ASCO GU 2024 and Annual ASCO Updates for the Prostate Cancer Support Group

September 9, 2024

Daniel E.C. Fein, MD
Hematology/Oncology, Genitourinary Oncology Program
Beth Israel Deaconess Medical Center
Instructor of Medicine, Harvard Medical School

Beth Israel Lahey Health

Beth Israel Deaconess Medical Center

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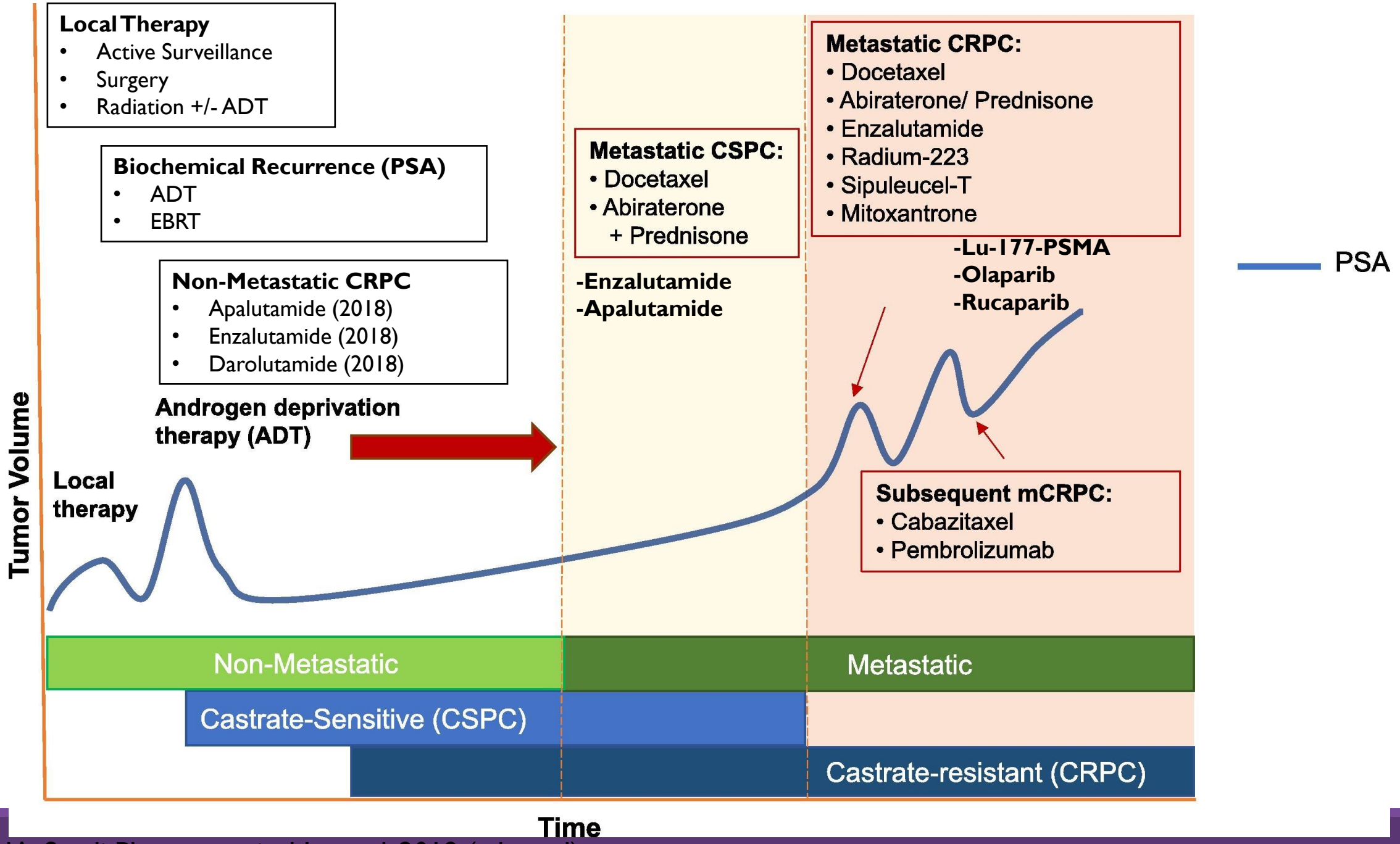
Moscone West



Alkhudair NA. Saudi Pharmaceutical Journal. 2019 (adapted)

The Drug Development Process

https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

The Drug Development Process

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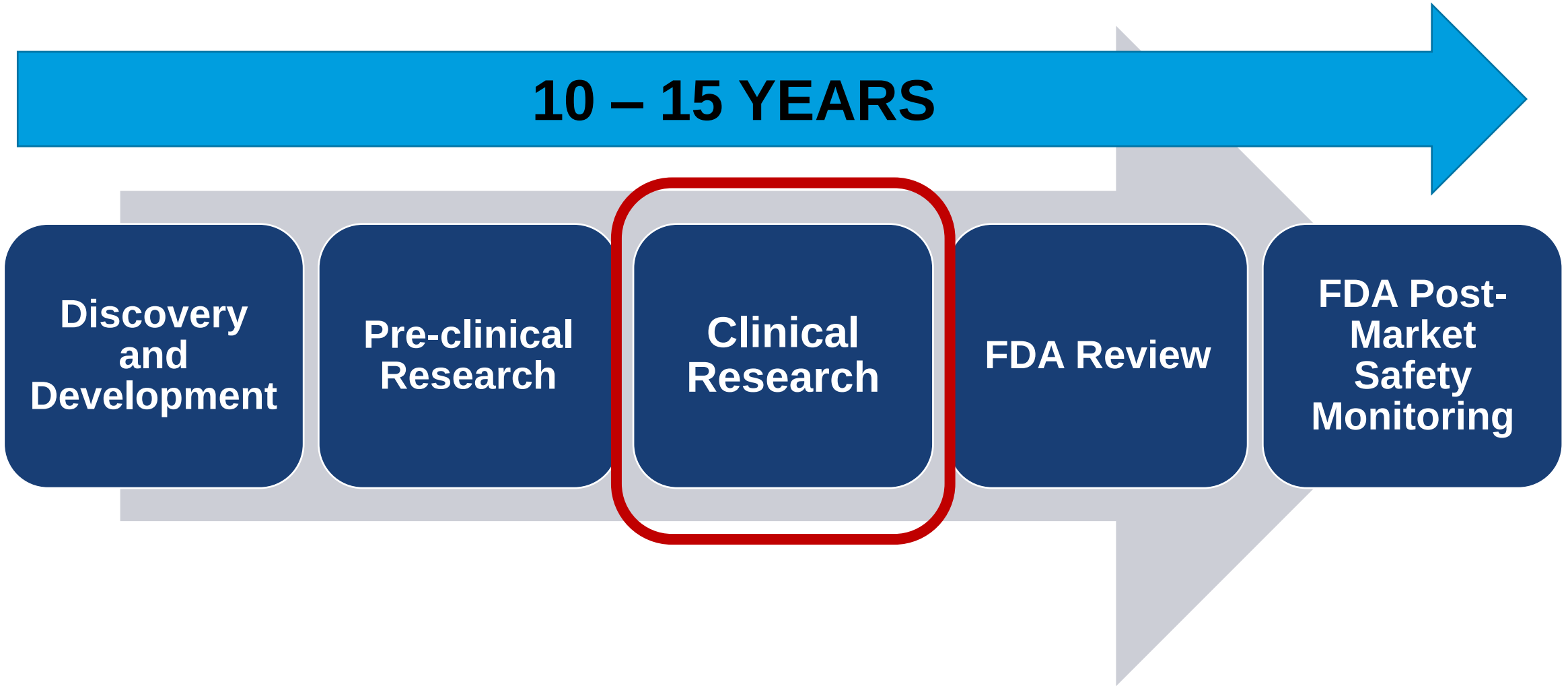

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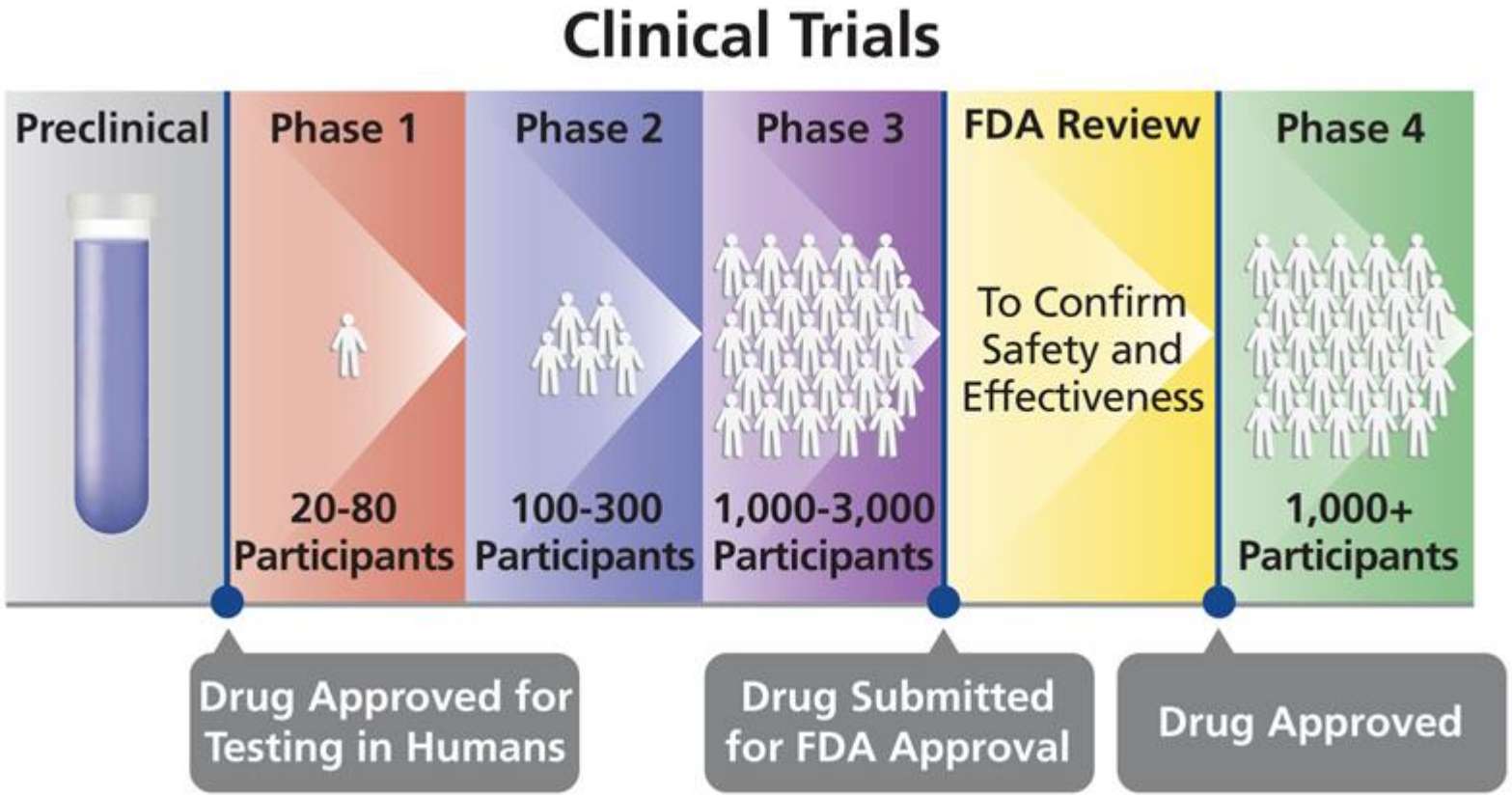
The Drug Development Process:
Clinical Research



Some important negative studies

“Metformin consumption does not alter rates of progression among men with low risk prostate cancer on active surveillance.”

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A randomized, double-blind, placebo-controlled trial of metformin in reducing progression among men on expectant management for low-risk prostate cancer: The MAST (Metformin Active Surveillance Trial) study.

- **What was it?** – A large double blinded placebo-controlled trial at 14 centers in Canada for patients with low risk localized prostate cancer
- **What did they do?** – They randomized 407 patients with low risk PC to receive ***Metformin 850mg twice daily*** or ***Placebo twice daily***
- **What did they see?** – There was no significant difference in progression-free survival between the two groups, no change in PSA. Increased risk of progression seen with metformin in BMI >30.
- **What does it mean?** – Despite some promising data from the laboratory and epidemiologic studies, Metformin does NOT reduce the change of PC progression in low risk disease.

Neil Fleshner, Rui Miguel Bernardino, Katherine Lajkosz…Anthony M Joshua. J Clin Oncol 42, 2024 (suppl 17; abstr LBA5002)

Updates in immunotherapy for prostate cancer

CONTACT-02- an immunotherapy phase 3 study for advanced castrate-resistant prostate cancer

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2024 ASCO GENITOURINARY CANCERS SYMPOSIUM

CONTACT-02: Coprimary PFS Data Favor Cabozantinib/Atezolizumab vs Additional Novel Hormonal Therapy in High-Risk mCRPC

January 25, 2024

Exelixis Announces Detailed Results of Phase 3 CONTACT-02 Pivotal Trial Evaluating Cabozantinib in Combination with Atezolizumab in Metastatic Castration-Resistant Prostate Cancer Presented at ASCO GU 2024

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– Cabozantinib in combination with atezolizumab reduced the risk of disease progression or death by 35% in patients with metastatic castration-resistant prostate cancer –

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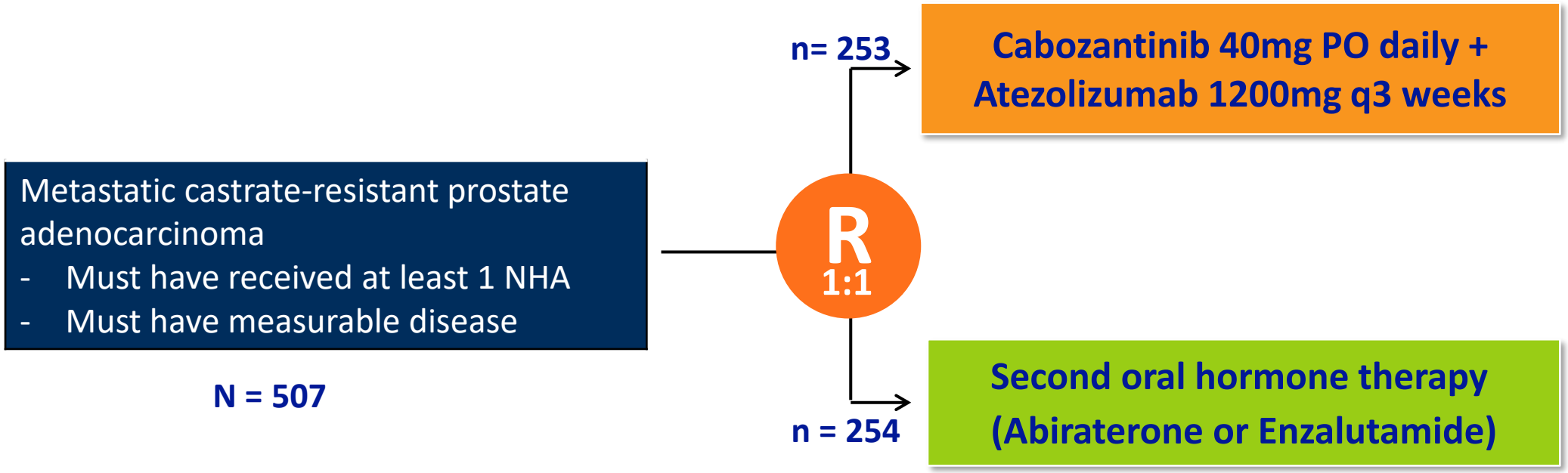
CONTACT-02- an immunotherapy phase 3 study for advanced castrate-resistant prostate cancer



Cabozantinib is an oral TKI (tyrosine kinase inhibitor) used in other cancers such as kidney cancer and liver cancer.

- Prolonged time to progression compared to prednisone by ~3 months and did NOT improve survival (*Phase 3 COMET-01 study, Journal Clin Oncol 2016*).

Atezolizumab is an IV immunotherapy used in other cancers such as bladder cancer and lung cancer.

Cabozantinib (oral TKI) + Atezolizumab (IV immunotherapy) prolonged progression free survival in patients with Liver or bone metastases and patients who received prior Docetaxel chemotherapy

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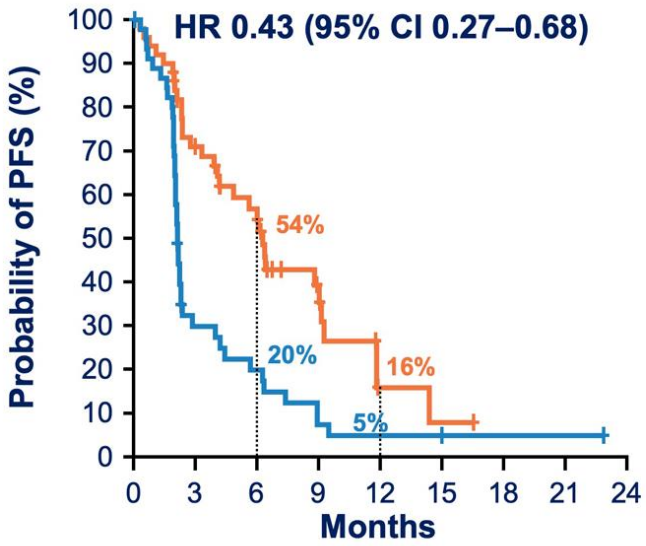
Liver Metastasis

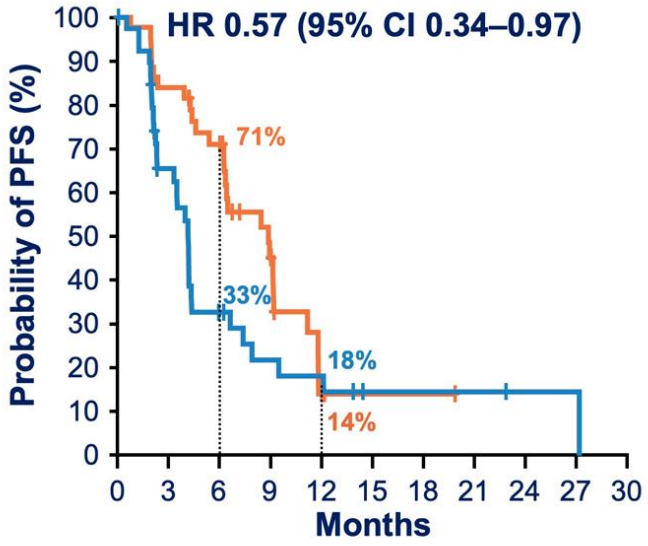
Reduction of risk† – 57%



	No. of Events	Median PFS mo (95% CI)
Cabo+Atezo (n=51)	32	6.2 (4.0–9.1)
Second NHT (n=48)	41	2.1 (2.0–2.3)

Prior Docetaxel

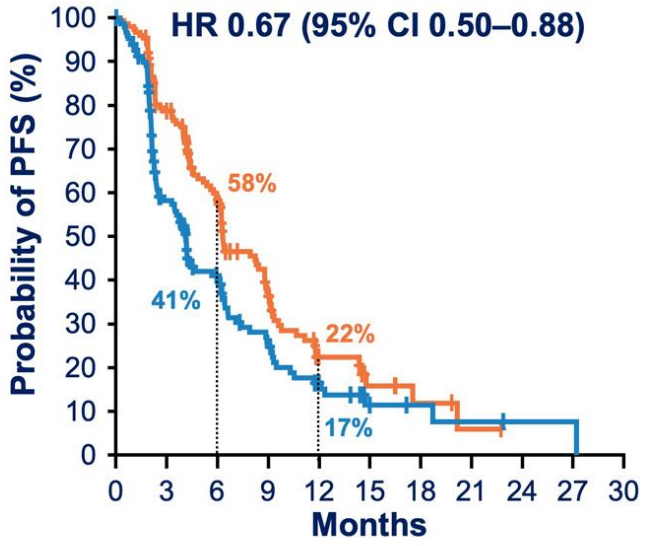
Reduction of risk† – 43%



	No. of Events	Median PFS mo (95% CI)
Cabo+Atezo (n=45)	27	8.8 (6.2–9.2)
Second NHT (n=44)	30	4.1 (2.3–4.3)

Bone Metastasis

Reduction of risk† – 33%



	No. of Events	Median PFS mo (95% CI)
Cabo+Atezo (n=162)	97	6.3 (6.0–8.8)
Second NHT (n=155)	104	4.1 (2.8–5.7)

*PFS ITT population. †Reduction of risk of progression or death with Cabo+Atezo vs second NHT.

Cabozantinib (oral TKI) + Atezolizumab (IV immunotherapy) - Should we use it?? Not right now.

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Many criticisms of CONTACT-02!!

1. **High screen fail rate** - ~40% who tried to enroll were unable to enroll – why?

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3. **("Partial" or "Complete Response") A second NHT doesn't work well after progression on the first, there are more effective options!**
   - Docetaxel or Cabazitaxel chemotherapy, Pluvicto (Lutetium PSMA)

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7. **Few patients were healthy enough to receive other treatments after!** - only 20-30% received other therapy, ~1% got Pluvicto

CONTACT-02- Look PAST the headline!

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DLL3- T cell engager – a new type of targeted immumotherapy for *Neuroendocrine prostate cancer*

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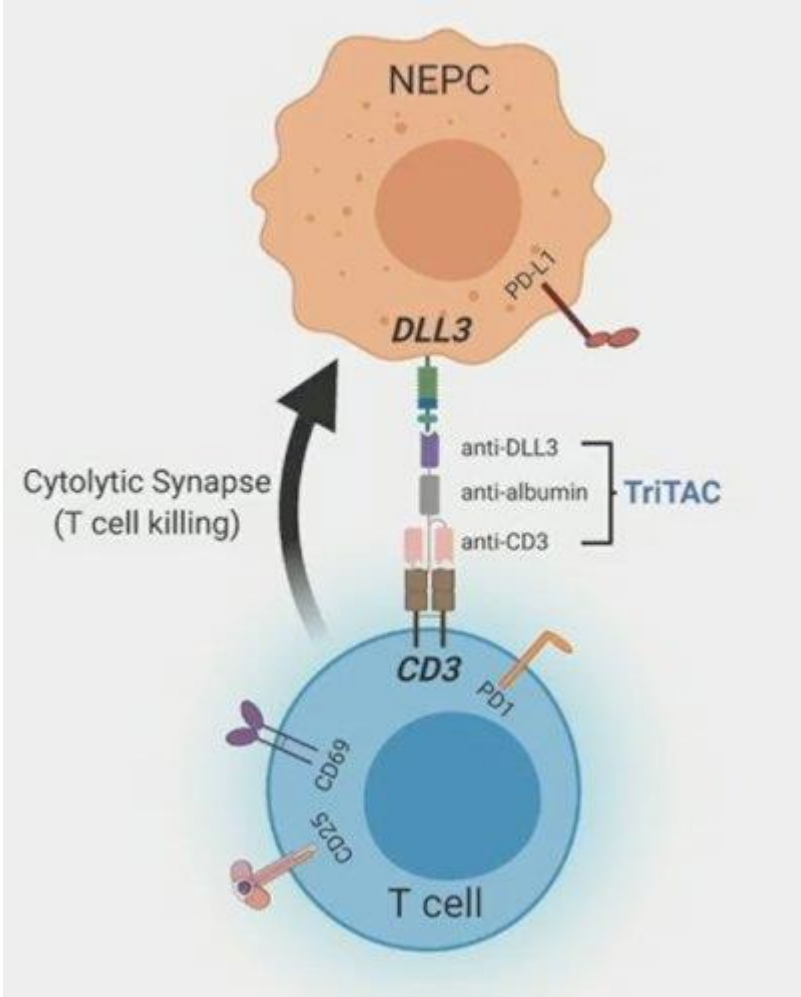
ASCO GU 2024: Interim Results from a Phase 1/2 Study of HPN328, a Tri-Specific, Half-Life Extended DLL3-Targeting T-Cell Engager, in Patients with Neuroendocrine Prostate Cancer and Other Neuroendocrine Neoplasms

- ***Neuroendocrine (small cell) prostate cancer*** (NEPC) is a rare variant of prostate cancer that is treated differently than the typical prostate adenocarcinoma
- Chemotherapy (Platinum+etoposide) is the current standard of care, similar to small cell lung cancer
- NEPC is typically much more aggressive than prostate adenocarcinoma and is more difficult to treat.



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Reference – presentation by Himisha Beltran, MD at ASCO GU 2024

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All Patients Treated (Dose Escalation + 1mg Dose Optimization; N=85)		
Diagnosis	n (%)	
All GU NEC NEPC	21 (24.7) 15 (17.6)	
SCLC	53 (62.4)	
Other NEC	11 (12.9)	
Baseline Characteristics	All tumors N = 85	GU NEC N = 21
Age (Years)		
Median	64	70
Range	41-81	44-81
Sex		
Female	35 (41.2)	3 (14.3)
Male	50 (58.8)	18 (85.7)
Race	n (%)	n (%)
White	76 (89.4)	18 (85.7)
Asian	4 (4.7)	1 (4.8)
American Indian or Alaska Native	1 (1.2)	0
Multiple	1 (1.2)	0
Other	1 (1.2)	1 (4.8)
Unknown	2 (2.4)	1 (4.8)
ECOG	n (%)	n (%)
0	37 (43.5)	12 (57.1)
1	48 (56.5)	9 (42.9)
# Prior Therapies*	n (%)	n (%)
Median	3	3
Range	1-7	1-7
PD(L)-1 Inhibitors	67 (78.8)	14 (66.7)
Sites of Metastases	n (%)	n (%)
Brain	35 (41.2)	2 (9.5)
Liver	44 (51.8)	13 (61.9)

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Adverse Events [a] N=85	All Grades, n (%)	Grade ≥3, n (%)
Any treatment-emergent AE	85 (100)	44 (51.8)
Any treatment-related AE	79 (92.9)	21 (24.7)
Treatment-Related AEs in ≥10% of subjects		
Cytokine release syndrome (CRS)	50 (58.8)	3 [c] (3.5)
Dysgeusia	30 (35.3)	0
Fatigue	28 (32.9)	1 (1.2)
Diarrhea	16 (18.8)	2 (2.4)
Nausea	15 (17.6)	0
Vomiting	12 (14.1)	0
Decreased appetite	11 (12.9)	0
Neutropenia [b]	8 (9.4)	4 (4.7)

Adverse Events of Special Interest

Adverse Events	Grade 1 n (%)	Grade 2 n (%)	Grade ≥3 n (%)
CRS	26 (30.6)	21 (24.7)	3 (3.5) [c]
ICANS [d]	6 (7.1)	2 (2.4)	0

- 67% of CRS events occurred following the first dose
- CRS Gr2+ was uncommon after 2nd or subsequent doses (N=4, all Gr2)

Data snapshot date: 08Dec2023
ICANS=Immune effector cell-associated neurotoxicity syndrome
[a] Grading per CTCAE v5.0, except cytokine release syndrome (grading per ASTCT 2019)
[b] Includes both neutropenia and neutrophil count decreased
[c] One event at 1 mg priming dose and 2 events at 2 mg priming dose prior to de-escalation of priming to 1 mg
[d] Immune effector cell encephalopathy (ICE) score for ICANS assessment performed at Screening and 6 times during Cycle 1; All events of ICANS were transient, none resulted in dose reduction

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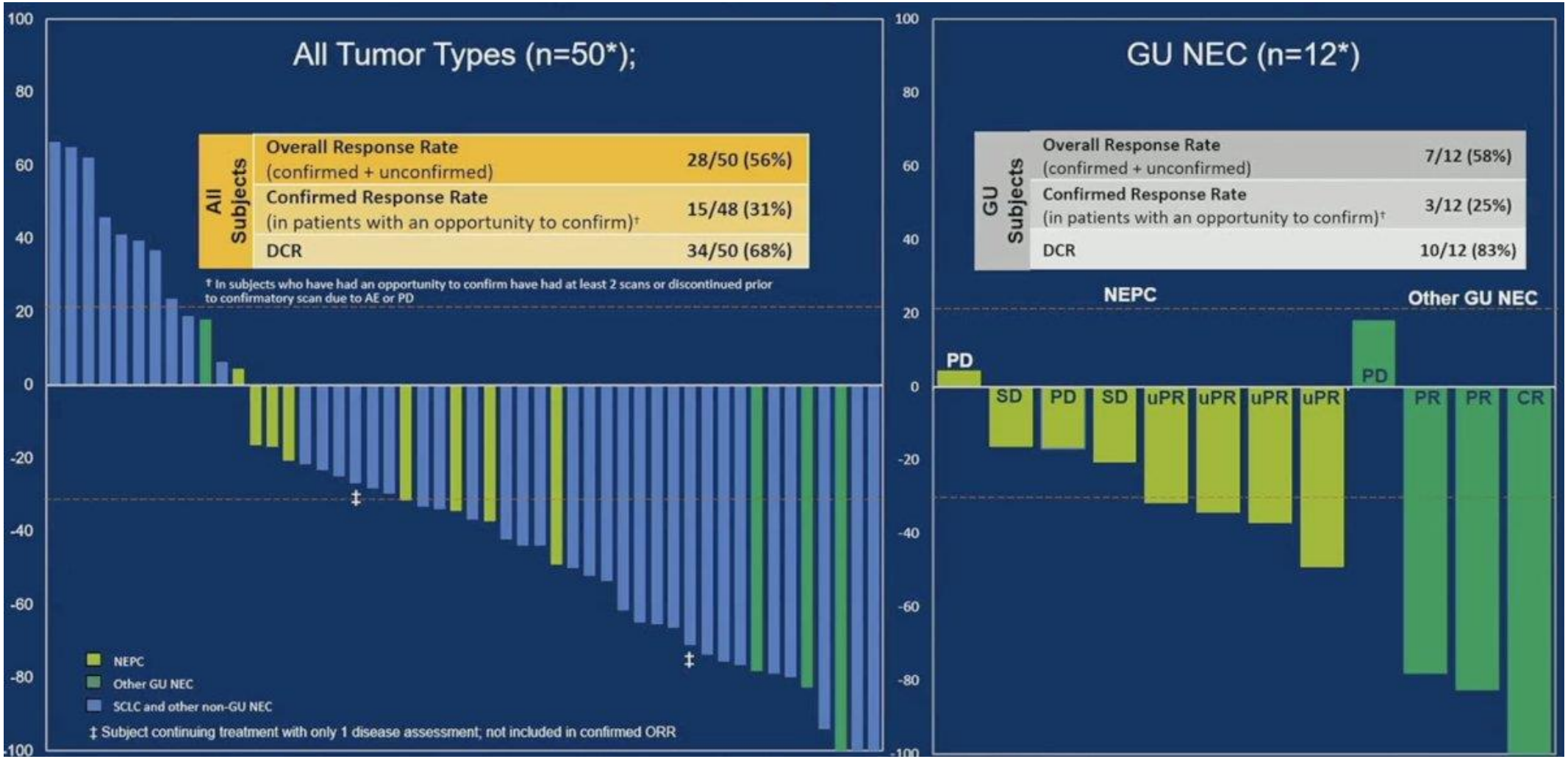

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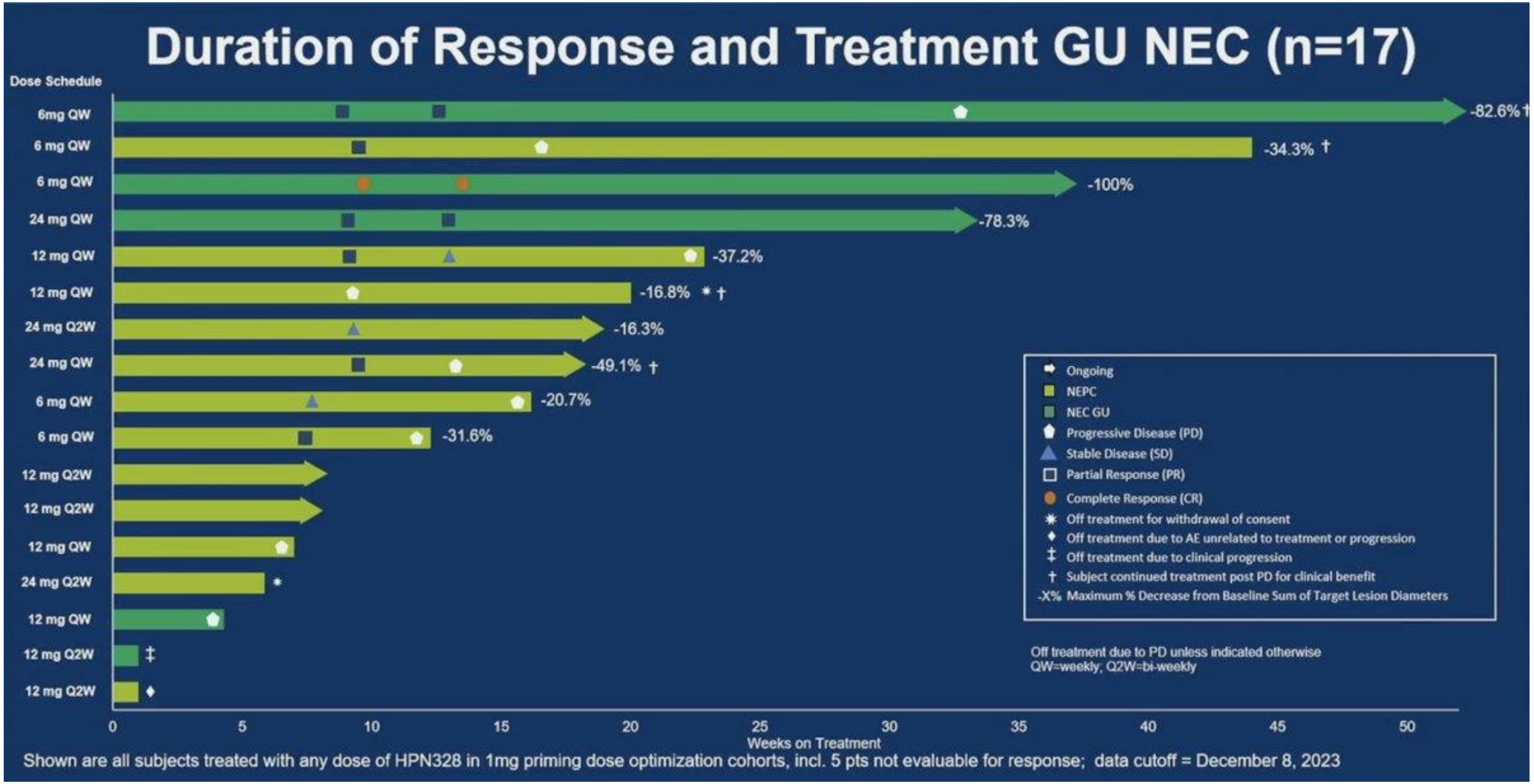

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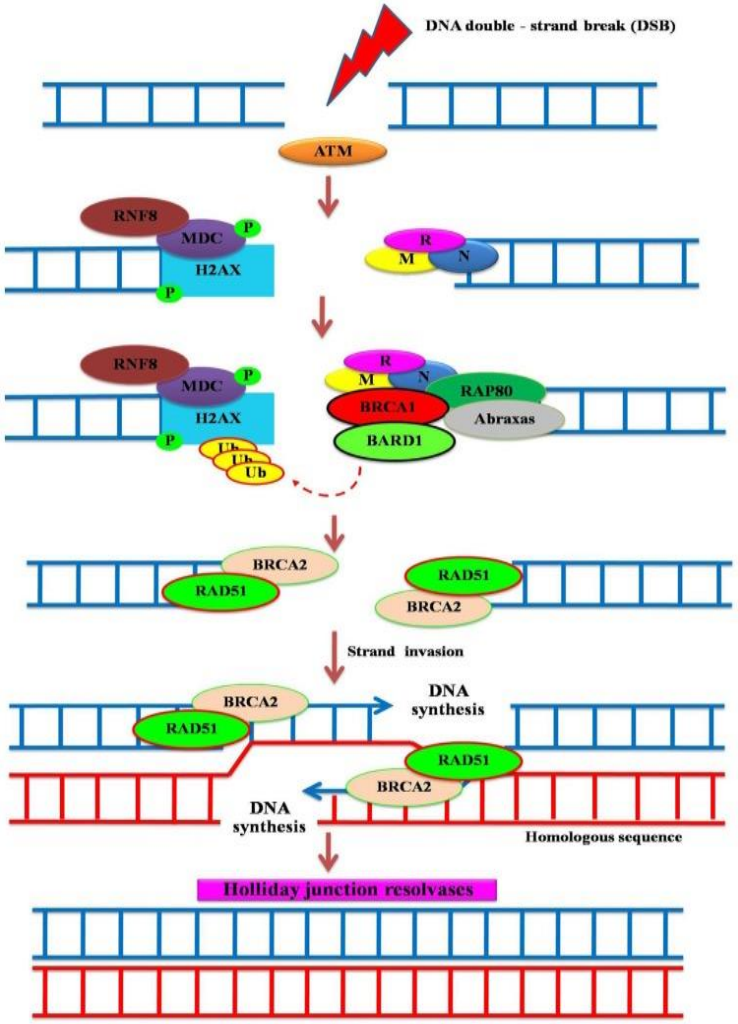
BRCA/HRR mutations and PARP inhibitors

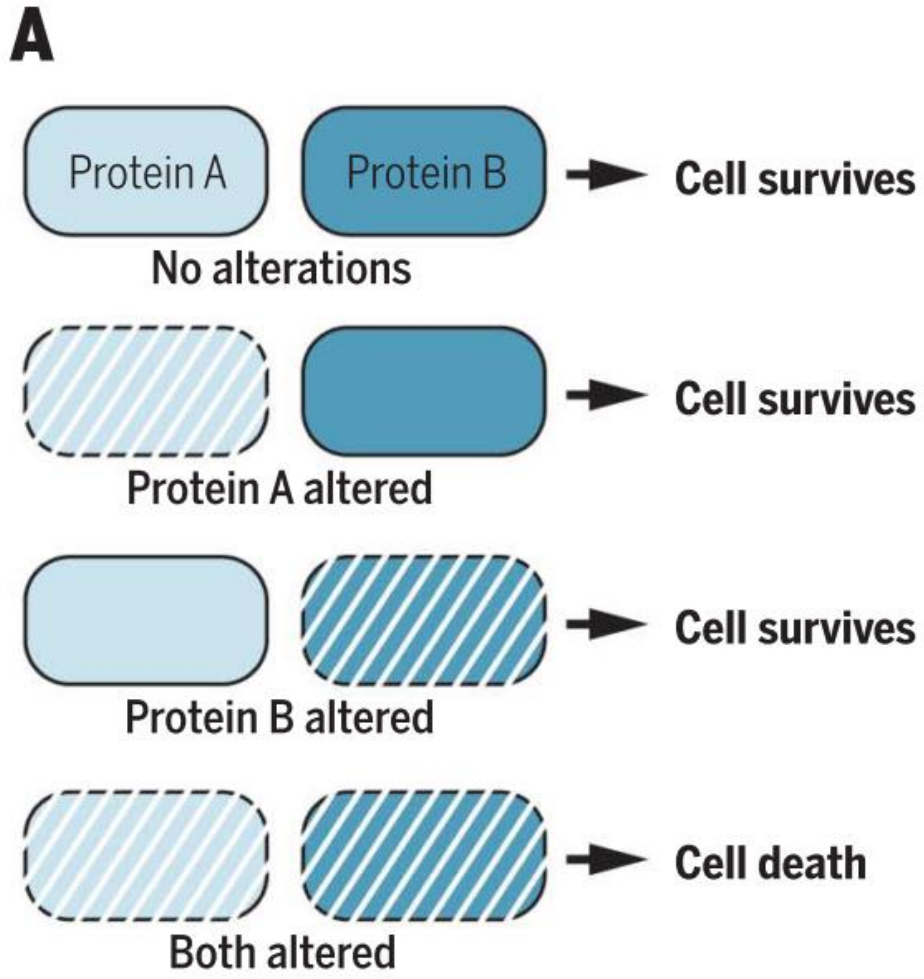
Homologous recombination repair (HRR) defects occur in approximately 20-30% of metastatic castrate resistant prostate cancers

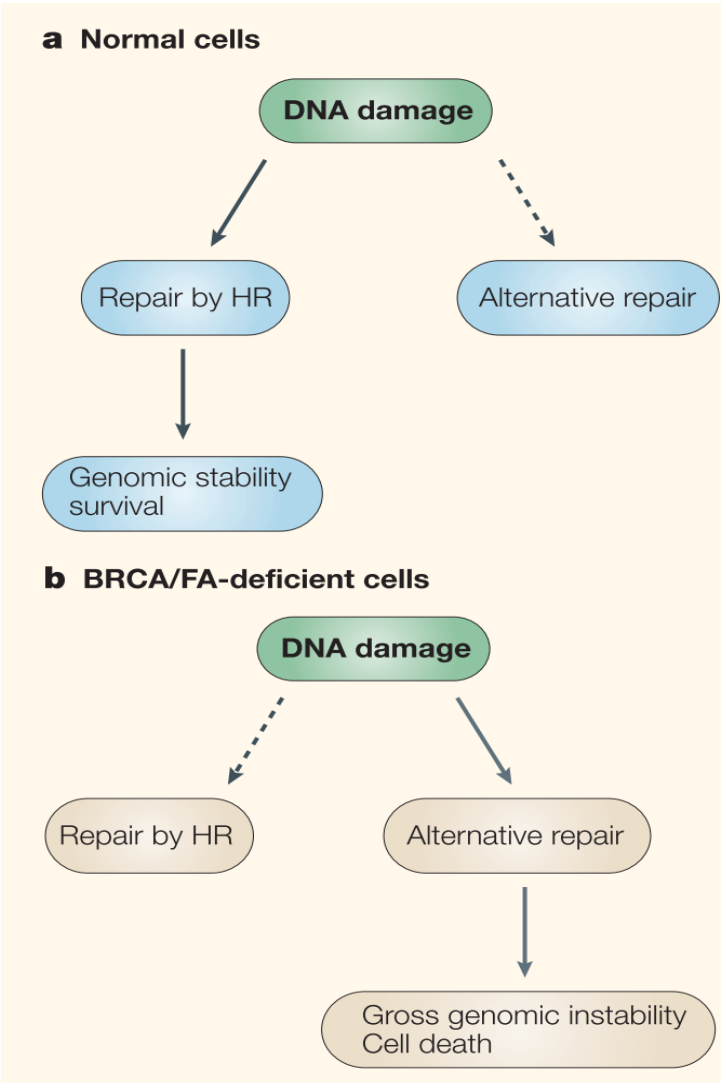


- Approximately 10% are from Germline mutations, i.e. DNA mutations the patient was born with that they could potentially pass on to children/grandchildren
- BRCA2 mutations can be associated with higher risk prostate cancer, with higher Gleason score, stage, and survival
- ***HRR Testing (Germline and Tumor [Somatic]) is recommended for ALL patients with metastatic castrate resistant prostate cancer!***

Robinson et al. Integrative Clinical Genomics of Advanced Prostate Cancer. Cell. 2015
Turner N, et al. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer. 2004

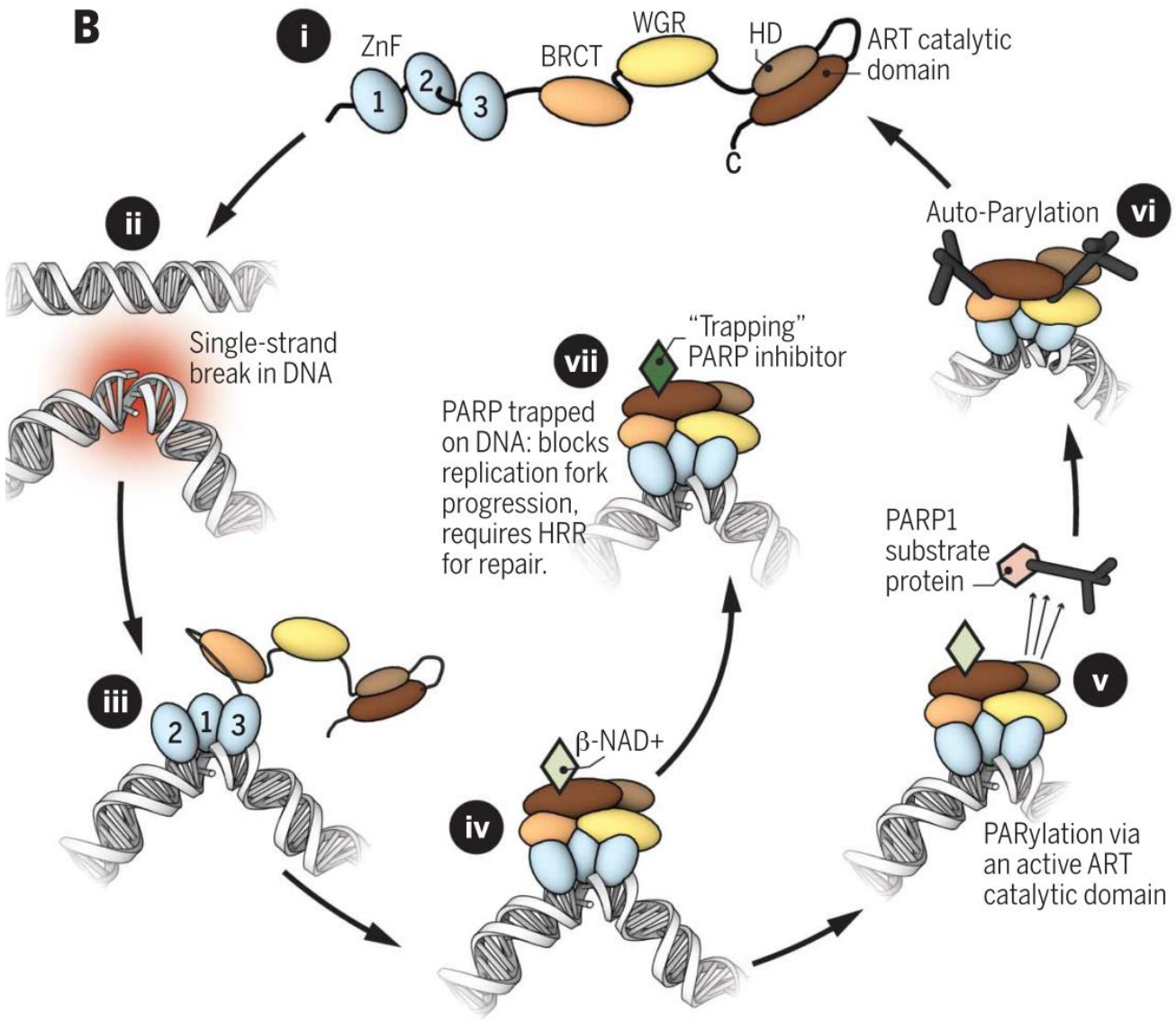
Synthetic Lethality - Inhibiting multiple pathways of DNA repair lead to cell death

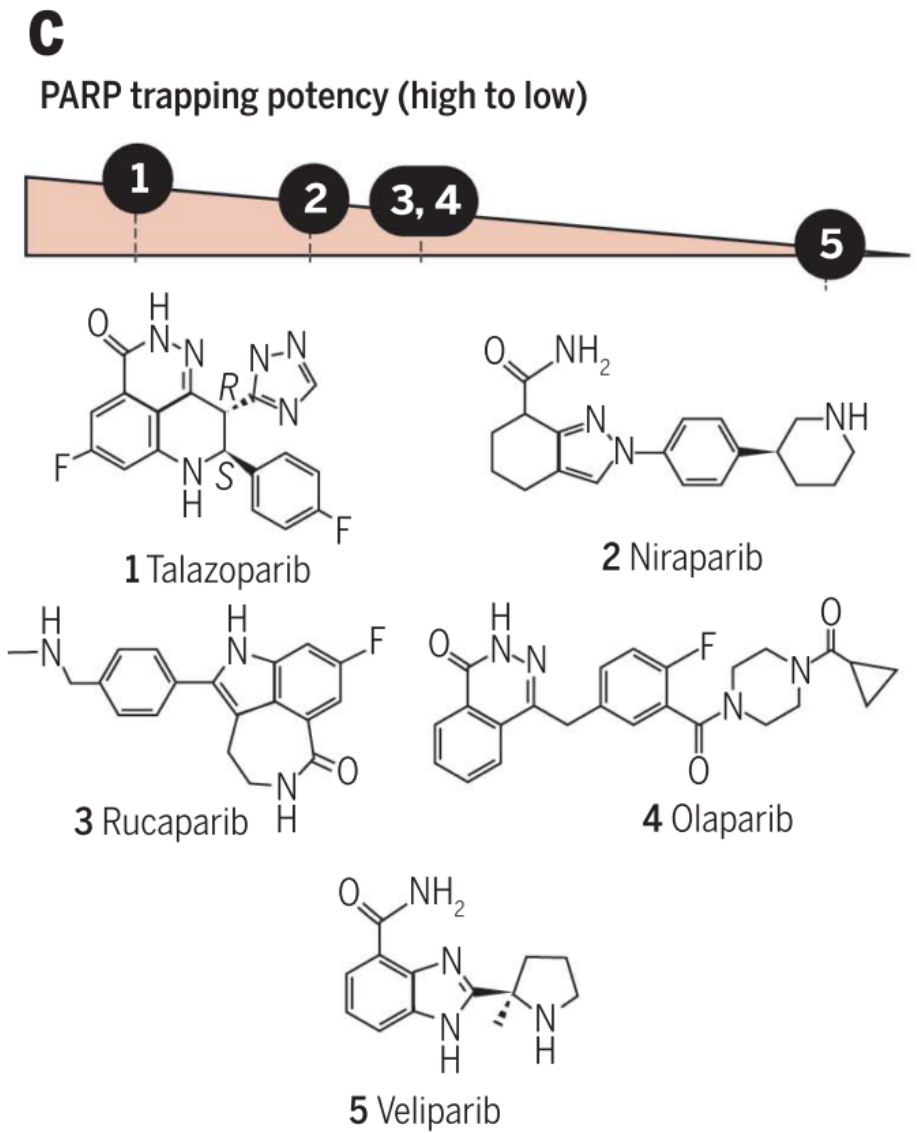




Turner N, et al. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer. 2004
Lord et al. Synthetic Lethality in the clinic. Science. 2017;355:1152–1158.

Blocking an alternative DNA repair – PARP inhibition





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PARP inhibitor combination FDA approvals in 2023

FDA D.I.S.C.O. Burst Edition: FDA approval of Lynparza (olaparib), with abiraterone and prednisone, for BRCA-mutated metastatic castration-resistant prostate cancer

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Podcast

Welcome back to the D.I.S.C.O., FDA's Drug Information Soundcast in Clinical Oncology, Burst Edition, brought to you by FDA's Division of Drug Information in partnership with FDA's Oncology Center of Excellence. Today we'll provide a quick update on a recent FDA cancer drug approval.

On May 31, 2023, the FDA approved olaparib (brand name Lynparza) with abiraterone and prednisone (or prednisolone) for adult patients with deleterious or suspected deleterious BRCA-mutated metastatic castration-resistant prostate cancer, as determined by an FDA-approved companion diagnostic test.

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On June 20, 2023, the Food and Drug Administration approved talazoparib (Talzenna, Pfizer, Inc.) with enzalutamide for homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC).

View full prescribing information for Talzenna

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View full prescribing i

FDA approves niraparib and abiraterone acetate plus prednisone for BRCA-mutated metastatic castration-resistant prostate cancer

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Three studies for PARP inhibitor combos – all slightly different and most for people who never had an oral hormone therapy

	Olaparib + abiraterone/prednisone	Talazoparib + enzalutamide	Niraparib + abiraterone/prednisone
Phase 3 study	PROpel[1]	TALAPRO-2[2]	MAGNITUDE[3]
Comparator	Placebo + AA/P	Placebo + Enzalutamide	Placebo + AA/P
Primary endpoint	rPFS (investigator assessed) in unselected patients	rPFS (BICR) in patients with DDR deficiencies and unselected patients	rPFS (1+3) Cohort 1: HRRm Cohort 2: No HRRm Cohort 3: Fixed dose, open label
HRR-deficient genes	ATM, BRCA1, BRCA2, BARD1, BRP1, CKD12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L	ATM, ATR, BRCA1, BRCA2, CHEK2, FANCL, MLH1, MRE11A, NBN, PALB2, RAD51C	ATM, BRCA1, BRCA2, CDK12, CHEK2, FANCA, HDAC2, PALB2
Prior ARPi	0.15%	8%	3.0%
Prior Docetaxel	23.7%	28.5%	19.3%

1. Saad F et al. 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. Lancet. 2023.
2. Agarwal N et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet. 2023.
3. Chi K et al. 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. Annals of Oncology. 2023.

PARP inhibitors can cause more side effects

MAGNITUDE HRR BM+: Summary of TEAEs

Overall summary, n (%)	NIRA + AAP n = 212	PBO + AAP n = 211
All TEAEs	210 (99.1)	199 (94.3)
Drug related	162 (76.4)	116 (55.0)
Grade 3/4 TEAEs	142 (67.0)	98 (46.4)
SAEs	76 (35.8)	52 (24.6)
Drug related[a]	24 (11.3)	6 (2.8)
Dose reduction due to an AE	42 (19.8)	7 (3.3)
Discontinuation of niraparib or placebo due to AE	23 (10.8)	10 (4.7)
All deaths within 30 days of last dose	19 (9.0)	19 (9.0)
Death due to prostate cancer	8 (3.8)	12 (5.7)
AE	11 (5.2)	7 (3.3)

- The most common AEs leading to dose reduction in the NIRA + AAP group were anemia (13.2%) and thrombocytopenia (2.8%)
- Median relative dose intensity was 99% in the NIRA + AAP group

AAP, abiraterone acetate + prednisone/prednisolone; AE, adverse event; BM, biomarker; HRR, homologous recombination repair; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]AE categorized as related if assessed by the investigator as related to niraparib, abiraterone acetate, or prednisone.

I have metastatic prostate cancer. Is a PARP inhibitor right for me?

1. Talk to your oncologist and make sure they have plans to have your tumor and germline tested for HRR mutations.

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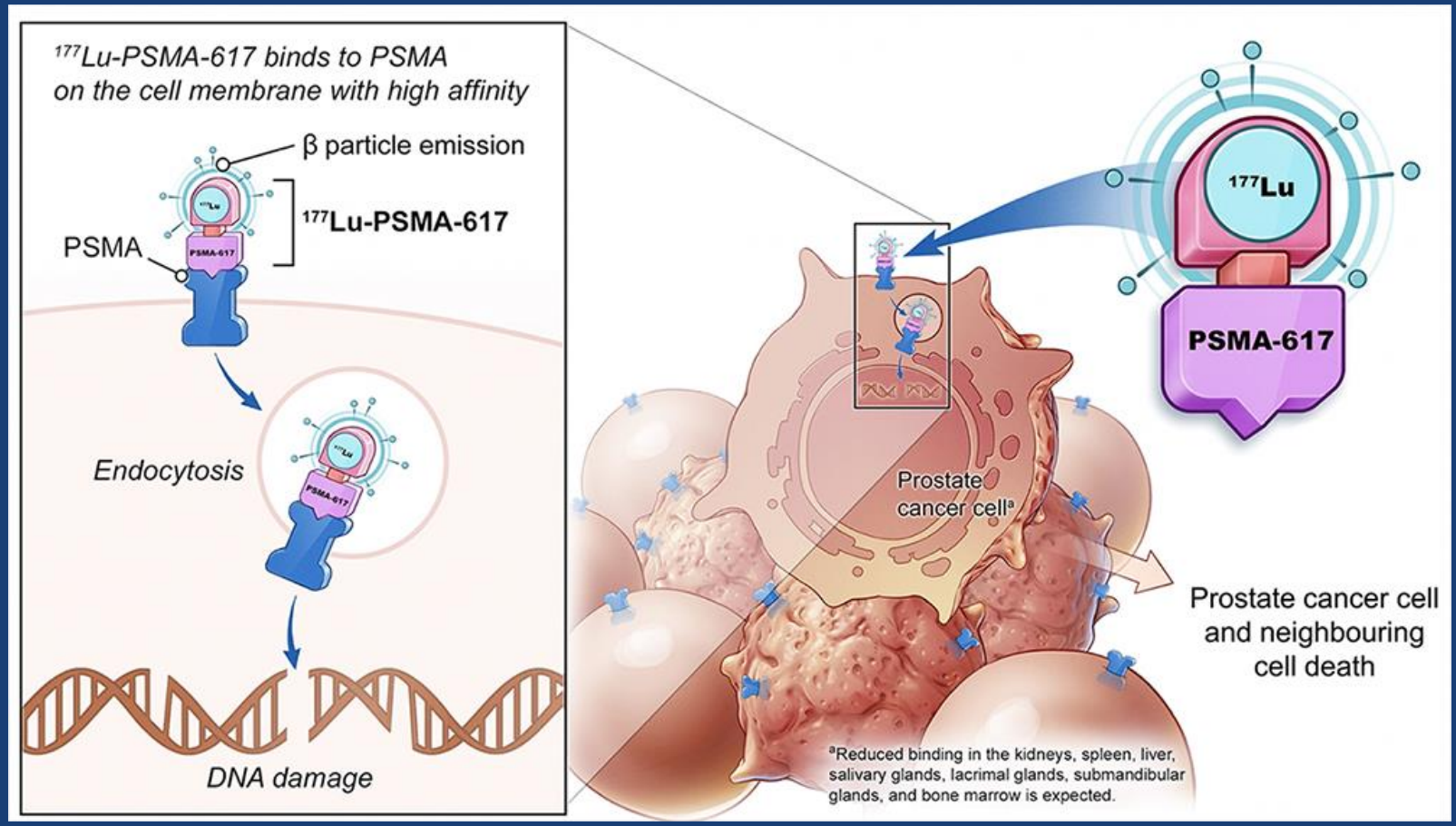
3. If you have taken an oral hormone therapy before, it's unclear if the new combos are better for you than just a PARP inhibitor alone
4. PARP inhibitors can cause more side effects (GI, low blood counts).

Updates for 177Lu-PSMA-617 and other Radio-ligand treatments



We need more treatments AFTER 177Lu-PSMA-617

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

FDA approves Pluvicto for metastatic castration-resistant prostate cancer

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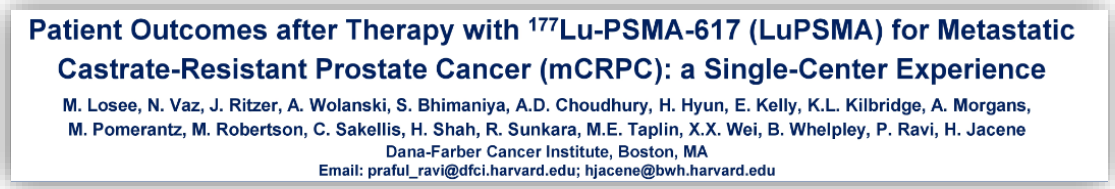
On March 23, 2022, the Food and Drug Administration approved Pluvicto (lutetium Lu 177 vipivotide tetraxetan, Advanced Accelerator Applications USA, Inc., a Novartis company) for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.



Patient Outcomes after Therapy with ^{177}Lu-PSMA-617 (LuPSMA) for Metastatic Castrate-Resistant Prostate Cancer (mCRPC): a Single-Center Experience

M. Losee, N. Vaz, J. Ritzer, A. Wolanski, S. Bhimaniya, A.D. Choudhury, H. Hyun, E. Kelly, K.L. Kilbridge, A. Morgans, M. Pomerantz, M. Robertson, C. Sakellis, H. Shah, R. Sunkara, M.E. Taplin, X.X. Wei, B. Whelpley, P. Ravi, H. Jacene
Dana-Farber Cancer Institute, Boston, MA
Email: praful_ravi@dfci.harvard.edu; hjacene@bwh.harvard.edu

- IRB-approved Prospective registry of all patients with mCRPC receiving standard of care LuPSMA between 06/2022 and 07/2023. (N=96)
- 44% of patients were able to receive another line of therapy after LuPSMA
- Most received chemotherapy (Cabazitaxel+/-platinum), only 36% had PSA response.

There are other Radio-pharmaceutical treatments for prostate cancer that are currently under developement

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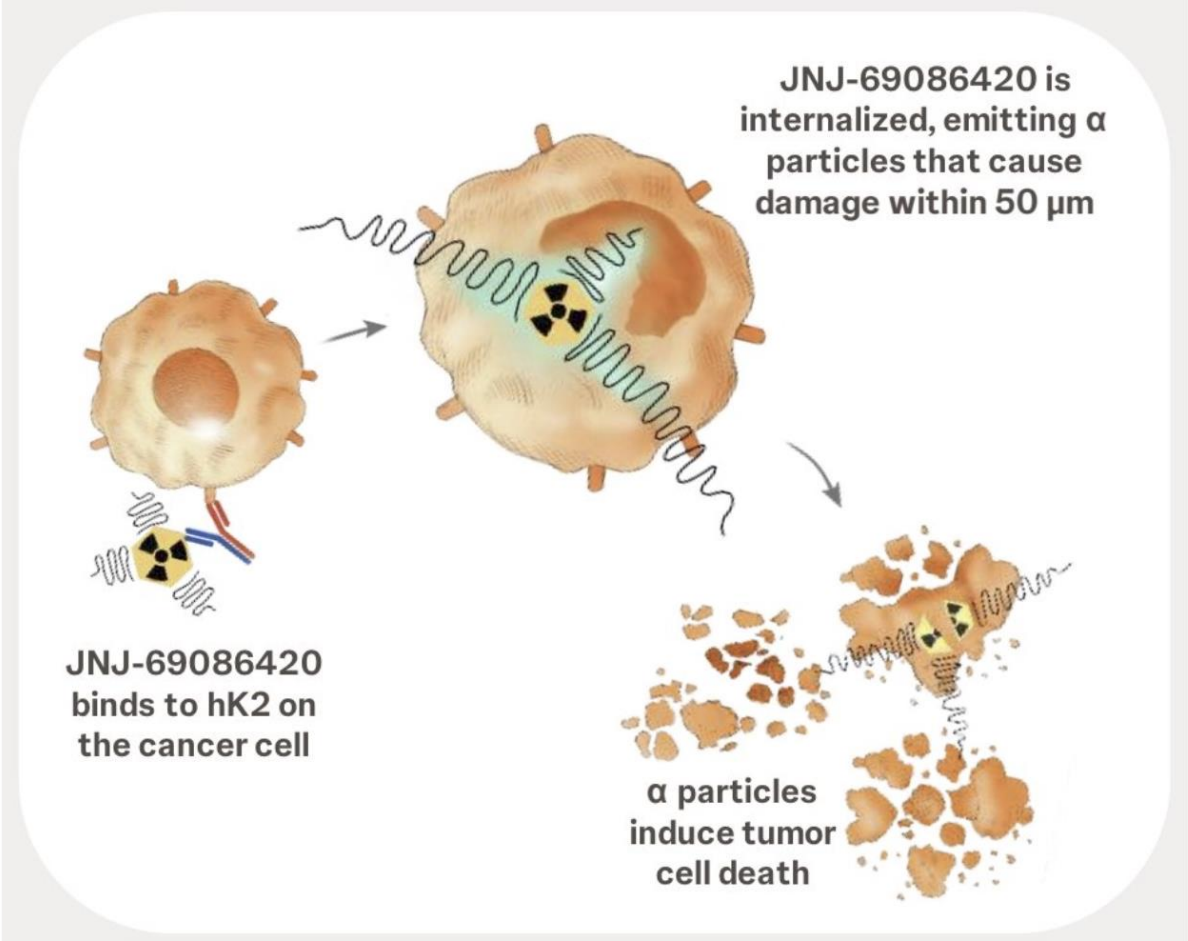
A phase 1 study of JNJ-69086420 (JNJ-6420), an actinium-225 (^{225}Ac) -labeled antibody targeting human kallikrein 2 (hK2), for metastatic castration-resistant prostate cancer (mCRPC).

Authors: Michael J. Morris, Jeffrey Y.C. Wong, Luke Nordquist, Russell Zelig Szmulewitz, Neeraj Agarwal, Edward F. Attiyeh, Steven I Max, ... SHOW ALL ..., and Oliver Sartor | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 16_suppl
https://doi.org/10.1200/JCO.2024.42.16_suppl.5010



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Publication: Journal of Clinical Onc
https://doi.org/10.1200/JCO.2024.4

Adverse Events	All participants N=75	
	Any grade (%)	Grade ≥3 (%)
Any TEAE (in ≥20%)	96.0	61.3
Thrombocytopenia	58.7	17.3
Fatigue	53.3	1.3
Anemia	48.0	25.3
Decreased appetite	41.3	4.0
Nausea	40.0	2.7
Leukopenia	29.3	8.0
Vomiting	29.3	2.7
Cough	24.0	1.3
Dyspnea	24.0	0
Diarrhea	22.7	1.3
Hypertension	20.0	9.3
Dry mouth	20.0	0
Back pain	20.0	2.7
ILD[a]	6.7	5.3
Serious TEAE/TRAE (%)	32.0/16.0	
TEAE/TRAE leading to discontinuation (%)	14.7/12.0	
TEAE/TRAE leading to death[b] (%)	6.7/5.3	

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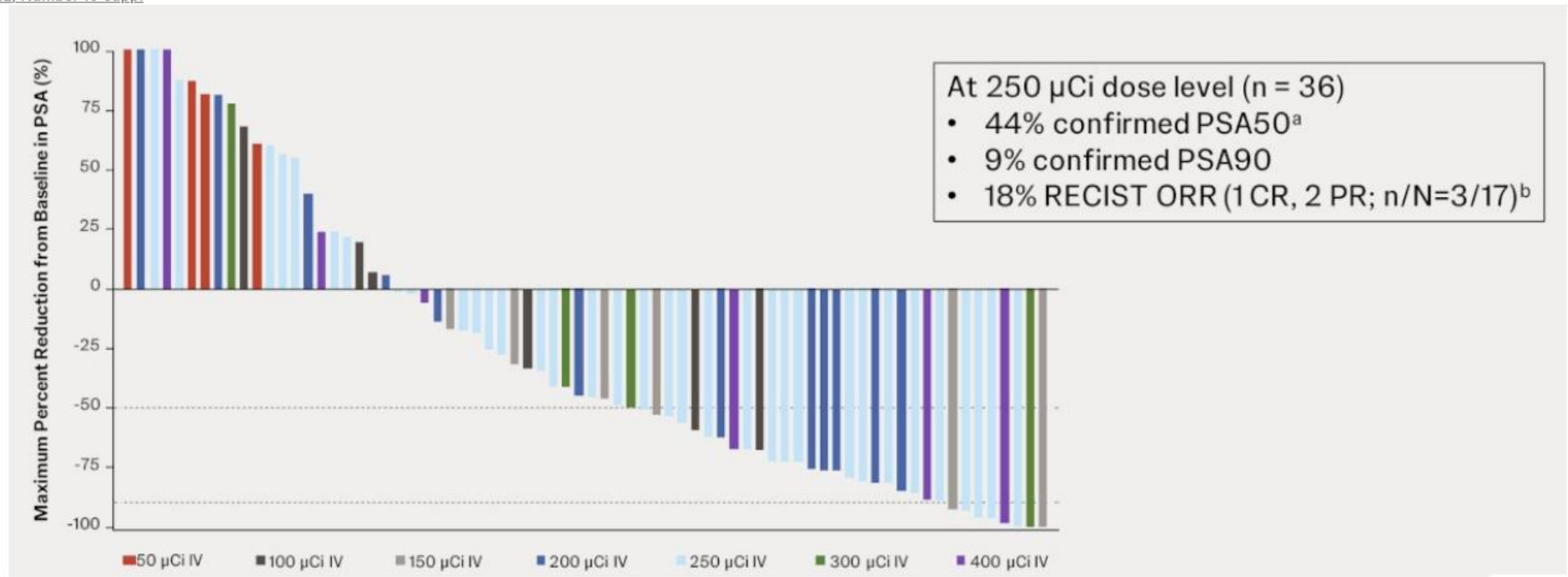

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Other prostate cancer treatment strategies in development

Androgen Receptor Degraders are a newer type of hormone therapy that are currently under development for prostate cancer

Beth Israel Deaconess Medical Center

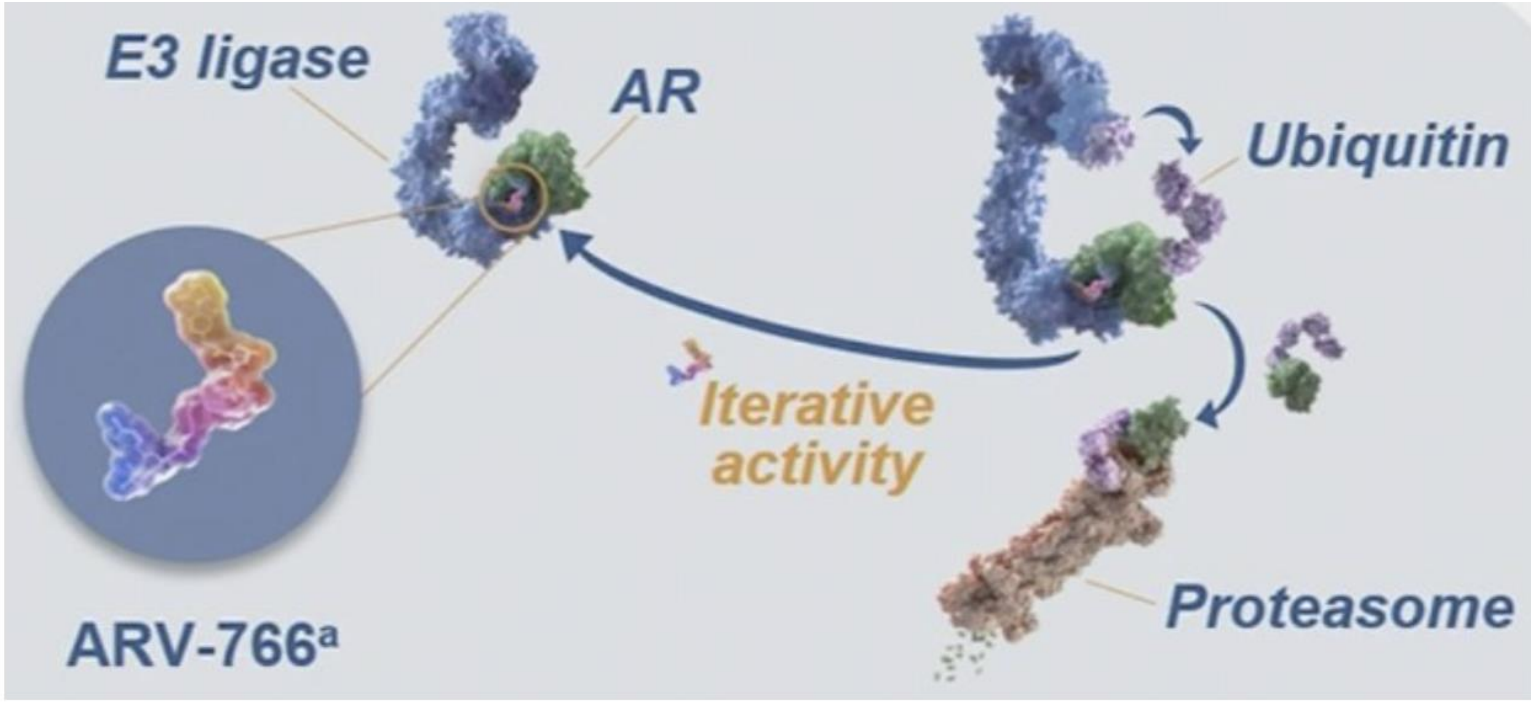
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

ARV-766, a proteolysis targeting chimera (PROTAC) androgen receptor (AR) degrader, in metastatic castration-resistant prostate cancer (mCRPC): Initial results of a phase 1/2 study.

Authors: Daniel P. Petrylak, Meredith McKean, Joshua Michael Lang, Xin Gao, Robert Dreicer, Daniel M. Geynisman, Tyler F. Ste , ... SHOW ALL ..., and Neal D. Shore | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 16_suppl
https://doi.org/10.1200/JCO.2024.42.16_suppl.5011

* In phase 1, there were no dose-limiting toxicities, and a maximum tolerated dose was not reached



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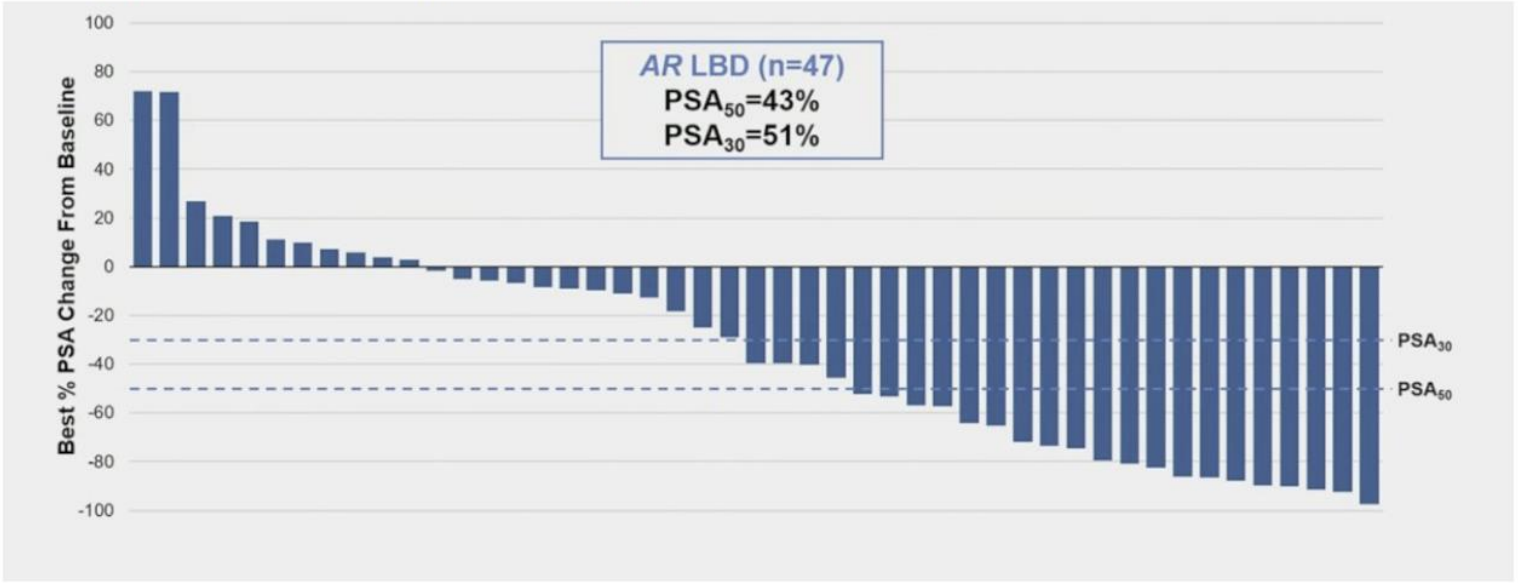
Among patients with *AR* ligand-binding domain mutations, PSA50 was 43% and PSA30 was 51%:



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Stay Tuned!