Immunotherapy and Exciting Updates in Advanced Prostate Cancer

13th Annual WCS

March 2, 2024

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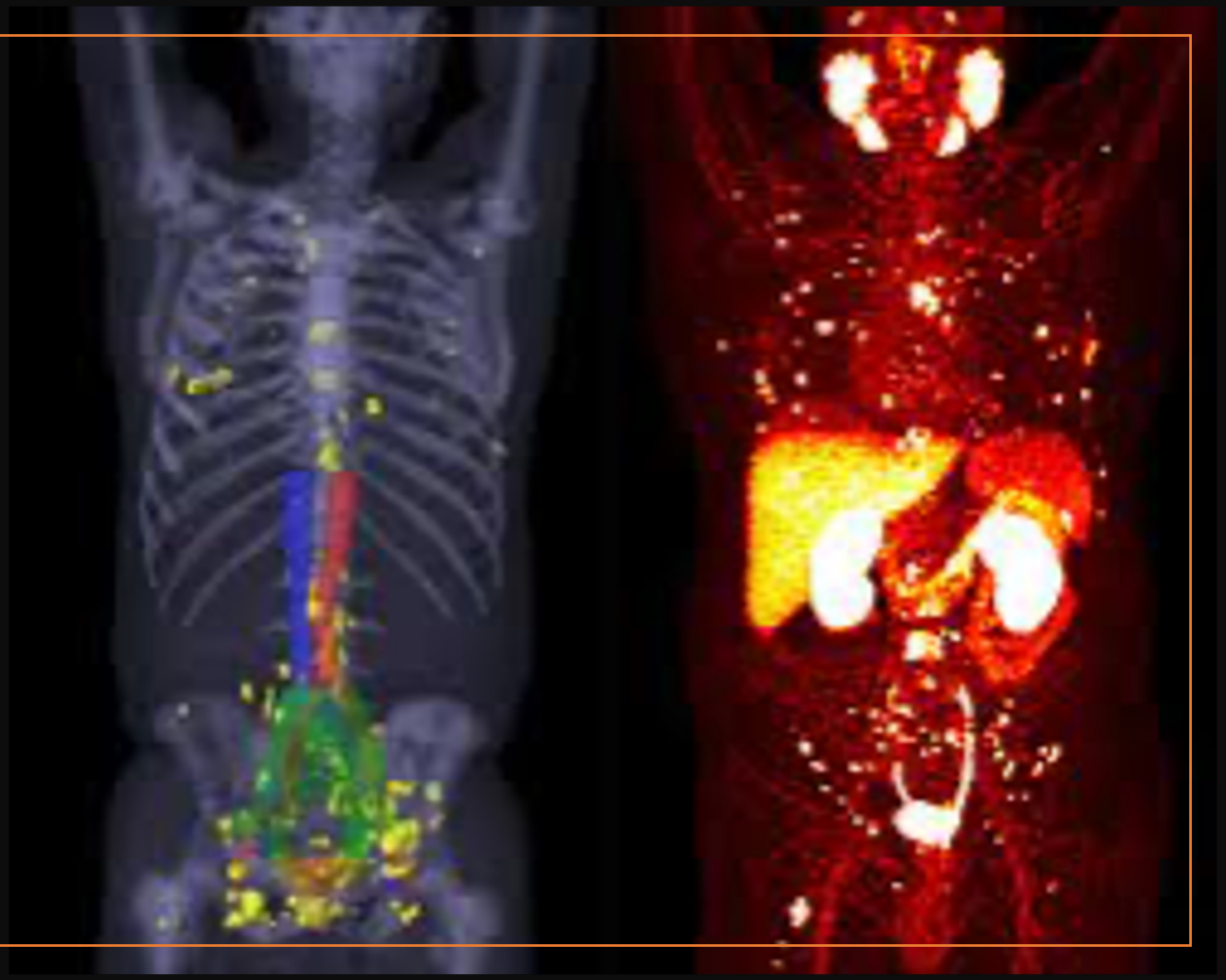
Genitourinary Oncology | UIC

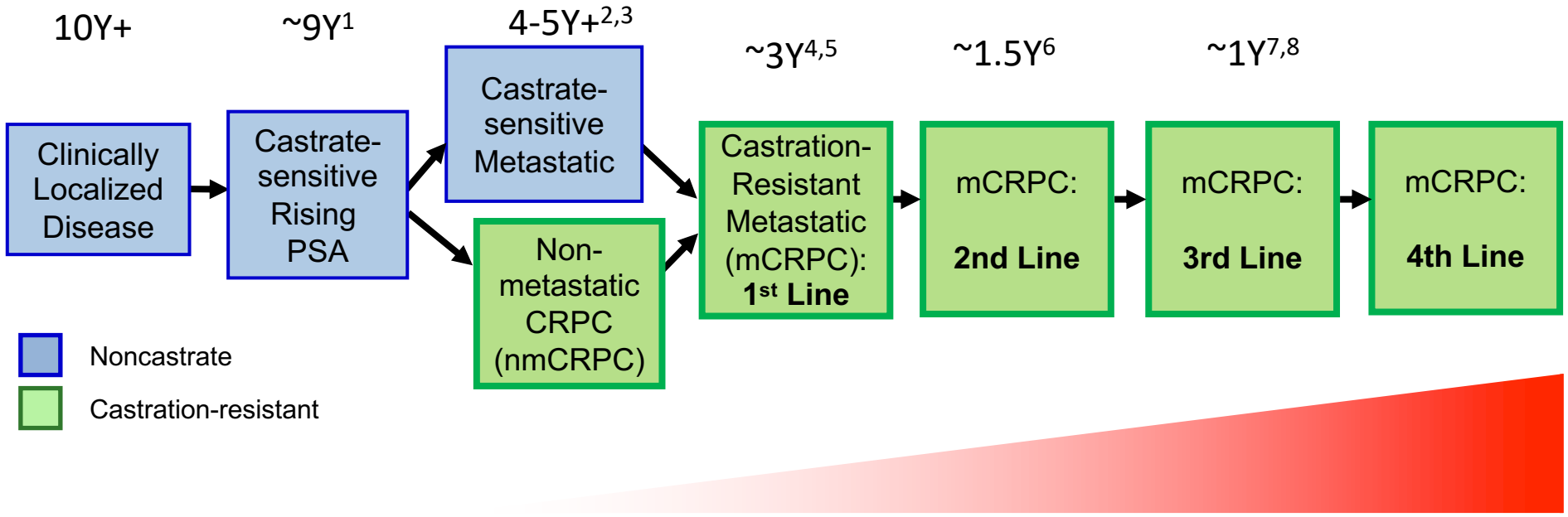


Imaging courtesy of HealthImaging.com

Outline

- Landscape of Advanced Disease Treatment Options
- Role for Genomic Sequencing and PARPi Regimens
- Radioligand Therapies
- Immunotherapy

Clinical States of Prostate Cancer



Death from Prostate Cancer

1. Crook et al, *NEJM,* 2012 [NCIC PR07]
2. Sweeney et al, *NEJM*, 2015 [CHAARTED]
3. Fizazi et al, *NEJM*, 2017 [LATITUDE]
4. Ryan et al, *Lanc Onc*, 2015 [COU-302]
5. Scher et al, *NEJM,* 2012 [AFFIRM]
6. deBono et al, *Lancet,* 2010 [TROPIC]
7. Smith et al, *JCO*, 2016 [COMET-I]
8. Mateo et al, *NEJM*, 2015 [TOPARP]

Modified from Scher ASCO 2015, Dr. Szmulewitz

Intensification of Systemic Therapy Earlier in the Disease Course of Castration Sensitive Prostate Cancer

Radiation to primary
Oligometastatic tx

Visceral metastases AND at least one bone lesion
OR
at least 4 bone lesions with at least one outside the axial skeleton

STAMPEDE M0: ADT + AAP
EMBARK: Enzalutamide +/- ADT

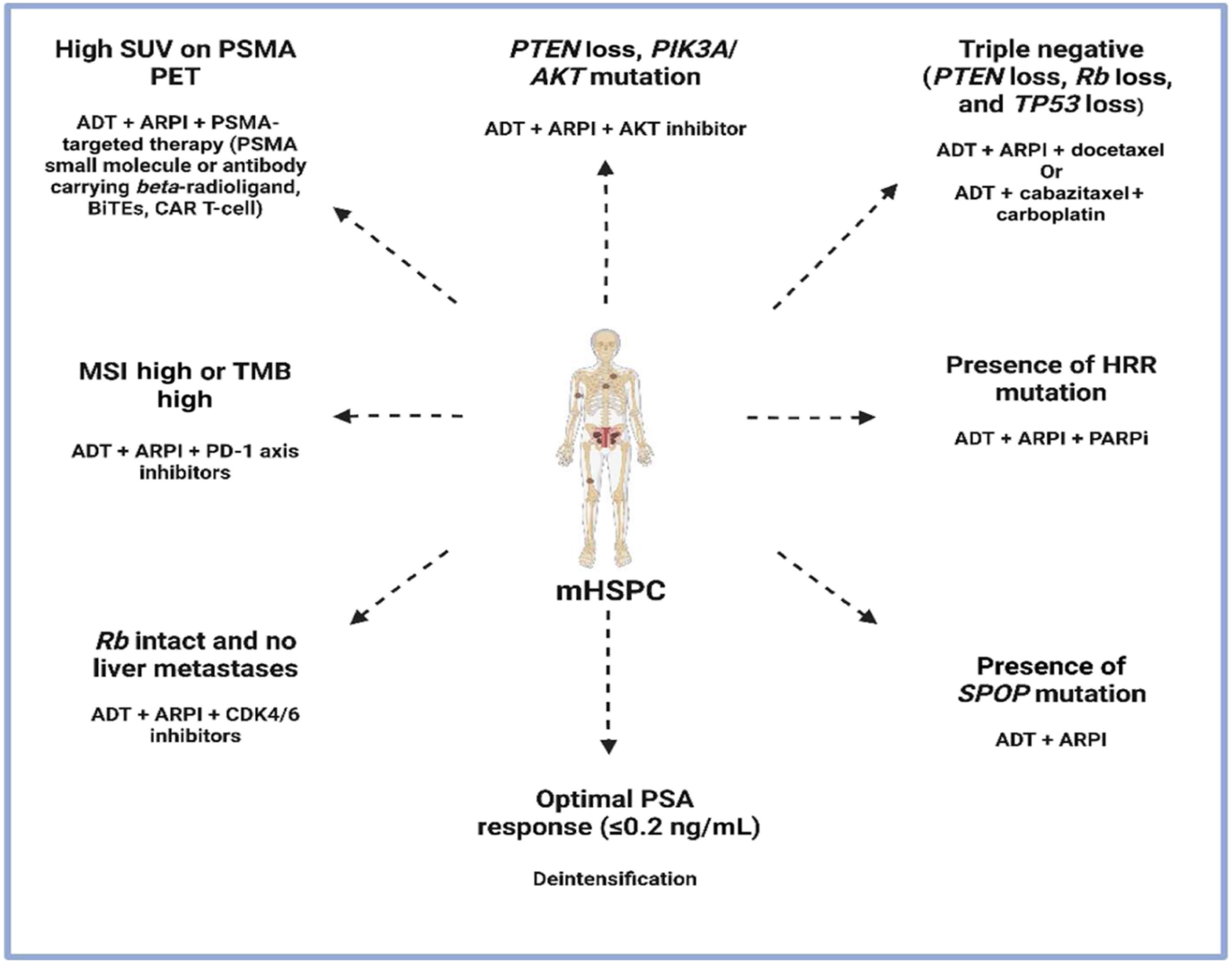
CHAARTED: docetaxel
STAMPEDE M1: abiraterone, docetaxel
LATTITUDE: abiraterone
ARCHES, ENZAMET: enzalutamide
TITAN: apalutamide

PEACE-1: Abiraterone + docetaxel
ARASENS: Darolutamide + docetaxel

What to do next??

Freedland NEJM 2023, Armstrong JCO 2022, Davis NEJM 2019, James Lancet 2016, Sweeney NEJM 2015, Chi NEJM 2019, Fizazi NEJM 2017, James NEJM 2017, Smith NEJM 2022, Fizazi Lancet 2022

Precision Medicine in PCa



MSI-H ~2-5%

PTEN loss ~40%
RB1 heterozygous loss ~30%
TP53 loss ~24-45%

BRCA2 ~3-7%
HRR ~10-20%

SPOP ~5%

Hamid et al
ASCO Educational Book 2023
DOI: 10.1200/EDBK_390166

Select mCSPC trials with triplets

Name	ARPI	Study Design	3rd agent	Biomarker
TALAPRO-3	Enzalutamide	Phase III	Talazoparib	HRR+
AMPLITUDE	Abiraterone	Phase III	Niraparib	HRR+
PSMAddition	Any ARPI	Phase III	Lu177-PSMA-617	PSMA PET+
CABIOS	Abiraterone	Phase Ib	Cabozantinib Nivolumab	
CASCARA	Abiraterone	Phase II	Cabazitaxel Carboplatin	
Capitello-281	Abiraterone	Phase III	Capivasertib	PTEN deficiency
CYCLONE-3	Abiraterone	Phase III	Abemaciclib	

Tawagi and Reizine 2023

mCSPC → mCRPC: Changing Landscape with entrance of PARPi

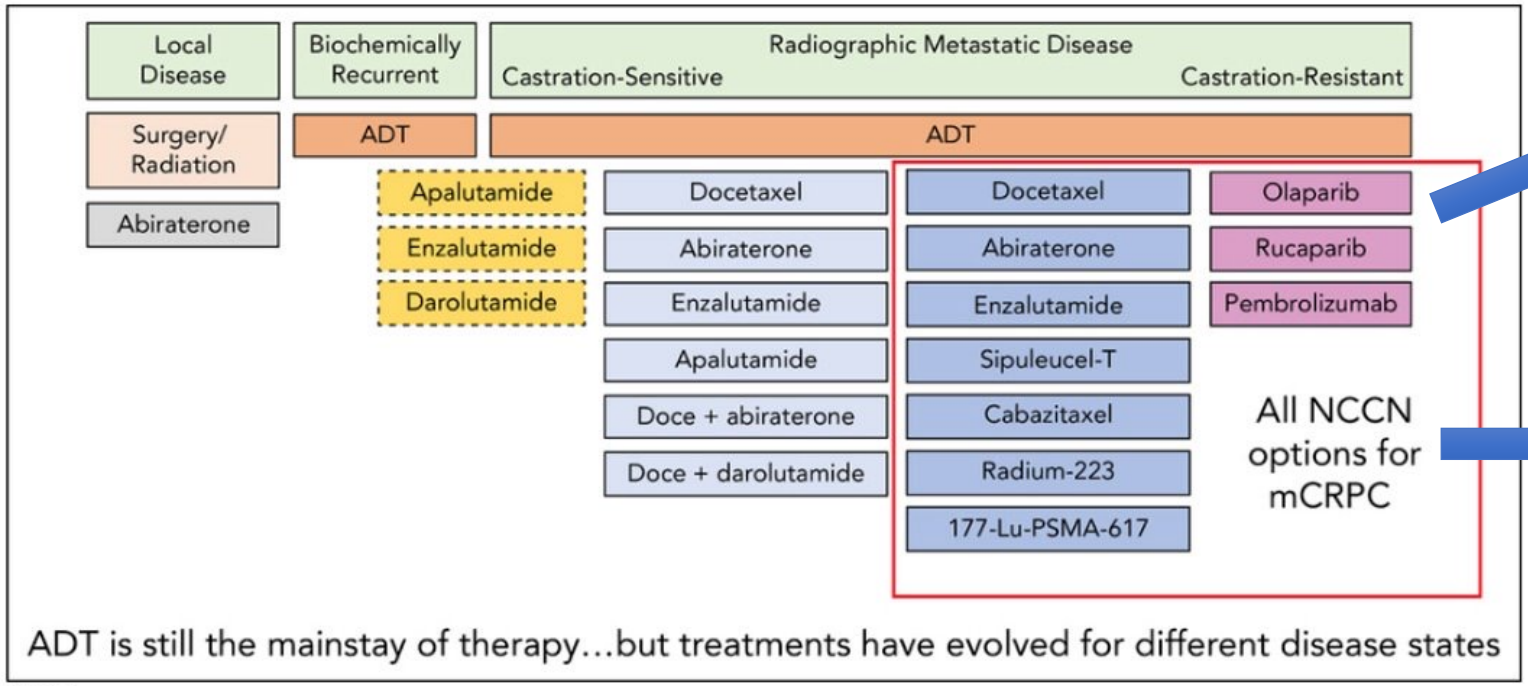


Figure 1.
Treatment landscape for advanced prostate cancer.

Abbreviations: ADT, androgen deprivation therapy; Doce, docetaxel; mCRPC, metastatic castration-resistant prostate cancer.

Data from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 1.2023. To view the most recent and complete version of these guidelines, visit www.nccn.org.

Citation: Journal of the National Comprehensive Cancer Network 21, 5.5; 10.6004/jnccn.2023.5004

May 2020	Rucaparib for 2L mCRPC w/ *BRCA1/2* muts TRITON-3
May 2020	Olaparib for 2L mCRPC w/ HRD PROfound
May 2023	Olaparib + abiraterone for 1L mCRPC w/ *BRCA1/2* only PROpel
June 2023	Talazoparib + Enzalutamide for 1L mCRPC w/ HRD+ cohort TALAPRO-2
August 2023	Niraparib + abiraterone for 1L mCRPC w/ *BRCA1/2* only MAGNITUDE

HRD mutations are prevalent in prostate cancer

6% germline in localized high risk

11.8% germline in metastatic

20% somatic in advanced disease

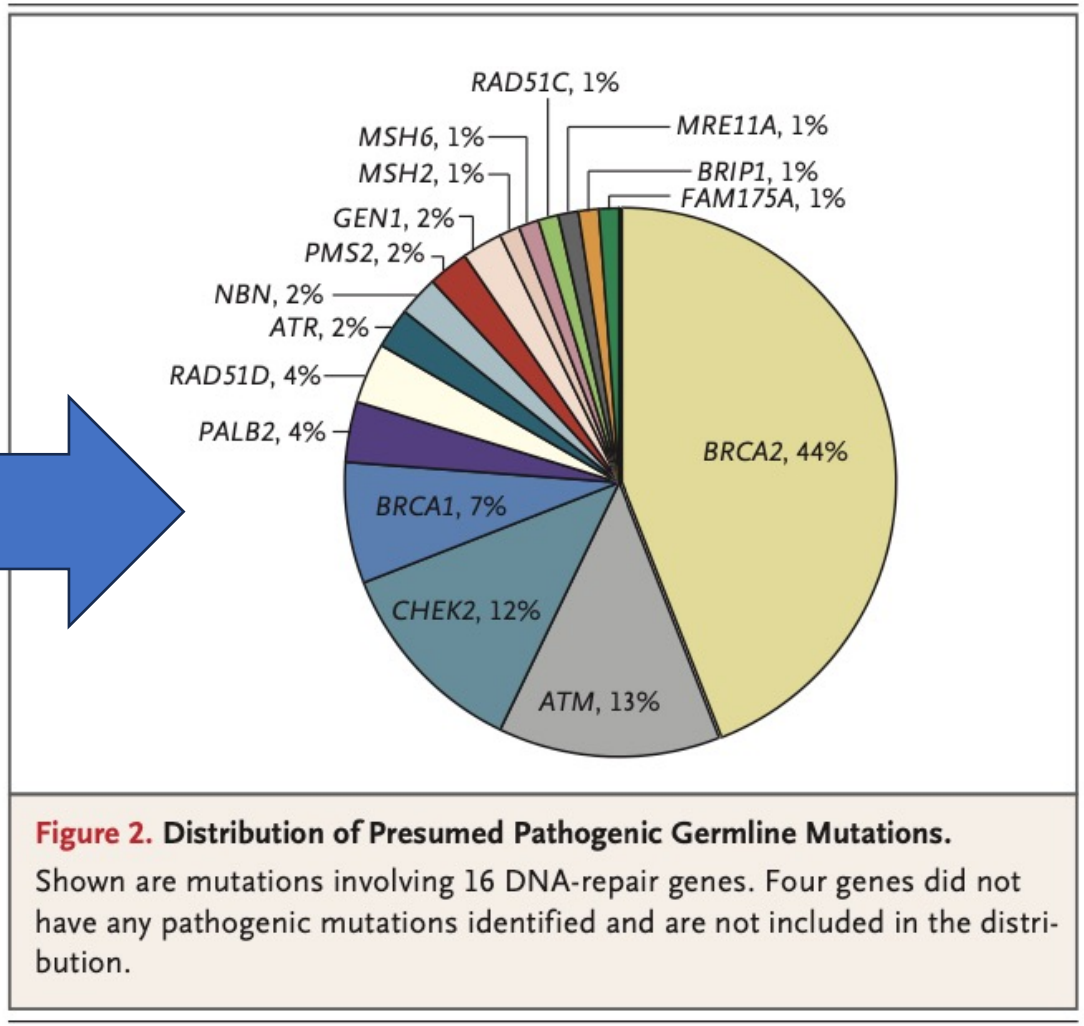


Figure 2. Distribution of Presumed Pathogenic Germline Mutations.
Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

Pritchard et al NEJM 2016

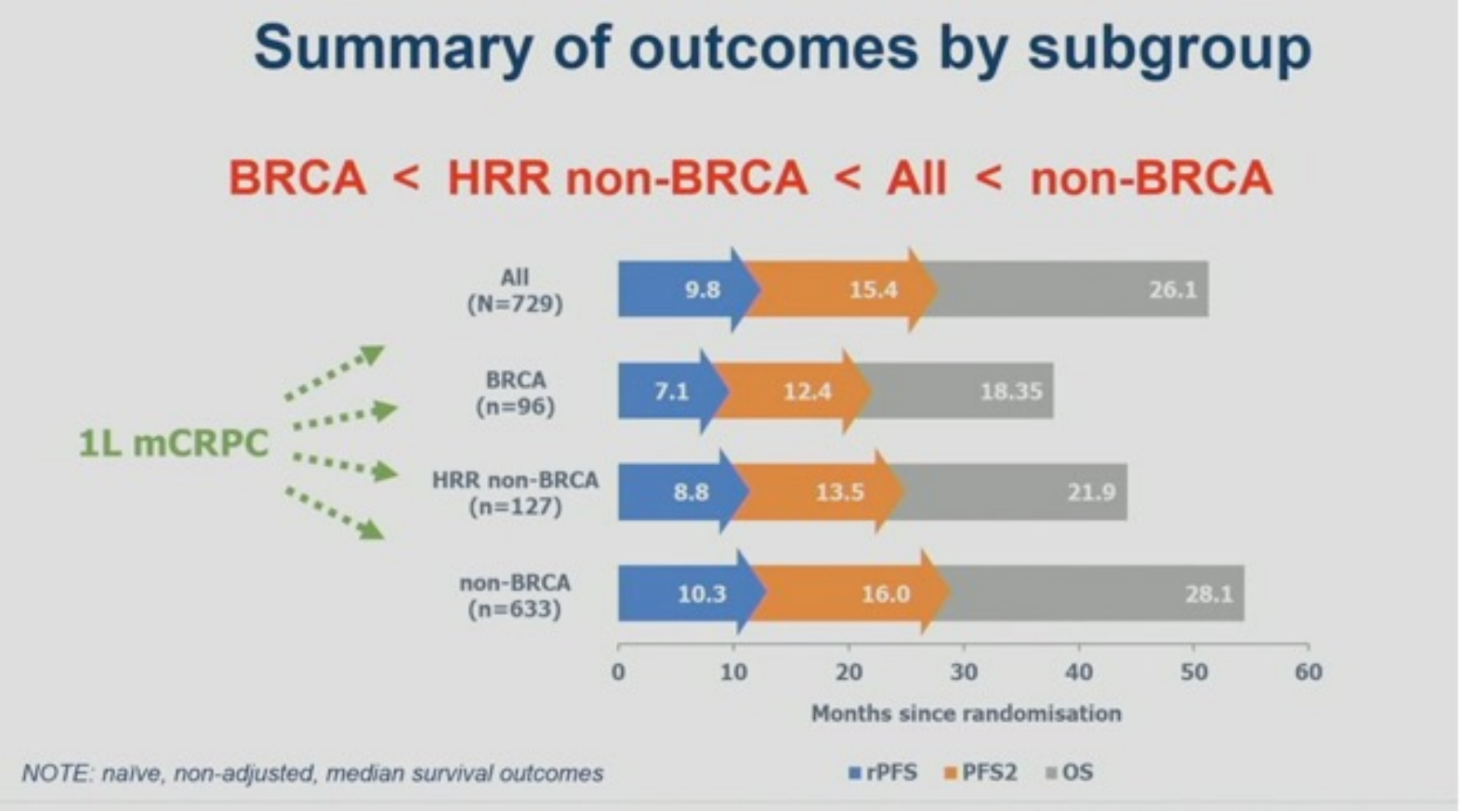
BRCA1/2m+ in prostate cancer have worse outcomes

CAPTURE Olmos et al ASCO 2023

- *Tested for:*
  ATM, BRCA1/2, BRIP1, CDK12, CHECK2, FANCA, HDAC2, PALB2, RAD51B, and *RAD54L*

- *BRCA1/2* - 13.2%
  Worse PFS, OS

- Irrespective of germline vs somatic; mono- vs bi-allelic



PARP inhibitors in Prostate cancer

- Poly (ADP-ribose) polymerase (PARP)
- Involved in DNA damage response (DDR) pathways
  - Nucleotide excision repair, base excision repair, mismatch repair, homologous recombination (HR), etc
- PARP Inhibition prevents cells from repairing damaged DNA
  - Accumulation of single-strand breaks
  - Entrapment of PARP-DNA complex
  - In cells harboring HR deficiencies: **Synthetic Lethality**

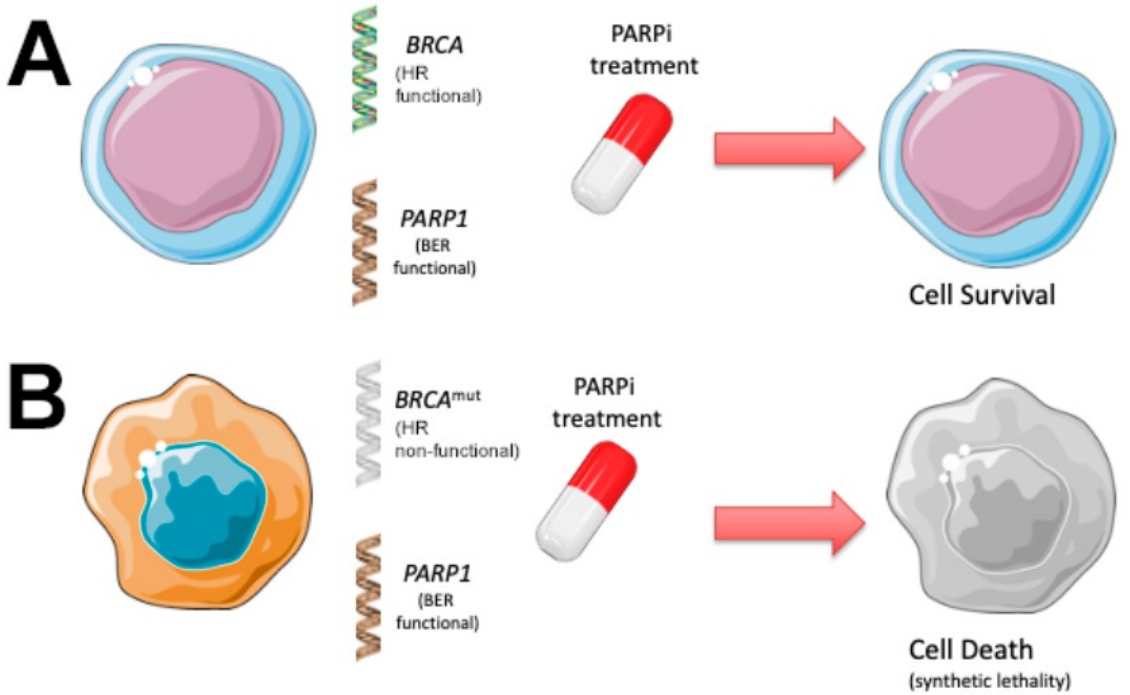


Figure 3. The principle of synthetic lethality—using PARP inhibitors (PARPi) to kill cancer cells with defects in DNA repair. (**A**) Normal cells without *BRCA* mutations have a functioning homologous recombination (HR) repair pathway and a functional base excision repair (BER) pathway. These cells remain alive when treated with PARPi. (**B**) Cancer cells with *BRCA* mutations have a non-functional HR pathway, but a functional BER pathway. When treated with PARPi, these cells are not able to repair DNA damage and subsequently undergo apoptosis.

Skelding et al, Cancers 2021

Guidelines support germline and somatic testing in most patients

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

Germline testing is recommended *in patients with a personal history of prostate cancer* in the following scenarios:

- **By prostate cancer stage or risk group (diagnosed at any age)**
  - **Metastatic, regional (node positive), very-high-risk localized, or high-risk localized prostate cancer**

- **By family history[a] and/or ancestry**
  - **≥1 first-, second-, or third-degree relative with:**
    - ◊ **breast cancer at age ≤50 y**
    - ◊ **colorectal or endometrial cancer at age ≤50 y**
    - ◊ **male (sex assigned at birth) breast cancer at any age**
    - ◊ **ovarian cancer at any age**
    - ◊ **exocrine pancreatic cancer at any age**
    - ◊ **metastatic, regional, very-high-risk, or high-risk prostate cancer at any age**
  - **≥1 first-degree relative (parent or sibling) with:**
    - ◊ **prostate cancer[b] at age ≤60 y**
  - **≥2 first-, second-, or third-degree relatives with:**
    - ◊ **breast cancer at any age**
    - ◊ **prostate cancer[b] at any age**
  - **≥3 first- or second-degree relatives with:**
    - ◊ **Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer**
  - **A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2,* and *EPCAM***
  - **Ashkenazi Jewish ancestry**
- **Personal history of breast cancer**

Germline testing may be considered *in patients with a personal history of prostate cancer* in the following scenarios:

- **By prostate cancer tumor characteristics (diagnosed at any age)**
  - ◊ **intermediate-risk prostate cancer with intraductal/cribriform histology[c]**
- **By prostate cancer[b] AND a prior personal history of any of the following cancers:**
  - ◊ **exocrine pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, and small intestinal**

[a] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family. See Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
[b] Family history of prostate cancer should not include relatives with clinically localized Grade Group 1 disease.
[c] Acinar prostate adenocarcinoma with invasive cribriform pattern, intraductal carcinoma of prostate, or ductal adenocarcinoma component have increased genomic instability, and germline testing may be considered.

Germline: almost all!

Somatic:

recommended in mCRPC

consider in mCSPC

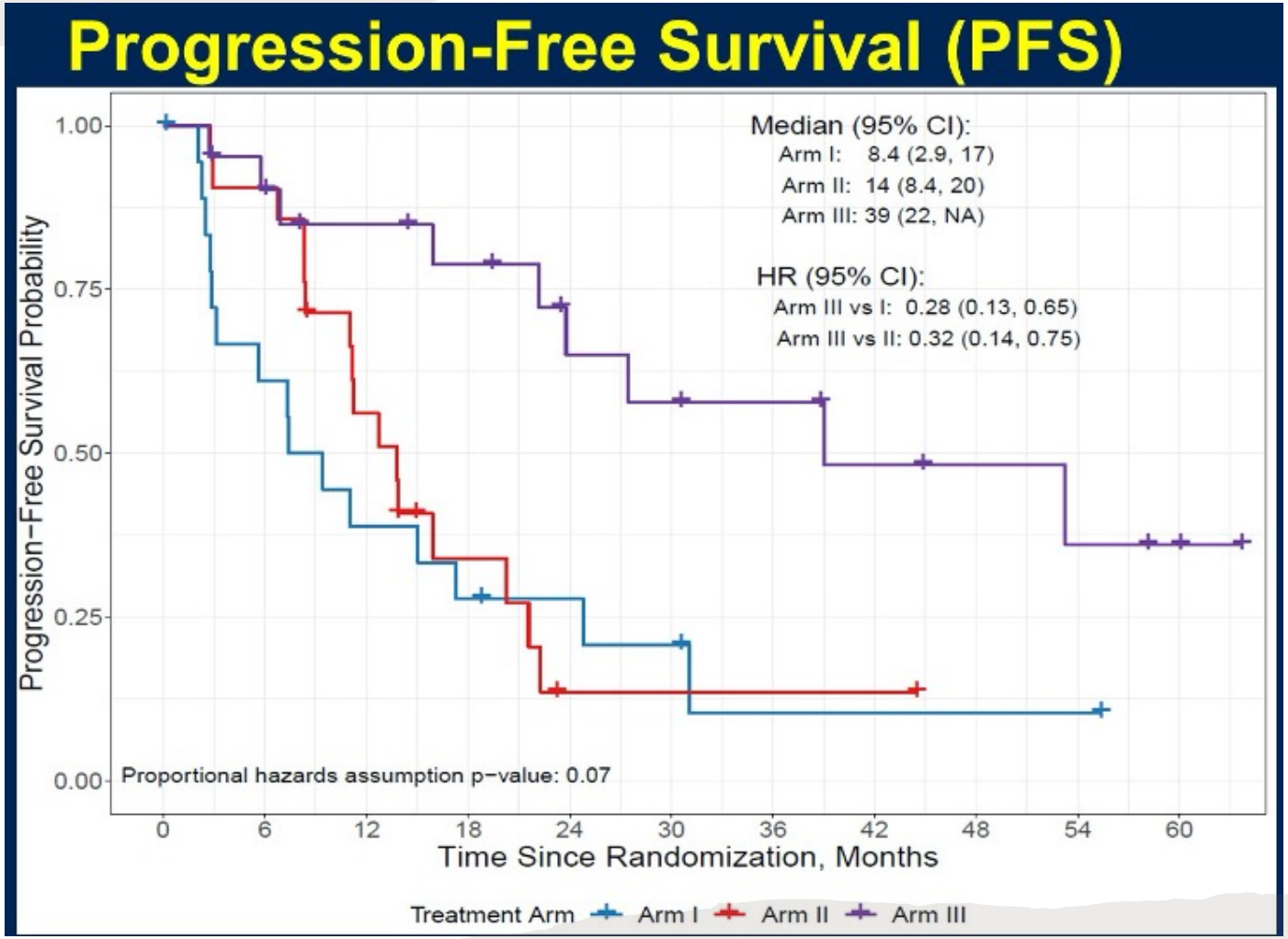
FDA approved PARPi Regimens in 1L mCRPC

	Olaparib	**Rucaparib**	**Olaparib + Abiraterone**	**Talazoparib + enzalutamide**	**Niraparib + Abiraterone**
Trial	PROfound NCT02987543	TRITON2 NCT02952534	Propel NCT03732820	Talapro-2 NCT03395197	MAGNITUDE NCT03748641
FDA approval	May 19, 2020	May 15, 2020	May 31, 2023	June 20, 2023	August 11, 2023
Biomarkers	**HRRm+** Cohort A: **BRCA1/2, ATM** Cohort B: **BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L**	**BRCA1/2m**	**BRCA1/2m** (n=85, 11% of ITT population)	**HRRm+** **ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C**	**BRCA1/2m**

N. Reizine 2023

BRCAAway: Phase 2 trial of sequential vs. combination tx

- Preclinical data suggests synergy between PARPi and AR-targeted tx
- mCRPC with BRCA1/2, ATM
- Olaparib vs. abiraterone/pred vs. combination
  - Crossover allowed
- Composite PFS in sequential arms was shorter than combination
  - suggesting **synergy** to **concurrent tx**



How to select a regimen for patients who received ARPI in CSPC?

Hussain et al GU ASCO 2024

PARPi Toxicities

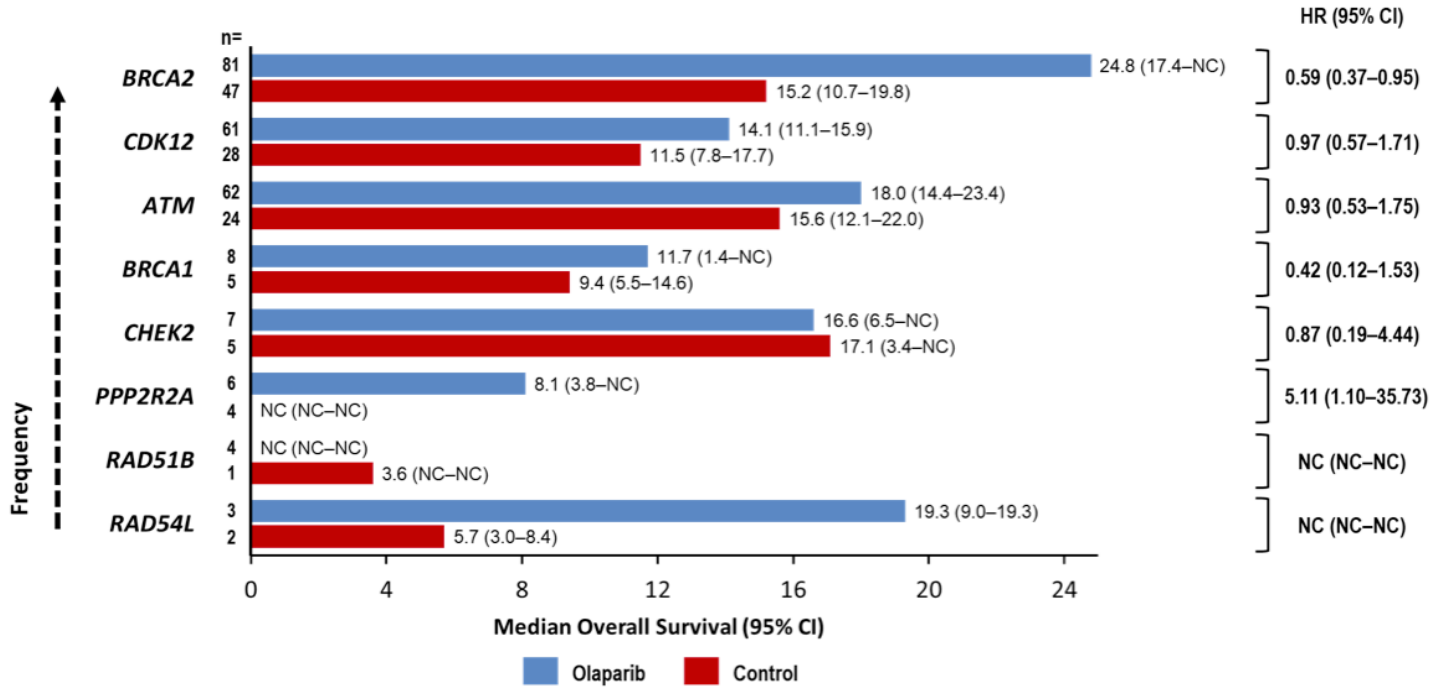
- 45% dose interruptions
  - 22% dose reductions
- 18% discontinue for AE
  - 4% death from AE

Event	Olaparib (N=256)	
	All Grades	Grade ≥3
		number
Adverse event		
Any	244 (95)	130 (51)
Anemia†	119 (46)	55 (21)
Nausea	106 (41)	3 (1)
Fatigue or asthenia	105 (41)	7 (3)
Decreased appetite	77 (30)	3 (1)
Diarrhea	54 (21)	2 (<1)
Vomiting	47 (18)	6 (2)
Constipation	45 (18)	0
Back pain	35 (14)	2 (<1)
Peripheral edema	32 (12)	0
Cough	28 (11)	0
Dyspnea	26 (10)	6 (2)
Arthralgia	24 (9)	1 (<1)
Urinary tract infection	18 (7)	4 (2)

de Bono et al NEJM 2020

Not all mutations respond equally to PARPi

Fig. S6. Gene-by-Gene Analysis of Overall Survival in Patients with Alterations in a Single HRR Gene. Data at the End of Each Bar are Median Overall Survival in Months (95% CI).



Note that for secondary and exploratory outcomes, which were not alpha controlled, definitive treatment effects may not be inferred.
CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NC, not calculable; n, number of patients

Hussain et al NEJM 2020, PROfound

JCO PO 2022

original reports

CANCER GENETICS

Germline Variant Spectrum Among African American Men Undergoing Prostate Cancer Germline Testing: Need for Equity in Genetic Testing

Veda N. Giri, MD[1,2]; Rebecca Hartman, MPH[3]; Mary Pritzlaff, MS, CGC[4]; Carrie Horton, MS, CGC[4]; and Scott W. Keith, PhD[3]

- 427 men tested using the 14-gene PCA panel: AA (n = 237, 56%) and White (n = 190, 44%)
- Pathogenic variant rate of 8.2%
  - AA men with lower rates then White (5.91% v 11.05%, P = .05).
- Difference in rates of variants of uncertain significance (VUSs) between AA and White men (25.32% v 16.32%; P = .02) and for carrying multiple VUSs (5.1% v 0.53%, P = .008).
- Germline evaluation in a cohort enriched for AA men highlights the **narrower spectrum of germline contribution to PCA** with **significantly higher rates of multiple VUSs in DNA repair genes**.

Not all individuals have the same incidence of actionable alterations

GU ASCO 2024

Prevalence of HRR gene mutations in patients with metastatic castration-resistant prostate cancer: Germline results from the Latin-American observational study PROSPECT.

Ray Manneh Kopp, Carmen Alaez Verson, Martin Angel, Arturo Delgado, Pedro H Isaacsson Velho, Alejandro Manduley, Melissa Barbieri, Carmen Vargas, Francisco Gonzalez, Pedro C. Barata; Sociedad de Oncología y Hematología del Cesar, Valledupar, Colombia; Instituto Nacional de Medicina Genómica, Ciudad De México, Mexico; Instituto Alexander Fleming, Buenos Aires, Argentina; Centro Médico Nacional Siglo XXI, Ciudad De México, Mexico; Hospital Moinhos de Vento, Porto Alegre, Brazil; Centro de Especialidades Urológicas de Panamá, Panama City, Panama; AstraZeneca Central America and Caribbean, San Jose, Costa Rica; AstraZeneca AG, Baar, Switzerland; AstraZeneca UK LTD, Cambridge, United Kingdom; Tulane University Medical School, New Orleans, LA

- Prevalence of germline HRR mutations found in this multinational Latin American population was lower than expected
- The most frequently mutated HRR genes differed from those from major trials including PROfound

Select mCRPC PARPi Combination Trials: Synergy?

	Drug Therapy	Study Name	Study Design	Trial Population	HRR Mutations	Primary Endpoint(s)
+ ICI	**Olaparib + pembrolizumab vs. enza./AAP**	**KEYLYNK-010**	Phase III, randomized	mCRPC	Unselected	overall survival, rPFS
+ ICI	**Olaparib + durvalumab**	**NCT03810105**	Phase II, single arm	Biochemically recurrent nmCRPC	Selected	# of patients with undetectable PSA
+ Radioligand	**Olaparib + 177Lu-PSMA**	**LuPARP**	Phase I, single arm	mCRPC	N/A	DLT, recommended phase II dose
+ Radioligand	**Olaparib + Radium-223 vs. Radium 223**	**COMRADE**	Phase I/II, randomized	mCRPC	N/A	rPFS, maximum tolerated dose
+ Radioligand	**Niraparib + Radium-223**	**NiraRad**	Phase Ib, single arm	mCRPC	Unselected	DLT
	Olaparib + AZD6738 (ATR inhibitor)	**TRAP**	Phase II, nonrandomized	mCRPC	Selected Tawagi and Reizine 2023	Rate of response, PSA response >50% decline

Tawagi and Reizine 2023

mCRPC: Changing Landscape with MANY options

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[iii,kkk,lll]

No prior docetaxel/no prior novel hormone therapy[mmm]

- Preferred regimens
  - Abiraterone[u,nnn,ooo] (category 1)
  - Docetaxel[fff,ppp] (category 1)
  - Enzalutamide[u] (category 1)
- Useful in certain circumstances
  - Niraparib/abiraterone[u,fff,zzz] for BRCA mutation (category 1)
  - Olaparib/abiraterone[u,fff,nnn,qqq] for BRCA mutation (category 1)
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Sipuleucel-T[fff,sss] (category 1)
  - Talazoparib/enzalutamide for HRRm[u,fff,yyy] (category 1)
- Other recommended regimens
  - Other secondary hormone therapy[u]

Prior novel hormone therapy/no prior docetaxel[mmm,ttt]

- Preferred regimens
  - Docetaxel (category 1)[fff]
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Niraparib/abiraterone[u,fff,zzz] for BRCA mutation (category 2B)
  - Olaparib for HRRm[uuu] (category 1)
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCA mutation[vvv]
  - Sipuleucel-T[fff,sss]
  - Talazoparib/enzalutamide for HRRm[u,fff,yyy] (category 2B)
- Other recommended regimens
  - Abiraterone[u,nnn]
  - Abiraterone[u] + dexamethasone[nnn,www]
  - Enzalutamide[u]
  - Other secondary hormone therapy[u]

Prior docetaxel/no prior novel hormone therapy[mmm]

- Preferred regimens
  - Abiraterone[u,nnn] (category 1)
  - Cabazitaxel[fff]
  - Enzalutamide[u] (category 1)
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff]
  - Niraparib/abiraterone[u,fff,zzz] for BRCA mutation
  - Olaparib/abiraterone[u,fff,nnn,qqq] for BRCA mutation
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Sipuleucel-T[fff,sss]
  - Talazoparib/enzalutamide for HRRm[u,fff,yyy]
- Other recommended regimens
  - Other secondary hormone therapy[u]

Prior docetaxel and prior novel hormone therapy[mmm,ttt]

- Useful in certain circumstances
  - Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases[xxx] (category 1)

(The following systemic therapies are category 2B if visceral metastases are present)

- Preferred regimens
  - Cabazitaxel[fff,ooo] (category 1)
  - Docetaxel rechallenge[fff]
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff]
  - Olaparib for HRRm[ooo,uuu] (category 1)
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff]
  - Radium-223[rrr] for symptomatic bone metastases[ooo] (category 1)
  - Rucaparib for BRCA mutation[vvv]
- Other recommended regimens
  - Abiraterone[u,nnn]
  - Enzalutamide[u]
  - Other secondary hormone therapy[u]

See Footnotes for Systemic Therapy M1 CRPC (PROS-15A).

March 23, 2022:

FDA approval of **177Lu-PSMA-617** for **PSMA+ mCRPC** who have received **prior ARPI** and **taxane**

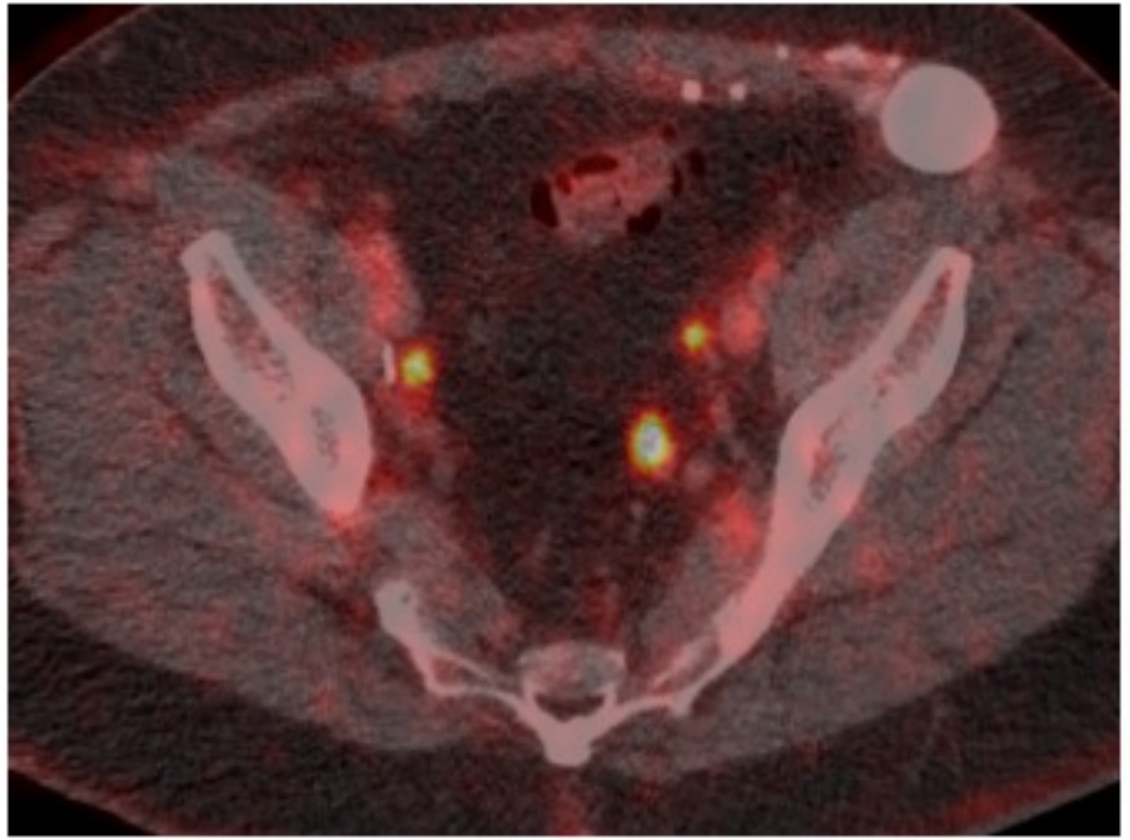
PSMA PET/CT

PSMA: cell membrane protein highly expressed on surface of PCa

Diagnostic radiotracers:
Ga-68 PSMA-11
F-18 piflufolast

Obtain scans in:
high, very high risk PCa,
biochemical recurrence,
mCRPC prior to PSMA-radioligand

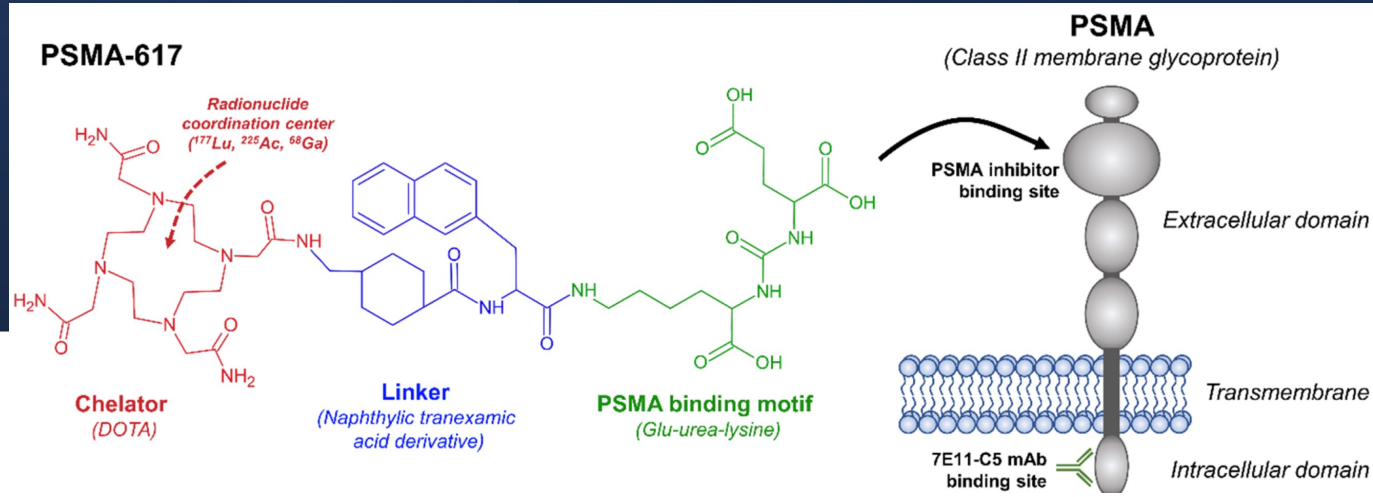
replacing conventional imaging?



~15% of PCa lesions are PSMA-negative

https://cancerecology.com/psma-imaging

177LuPSMA Radioligand



Beta particle radiation taken up by PSMA-positive cells and surrounding tissues

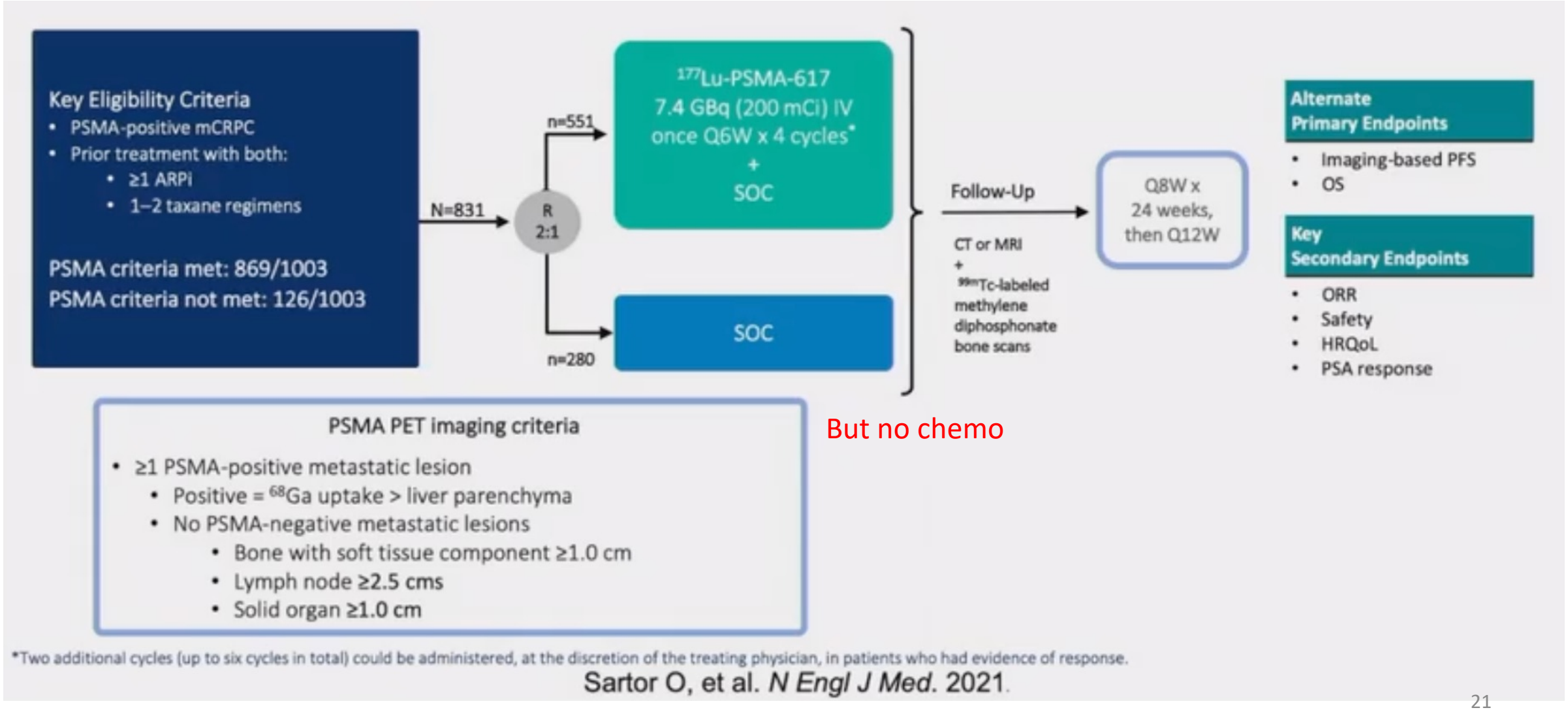
Internalization of radioligand results in accumulation of radioactivity in tumor tissue and irradiation

6 injections (~20 minutes) q4-6 weeks

Hydration is important

AEs: salivary gland xerostomia, long-term renal toxicities

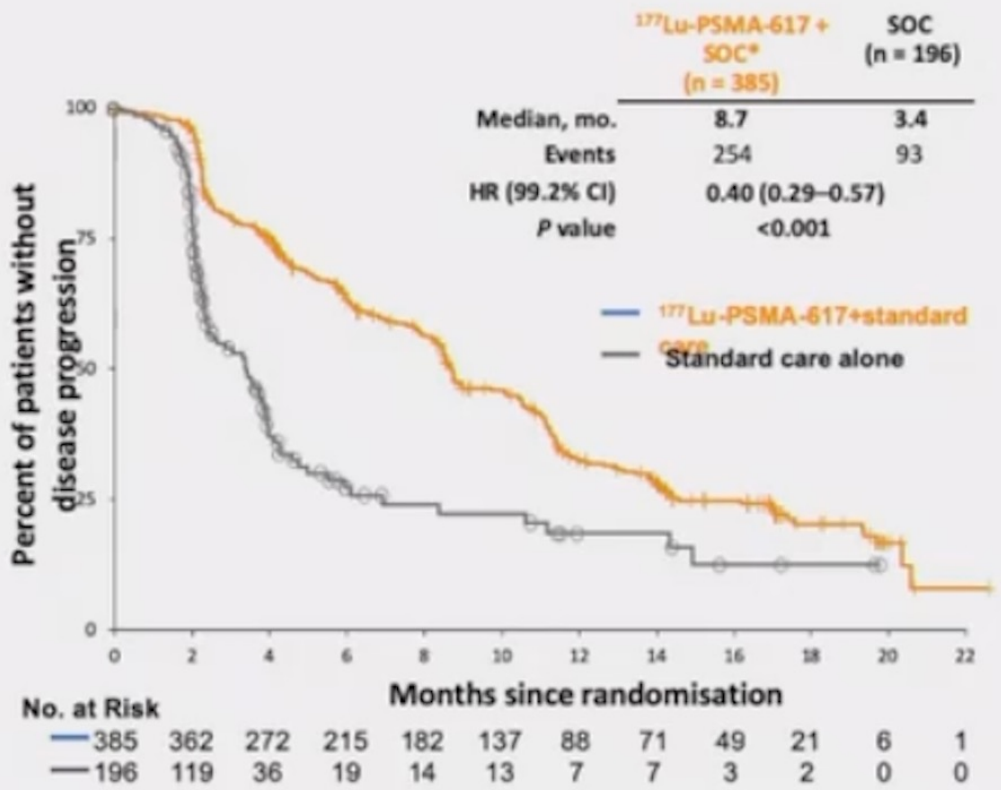
VISION: 177-Lu-PSMA-617 for Late Stage mCRPC

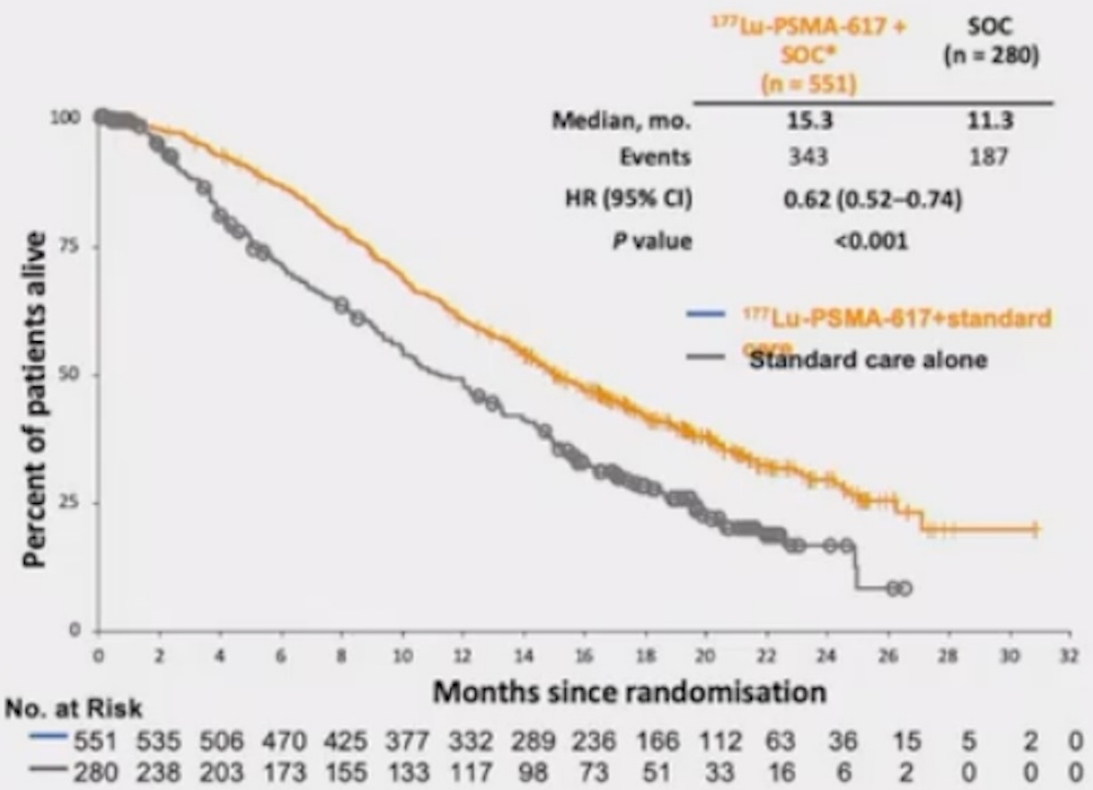


But no chemo

*Two additional cycles (up to six cycles in total) could be administered, at the discretion of the treating physician, in patients who had evidence of response.

Sartor O, et al. *N Engl J Med*. 2021.



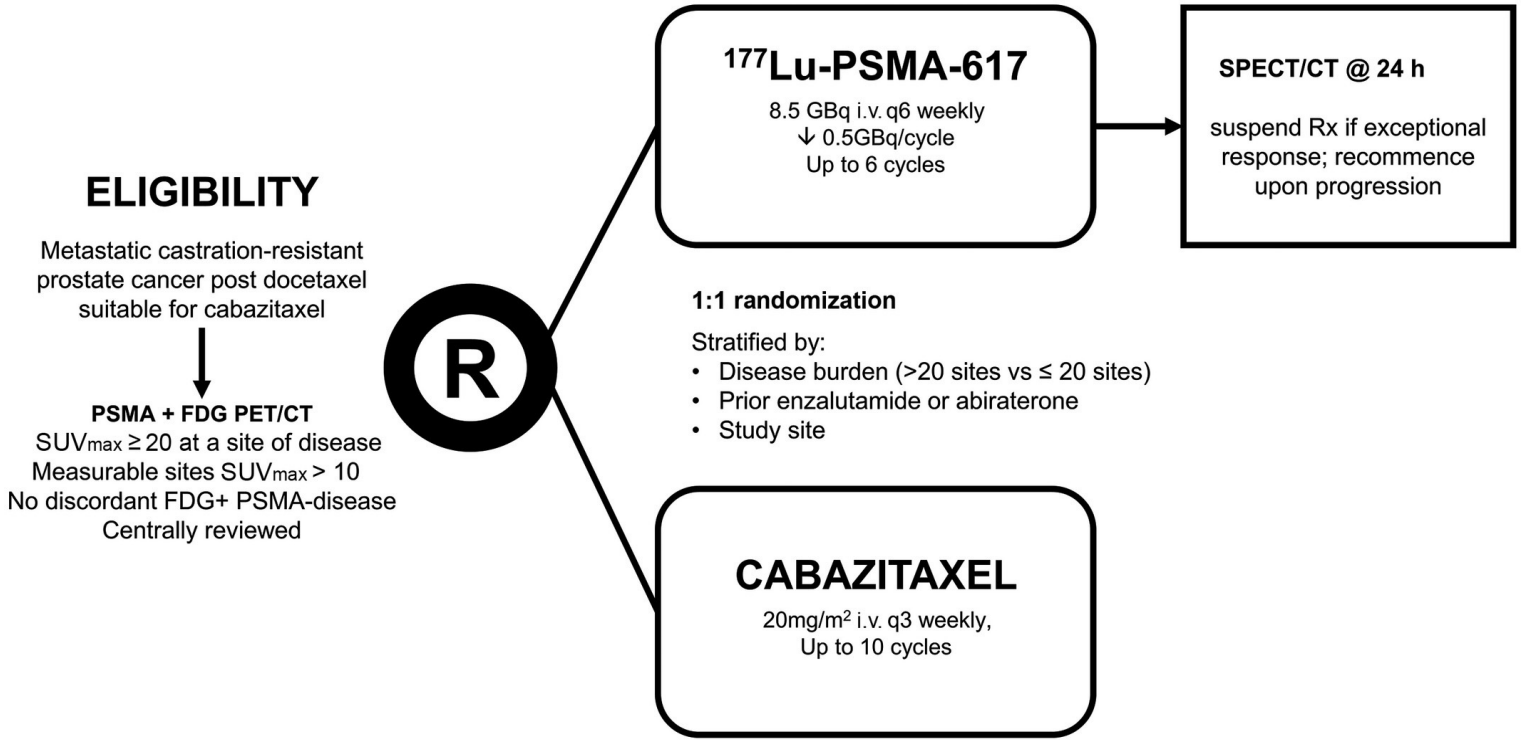


15.3 vs. 11.3m

Sartor O, et al. *N Engl J Med*. 2021.

VISION: 177-Lu-PSMA-617 for Late Stage mCRPC

TheraP: randomized Ph2 in mCRPC



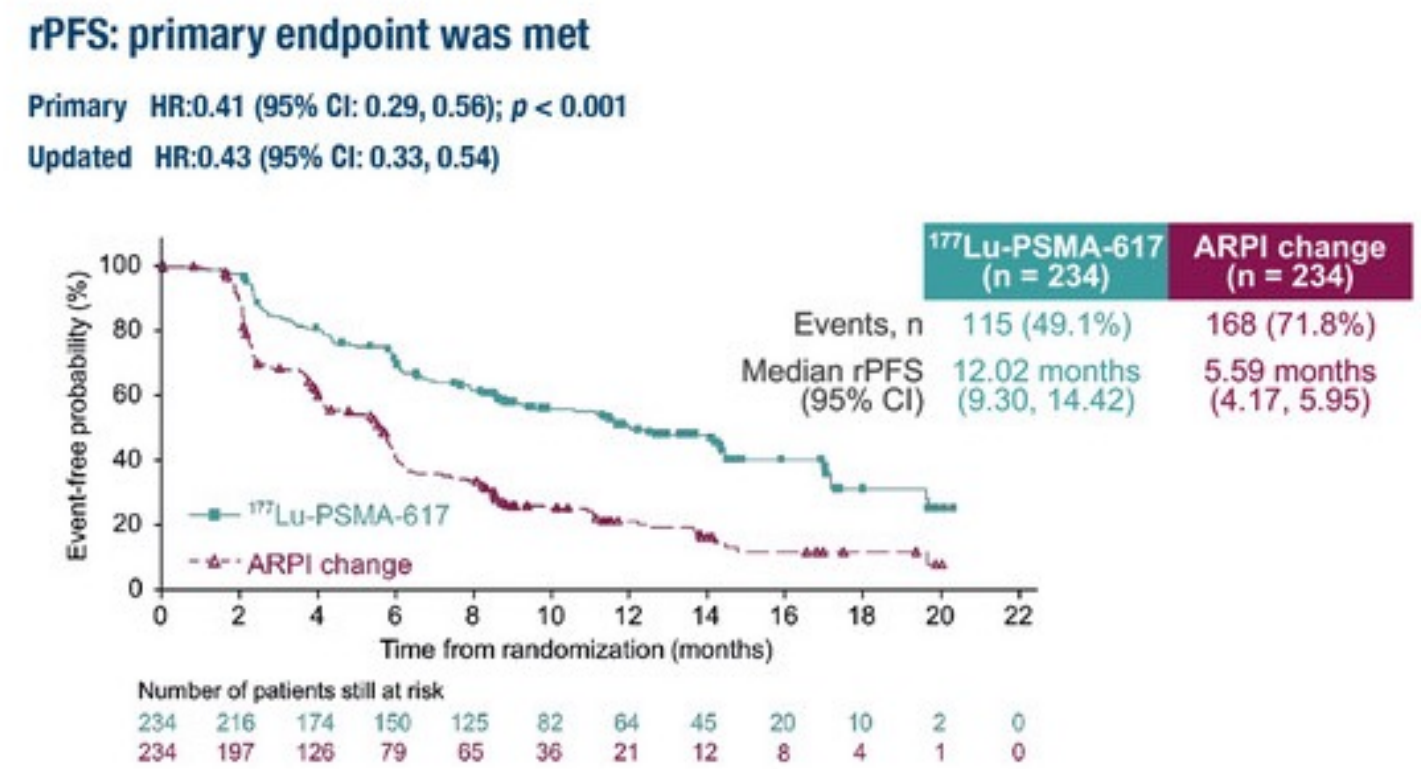
Hofman et al Lancet 2024

- Secondary Outcome of OS
- Median follow up 35.7 m
- Higher ORR
- mOS similar between groups
- Lower Aes
- Better QoL/PROs

LuPSMA resulted in higher response rates (BCR, imaging), longer PFS, and reduced G3/4 toxicities compared to cabazitaxel

BJU International, Volume: 124, Issue: S1, Pages: 5-13, First published: 22 October 2019, DOI: (10.1111/bju.14876)

PSMA radioligand pre-chemo: PSMAfore



- **Control arm = ARPI change**
- **84% crossover**
- **OS data immature**

Sartor et al, 2023

Figure. The PSMAfore trial met its primary endpoint, with a significant improvement in rPFS with 177Lu-PSMA-617 compared with ARPI change in mCRPC (ESMO Congress 2023, LBA13)

PSMA radioligand in earlier settings

Drug Therapy	Study Name	Study Design	Trial Population
LuPSMA before prostatectomy	Lutectomy	Phase I/II	High-risk localized or locoregional PCa
LuPSMA before SBRT vs. SBRT alone	LUNAR	Phase II	Oligorecurrent PCa
LuPSMA + EBRT	ProstACT TARGET	Phase II	Oligorecurrent PCa
LuPSMA + SABR vs. SABR alone	POPSTAR II	Phase II	Oligomestastatic PCa
LuPSMA + SOC vs. SOC alone	PSMAddition	Phase III	mHSPC
LuPSMA + Docetaxel vs Docetaxel alone	UpfrontPSMA	Phase II	mHSPC
LuPSMA vs. SOC	Bullseye	Phase II	Oligometastatic mHSPC

Improve efficacy in more homogenous population?

Tawagi and Reizine 2023

PSMA radioligand in combination regimens

Drug Therapy	Study Name	Study Design	Trial Population
Enzalutamide + LuPSMA vs Enzalutamide alone	ENZA-p	Phase II	mCRPC
LuPSMA after ARSI progression	SPLASH	Phase III	mCRPC
LuPSMA vs ARSI	ECLIPSE	Phase III	mCRPC
Abemaciclib before LuPSMA	UPLIFT	Phase I/II	mCRPC
LuPSMA vs LuPSMA with Ipilimumab + Nivolumab	EVOLUTION/ANZUP2001	Phase II	mCRPC
LuPSMA + Pembrolizumab	PRINCE	Phase I/II	mCRPC
LuPSMA + Cabazitaxel	LuCAB	Phase I/II	mCRPC
LuPSMA + Cabozantinib	CaboLu	Phase Ib	mCRPC
LuPSMA + Olaparib	LuPARP	Phase I	mCRPC

Tawagi and Reizine 2023

ICI, PARPi?
PSMA upregulation?
Timing/significance of sequencing with other therapies?

Outstanding questions re: LuPSMA

How to monitor response on therapy?

What is the role of imaging in treatment selection?

- And re-treatment?

What is the optimal dose?

- Adaptive strategies?

How to sequence with other therapies?

How to manage toxicities?

How to prevent and overcome resistance?

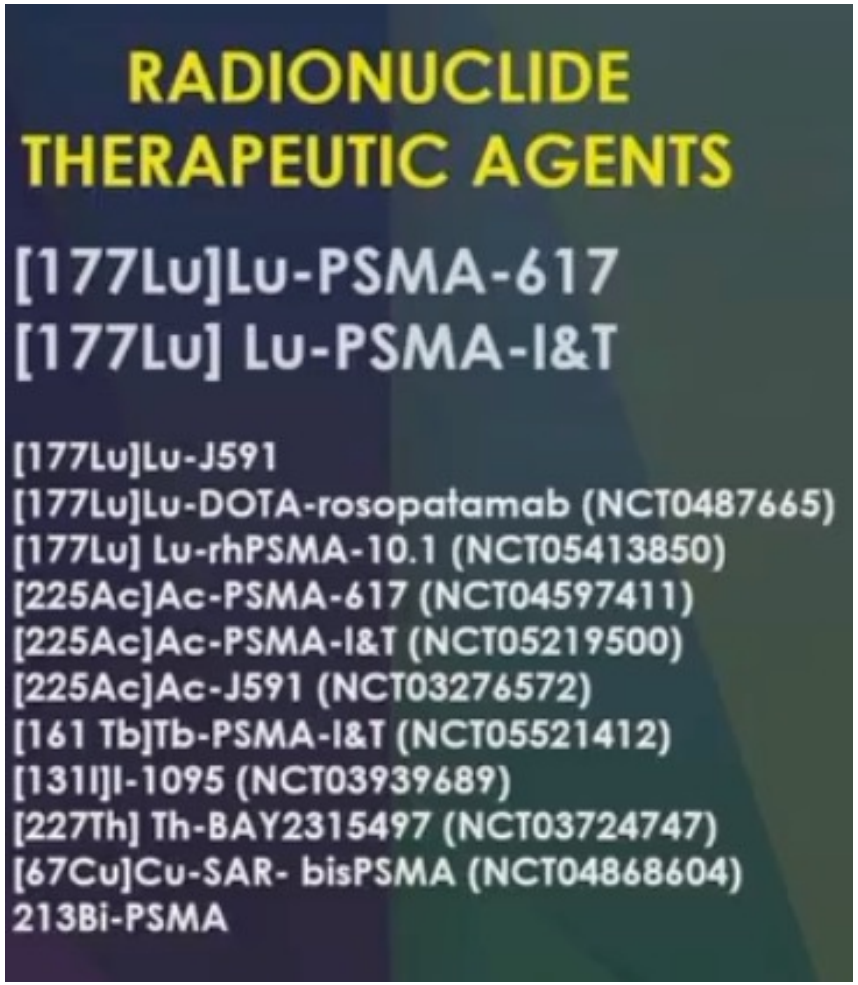
- 1/3 do not respond

What is the role of other radioligands?

- Alpha: higher energy transfer/more potent

Equitable Access to Theranostics*

- Availability, NM access, cost



Gopanath Gnanasegaran IUCS 2023

mCRPC: Changing Landscape with MANY options …but limited role of Immunotherapy

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[iii,kkk,lll]

No prior docetaxel/no prior novel hormone therapy[mmm]	Prior novel hormone therapy/no prior docetaxel[mmm,ttt]
• Preferred regimens ▸ Abiraterone[u,nnn,ooo] (category 1) ▸ Docetaxel[fff,ppp] (category 1) ▸ Enzalutamide[u] (category 1) • Useful in certain circumstances ▸ Niraparib/abiraterone[u,fff,zzz] for BRCA mutation (category 1) ▸ Olaparib/abiraterone[u,fff,nnn,qqq] for BRCA mutation (category 1) ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[fff,sss] (category 1) ▸ Talazoparib/enzalutamide for HRRm[u,fff,yyy] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[u]	• Preferred regimens ▸ Docetaxel (category 1)[fff] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Niraparib/abiraterone[u,fff,zzz] for BRCA mutation (category 2B) ▸ Olaparib for HRRm[uuu] (category 1) ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Rucaparib for BRCA mutation[vvv] ▸ Sipuleucel-T[fff,sss] ▸ Talazoparib/enzalutamide for HRRm[u,fff,yyy] (category 2B) • Other recommended regimens ▸ Abiraterone[u,nnn] ▸ Abiraterone[u] + dexamethasone[nnn,www] ▸ Enzalutamide[u] ▸ Other secondary hormone therapy[u]
Prior docetaxel/no prior novel hormone therapy[mmm]	**Prior docetaxel and prior novel hormone therapy**[mmm,ttt]
• Preferred regimens ▸ Abiraterone[u,nnn] (category 1) ▸ Cabazitaxel[fff] ▸ Enzalutamide[u] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff] ▸ Niraparib/abiraterone[u,fff,zzz] for BRCA mutation ▸ Olaparib/abiraterone[u,fff,nnn,qqq] for BRCA mutation ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[fff,sss] ▸ Talazoparib/enzalutamide for HRRm[u,fff,yyy] • Other recommended regimens ▸ Other secondary hormone therapy[u]	• Useful in certain circumstances ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases[xxx] (category 1) (The following systemic therapies are category 2B if visceral metastases are present) • Preferred regimens ▸ Cabazitaxel[fff,ooo] (category 1) ▸ Docetaxel rechallenge[fff] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff] ▸ Olaparib for HRRm[ooo,uuu] (category 1) ▸ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff] ▸ Radium-223[rrr] for symptomatic bone metastases[ooo] (category 1) ▸ Rucaparib for BRCA mutation[vvv] • Other recommended regimens ▸ Abiraterone[u,nnn] ▸ Enzalutamide[u] ▸ Other secondary hormone therapy[u]

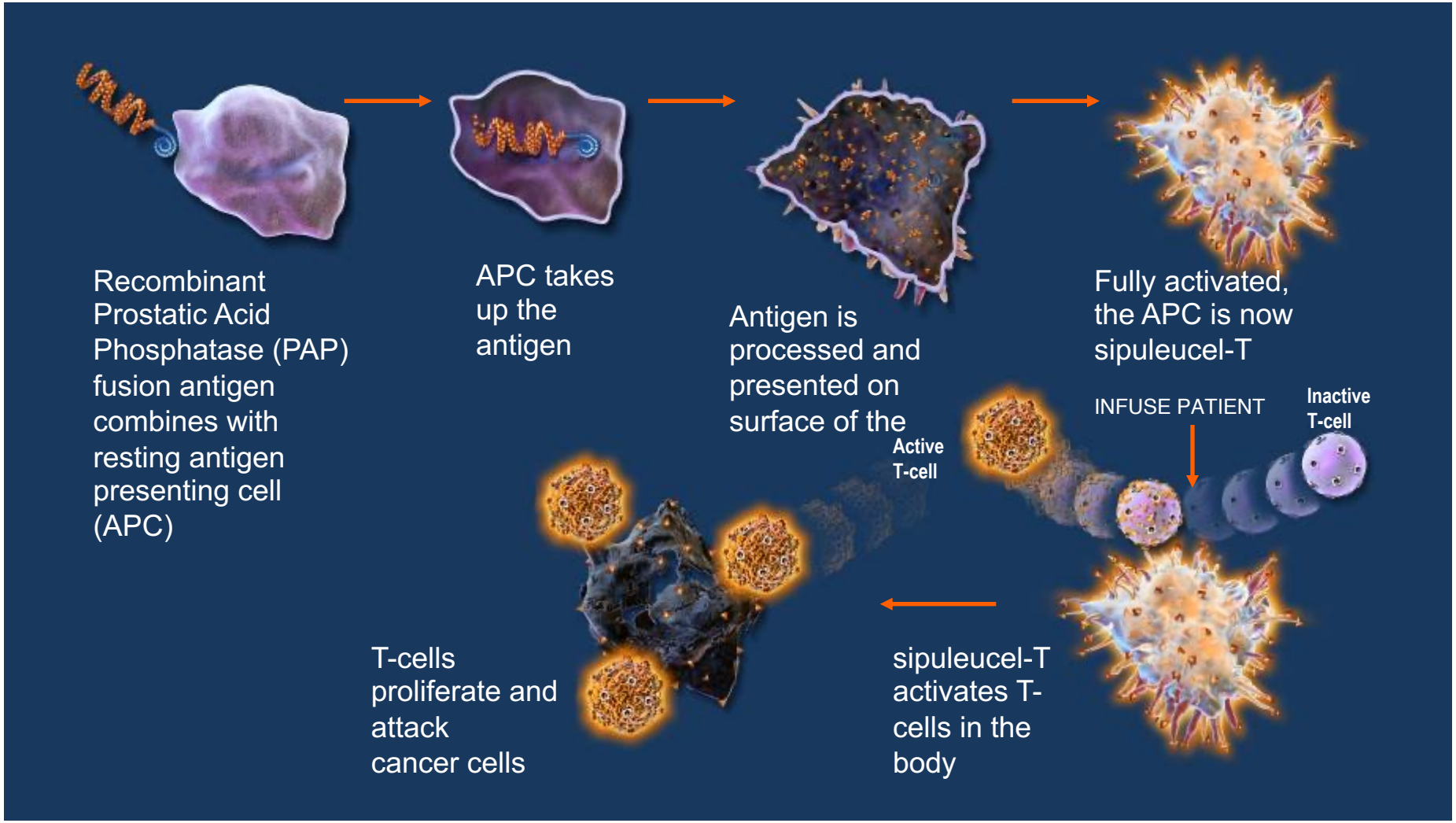
See Footnotes for Systemic Therapy M1 CRPC (PROS-15A).

Sipuleucel-T

Pembrolizumab for MSI-H/dMMR/high TMB (2-5%)

Sipuleucel-T

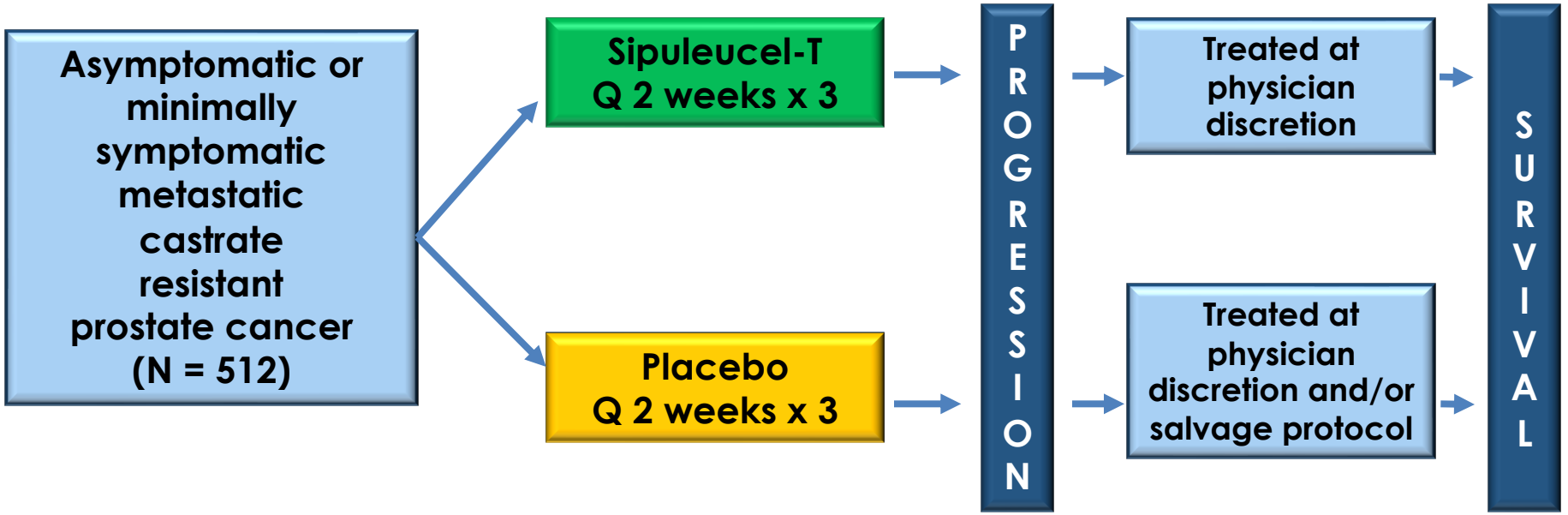
One of the first immunotherapies!



P. Kantoff GU ASCO 2010

Randomized Phase 3 IMPACT Trial

(IMmunotherapy Prostate AdenoCarcinoma Treatment)



Primary endpoint: Overall survival
Secondary endpoint: Objective disease progression

Kantoff PW, Higano CS, Shore ND, et al. *N Engl J Med*. 2010;363:411-422.

Sipuleucel T: IMPACT Overall Survival

36.5 mo median f/u

HR = 0.759 (95% CI: 0.606, 0.951)

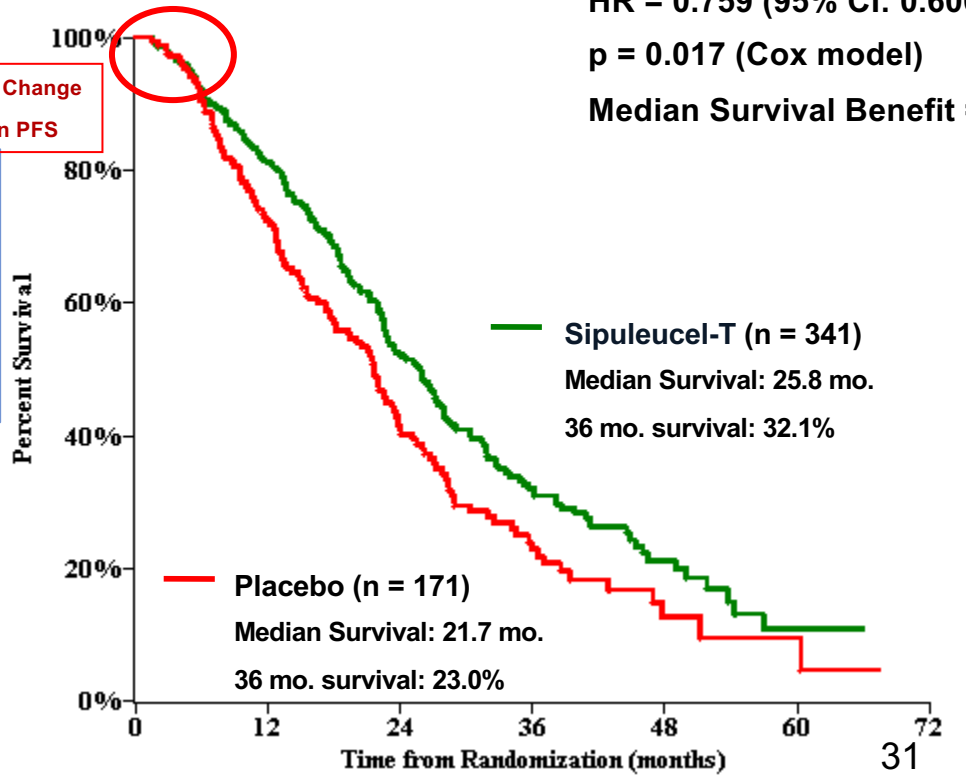
p = 0.017 (Cox model)

Median Survival Benefit = 4.1 months

No Change in PFS

PFS: 14.6 vs. 14.4 wks

HR 0.95



Courtesy of P. Kantoff, presented GU ASCO 2010

Szmulewitz, 2017

Challenges

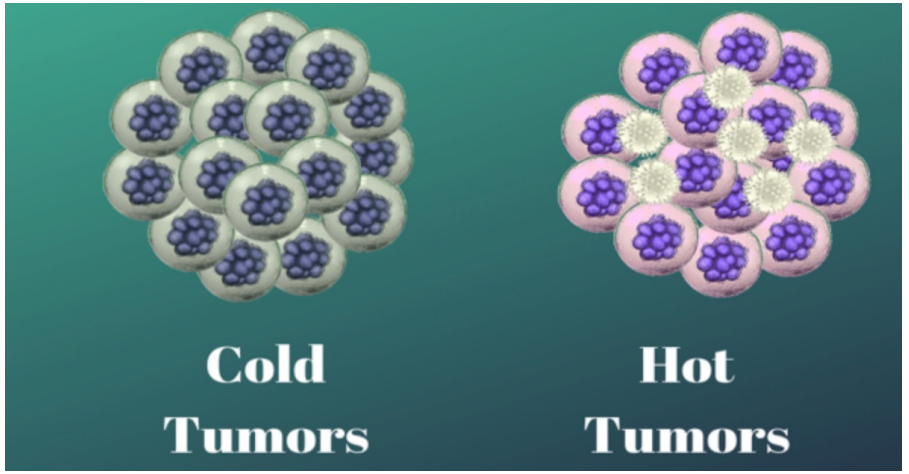
- Vague mechanism of action with few PSA declines (1-3%)
- Approved only for asymptomatic or minimally symptomatic cases
- No documented delay in time to progression
- Difficult to predict who will benefit (Lack of Predictive and Response biomarkers)
- Cost/benefit ratio
- Agents with other MOAs have been developed that do provide objective responses

Differences in genomic, transcriptomic, and immune landscape of PCa based on site of metastasis

Swami et al
GU ASCO 2024

Prostate Cancer is typically considered an immunologically “cold” tumor

- Low TMB
- Low PDL1
- Sparse T-cell infiltration
- Immunosuppressive TME



Sites of metastasis is prognostic
(LN > Bone > Lung > Liver)

GU ASCO 2024
Swami et al
Real-world Data set (Caris)
n=6,074

Comprehensively characterized molecular and immune landscape of PCa based on metastatic site

Metastatic and primary sites were similar in TMB-H and dMMR/MSI-H frequency

- TME of liver was less enriched with macrophages M2, NK cells, Tregs, B cells and neutrophils
- TME of lung was less enriched with NK cells and more with Tregs

Halabi et al JCO 2016

Wang et al Am J Clin Exp Urol 2022

Targeting PD1/PDL1 for mCRPC

ICI has Modest activity in unselected individuals with PCa

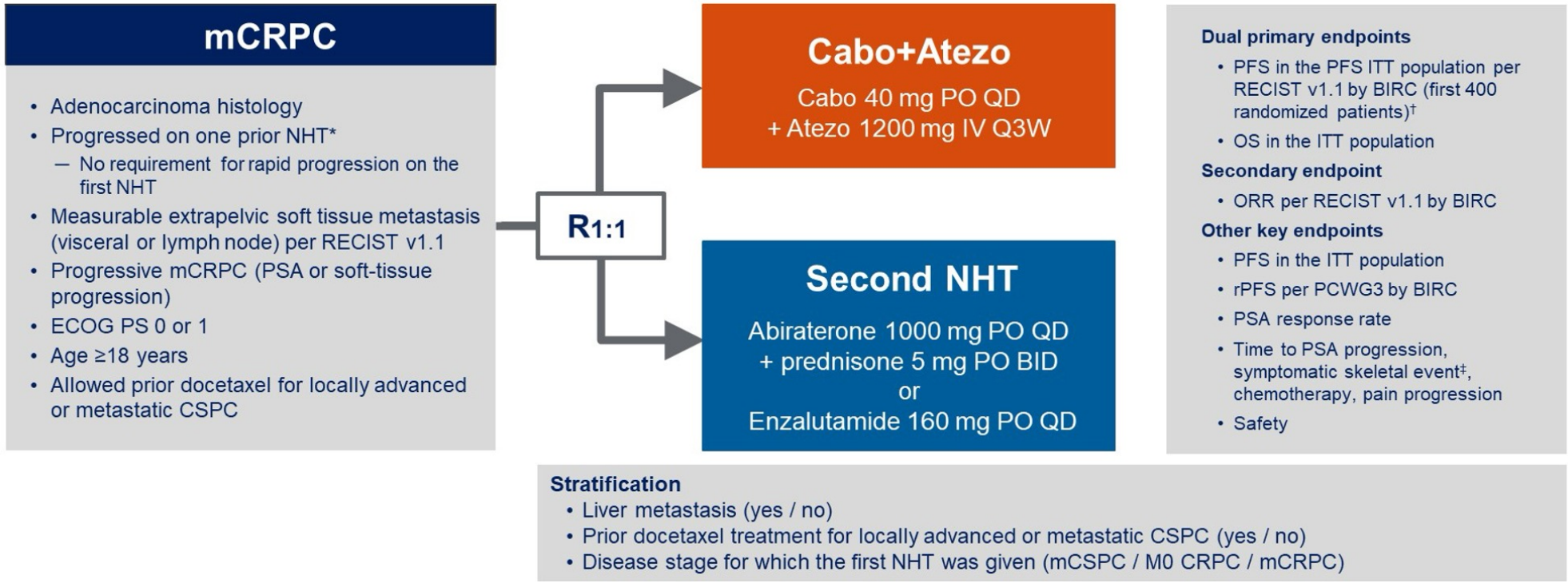
Combination strategies: negative for rPFS, OS in Phase 3 trials

IMbassador250: Atezolizumab + Enzalutamide	Keynote-921: Pembrolizumab + Docetaxel	Keylynk-010: Pembrolizumab + Olaparib	Keynote-641: Pembrolizumab + Enzalutamide

Phase 3 Contact-02 Study: Cabozantinib + Atezolizumab vs. Second NHT in mCRPC

Agarwal et al, ASCO GU 2024

- Cabozantinib: TKI
  - VEGFR2, c-MET, RET, etc
  - Immunomodulatory effects
- COMET-1: Cabozantinib improved rPFS with no difference in OS in mCRPC
  - post ARPI and docetaxel
- COSMIC-021: Phase 1b Cabozantinib + atezolizumab in mCRPC

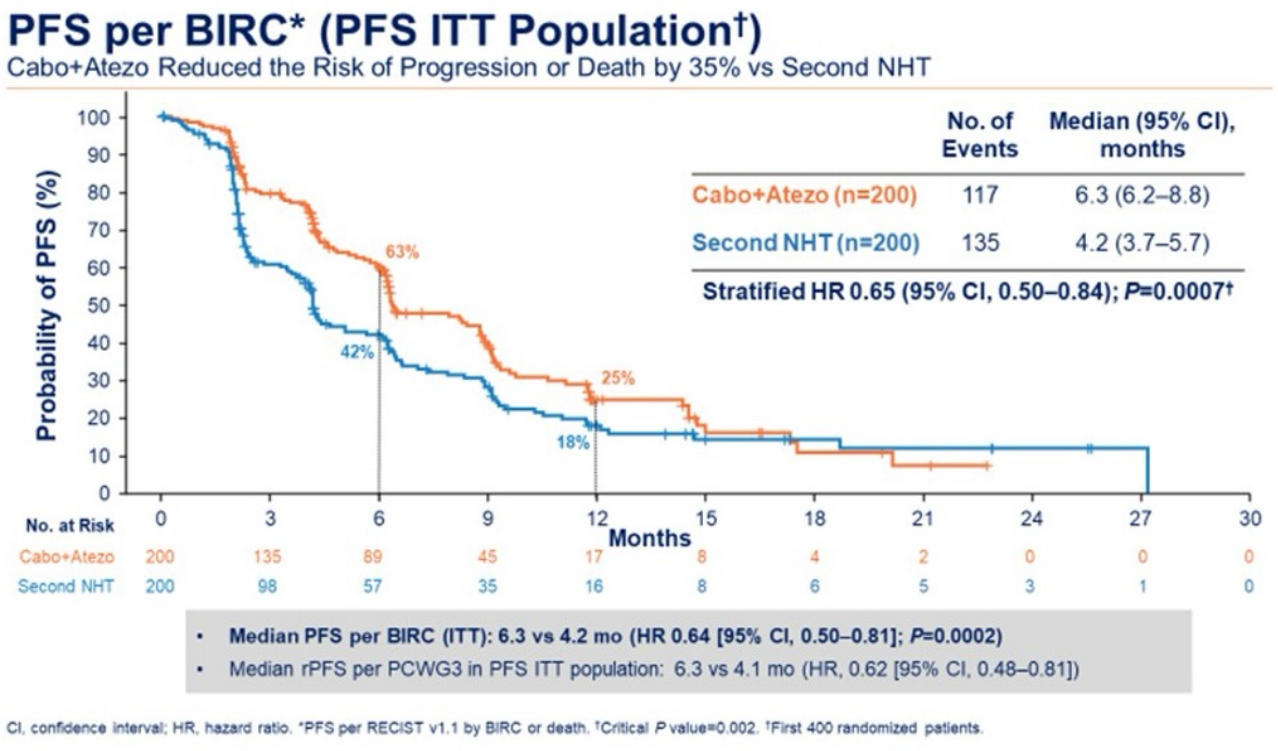


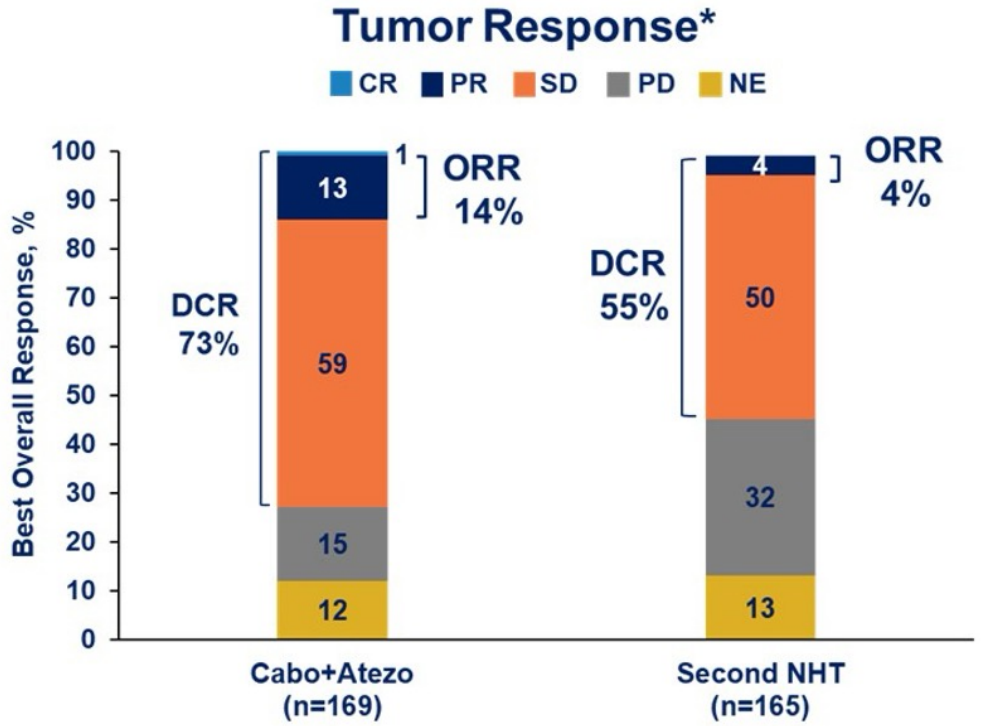
Smith et al JCO 2016

Apolo et al Lancet Oncol 2020

Phase 3 Contact-02 Study: Cabozantinib + Atezolizumab vs. Second NHT in mCRPC

Agarwal et al, ASCO GU 2024





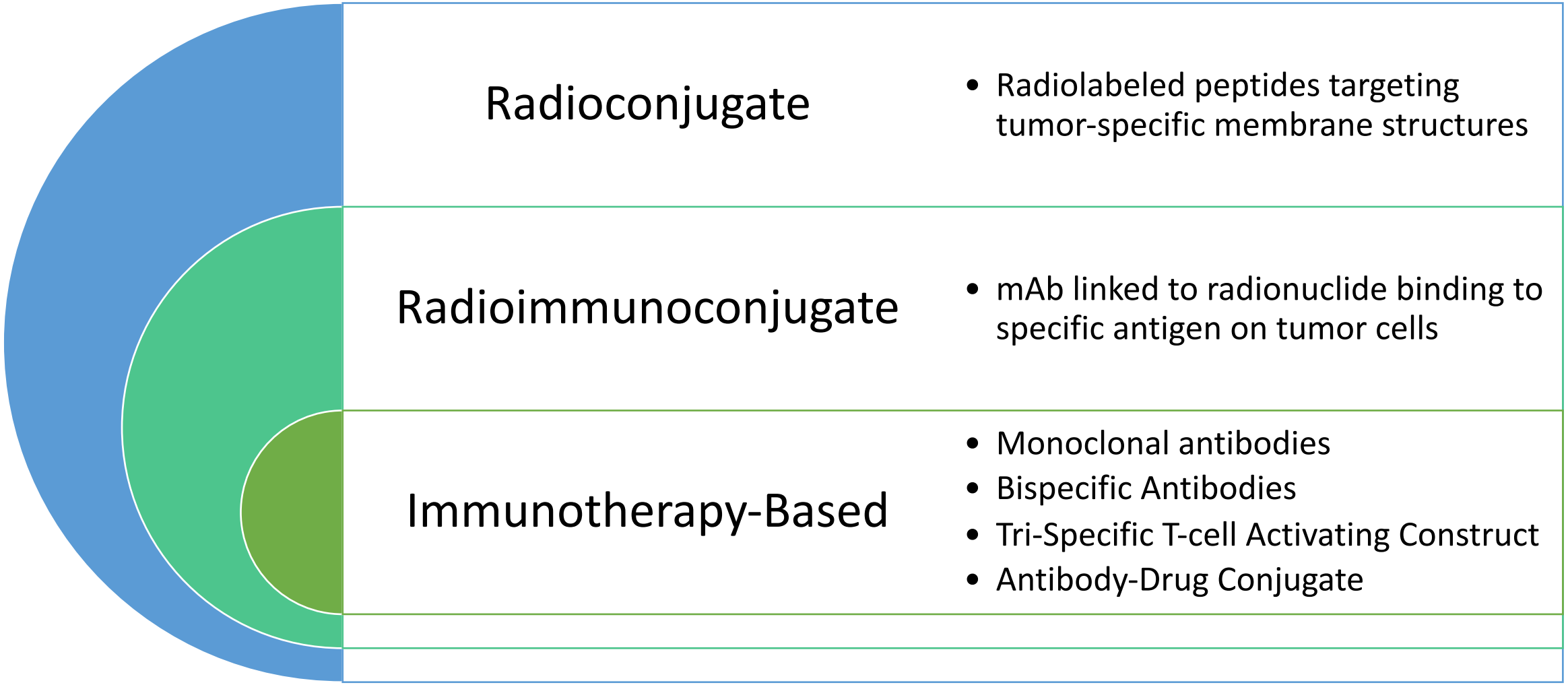
First positive trial for immunotherapy combination in mCRPC

Limitations of CONTACT-02 Results

- Is ARPI an acceptable control arm in mCRPC?
  - Measurable disease, 40% visceral
  - Low rate of subsequent therapy received
- Applicable to real-world patients?
  - 40% screen failure rate for enrollment
- rPFS benefit is modest
  - No difference in OS
  - No difference in PROs (Pain, QoL deterioration)
- AEs were significant (delays/reductions in 40-60%)
- Contribution of Cabozantinib alone vs. combination regimen?

TRIAL	STUDY DRUGS	RPFS (MONTHS)
COMET-1	Cabozantinib alone	6.6
COSMIC-021	Cabozantinib + atezolizumab	5.5
CONTACT-02	Cabozantinib + atezolizumab	6.3

Clinical Trials and Novel Therapies in PCa

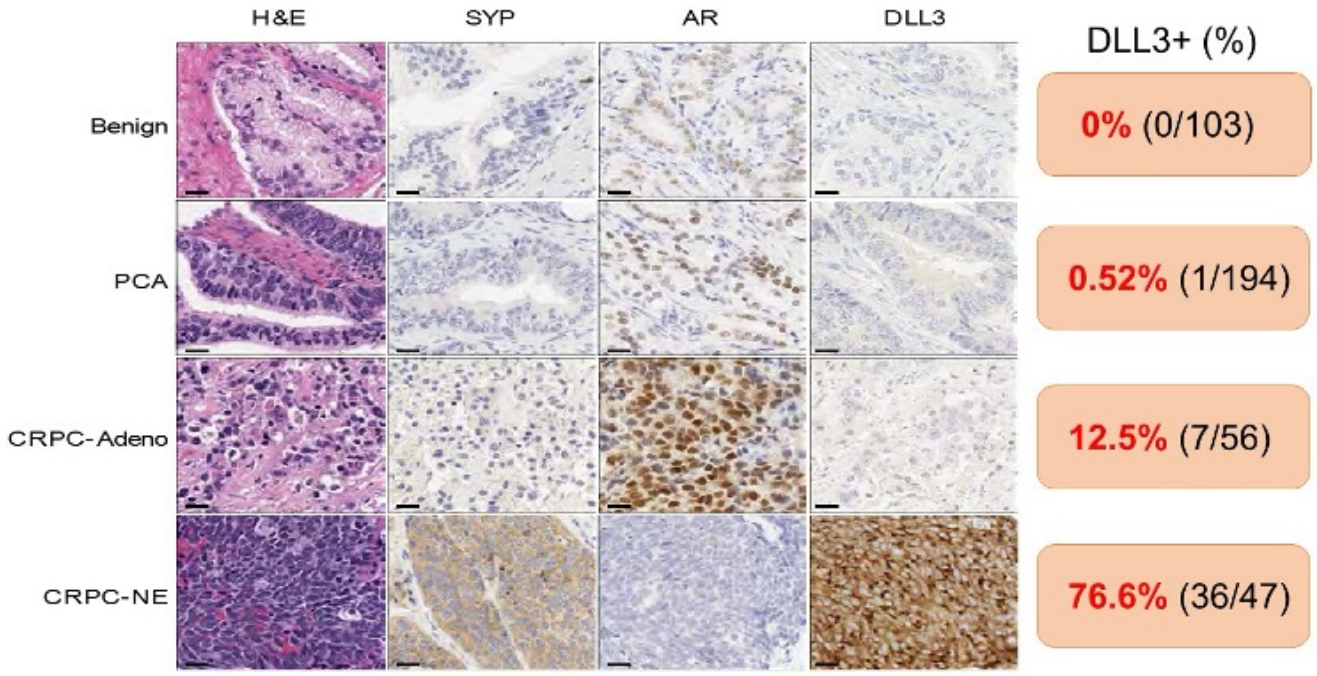


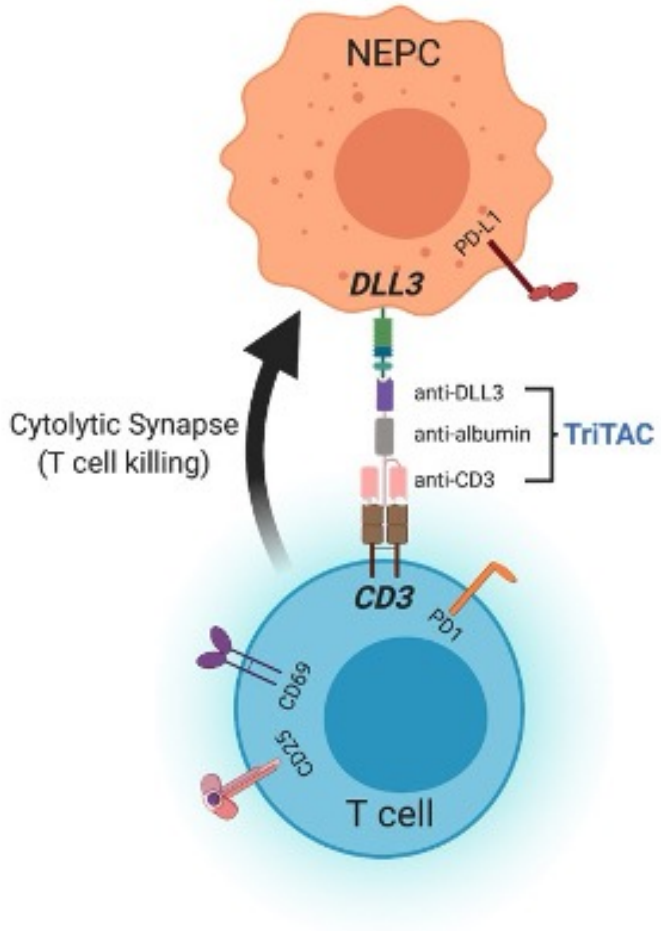
HPN328: Tri-specific DLL-3 Targeting T-Cell Engager in NEPC

Beltran et al GU ASCO 2024

CANCER

Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer





Puca L et al, Sci Transl Med 2019

Harpoon Therapeutics

HPN328: Tri-specific DLL-3 Targeting T-Cell Engager in NEPC

Beltran et al GU ASCO 2024

Trial Design
N=85; 3+3 design
DLL3 pre-screen not required
HPN328 is weekly or biweekly

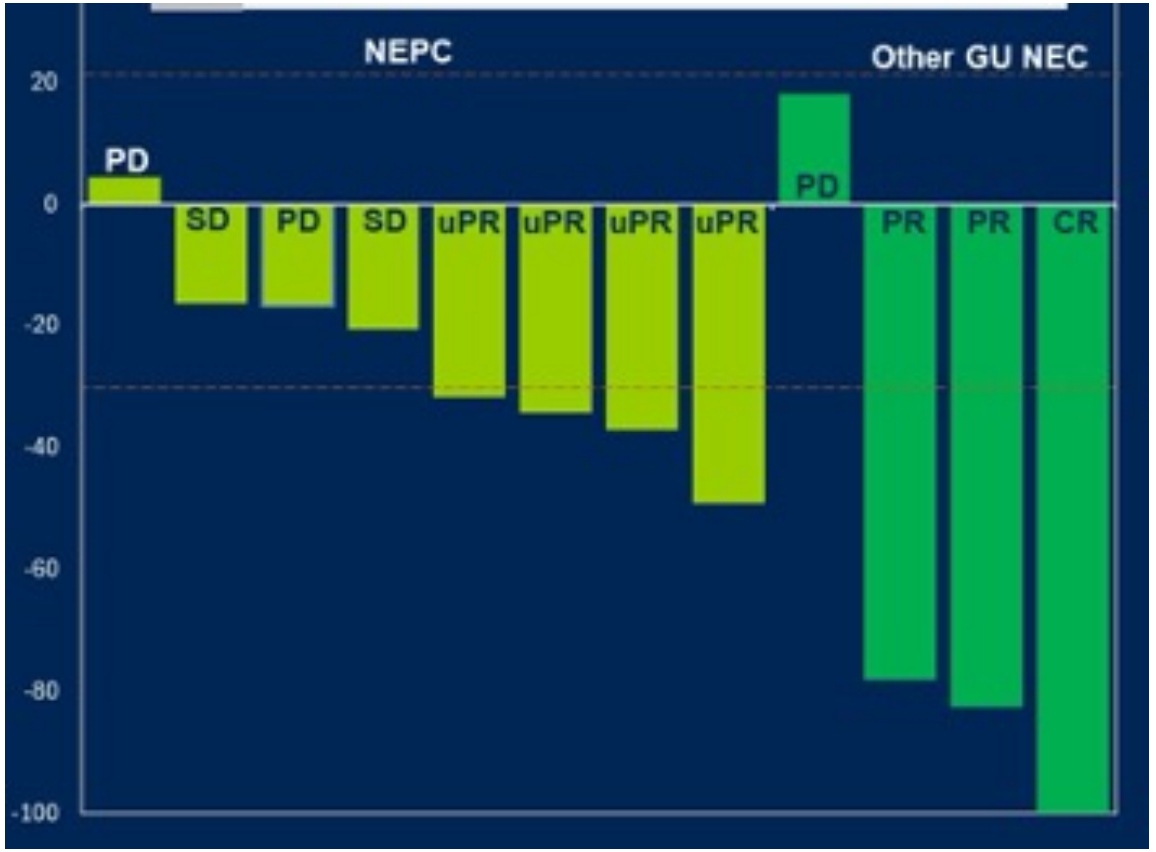
Objectives
Safety, tolerability
Dosing
Preliminary anti-tumor activity

Target Population
Relapsed/refractory NEPC
Other DLL3+ high grade neuroendocrine neoplasms (SCLC)

Results
AEs: G3 CRS in escalation
No DLTs at target doses

All n=50 ORR 28/50 (56%)
GU n=12 ORR 7/12 (58%)

- DLL3 expression 20-100%
- No obvious correlation between %positivity + response



Is DLL3 heterogeneity important?
Potential for combination strategies?
Mono-tx dose optimization ongoing to inform Phase 2 Dose

Summary for Advanced Prostate Cancer

Landscape of Advanced Disease Treatment Options
Early Intensification is the Trend

There is a Role for Genomic Sequencing in all
Need to improve Personalized Treatment Strategies

PARPi have an established role in Advanced PCa
But thus far benefits only limited populations

Radioligand therapies are firmly in the standard of care
Combination and earlier strategies are the future

Immunotherapy remains a work in progress
But with exciting avenues to explore

Thank you!