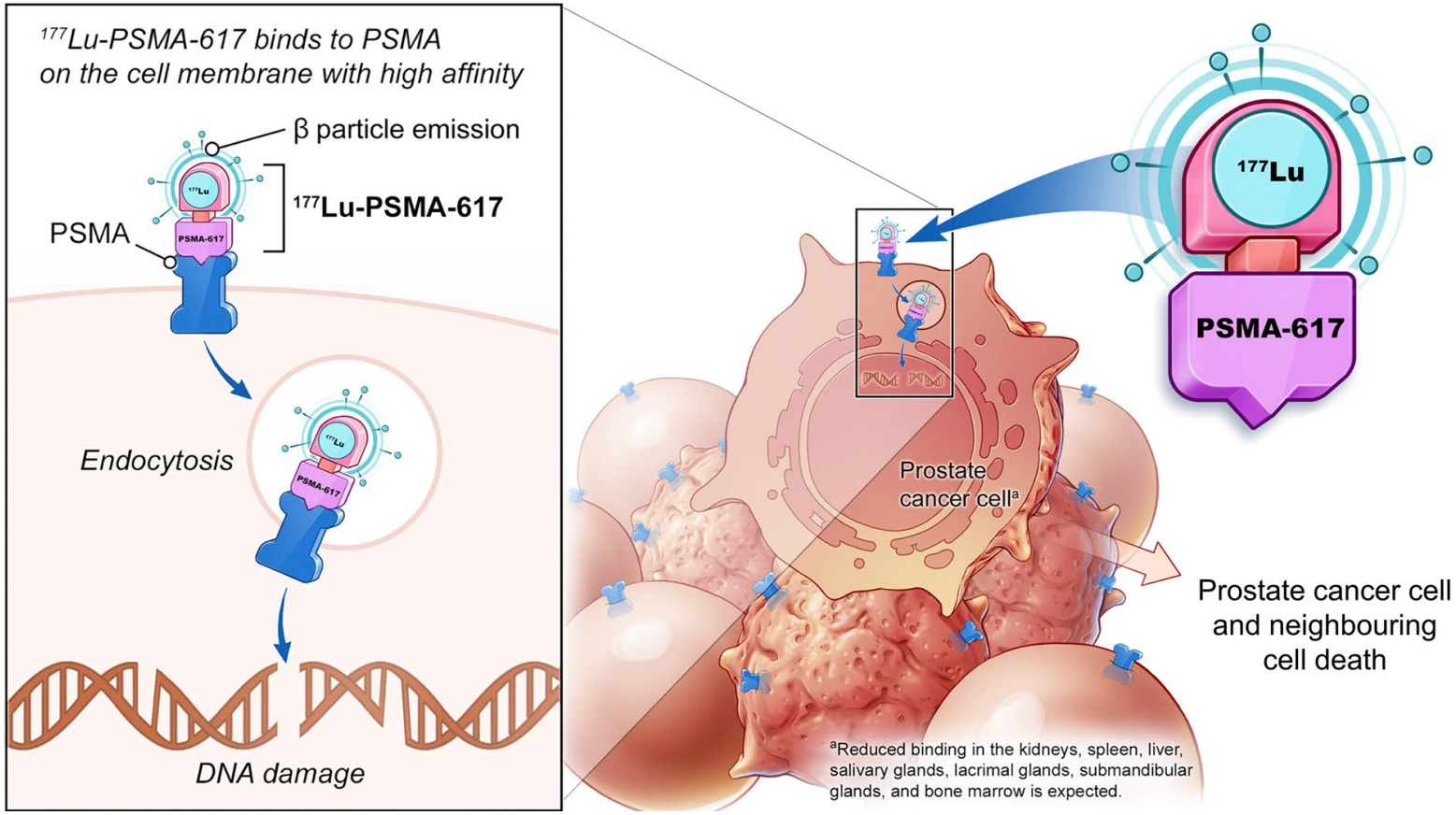
PSMA: Target for imaging and therapy

- Transmembrane carboxypeptidase
- Highly expressed in prostate cancer including metastatic lesions
- Relatively restricted normal expression
  - E.g. salivary and lacrimal glands
- Excellent target for PET imaging



Evans JC, *et al. Br J Pharmacol* 2016; 173: 3041-79.

^{177}Lu-PSMA-617 Radioligand therapy



Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4).

VISION trial for patients with PSMA+ mCRPC

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

2:1

Protocol-permitted SOC + ^{177}Lu-PSMA-617
7.4 GBq (200 mCi) every 6 weeks
4 cycles, increasable to 6

Protocol-permitted SOC alone

Treatment → Follow-up → Final analysis

- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)

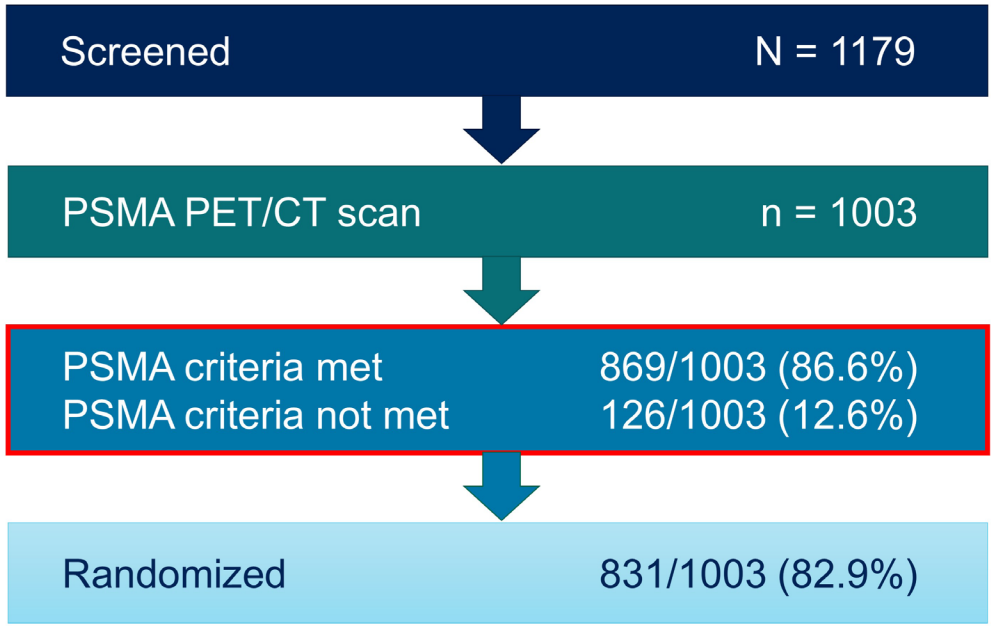
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4). Sartor O, et al. *NEJM* 2021.

VISION trial for patients with PSMA+ mCRPC

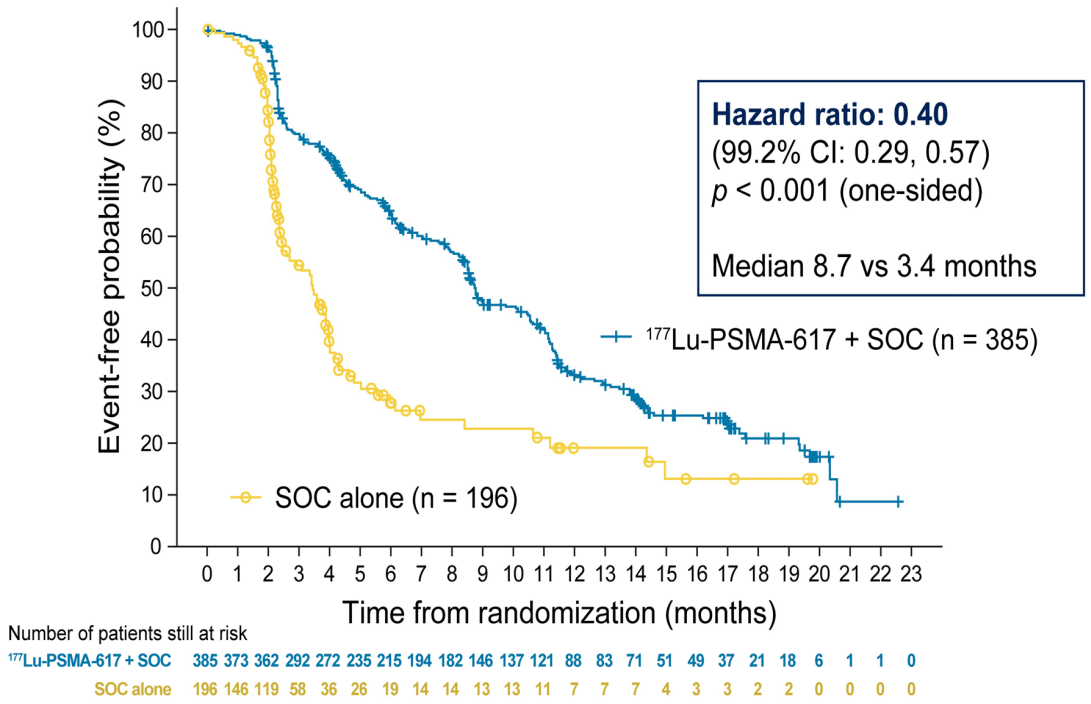
^{68}Ga-PSMA-11 PET/CT: ~87% of patients scanned met the VISION imaging criteria for PSMA-positive mCRPC

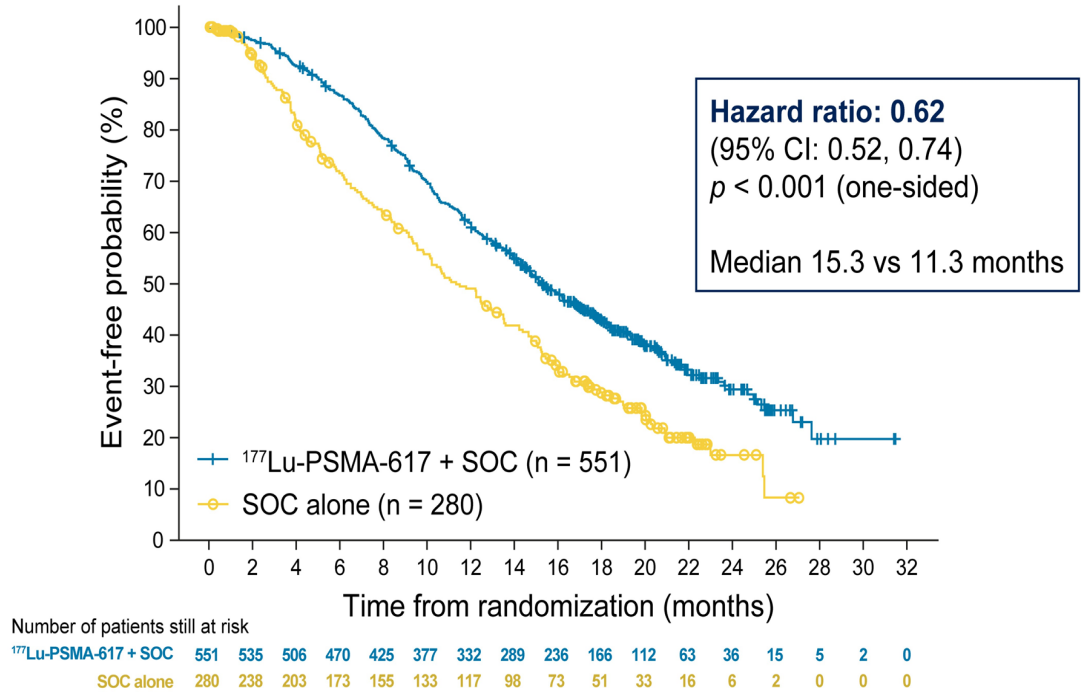
Patient disposition in screening



Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4). Sartor O, et al. *NEJM* 2021.

VISION trial: rPFS and OS



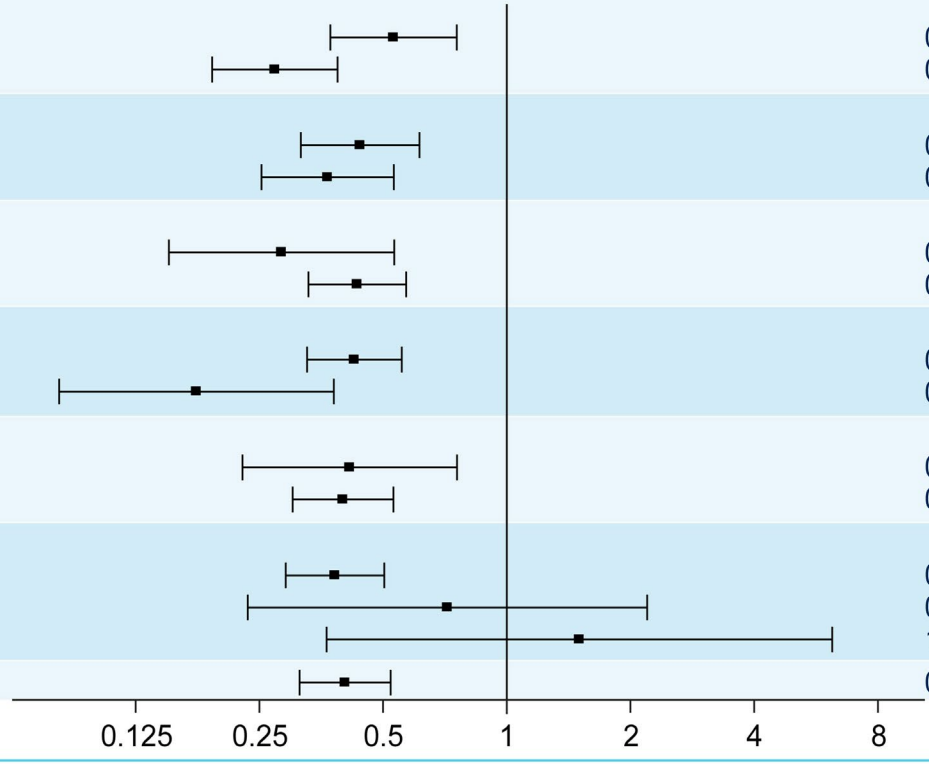


Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4) .

Sartor O, et al. *NEJM* 2021.

VISION trial: rPFS forest plot

Subgroup	^{177}Lu-PSMA-617 + SOC (n = 385)	SOC alone (n = 196)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned SOC			
Yes	170	107	0.53 (0.37, 0.76)
No	215	89	0.27 (0.19, 0.39)
LDH			
≤ 260 IU/L	244	120	0.44 (0.32, 0.61)
> 260 IU/L	140	75	0.37 (0.25, 0.53)
Liver metastases			
Yes	37	22	0.28 (0.15, 0.53)
No	348	174	0.43 (0.33, 0.57)
ECOG score			
0 or 1	352	179	0.43 (0.33, 0.56)
2	33	17	0.18 (0.08, 0.38)
Age			
< 65 years	96	39	0.42 (0.23, 0.76)
≥ 65 years	289	157	0.40 (0.30, 0.53)
Race			
White	336	166	0.38 (0.29, 0.50)
African American or Black	29	14	0.72 (0.23, 2.20)
Asian	6	9	1.50 (0.36, 6.19)
All patients	385	196	0.40 (0.31, 0.52)



Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4) . Sartor O, et al. *NEJM* 2021.

VISION trial: Adverse Events

Table 2. Adverse Events.*

Event	^{177}Lu-PSMA-617 plus Standard Care (N=529)		Standard Care Alone (N=205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)

Sartor O, et al. *NEJM* 2021.

^{177}Lutetium–PSMA–617: FDA Approved!

FDA Approves ^{177}Lu-PSMA-617 for the Treatment of mCRPC

Press Release — March 23, 2022

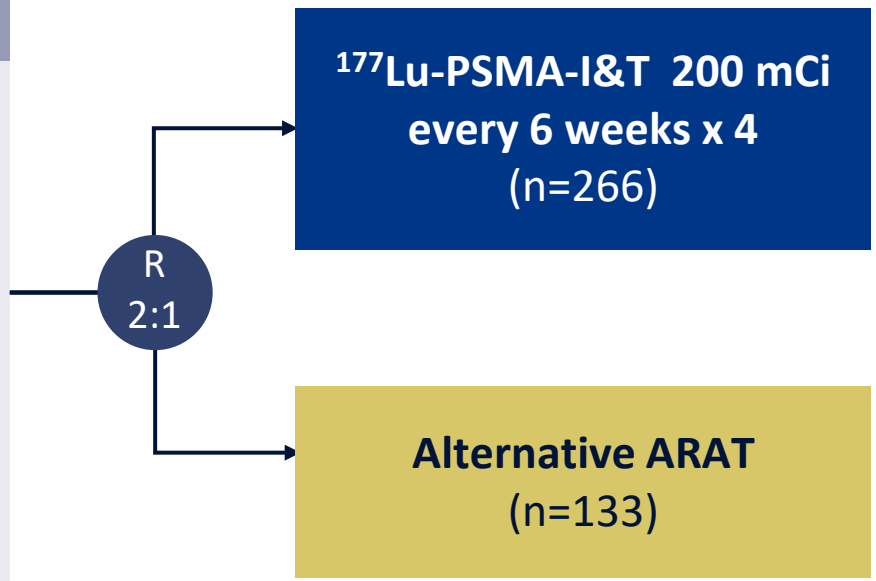
"On March 23, 2022, the Food and Drug Administration approved [the radio-ligand therapy, ^{177}Lu-PSMA-617] for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

On the same day, the FDA approved gallium Ga 68 gozetotide, a radioactive diagnostic agent for positron emission tomography (PET) of PSMA-positive lesions, including selection of patients with metastatic prostate cancer for whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated. Gallium Ga 68 gozetotide is the first radioactive diagnostic agent approved for patient selection in the use of a radioligand therapeutic agent. "

^{177}Lu–PSMA–I&T: The ECLIPSE trial

Patient population

- mCRPC with progression per PCWG3 guidelines
- Only one prior ARAT (abiraterone, enzalutamide, darolutamide, apalutamide)
- No prior chemo treatment
- No prior radioligands
- ECOG PS 0–2
- Positive PSMA-PET scan



Estimated primary completion:
Jan 2024

Primary endpoint

- rPFS

Key secondary endpoints

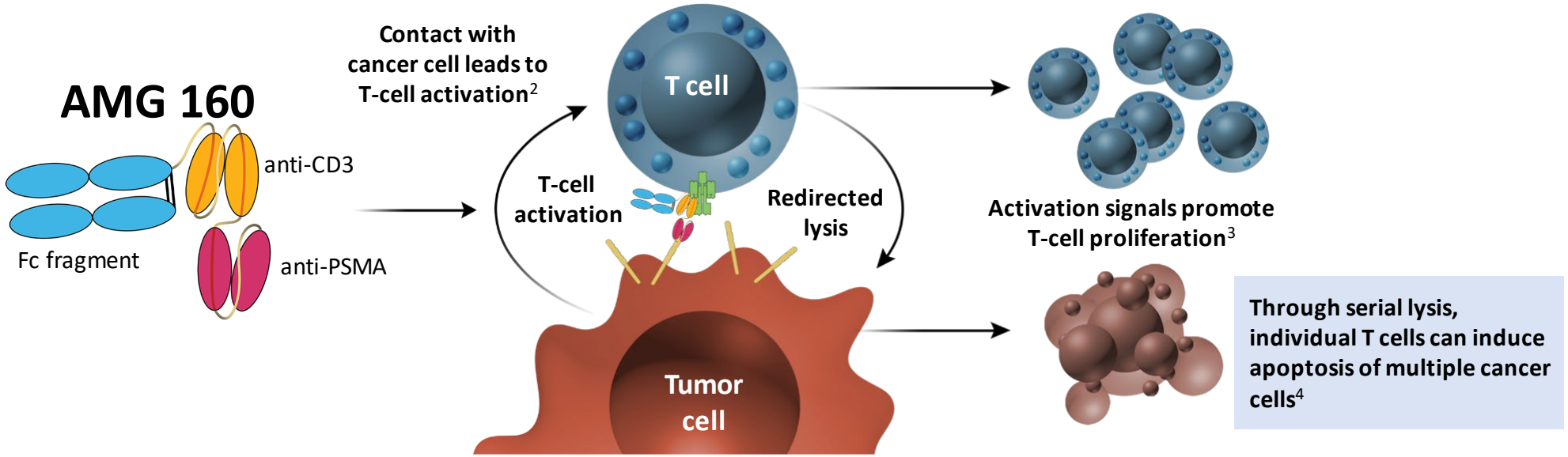
- OS
- Overall PFS
- PFS-2 (second PFS)
- PSA response rate
- Time to first SSE
- QOL (EORTC QLQ-C30)

Key correlative endpoint

- Dosimetry
- PKs (pharmacokinetics)

PSMA–Targeted BiTEs (AMG160)

Amgen BiTE® (Bispecific T-cell Engager)



- BiTE molecules engage a patient's own T cells to attack and eradicate cancer cells[1]
  - T-cell activation induces transient cytokine release and tumor killing[1]
- Blinatumomab (BLINCYTO®, Amgen Inc.) is the first and only bispecific immunotherapy approved in oncology worldwide[1]
- **AMG 160** is a **half-life extended** PSMA x CD3 BiTE immunotherapy for mCRPC

Tran, Ben *et al.* ESMO 2021, Sept 19-21.

Amgen BiTE® (Bispecific T-cell Engager)

Inclusion Criteria

- Histologically or cytologically confirmed mCRPC refractory to novel hormonal therapy **and**
  - Have failed 1–2 taxane regimens; **or**
  - Patient deemed unsuitable for or has refused taxanes
- Evidence of progressive disease per PCWG3

Exclusion Criteria

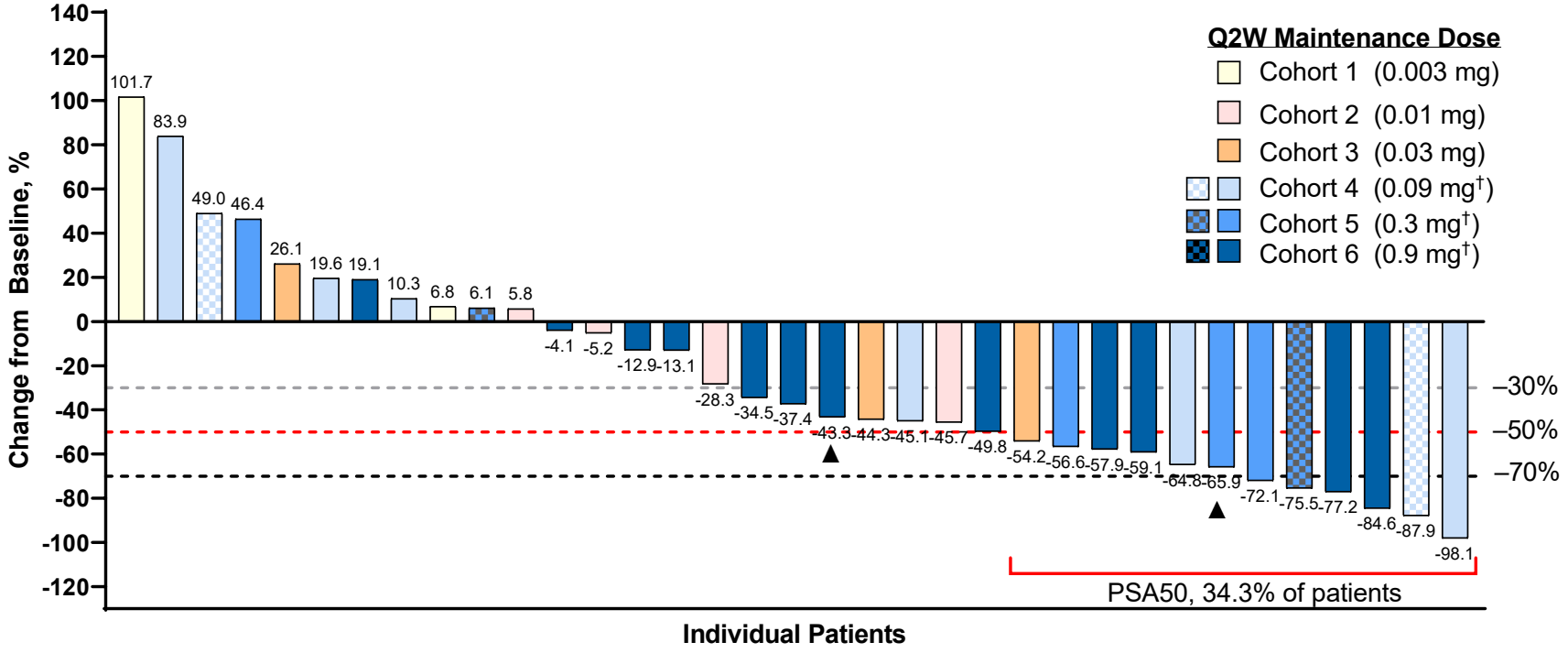
- Active autoimmune disease or requiring immunosuppressive therapy
- Prior PSMA–targeted therapy (patients treated with PSMA radionuclide therapy may be eligible)
- CNS metastases, leptomeningeal disease, or spinal cord compression

Baseline Demographics	All (N = 43)
Median (range) age, y	66.0 (49–78)
Race, n (%)	
Asian	2 (4.7)
Black	2 (4.7)
White	34 (79.1)
Other	5 (11.6)
Prior lines of therapy, n (%)	
1	2 (4.7)
2	4 (9.3)
3	9 (20.9)
≥ 4	26 (60.5)
Median (range)	4 (1–9)
Median (range) PSA at baseline, µg/L	79.2 (0.1–4035.0)
RECIST-measurable disease, n (%)	15 (34.9%)

Tran, Ben *et al.* ESMO 2021, Sept 19-21.

Amgen BiTE® (Bispecific T-cell Engager)

- PSA reductions > 50% occurred in 12/35 (34.3%) evaluable patients



Tran, Ben *et al.* ESMO 2021, Sept 19-21.

Amgen BiTE® (Bispecific T-cell Engager)

Cytokine Release Syndrome

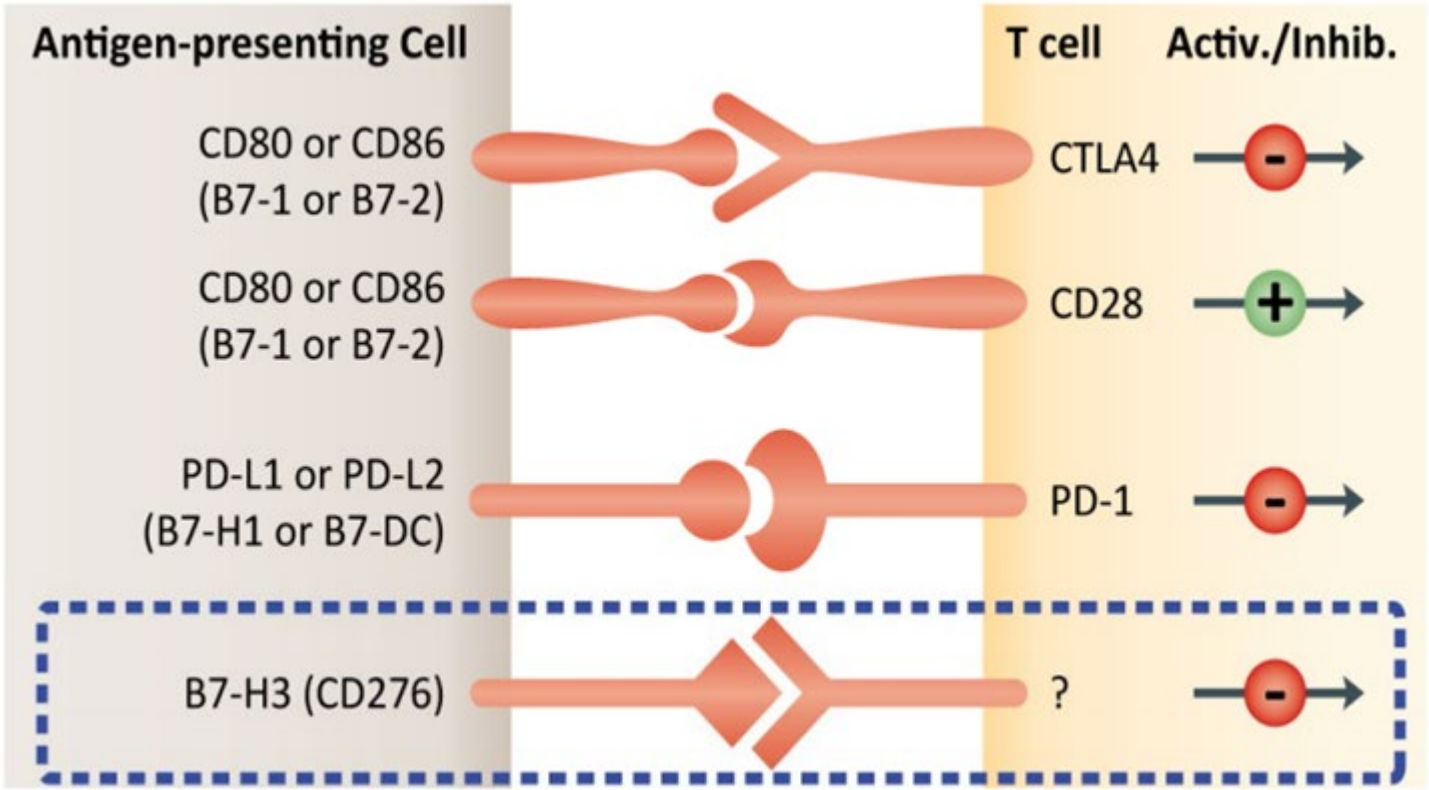
- CRS was reversible, manageable, most severe in cycle 1 and associated with fever, hypotension, transient transaminitis, nausea/vomiting and/or diarrhea (Lee 2014 grading)
  - No grade 4/5 CRS events or treatment discontinuations
  - 26 (60.5%) patients had grade 2 CRS as worst grade (hypotension: 15 [34.9%]; transaminitis: 13 [30.2%])*
  - 11 (25.6%) patients had grade 3 CRS as worst grade (hypotension: 6 [14.0%]; transaminitis: 10 [23.3%])*
    - Transaminitis events were short-term AST/ALT elevations not associated with long-term hepatic dysfunction
  - 4 (9.3%) patients experienced reversible atrial fibrillation in setting of CRS/tachycardia

CRS Grading (Lee 2014)			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4†**
Fever, nausea, fatigue, etc, requiring symptomatic treatment only	Grade 1 CRS symptoms and • O_2 requirement $< 40\%$ • Intravenous fluids or low-dose vasopressor for hypotension • Grade 3 transaminitis	Grade 1 CRS symptoms and • O_2 requirement $\geq 40\%$ • High-dose or multiple vasopressors for hypotension • Grade 4 transaminitis	Grade 1 CRS symptoms and • Requirement for ventilator • Grade 4 organ toxicity (excluding transaminitis)

Tran, Ben *et al.* ESMO 2021, Sept 19-21.

B7-H3–Targeted Therapies

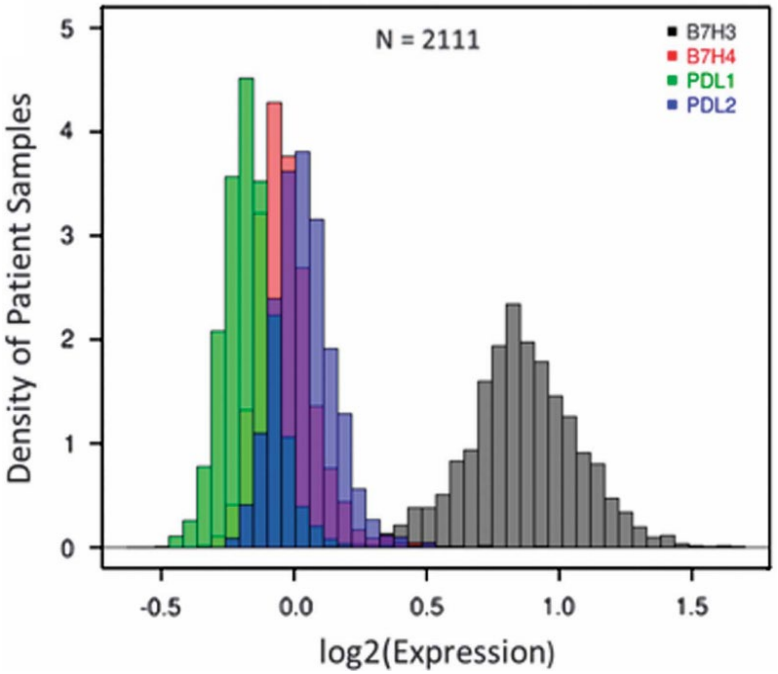
B7-H3: Member of B7 family of immune checkpoints



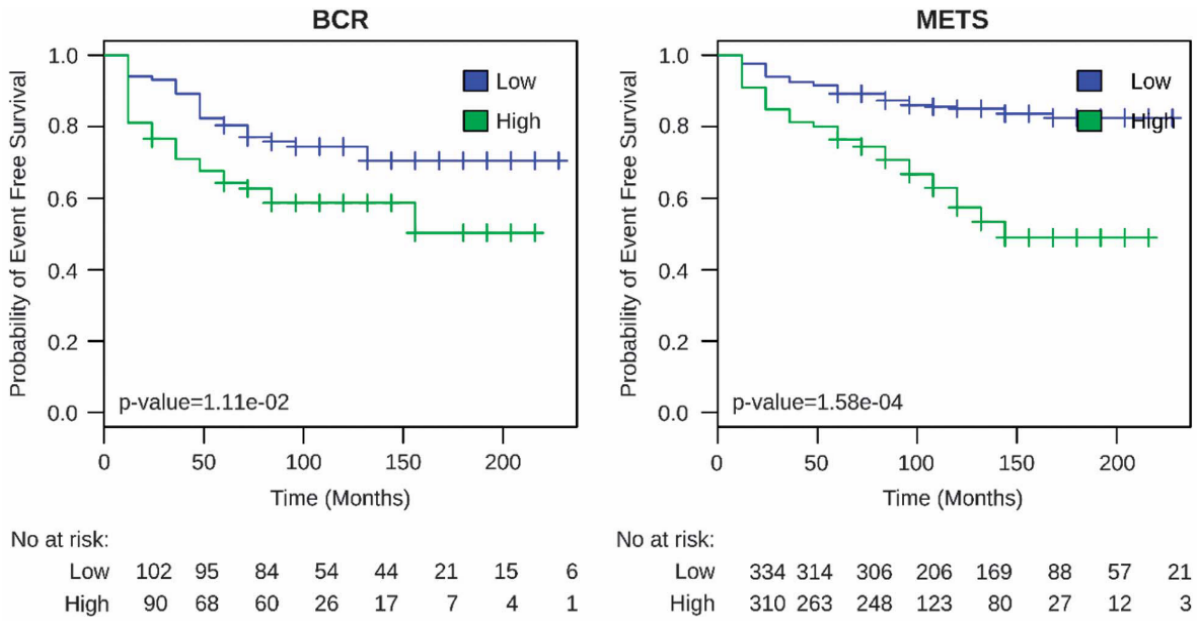
Expressed by 90% of prostate cancers (higher expression in mCRPC than in localized PCa).

Pardoll D, *et al. Nature 2012*.

B7-H3, compared to other checkpoints, in PCa



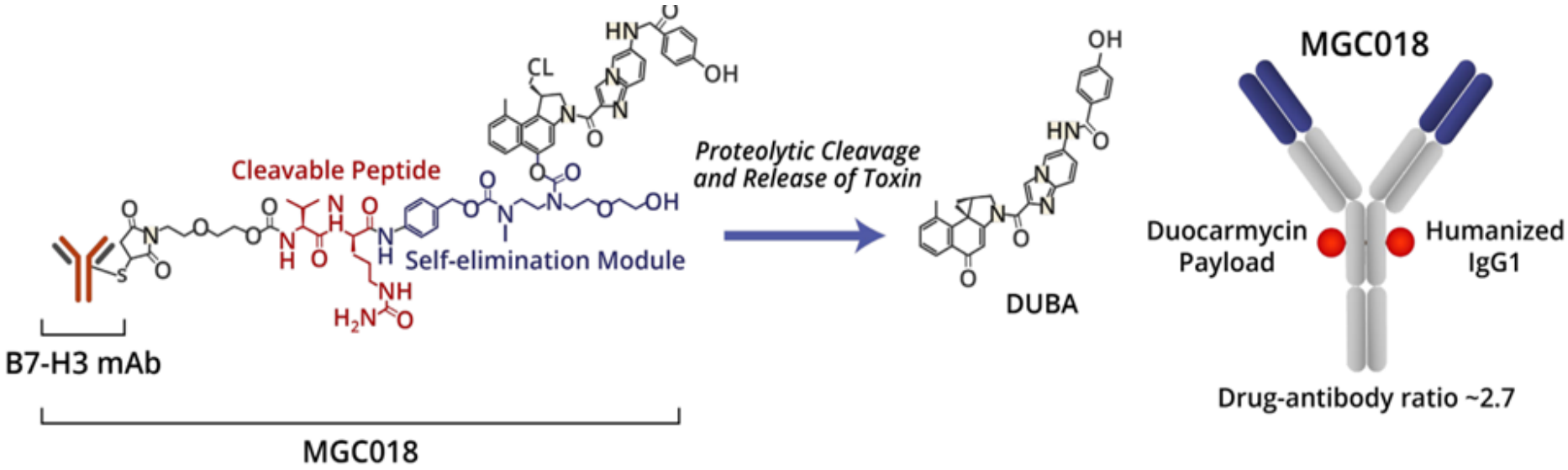
RNA expression distributions of B7-H3, B7-H4, PD-L1 and PD-L2 in a prospective radical prostatectomy (RP) cohort (n=2111).



Kaplan–Meier curves for biochemical recurrence (BCR) and clinical metastasis (METS) with low and high B7-H3 RNA expression.

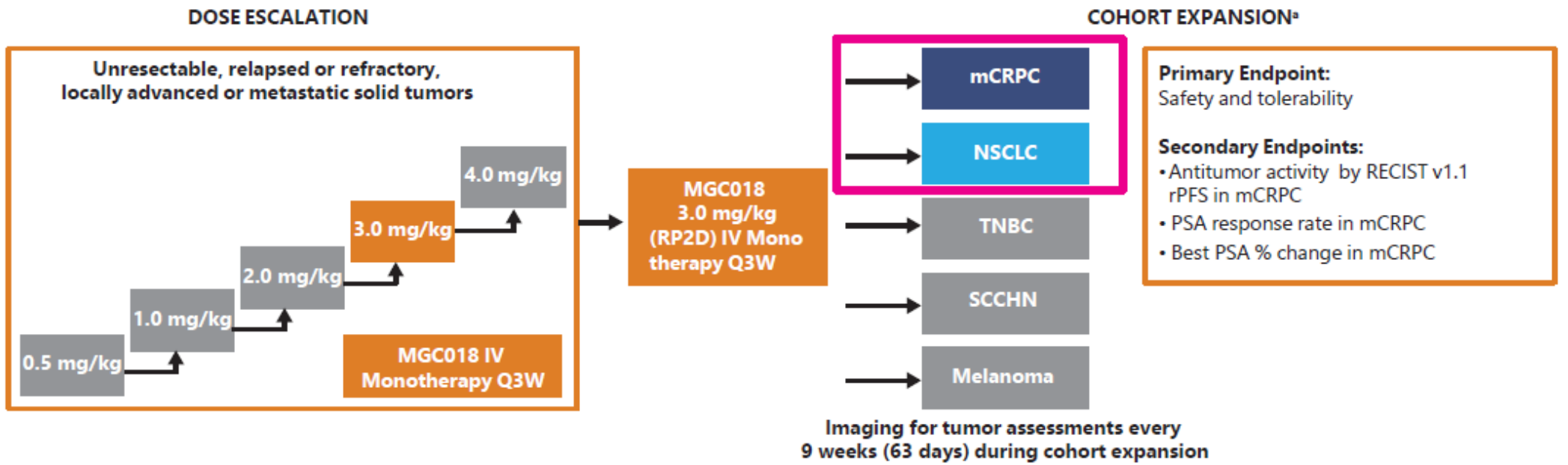
Benzon B, et al. *Prostate Cancer Prostatic Diseases* 2017.

MGC 018 is a B7-H3–directed ADC



Jang S, *et al.* J Clin Oncol 39; 2021 (ASCO abstract 2631).

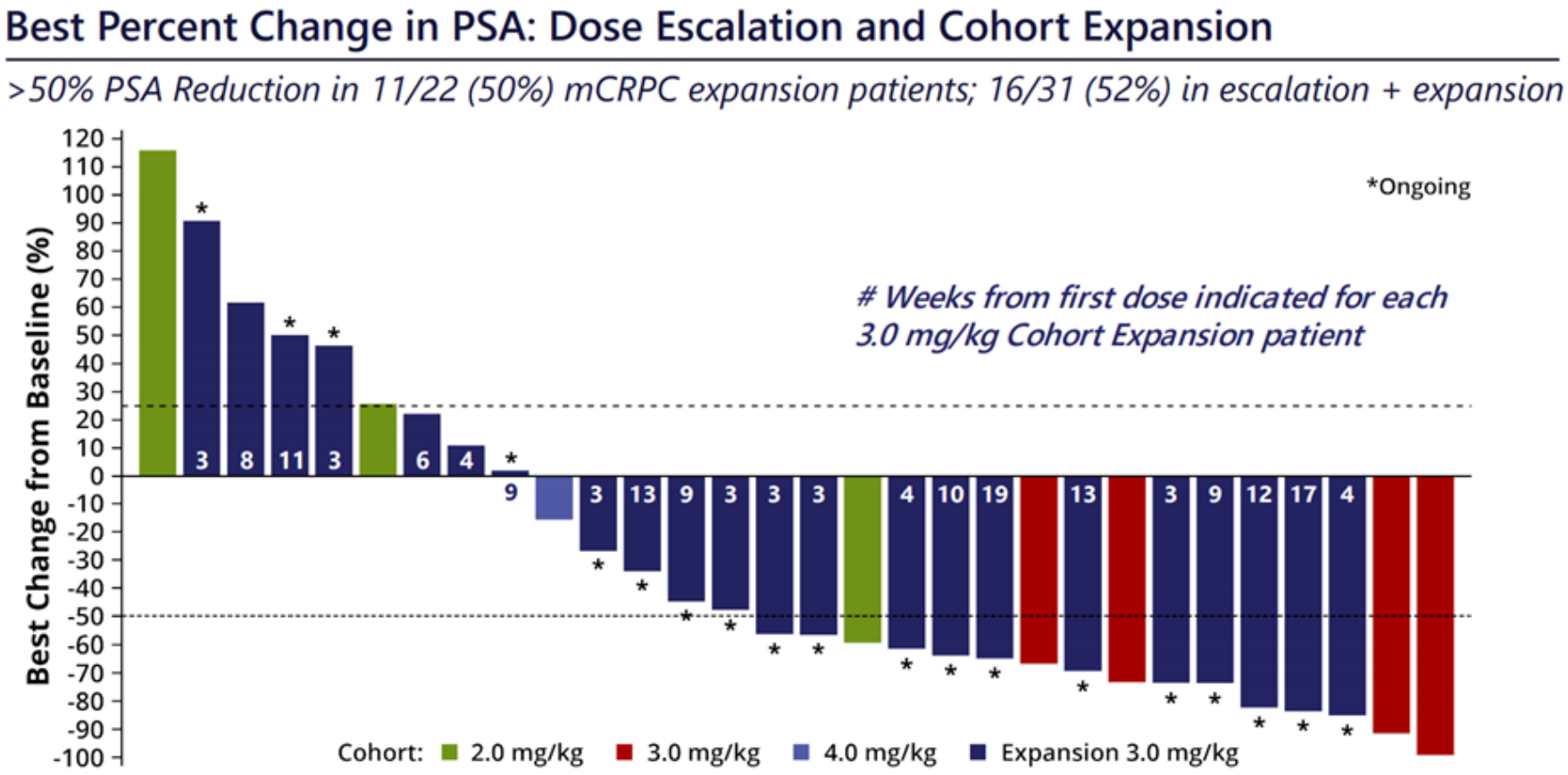
MGC 018 clinical trial: Phase 1b



[a]Enrollment for the mCRPC, NSCLC, and TNBC cohorts opened in 2020, whereas the SCCHN and melanoma cohorts opened in May 2021.
IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; NSCLC, non–small cell lung cancer; PSA, prostate-specific antigen; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; rPFS, radiographic progression-free survival; SCCHN, squamous cell cancer of head and neck; TNBC, triple-negative breast cancer.

Jang S, *et al.* J Clin Oncol 39; 2021 (ASCO abstract 2631).

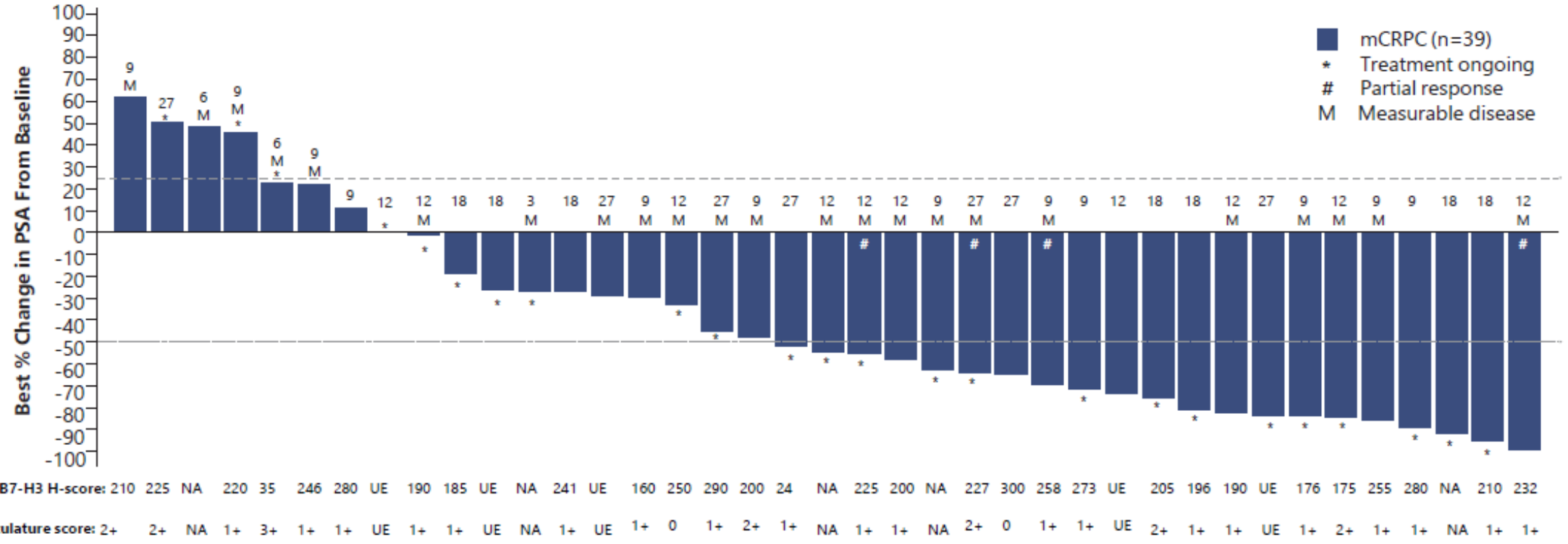
MGC 018 clinical trial: Phase 1b



Jang S, *et al.* J Clin Oncol 39; 2021 (ASCO abstract 2631).

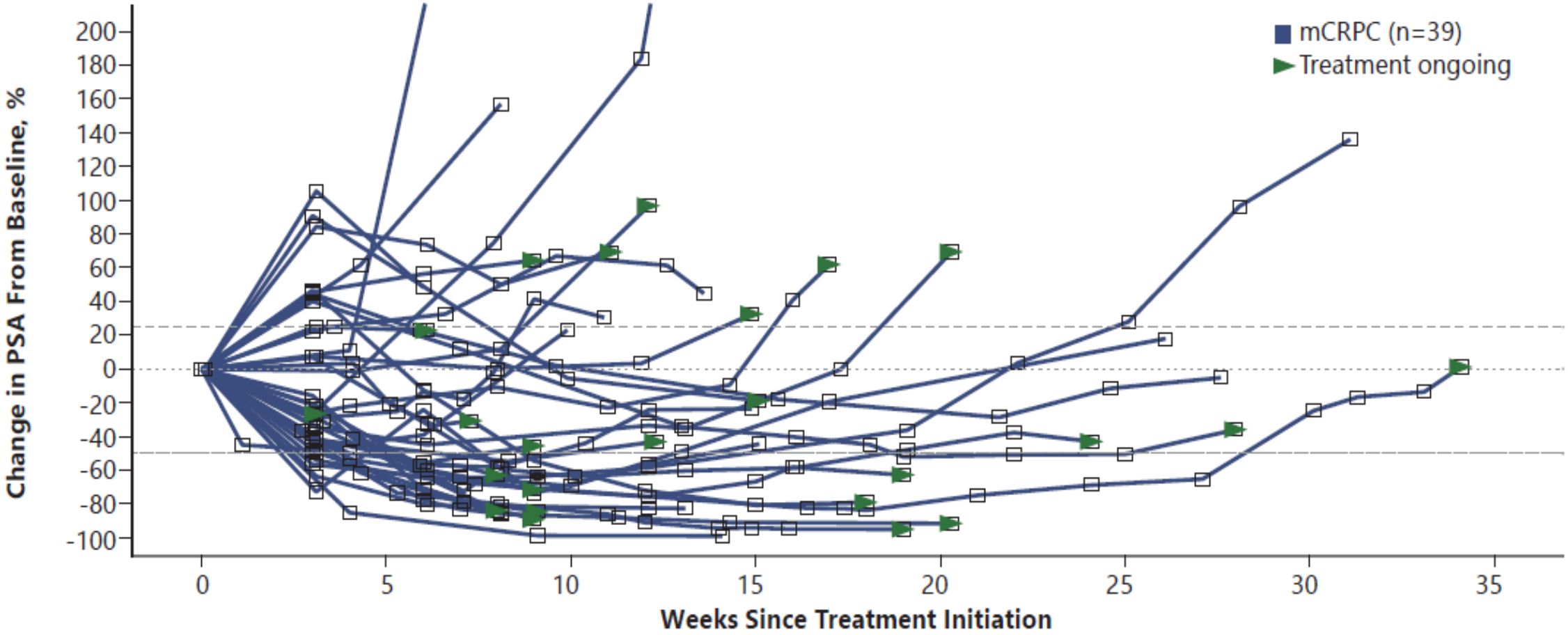
MGC 018 clinical trial: Phase 2 expansion

- In mCRPC cohort, 39 patients were evaluable for PSA response:
  - Twenty-one of 39 patients (53.8%) had reductions in PSA from baseline of more than 50%
  - Twenty-four of 39 patients (61.5%) remained on treatment



Shenderov E, *et al.* ESMO 2021 (abstract #620P).

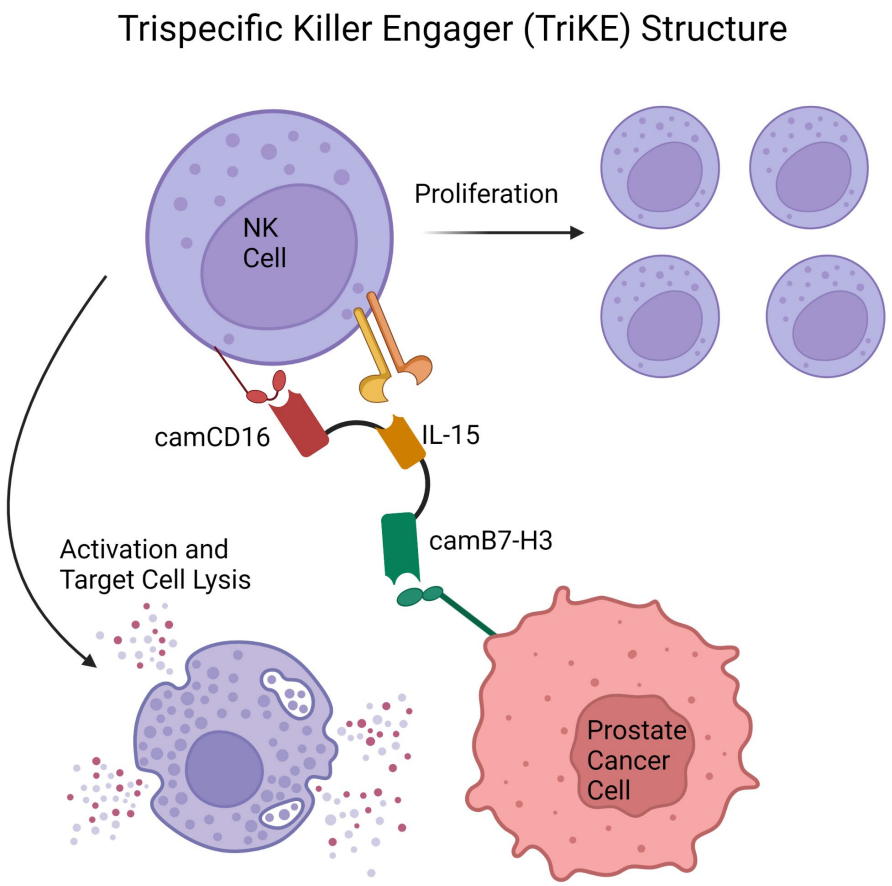
MGC 018 clinical trial: Phase 2 expansion



Shenderov E, *et al.* ESMO 2021 (abstract #620P).

B7-H3–targeted TriKE

Nick Zorko, MD PhD



- Clinical-grade batch of B7-H3 TriKE (GTB-5550) currently in production.
- Goal for FDA-IND application in Q1/2 of 2023.
- First-in-human Phase 1/2 clinical trial for B7-H3+ cancers with prostate-specific arm in Q3/4 2023.

Conclusions

- Germline and somatic DNA-repair mutations are common in mCRPC patients
- HRR mutations sensitize to PARP inhibitors, and perhaps Platinums and Radium-223
- MMR mutations, TMB >10 muts/Mb (and perhaps *CDK12* mutations) sensitize to PD-1 inhibitors
- PSMA is a target for imaging (PET) and therapy (^{177}Lu-PSMA)
- Novel BiTEs, targeting PSMA, are in development
- B7-H3 may be a relevant therapeutic target in PCa

Thank You !

Masonic Cancer Center

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