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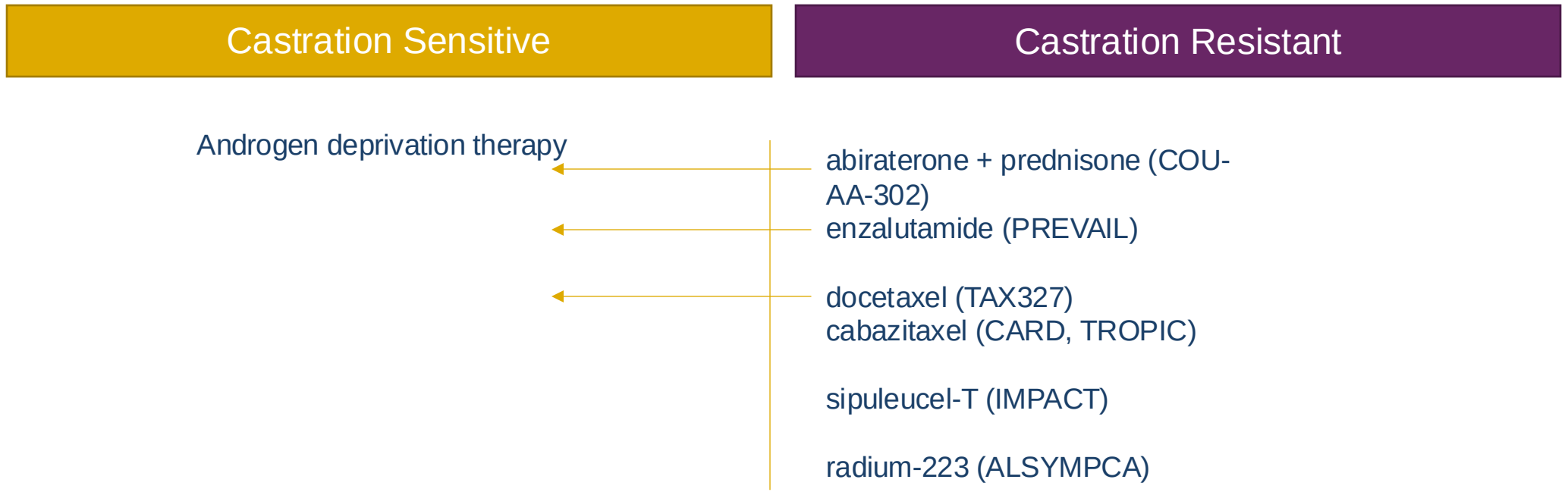
COMPREHENSIVE
CANCER CENTER

Castration Resistant Prostate Cancer: What is the optimal strategy?

Mamta Parikh, MD, MS

Associate Professor

CRPC therapeutic development: exists in the context of what came before



CRPC therapies: the context in which our patients live

Androgen deprivation therapy (ADT)

Castration Sensitive

High volume

docetaxel + abiraterone + prednisone (PEACE-1)

docetaxel + darolutamide (ARASENS)

docetaxel (CHAARTED)

abiraterone + prednisone (STAMPEDE/LATITUDE)

enzalutamide (ENZAMET/ARCHES)

apalutamide (TITAN)

Castration Resistant

abiraterone + prednisone (COU-AA-302)
enzalutamide (PREVAIL)

docetaxel (TAX327)
cabazitaxel (CARD, TROPIC)

sipuleucel-T (IMPACT)

radium-223 (ALSYMPCA)

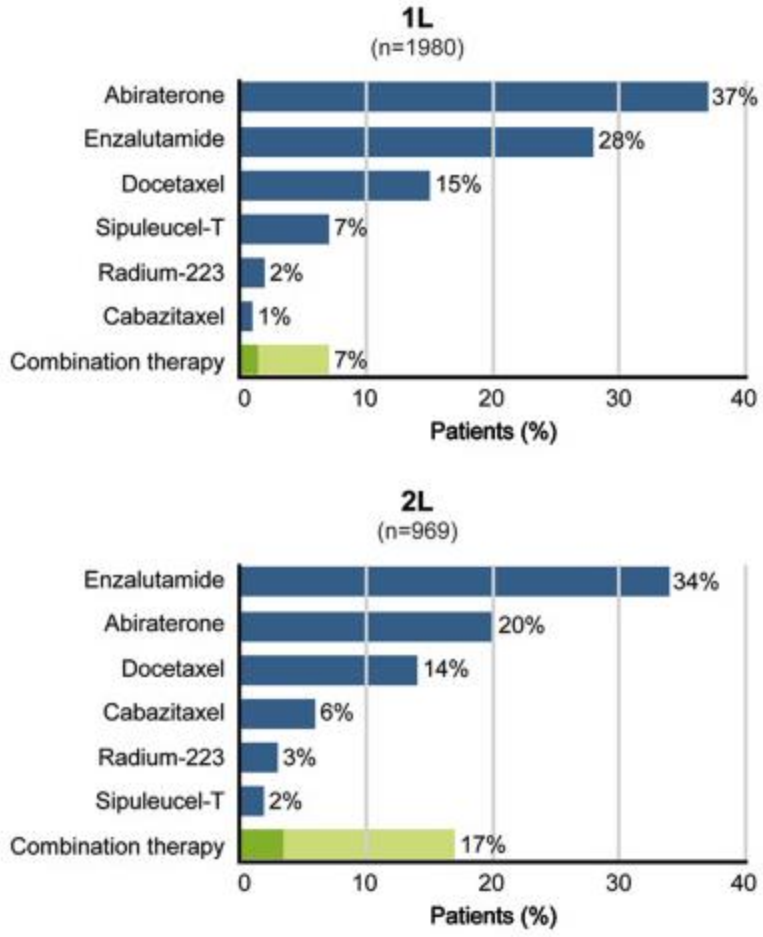
HRR deficient:
olaparib +/- abiraterone
niraparib + abiraterone
rucaparib
talazoparib + enzalutamide

taxane/ARPI refractory:
Lu 177 vipivotide tetraxetan (VISION)

How do we treat mCRPC given these new advances in mHSPC? → Still a lot of options but what is the optimal strategy and sequence?

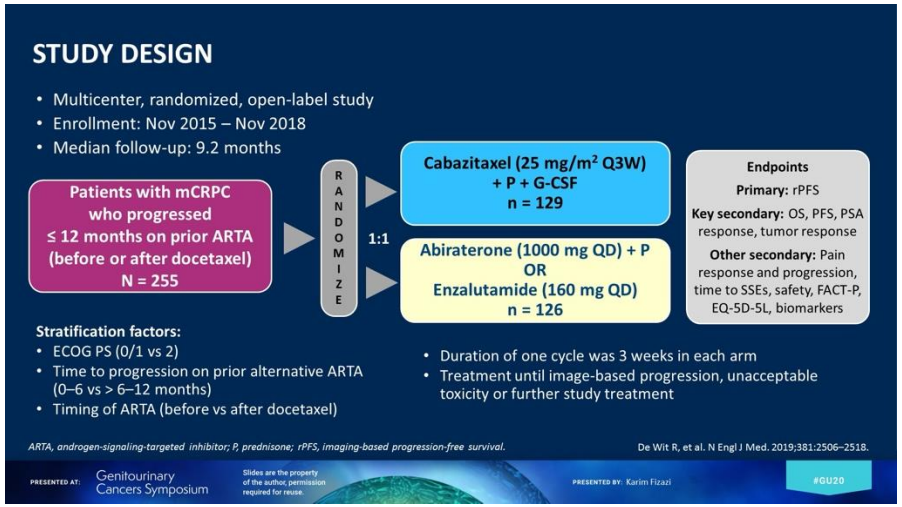
Still some relevant data from prior CRPC era: CARD

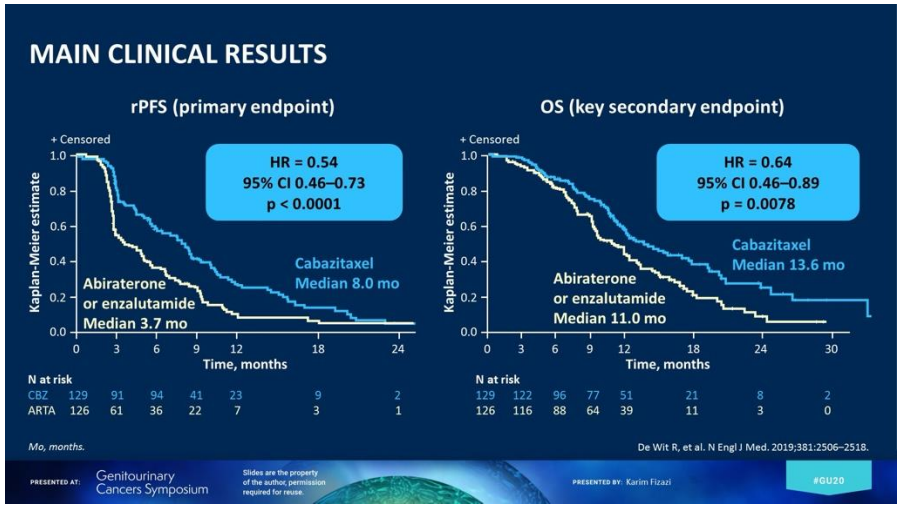
Flatiron RWD analysis



George DJ, et al Clin Genitourin Cancer 2020; 18:284-294

Chemotherapy should be considered for patients after progression on an ARPi



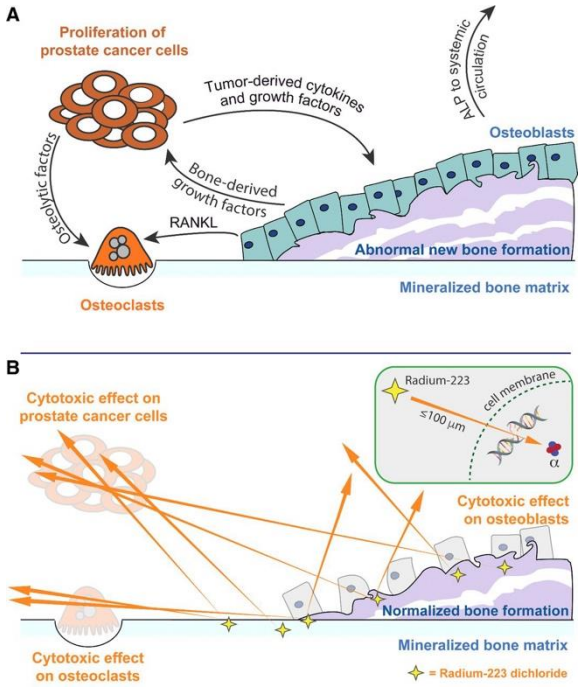


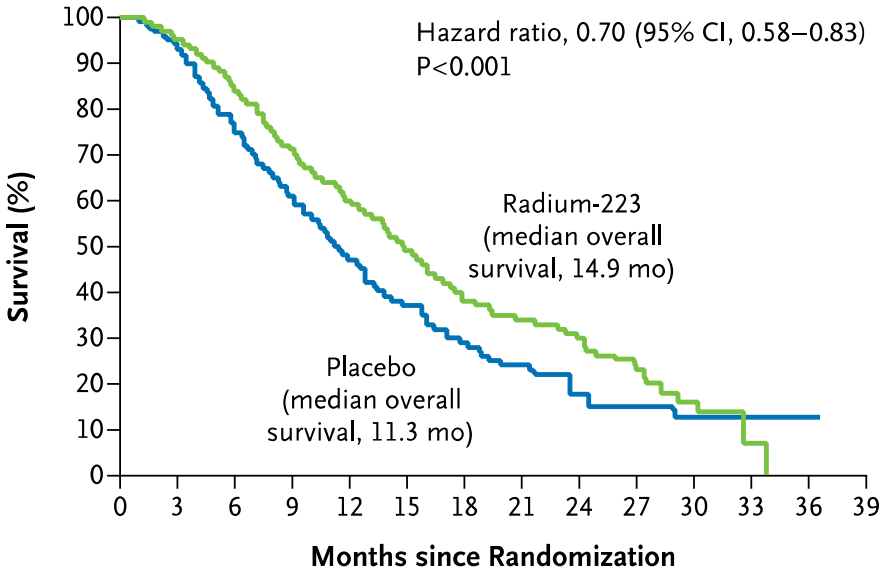
De Wit N Engl J Med 2019; 381: 2506-2518

Radioligand therapies/Theranostics

- Phase III ALSYPMCA
  - patients with symptomatic skeletal mets, no bulky LAD/visceral disease
  - ~60% of patients with prior taxane
  - OS improvement, delays time to first symptomatic skeletal event (15.6 v 9.8 months, HR: 0.66 [0.52-0.3; p<0.001])

- Can other radioligand therapies can be employed?
  - [^{177}Lu]-Lu-PSMA-617



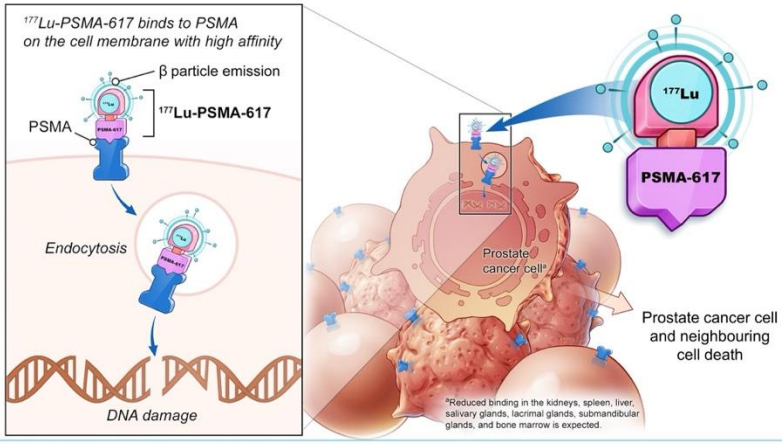


Parker et al N Engl J Med 2013; 369:213-223

Phase III VISION study

3

^{177}Lu-PSMA-617 targeted radioligand therapy



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Open-label study of protocol-permitted standard of care ± ^{177}Lu-PSMA-617 in adults with PSMA-positive 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

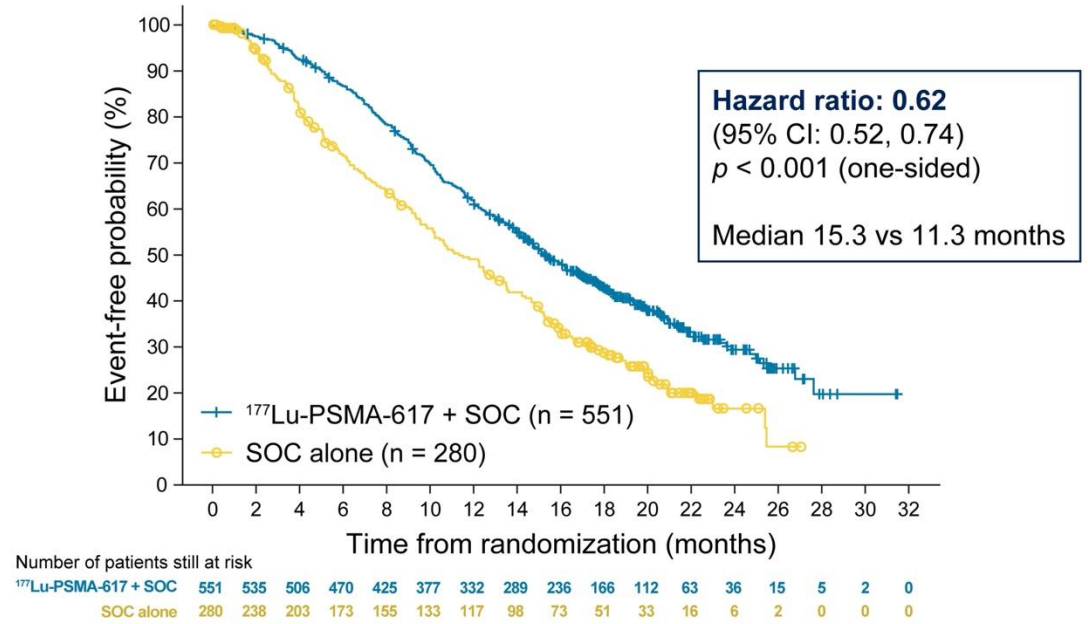
Overall survival in taxane-pretreated patients

16

Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients
(N = 831)



Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
SOC alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

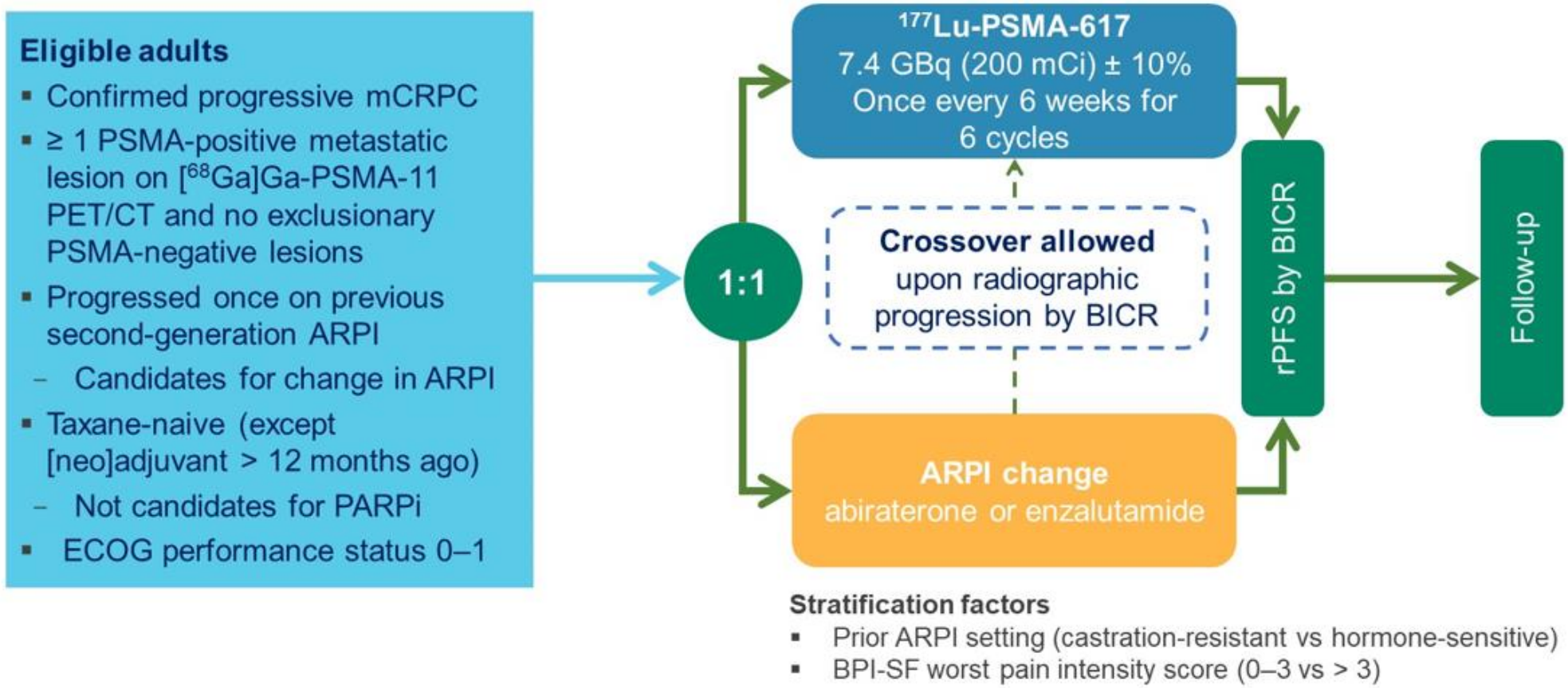
Presented By: **Michael J. Morris**

2021 ASCO ANNUAL MEETING

- 16.6 v 22.4% of patients went on to receive taxanes
- 25.2 v 32.1 % of patients went on to receive any further systemic therapy

What about taxane-naïve patients?

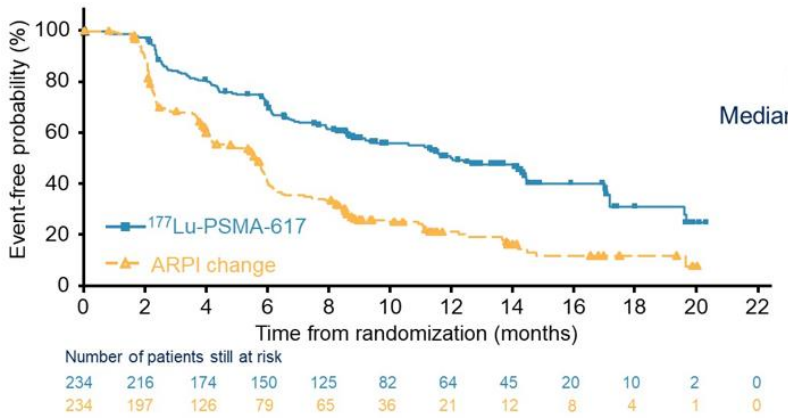
PSMAfore Study



Progression Free Survival in taxane-naïve mCRPC

Primary analysis[a] HR: 0.41 (95% CI: 0.29, 0.56); $p < 0.0001$

Second interim analysis[b] HR: 0.43 (95% CI: 0.33, 0.54)



	177Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median, months (95% CI)	12.02 (9.30, 14.42)	5.59 (4.17, 5.95)

No benefit in OS (57.3% cross-over rate)

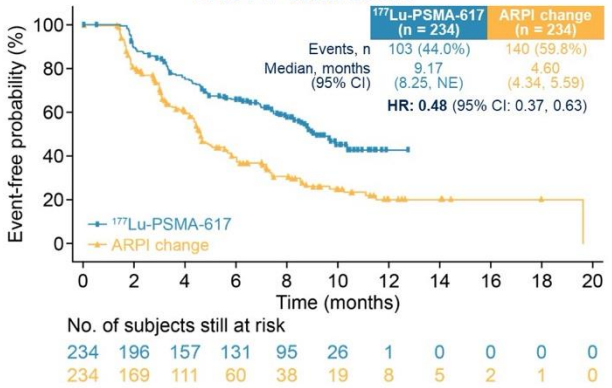
- ^{177}Lu-PSMA-617 delayed cancer deterioration with maintenance of QoL
- among responders, higher QoL and lower pain scores in ^{177}Lu-PSMA-617 arm
- has not resulted in change to label as of yet

Second interim OS analysis

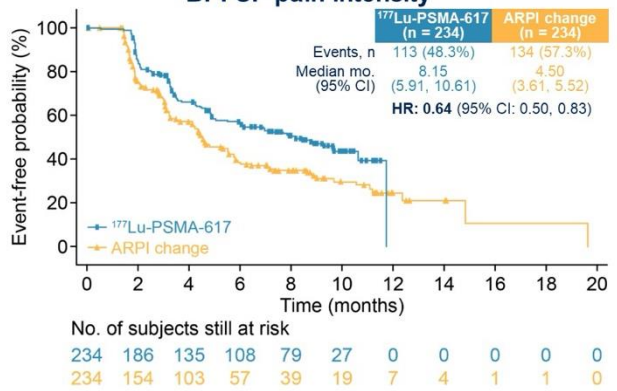
Non-composite *post hoc* HRQoL and pain

***Post hoc* analysis:**
Non-composite time to worsening in FACT-P and BPI-SF excluding clinical progression and death

FACT-P total score



BPI-SF pain intensity



Clinical progression was investigator-assessed as: cancer-related pain escalation, immediate need for new treatment, ECOG status deterioration or progression requiring treatment discontinuation
ARPI, androgen receptor pathway inhibitor; BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; HRQoL, health-related quality of life; NE, not estimable; PSMA, prostate-specific membrane antigen

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Prof. Karim Fizazi

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Targeted approaches

- PARPi (+/- ARPi)
- PROTAC
- Tumor-informed analysis of TRANSFOMER

PARPi efficacy in mCRPC

higher ORR with ARPi combinations, **but** low rates of prior ARPi exposure, and additive toxicity (?)

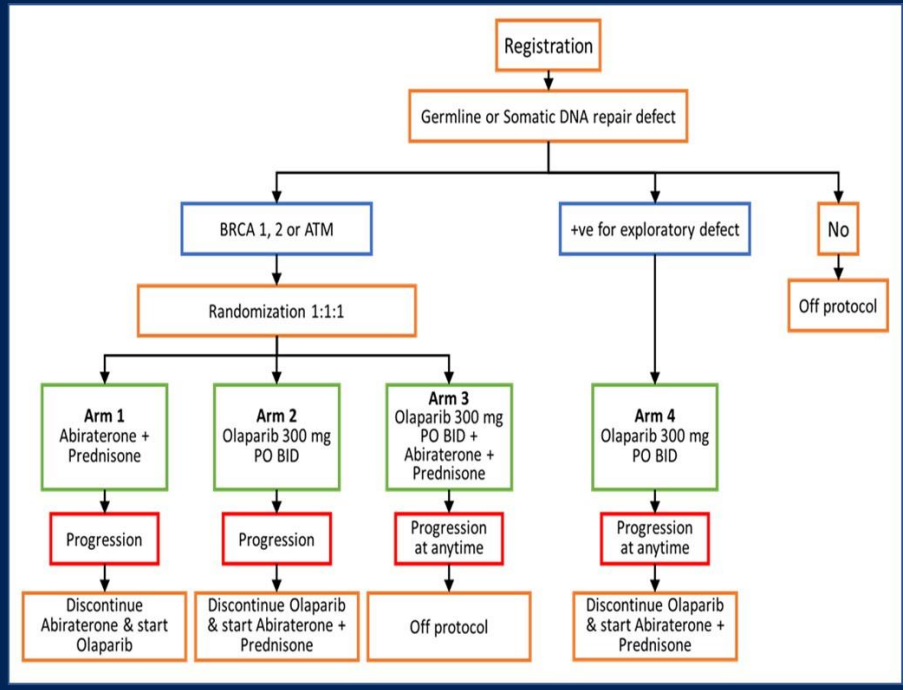
Treatment	Mutations	ORR	Median PFS (months)	Median OS (months)
olaparib (PROfound)	BRCA, ATM	33%	7.4	19.1
rucaparib (TRITON3)	BRCA	45%	11.2	--
	ATM	0%	8.1	--
abiraterone + olaparib (PROpel)	BRCAm	--	NR	--
	All	58.4%	24.8	42.1
abiraterone + niraparib (MAGNITUDE)	BRCA1/2	51.8%	16.6	NR
enzalutamide + talazoparib (TALAPRO-2)	Overall	62%	NR	NR
	HRRm	79%	27.9	NR

N Agarwal et al Lancet 2023; K Chi et al J Clin Oncol 2023; F Saad et al Lancet Oncol 2023; N Clarke et al NEJM Evid 2022; J de Bono et al N Engl J Med 2020; K Fizazi N Engl J Med 2023

BRCAAway

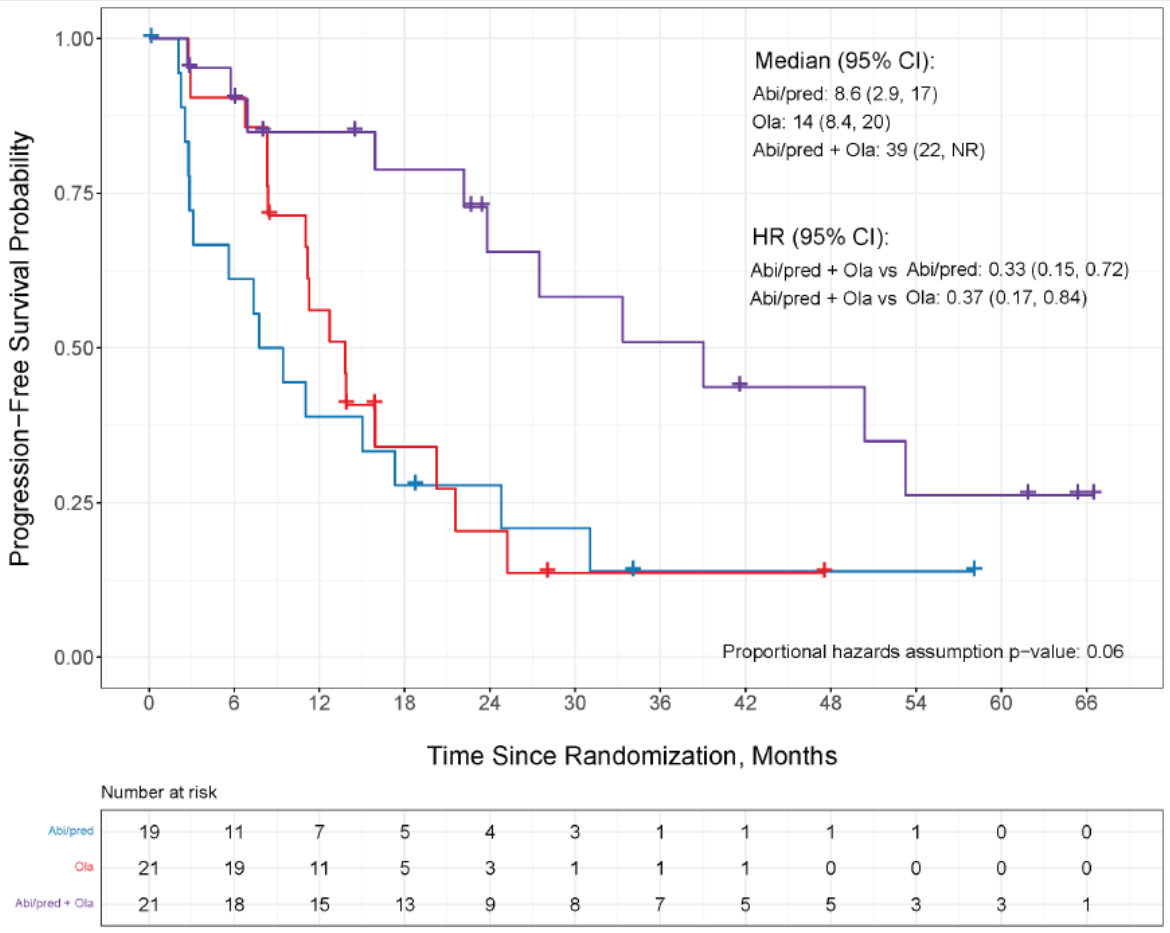
Methods & Study Design

- **Eligibility:** mCRPC, no prior exposure to PARP-I, AR-I, or chemotherapy for mCRPC, washout of antiandrogen (for mHSPC), radiation, and other investigational agents.
- Eligible pts underwent tumor next-generation sequencing (NGS) & germline testing; pts with inactivating BRCA1/2 and/or ATM alterations were randomized 1:1:1 to:
  - Arm I: abiraterone (1000 mg qd) + prednisone (5mg bid),
  - Arm II: olaparib (300 mg bid)
  - Arm III: olaparib + abiraterone/prednisone
- Arm I and II pts could cross over at progression.



PRESENTED BY: Maha Hussain, MD, FACP, FASCO

Combination therapy leads to longer median PFS



	Arm I (n = 19)	Arm II (n = 21)	Arm III (n = 21)
Median PFS, months (95% CI)	**8.4 (2.9, 17)**	**14 (8.4, 20)**	**39 (22, NR)**
Objective RR, % (95% CI)	**22** (6.4, 48)	**14** (3, 36)	**33** (15, 57)
PSA RR, % (95% CI)	**61** (36, 83)	**67** (43, 85)	**95** (76, 100)
Undetectable PSA RR, % (95% CI)	**17** (3.6, 41)	**14** (3, 36)	**33** (15, 57)

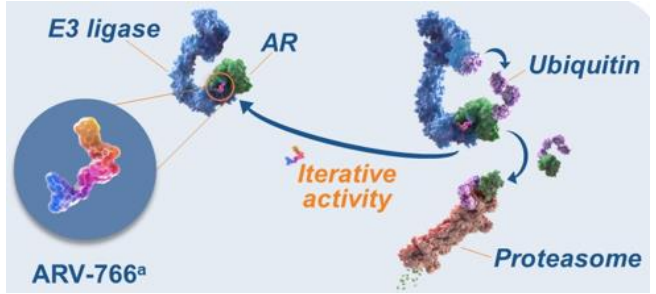
Grade 3 and higher AEs similar across groups (14-21%)

All grade:
- abi/pred: 58%
- olaparib: 90%
- abi/pred + olaparib: 95%

Hussain et al Clin Cancer Res 2024

ARV-766 PROTAC

- 20-25% of men with mCRPC develop mutations in AR LBDs
  - L720H, H875Y, and T878A common & associated with poor prognosis



Phase 1 dose escalation (part A)	Phase 2 cohort expansion (part B)
Key eligibility criteria • Progressive mCRPC • Ongoing ADT • ≥2 prior systemic therapies (including ≥1 ARPI)	**Key eligibility criteria** • Progressive mCRPC • Ongoing ADT • 1–3 prior ARPIs • ≤2 prior chemotherapy regimens
Treatment • Ascending doses of ARV-766 (20–500 mg orally QD)	**Treatment** • ARV-766 100 mg or 300 mg orally QD (1:1 randomization)
Primary objective • Safety and tolerability of ARV-766 to select RP2Ds	**Primary objective** • Evaluate the antitumor activity of ARV-766

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ARV-766 monotherapy: patient characteristics & safety

- n=123
  - AR LBD, n=53
- Median prior lines of therapy: 4
- In AR LBD cohort:
  - Prior abiraterone only- 36%
  - AR antagonist only- 9%
  - ≥ 2 ARPis- 55%
  - prior taxane- 58%
- No DLTs observed, MTD not reached in Phase I/Part A

TRAEs in ≥10% of patients, n (%)	Total (N=123)			
	Total	Grade 1	Grade 2	Grade 3
Fatigue	41 (33)	26 (21)	12 (10)	3 (2)
Nausea	25 (20)	16 (13)	8 (7)	1 (1)
Diarrhea	19 (15)	13 (11)	5 (4)	1 (1)
Increased blood creatinine	18 (15)	14 (11)	4 (3)	0
Alopecia	17 (14)	14 (11)	3 (2)	NA
Decreased appetite	13 (11)	4 (3)	9 (7)	0

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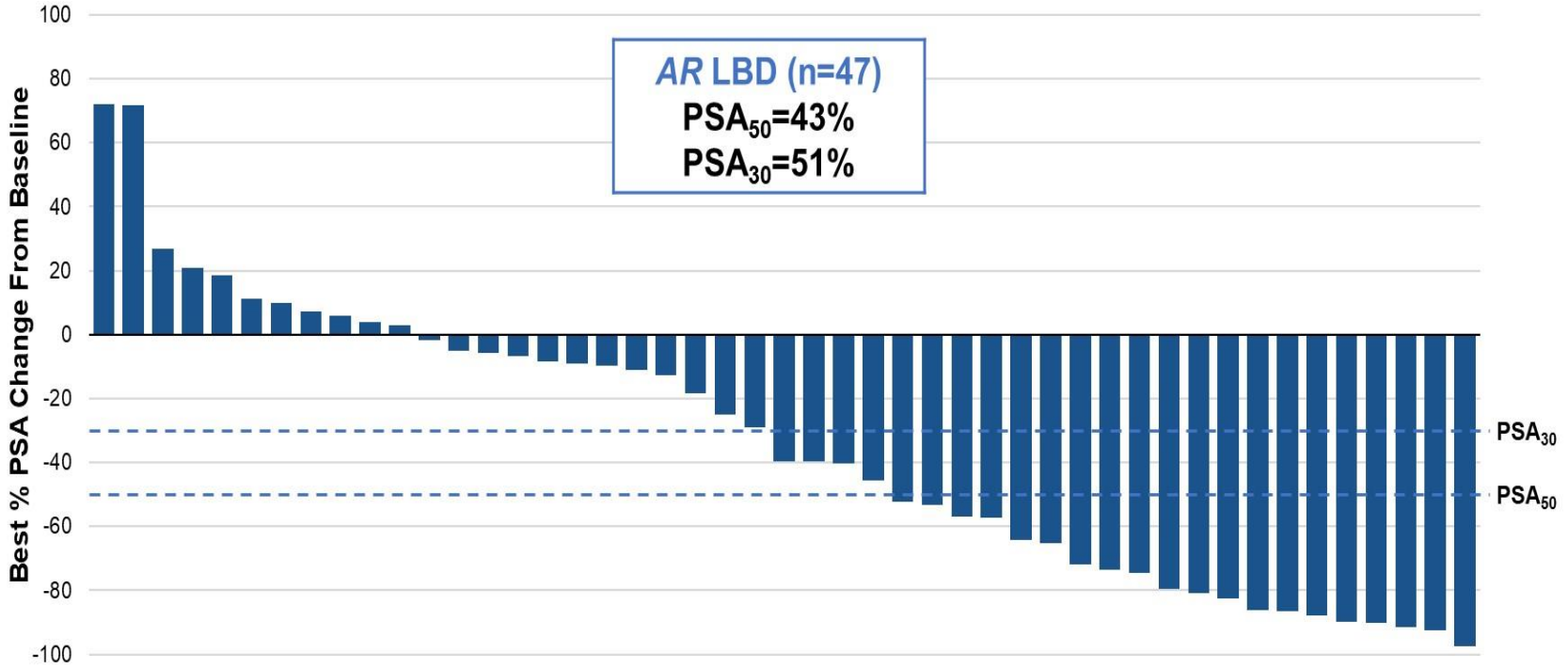
ARV-766 Monotherapy: Best Declines in PSA in Patients With *AR* LBD Mutations[a]



[a]Includes patients with ≥1 month of PSA follow-up.

AR=androgen receptor; LBD=ligand-binding domain; PSA=prostate-specific antigen; PSA_{30}=best PSA declines ≥30%; PSA_{50}=best PSA declines ≥50%.

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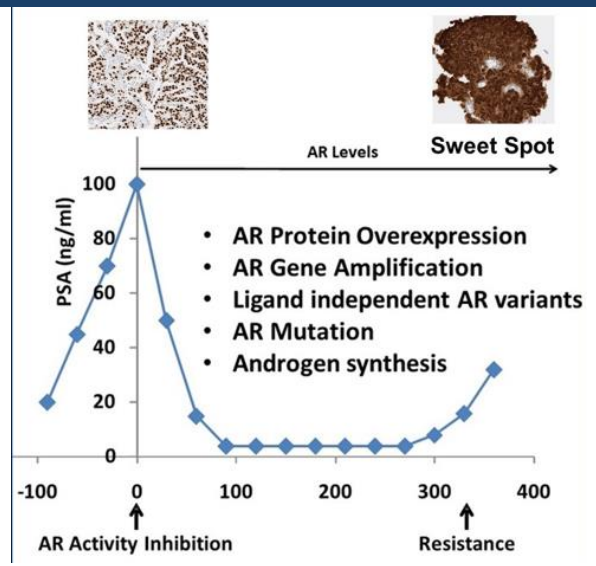
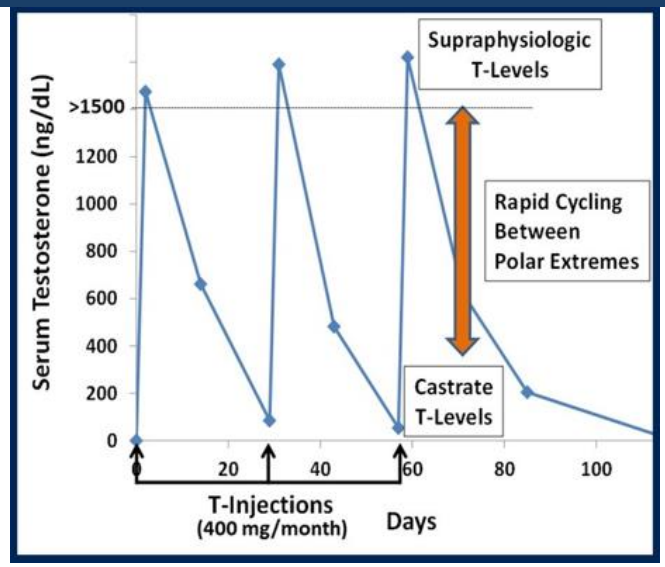
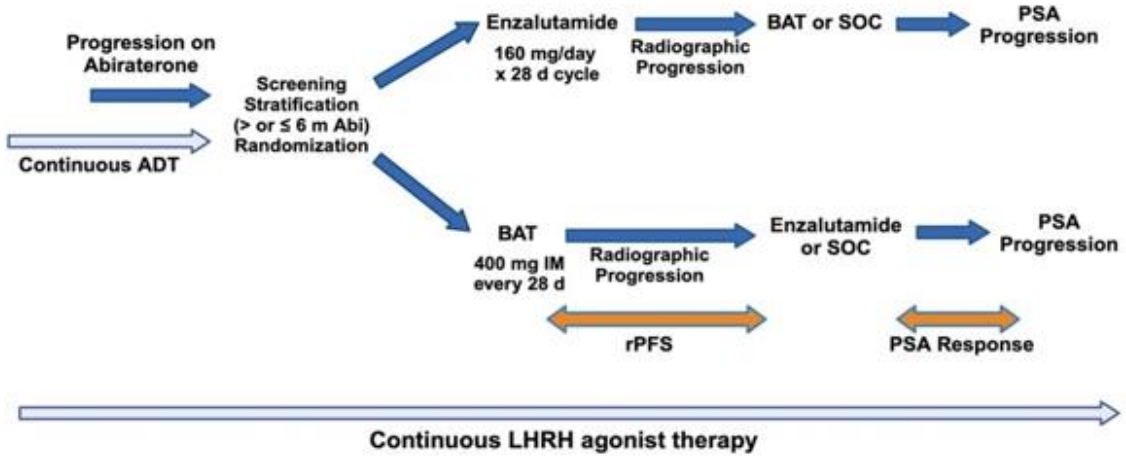
TRANSFORMER





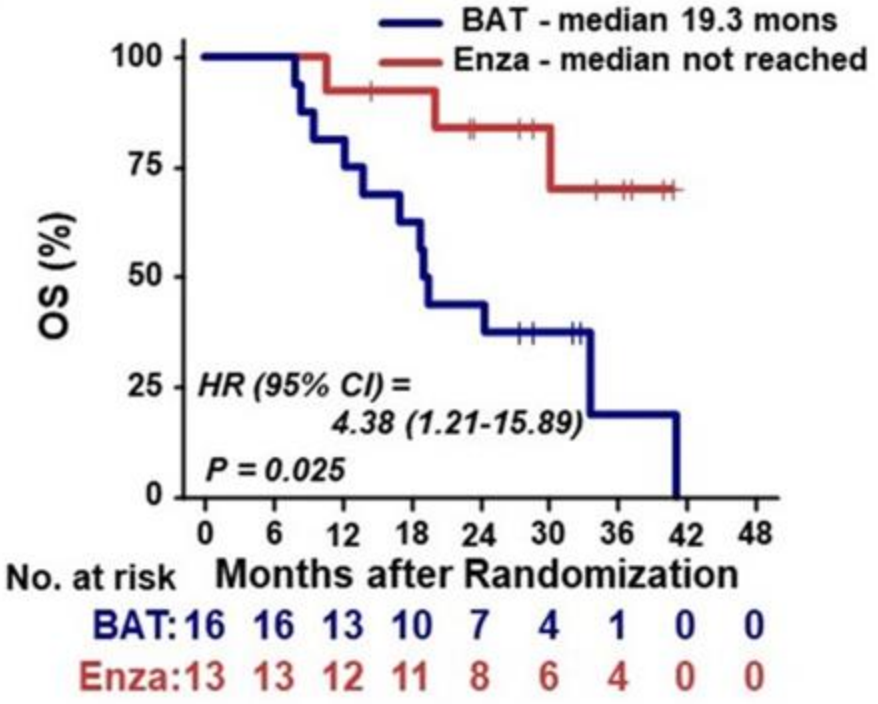


no significant differences in PFS, PSA_{50}, OR, OS in BAT versus enzalutamide

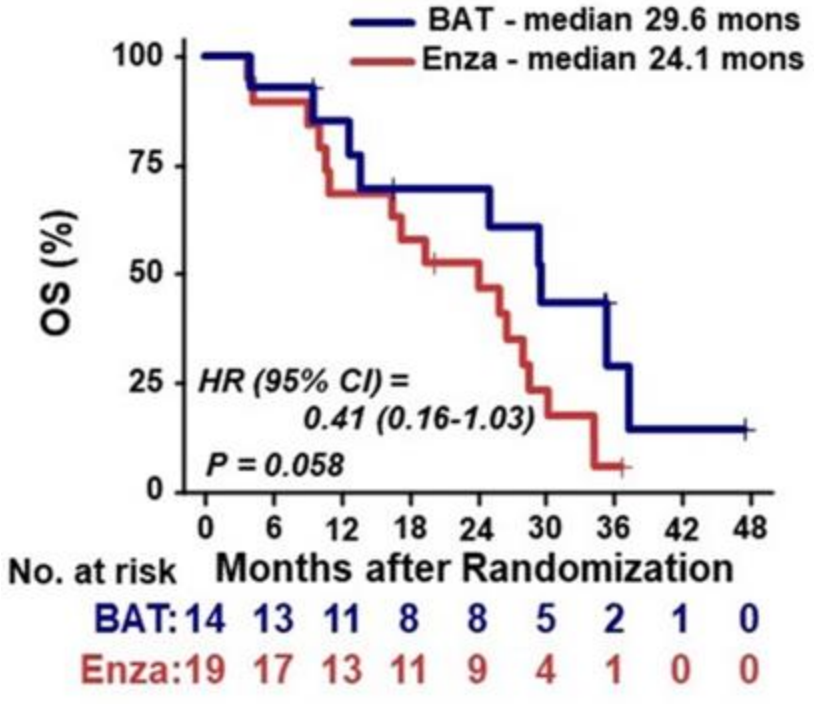
Denmeade ASCO 2024

Lack of AR alterations predicts worse outcomes with BAT

OS with no AR alterations



OS with AR alterations



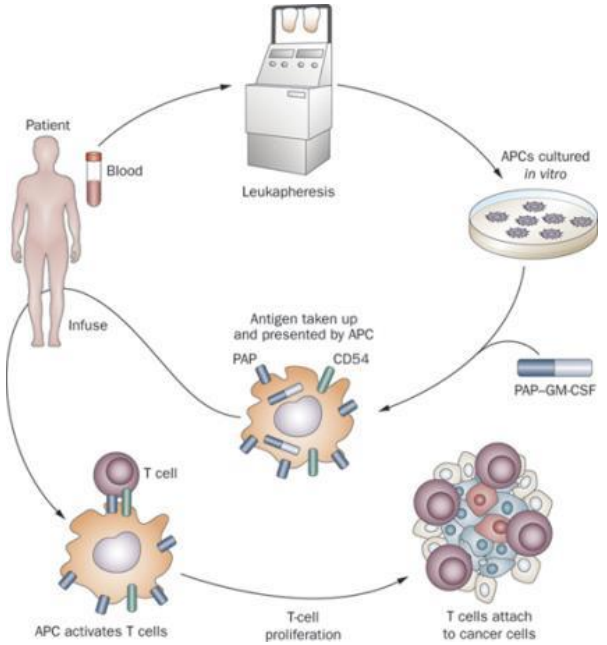
- Similar trends seen with PFS
- Further trials with BAT open and accruing: STEP-UP, APEX, BATRAD (+Radium-223), AcroBAT (oral testosterone)

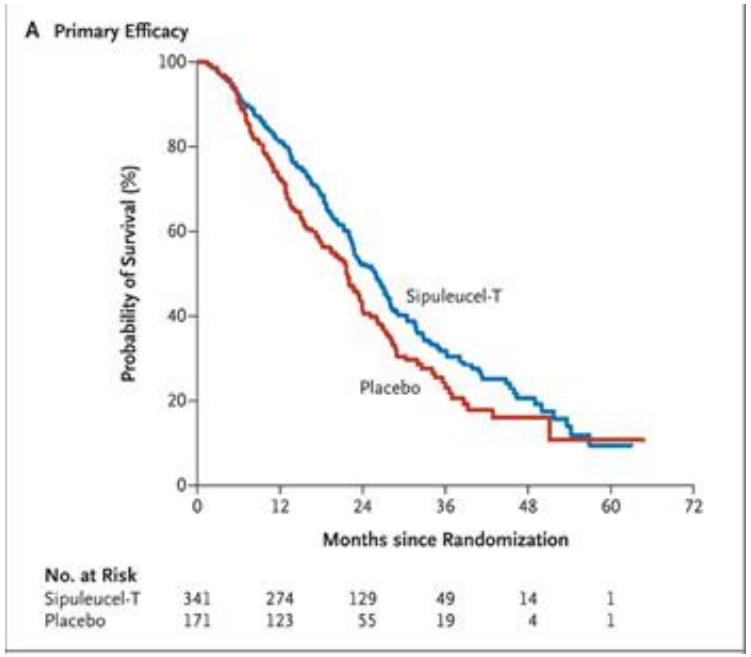
Denmeade ASCO 2024

Immunotherapy

- IMPACT Phase III
  - asymptomatic patients with mCRPC
  - prior to modern ARPi
  - ~15% prior taxane
  - OS benefit (25.8 v 21.7 months), no PFS or PSA response benefit

- Can we use immune-based approaches to optimize prostate cancer treatment?
  - BiTE therapies
  - CAR-T cells

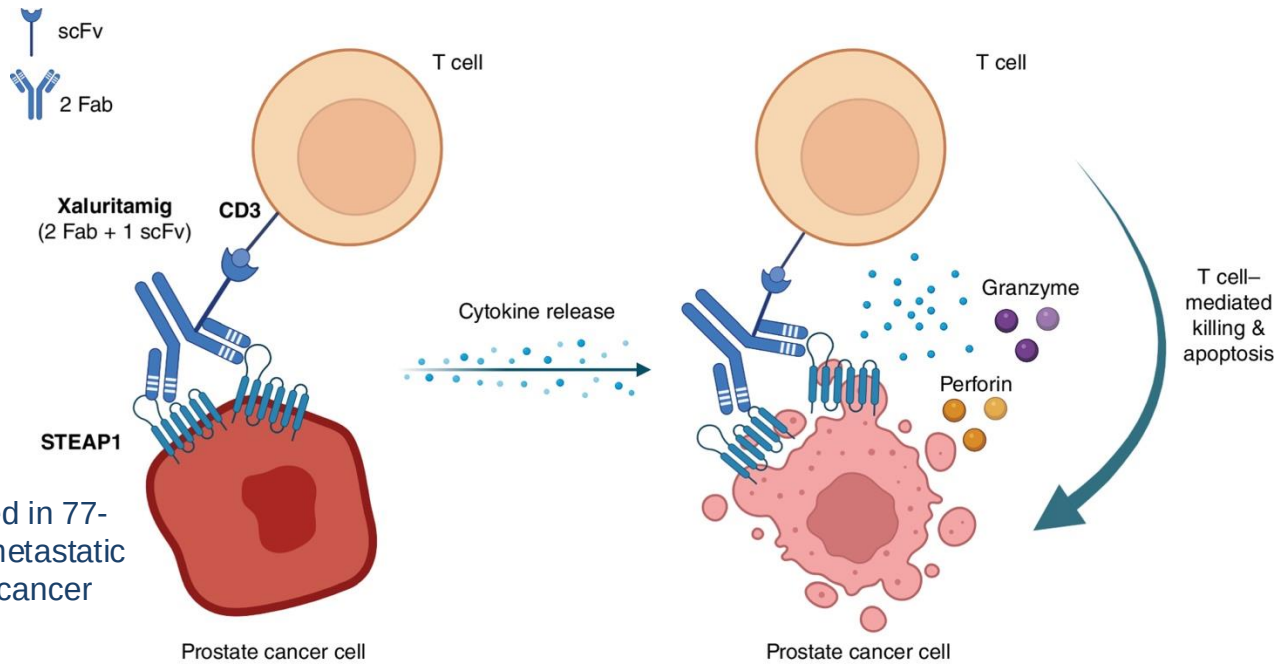




22% relative reduction in risk of death
HR: 0.78; 95% CI 0.61-0.98; p=0.03

Kantoff et al N Engl J Med 2010; 363: 411-422

STEAP1 Bispecific T-cell Engager (BiTE)- Xaluritamig



expressed in 77-83% of metastatic prostate cancer

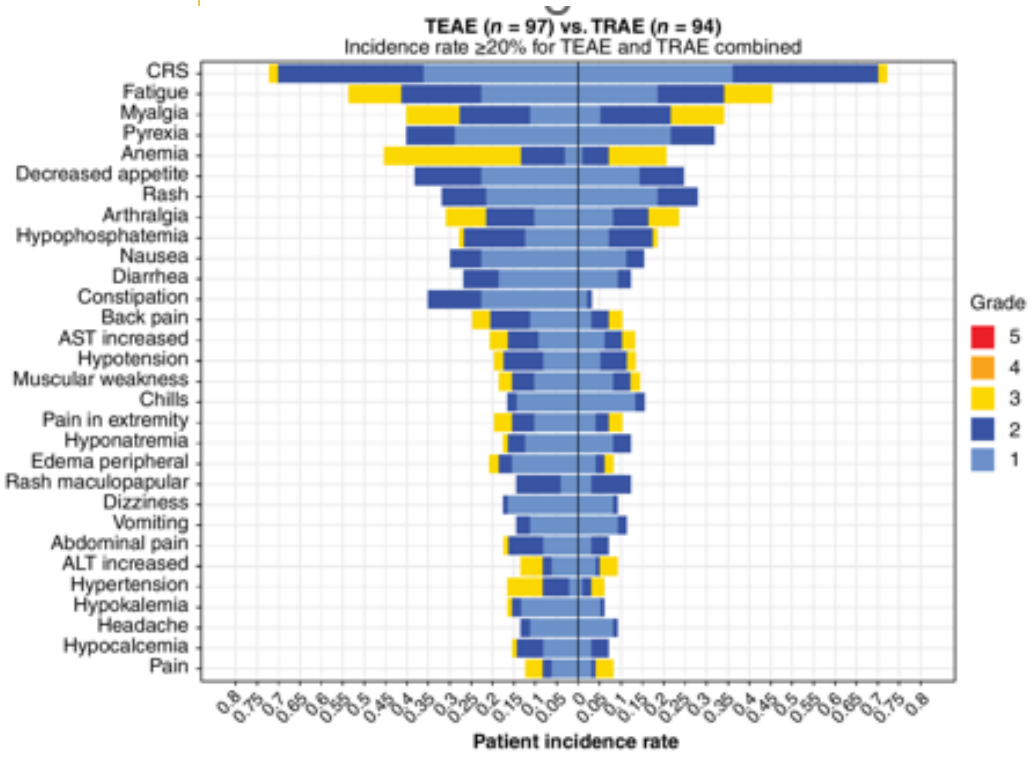
Phase I monotherapy dose-escalation study

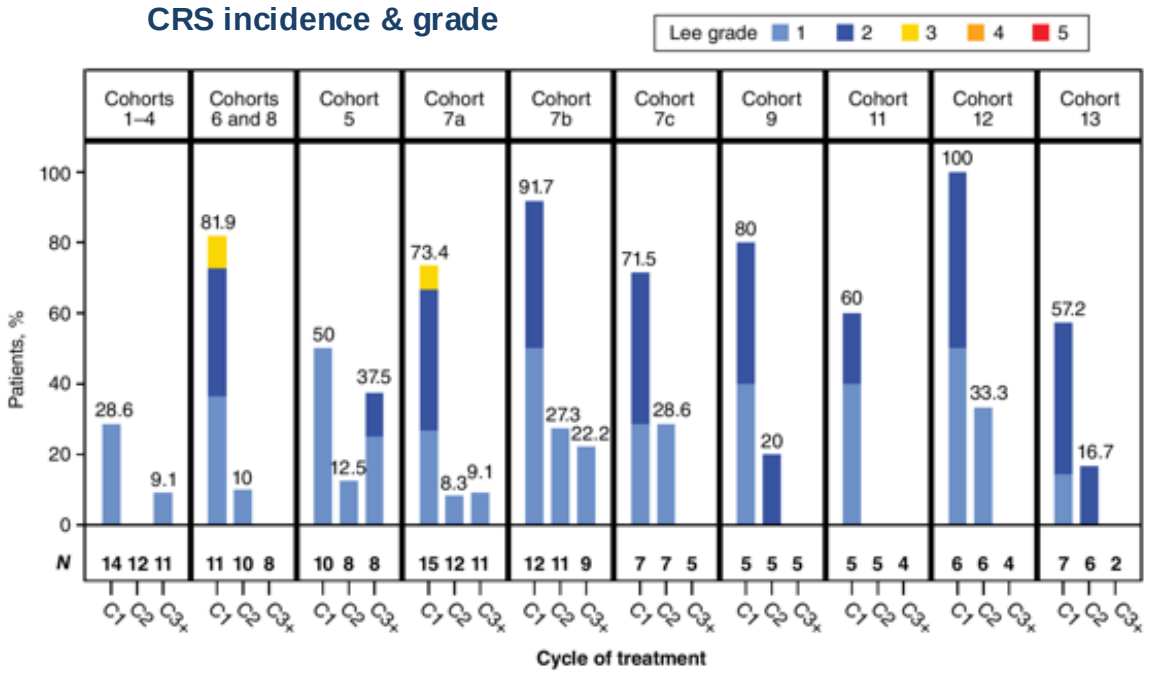
Key patient characteristics:

- 96% ECOG 0
- Most patients had at least 3 prior lines of therapy:
  - 3: 26%
  - 4: 26%
  - ≥ 5: 28%
- 15% with no prior taxane
- 4% with prior PSMA-targeting radioligand therapy
- 53% with visceral mets

WK Kelly et al Cancer Discovery 2024

Xaluritamig safety





MTD: 1.5 mg IV weekly (3-step)- cohorts 11/12

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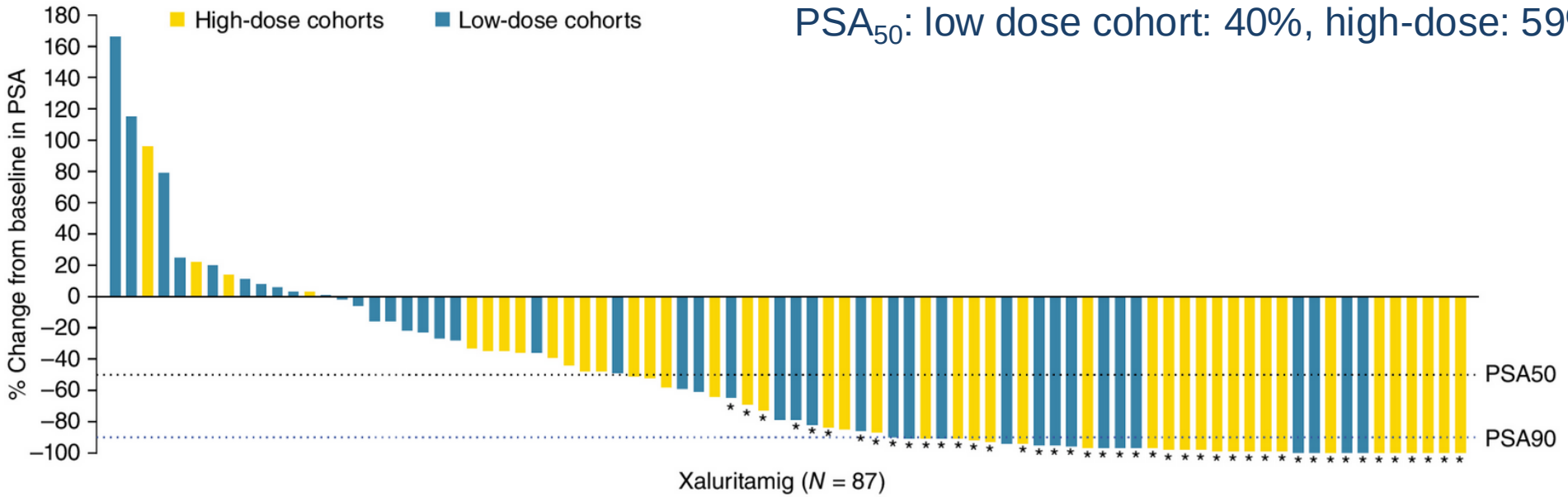
Xaluritamig efficacy



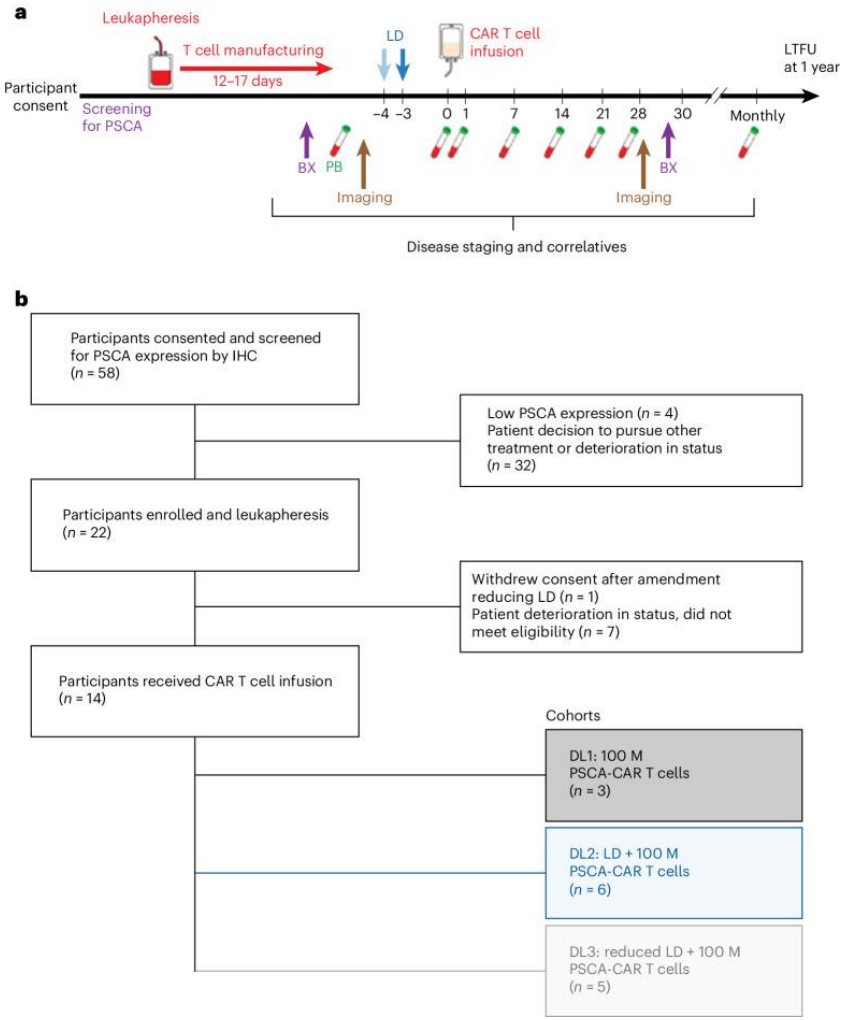
PSA_{50}: low dose cohort: 40%, high-dose: 59%

- DCR was 63% in low dose cohort and 79% in high dose cohort
  - PR: 3% in low dose cohort, 41% in high dose cohort

WK Kelly et al Cancer Discovery 2024

PSCA CAR-T cell therapy

- Prostate stem cell antigen (PSCA)- commonly and robustly expressed tumor associated antigen
- Phase I study at CoH to evaluate safety and DLTs associated with PSCA CART (primary endpoints)
- Secondary endpoints:
  - expansion & persistence of CART cells
  - disease response
  - Survival
- n=14
- Most patients had received prior enzalutamide or abiraterone (or bother), most patients had received a prior taxane.
- 20% had visceral disease, 20% had lymph node only disease

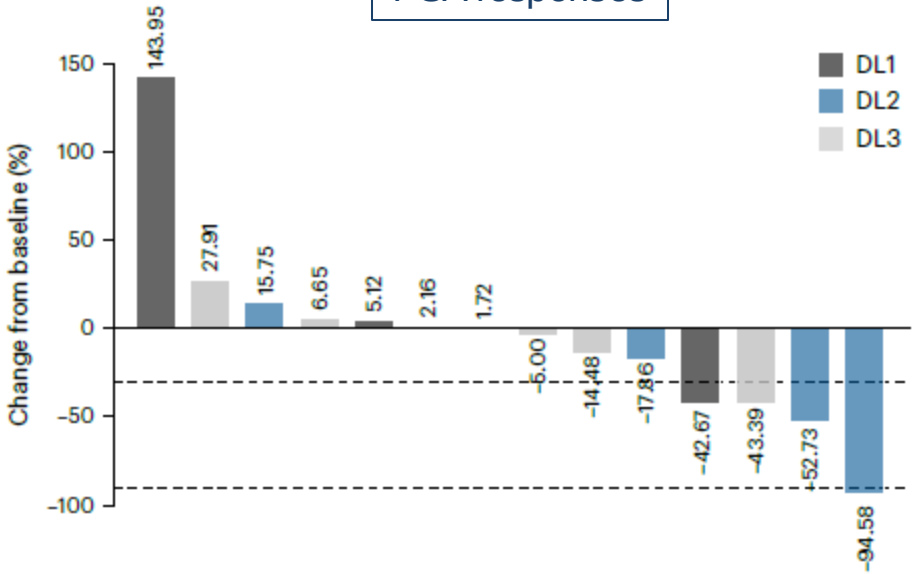


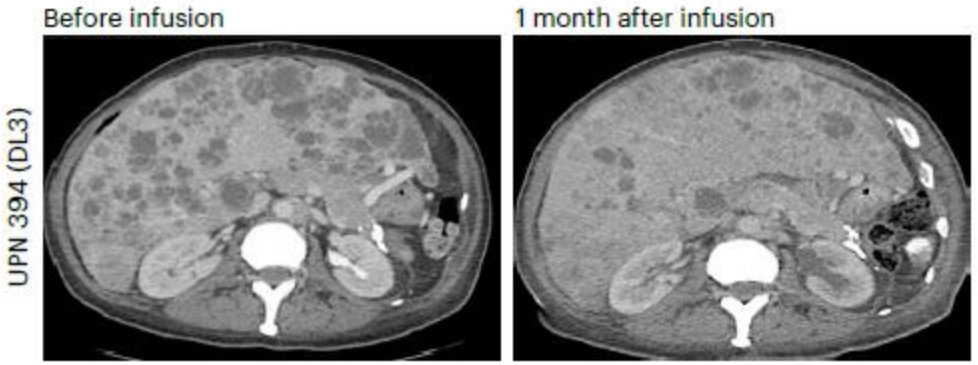
T Dorff et al Nat Med 2024

PSCA CAR-T cell therapy Results

- Safety:
  - Maximum CRS was Grade 2
  - 2 DLTs of non-infectious cystitis at DL2 → led to amendment for reduced lymphodepletion dose
  - No DLTs at DL3 (n=5)
    - 50% CRS
    - 60% Grade 3+ neutropenia

PSA responses





T Dorff et al Nat Med 2024

The optimal strategy is **personalized**

Castration Resistant Prostate Cancer

abiraterone + prednisone (COU-AA-302)
enzalutamide (PREVAIL)

docetaxel (TAX327)
cabazitaxel (CARD, TROPIC)

sipuleucel-T (IMPACT)

radium-223 (ALSYMPCA)

HRR deficient:
olaparib +/- abiraterone
niraparib + abiraterone
rucaparib
talazoparib + enzalutamide

taxane/ARPI refractory:
Lu 177 vipivotide tetraxetan (VISION)

Considerations:
- therapy received in the hormone-sensitive context
- HRRm status (and possibly others soon like AR LBD)
- taxane candidacy
- current cancer-related symptoms
- **clinical trial candidacy**
- quality of life
- financial toxicity

Thank you