Precision Oncology For Metastatic Castration-Resistant Prostate Cancer

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What is mCRPC?

- Shows resistance to standard ADT and ARPI's

Mechanisms include;

- Mutations in Androgen Receptor (AR)
- High Heterogeneity
- Switch to a neuroendocrine subtype - emergent neuroendocrine prostate cancer (t-NEPC)

Precision Oncology Tools For mCRPC

(1) Tumour DNA Sequencing

(2) HER2 IHC testing

(3) Tumour RNA Expression Testing

Tumour DNA Sequencing For mCRPC

(1) Parp Inhibitors (PARPi's)

(2) High Tumour Mutation Burden (TMB)

PARP Inhibitors For mCRPC

PARP inhibitors trap the PARP-1 protein at DNA mutations preventing DNA repair, replication, and transcription.

Results in increased DNA single-strand breaks (SSBs) which are converted into toxic double-strand breaks (DSBs).

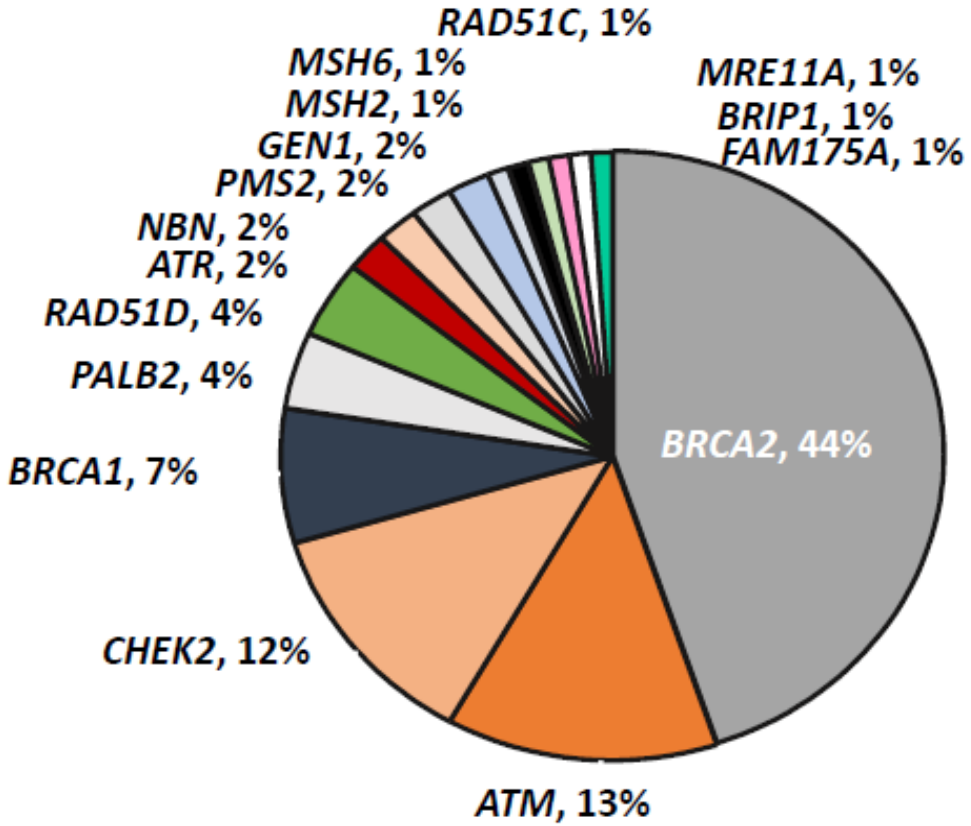
The cancer cell cannot repair the DSBs and dies.

PARPi's For mCRPC

In order for these drugs to work, the tumour must have mutations in Homologous Recombination Repair (HRR) genes.

The following slide shows the HRR genes and their rate of occurrence in mCRPC's.

HRR Genes Targeted By PARPi's



Pritchard. NEJM. 2016;375:443.

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FDA Approved PARPi's For mCRPC

Olaparib - Approved in 2020 for mCRPC who have genomic alterations in specific HRR genes and in combination with Abiraterone for BRCA-mutated mCRPC patients.

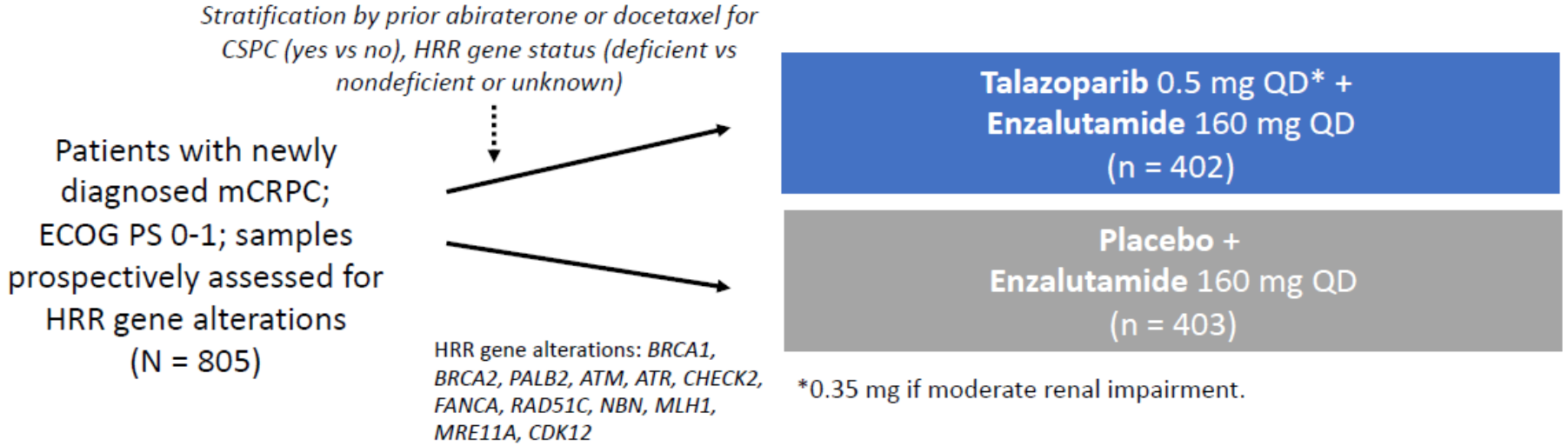
Rucaparib - Approved for mCRPC with mutated BRCA1/BRCA2.

Talazoparib - Approved in combination with Enzalutamide for patients with HRR gene-mutated mCRPC.

Niraparib - Approved in combination with Abiraterone for BRCA-mutated mCRPC.

TALAPRO-2
First-Line Enzalutamide ± Talazoparib for mCRPC

- Randomized, double-blind, placebo-controlled phase III trial

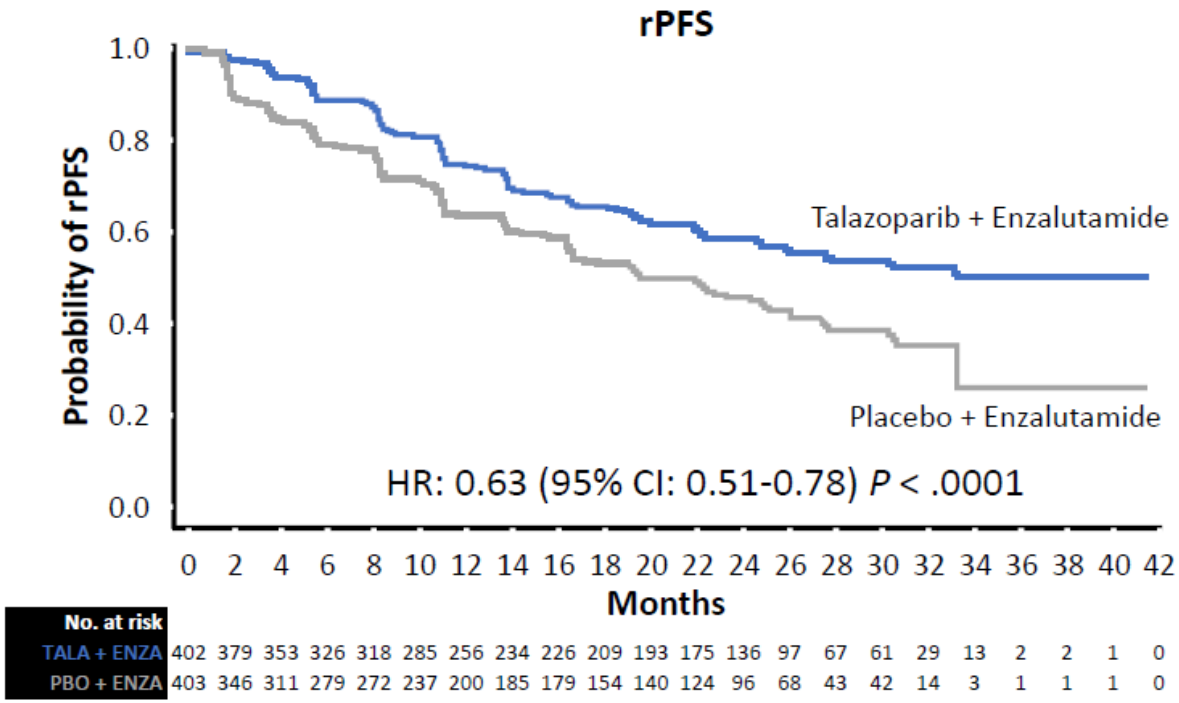


*0.35 mg if moderate renal impairment.

- **Primary endpoint:** rPFS by BICR
- **Key secondary endpoint**: OS
- **Other secondary endpoints:** time to cytotoxic chemotherapy, PFS2 (by investigator), ORR, PROs, safety

Agarwal. ASCO GU 2023. Abstr LBA17.

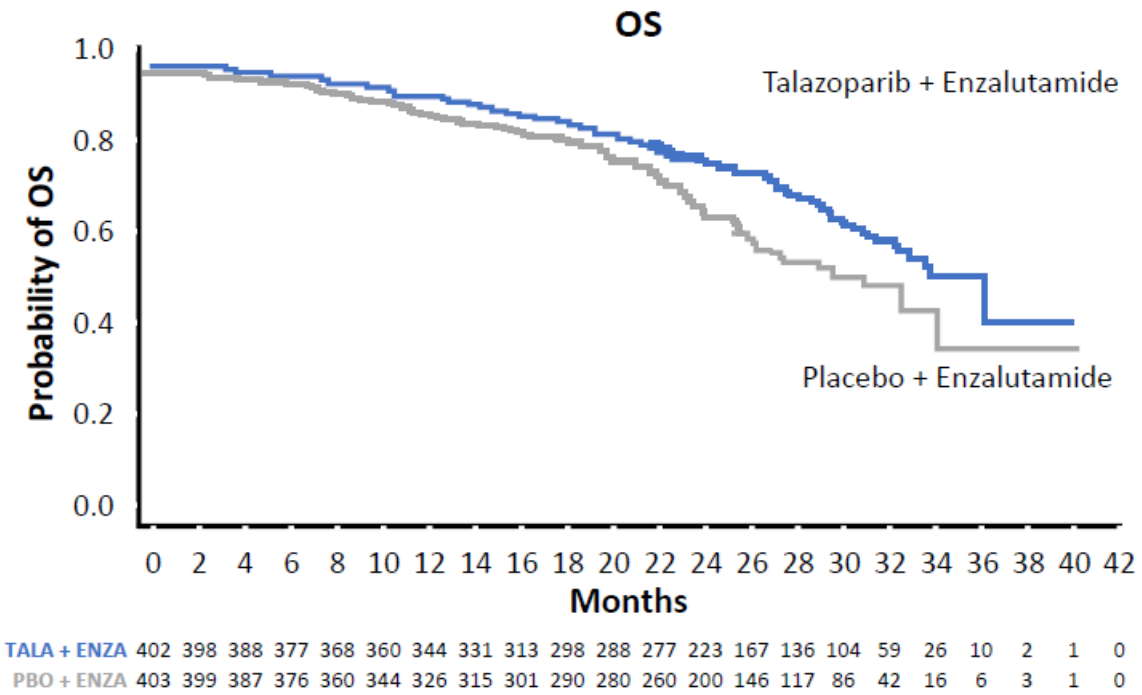
TALAPRO-2
rPFS by BICR



	Talazoparib + Enzalutamide (n = 402)	Placebo + Enzalutamide (n = 403)
Events, n	151	191
Median rPFS, mo	NR (27.5-NR)	21.9 (16.6-25.1)
Median f/u, mo	24.9	24.6

- Investigator assessed rPFS HR: 0.64 (95% CI: 0.50-0.91) *P* < .001

TALAPRO-2
Overall survival in HRR MUT+ subgroup



	Talazoparib + Enzalutamide (n = 200)	Placebo + Enzalutamide (n = 199)
Events, n	43	53
Median OS, mo	NR(36.4-NR)	33.7 (27.6-NR)

HR: 0.69 (95% CI: 0.46-1.03) *P* = .068

- OS data at 24% mature; additional follow-up is needed

Agarwal N et al. The Lancet. 2023. doi.org/10.1016/S0140-6736(23)01055-3

PROpel
First-line Abiraterone/Prednisone ± Olaparib in mCRPC

- International, randomized, double-blind phase III study

Stratified by metastatic disease sites (bone only vs visceral vs other); taxane for mHSPC (yes vs no)

Patients with mCRPC
- No prior tx for mCRPC
- Ongoing ADT
- Docetaxel for mHSPC allowed
- No prior abiraterone
- ECOG PS 0/1
- **No screening for HRR mutations required**, but optional biopsies and blood collected for NGS testing

(N = 796)

Olaparib 300 mg BID + **Abiraterone** 1000 mg QD + **Prednisone/Prednisolone** 5 mg BID (n = 399)

Placebo + **Abiraterone** 1000 mg QD + **Prednisone/Prednisolone** 5 mg BID (n = 397)

Until radiographic progression or unacceptable toxicity

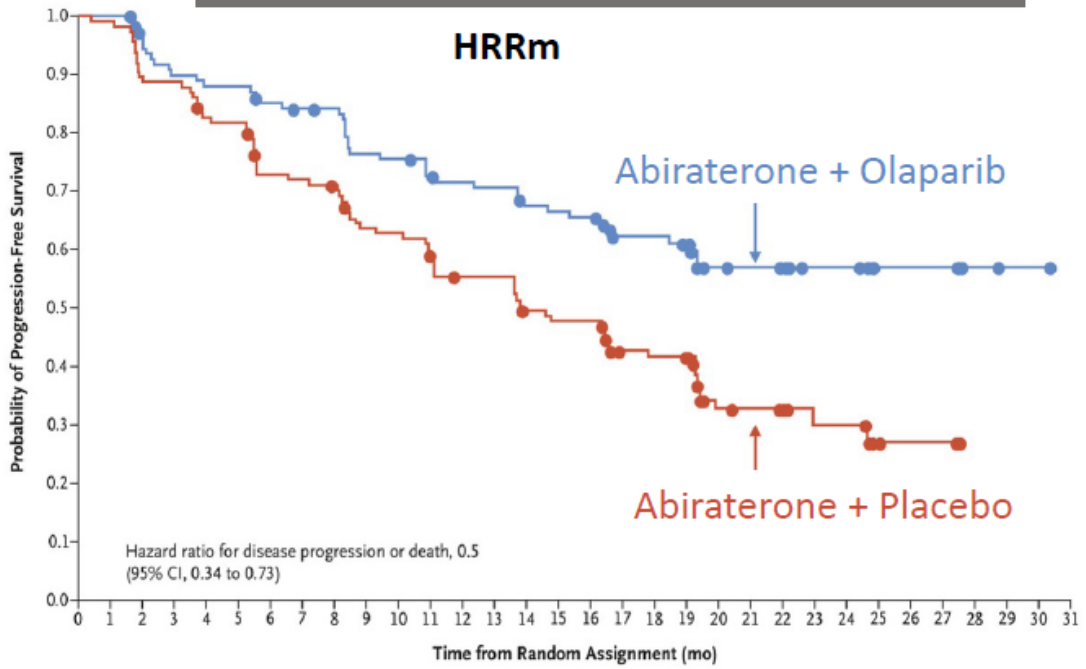
Crossover from placebo to olaparib not permitted

- **Primary endpoint**: rPFS by investigator
- **Key secondary endpoints**: OS, time to subsequent therapy or death, PFS2, ORR, HRRm prevalence (retrospectively assessed), HRQoL, safety

PROpel
rPFS by HRR status

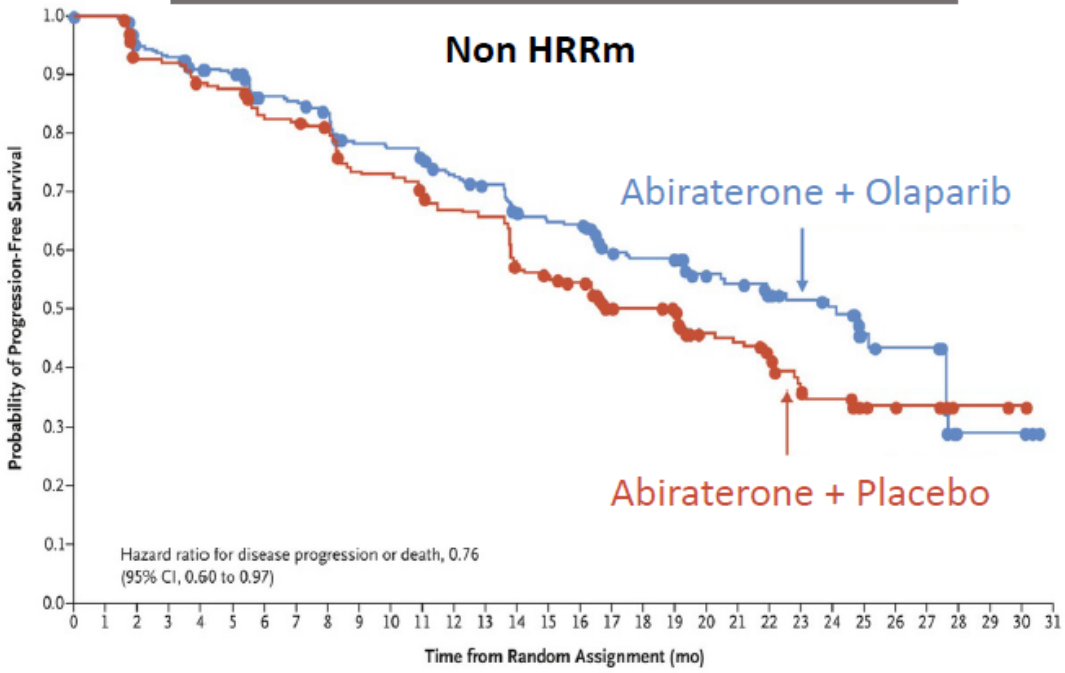
	Abi + Ola (n = 111)	Abi + Placebo (n = 115)
Events, n (%)	43 (38.7)	73 (63.5)
Median rPFS, mo	NR	13.9
	HR: 0.5 (95% CI: 0.34-0.73)	

HRRm



	Abi + Ola (n = 279)	Abi + Placebo (n = 273)
Events, n (%)	119 (42.7)	149 (54.6)
Median rPFS, mo	24.1	19.0
	HR: 0.76 (95% CI: 0.60-0.97)	

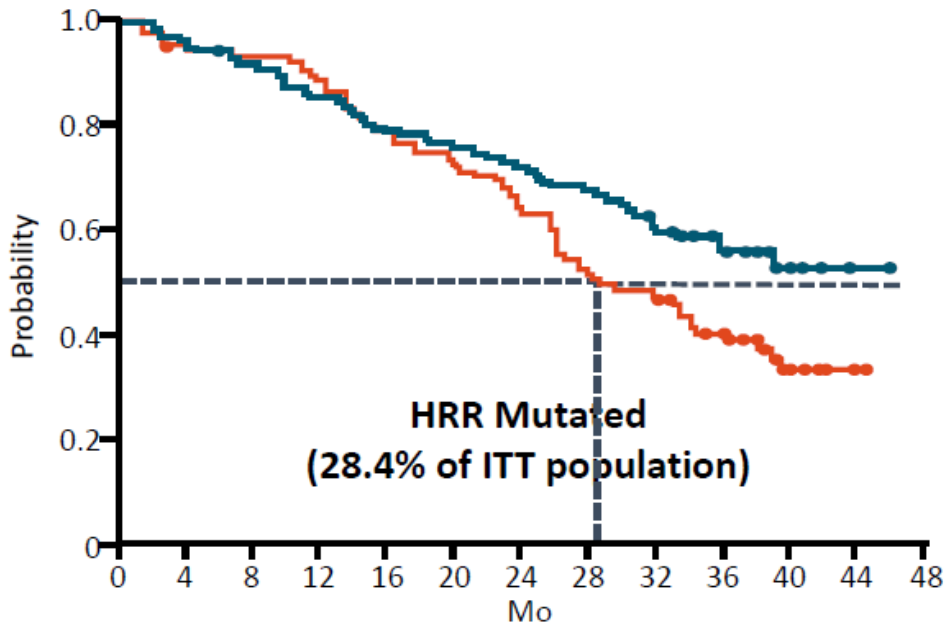
Non HRRm



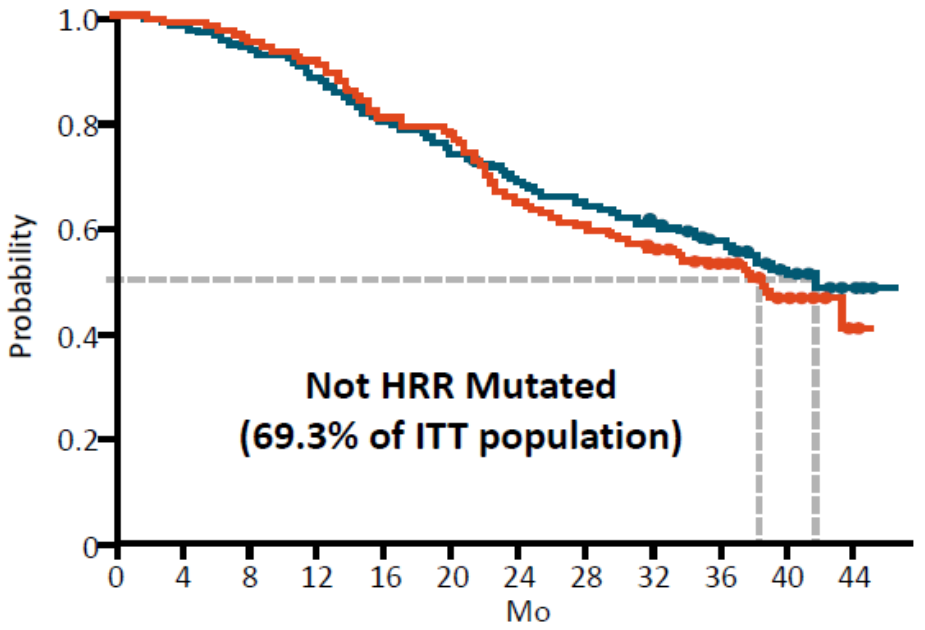
Clarke. NEJM Evid. 2022;1.

PROpel
OS by HRR status

	Abi + Ola (n = 111)	Abi + Placebo (n = 115)
Median OS, mo	NR	28.5
	HR: 0.66 (95% CI: 0.45-0.95)	



	Abi + Ola (n = 279)	Abi + Placebo (n = 273)
Median OS, mo	42.1	38.9
	HR: 0.89 (95% CI: 0.70-1.14)	



Clarke. ASCO GU 2023. Abstr LBA16.

ASCO® Genitourinary Cancers Symposium

Abstract # 19

BRCAAway: A Randomized Phase 2 Trial of Abiraterone, Olaparib, or Abiraterone + Olaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) bearing Homologous Recombination-Repair Mutations (HRRm)

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pcctc
The Prostate Cancer Clinical Trials Consortium

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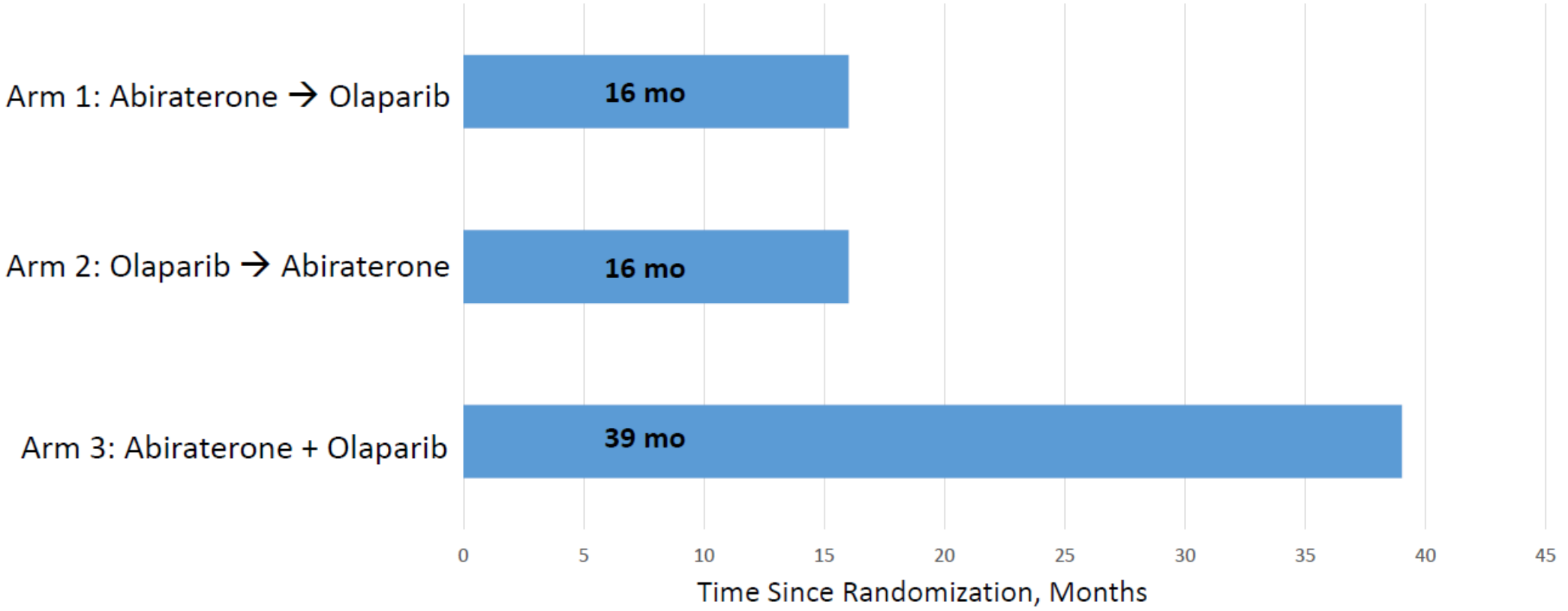
Median PFS from Randomization to End of Crossover Treatment



Hussain M., ASCO GU 2024

High Tumour Mutation Burden (TMB) For mCRPC

A tumor is identified as having a high TMB when it has at least 10 mutations per megabase (mut/Mb).

Pembrolizumab (a form of immune therapy) is approved for mCRPC as part of the tumour agnostic approval for patients with mismatch repair deficient (dMMR), microsatellite instability high (MSI-H) or high tumor mutational burden (TMB) (≥10 mutations per mega base (mut/Mb)) who have progressed.

Comparative Effectiveness of Immune Checkpoint Inhibitors vs Chemotherapy by Tumor Mutational Burden in Metastatic Castration-Resistant Prostate Cancer

Ryon P. Graf, PhD[1]; Virginia Fisher, PhD[1]; Janick Weberpals, RPh, PhD[2]; et al.

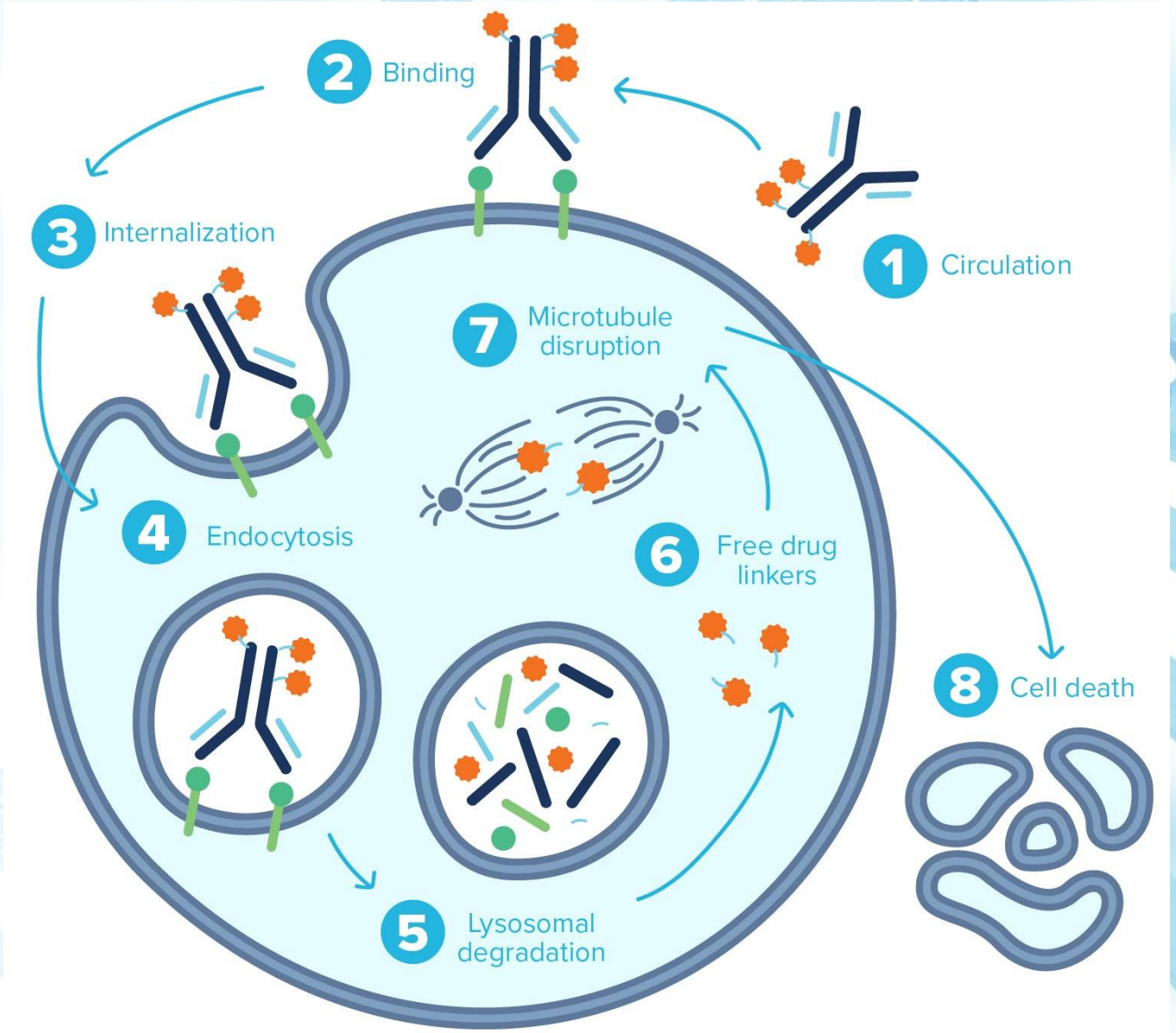
In this comparative effectiveness study of 741 patients with mCRPC, patients with TMB of 10 mutations per megabase (mt/Mb) or greater had significantly longer time to next treatment and overall survival with ICIs vs Taxanes.

Antibody Drug Conjugates; HER2 IHC testing; and Tumour RNA expression testing for mCRPC

HER2 is a cell receptor that is over-expressed in a variety of cancers.

What is an Antibody Drug Conjugate (ADC)?

ADC Mechanism



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Because ADC's like T-DXd target unique receptors or cell antigens, they can be used on any cancer that expresses HER2.

Additionally, the bystander effect of T-DXd allows it to work in HER2–low, or tumours that don't have the HER2 receptor on every tumour cell.

T-DXd is only one of many ADC and we see new ones coming out weekly!

August 31, 2023 - FDA Grants Breakthrough Therapy Designations to Trastuzumab Deruxtecan (T-DXd) for HER2+ Solid Tumors

The FDA has granted 2 breakthrough therapy designations to fam-Trastuzumab deruxtecan-nxki (Enhertu) for the treatment of patients with unresectable or metastatic HER2-positive solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options.

Case Example: Patient with Advanced Prostate Cancer Benefiting from T-DXd

60yr old with high-volume metastatic prostate cancer initially received ADT/docetaxel but progressed.

Treated consecutively with six additional lines of therapy, which each elicited a transient response followed by rapid progression.

He subsequently developed symptomatic brain metastases and had craniotomy with tumor resection followed by radiotherapy.

Histopathology was consistent with transformation to t-NEPC, a particularly aggressive subtype of the already mCRPC.

IHC for HER2 showed strong expression in both the primary prostate tumor and the brain metastasis.

After 4 cycles of T-Dxd, there was a 57% overall reduction in tumor volume across sites, including the brain. In addition, computed tomography showed stable bone metastases.

Blood counts and lactate dehydrogenase level normalized, and his performance status improved, despite being recommended for palliative hospice care several months earlier.

RNA expression testing determines what ADCs will work for you with a single test.

To find out more about RNA Expression testing of 20,813 Genes and identify all possible approved ADC therapies for your cancer, visit.
https://youtu.be/HU_1uaWxNOs?si=hDzVIFp6jhJXQK6X

Educational Video on ADCs.
https://www.youtube.com/watch?v=7_cR73Ga6Sg&t=1786s

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