UT Southwestern
Simmons Cancer Center

Lutetium-177 PSMA Radioligand Therapy for Treatment of Advanced Prostate Cancer

Kevin Courtney, MD, PhD
Associate Professor of Internal Medicine
Director of Genitourinary Medical Oncology
Division of Hematology/Oncology
UT Southwestern Medical Center
Co-Leader, Genitourinary Oncology Disease Oriented Team
UTSW Harold C. Simons Comprehensive Cancer Center

Disclosures

- Advisory board meeting: Novartis
- Research funding to my institution for clinical trial activities: Astellas Pharma, Lilly, Stemline Therapeutics, Clovis Oncology, Exelixis, Amgen, Harpoon Therapeutics, Pfizer, Novartis, Myovant Sciences, Celgene / Bristol-Myers Squibb, AstraZeneca, Janssen

Educational Objectives: First Attendance Verification Code: **4532**

- Identify patients with metastatic castration resistant prostate cancer who are appropriate for consideration for treatment with lutetium Lu 177 vipivotide tetraxetan under current FDA approval guidelines
- Define PSMA PET selection criteria for treatment with lutetium Lu 177 vipivotide tetraxetan
- Identify adverse events associated with Lu 177 PSMA radioligand therapy

Patients appropriate for treatment with lutetium Lu 177 vipivotide tetraxetan under current FDA approval guidelines

- "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.
- On the same day, the FDA approved Locametz (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. Locametz is the first radioactive diagnostic agent approved for patient selection in the use of a radioligand therapeutic agent.
- Patients with previously treated mCRPC should be selected for treatment with Pluvicto using Locametz or another approved PSMA-11 imaging agent based on PSMA expression in tumors. PSMA-positive mCRPC was defined as having at least one tumor lesion with gallium Ga 68 gozetotide uptake greater than normal liver. Patients were excluded from enrollment if any lesions exceeding certain size criteria in the short axis had uptake less than or equal to uptake in normal liver"
-

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pluvicto-metastatic-castration-resistant-prostate-cancer. Accessed April 11, 2024.
Sartor, O. et al, NEJM, 2021, 385(12):1091-1103

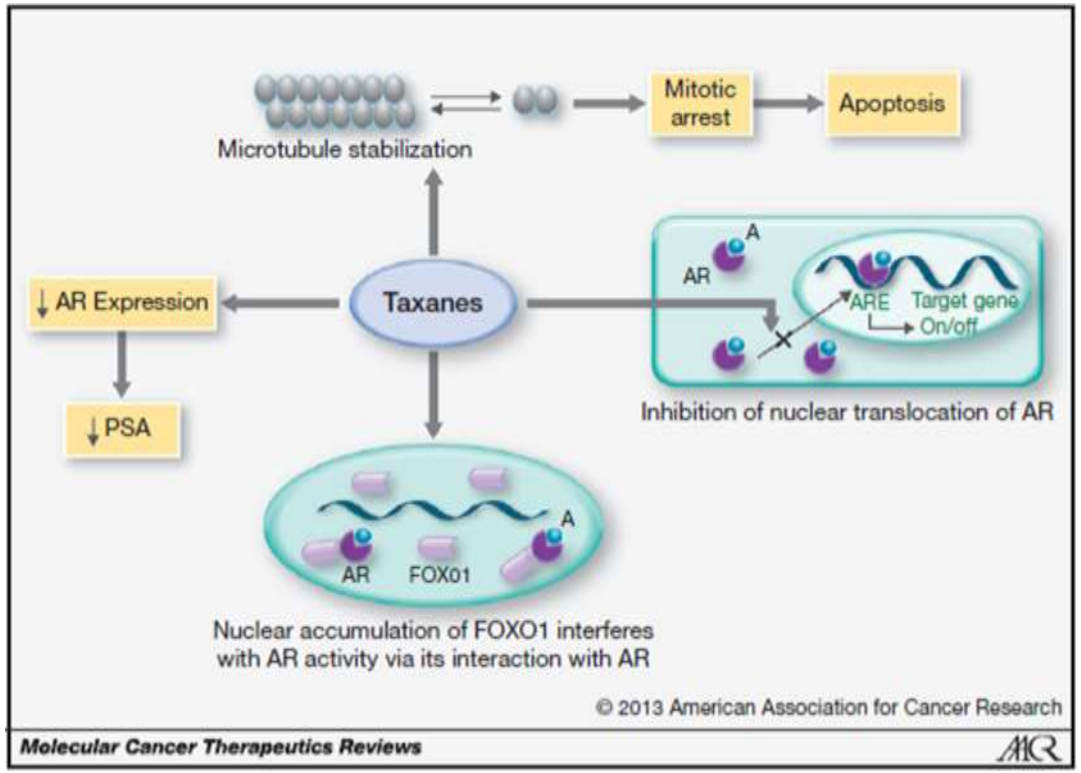
Enhancing castration therapy to treat metastatic prostate cancer

- Castration therapy leads to objective responses in 80-90% of men
- Highly variable duration of efficacy
- Median time to prostate cancer progression: 2-3 years
- How can we prolong the progression free survival and overall survival time for patients with metastatic prostate cancer with the addition of other systemic therapies to castration therapy?

Mechanisms of prostate cancer progression and castration resistance and targets for therapy

- Microtubule polymerization / AR nuclear translocation (taxanes)
- Persistent androgen signaling despite castration therapy
- Immune escape
- Homologous recombination defects
- Interactions with the bone microenvironment
- Prostate specific membrane antigen (PSMA)

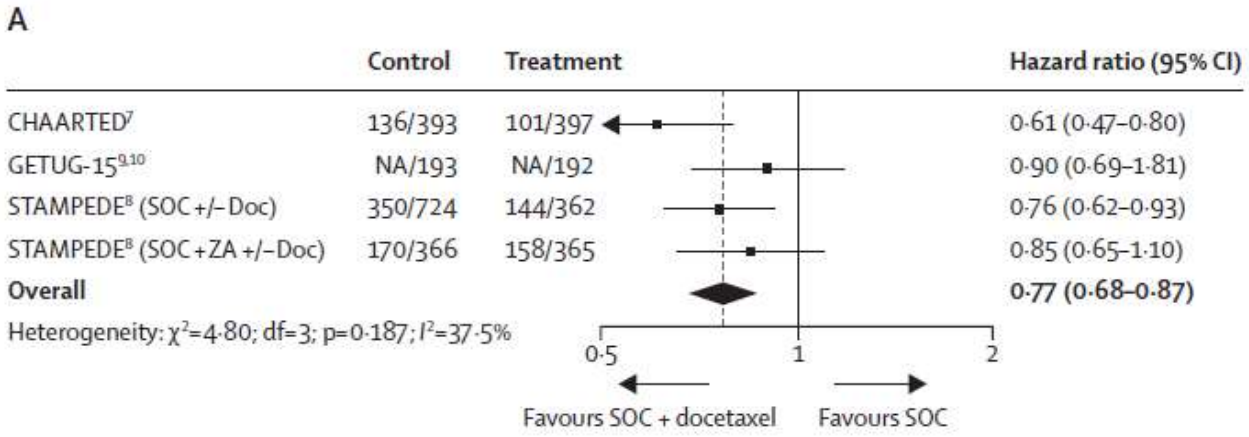
Microtubule stabilization as a rational therapeutic target in prostate cancer: taxanes



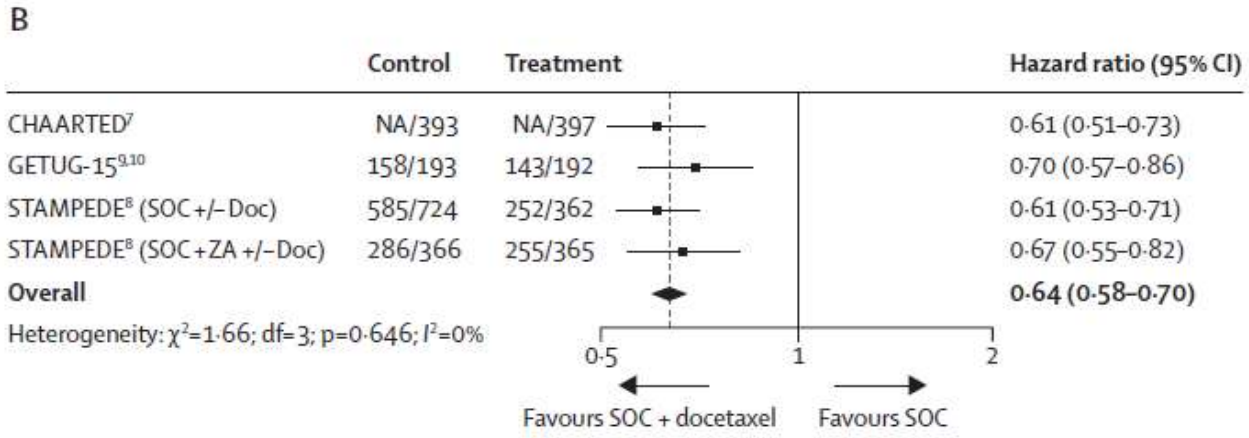
Mistry SJ and WK Oh. (2013) Mol Cancer Ther; 12:555-66.

Docetaxel improves failure-free survival and OS in men with metastatic castration - sensitive prostate cancer starting ADT

A: Docetaxel impact on OS in M1 disease



B: Docetaxel impact on Failure-free survival in M1 disease



Vale CL et al (2016) Lancet Oncol; 17:243-56.

Docetaxel for mCRPC

- TAX 327: Phase III study of 1006 men with mCRPC received prednisone 5 mg bid and randomized to docetaxel 75 mg/m2 q 3 weeks vs 30 mg/m2 weekly for 5/6 weeks vs mitoxantrone 12 mg/m2 q 3 weeks
- Medians OS: 18.9 mos vs 17.4 mos vs 16.5 mos (HR 0.76, p = 0.009 for q 3 week docetaxel)
- Increased PSA response rate, decreased pain, and improved QoL with docetaxel

- SWOG 99-16: Phase III study of men randomized to 21-day cycles of 280 mg estramustine (estradiol-linked nitrogen-mustard) tid days 1-5 and 60 mg/m2 docetaxel on day 2 and 60 mg dexamethasone in 3 divided doses pre-docetaxel vs. mitoxantrone 12 mg/m2 day 1 plus prednisone 5 mg bid
- Median OS 17.5 vs 15.6 mos, HR 0.80, P=0.02
- Improved median TTP and PSA response rate with docetaxel

Tannock IF et al., NEJM 2004; 351:1502.
Petrylak DP, et al., N Engl J Med 2004; 351:1513-1520

Cabazitaxel for mCRPC

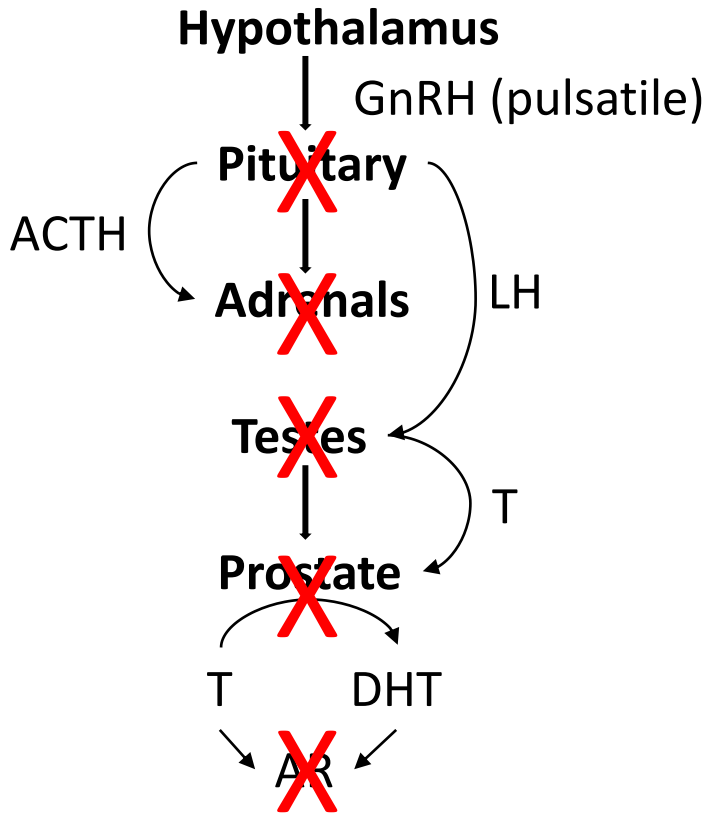
- Cabazitaxel: docetaxel derivative with decreased affinity for P-glycoprotein efflux pump and improved ability to cross blood-brain barrier; unique alterations in prostate cancer cells *in vitro* by expression profiling

- TROPIC phase III study:
  - 755 men with mCRPC following docetaxel treatment treated with prednisone 10 mg daily and randomized to 25 mg/m2 cabazitaxel q 3 weeks vs mitoxantrone 12 mg/m2 q 3 weeks
  - Median OS: 15.1 mos vs 12.7 mos, HR 0.70 (95% CI 0.59-0.83, p<0.001)
  - 82% in cabazitaxel group with grade $\geq$ 3 neutropenia, 6% grade $\geq$ 3 diarrhea, 8% febrile neutropenia
  - Growth factor support required

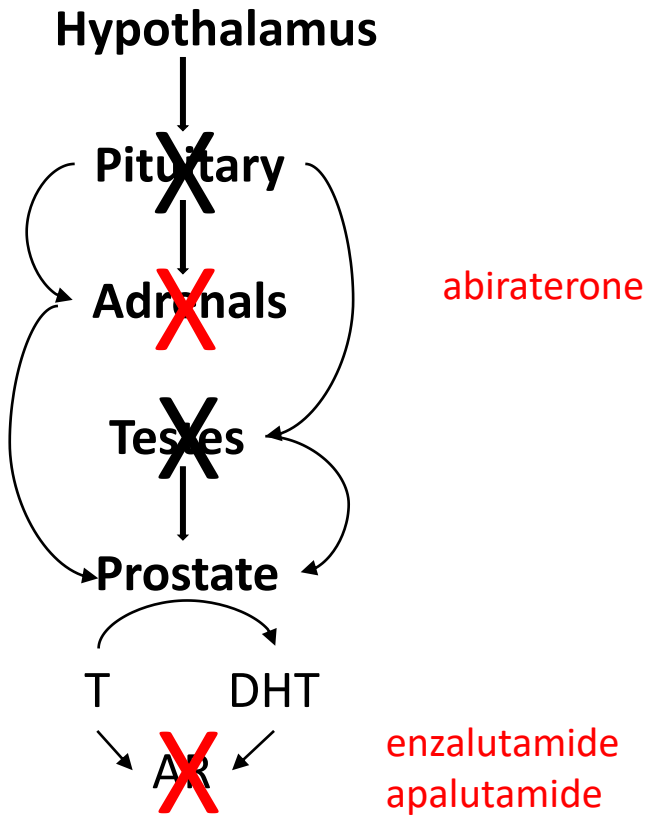
de Bono JS et al. Lancet 2010; 376:1147
De Leeuw R et al. Clin Cancer Res 2015; 21:795

Methods of androgen signaling inhibition

- Orchiectomy (surgical castration)
- GnRH agonist / antagonist (eg: leuprolide / degarelix / relugolix)
- Antiandrogen (block androgen receptor)
- CYP17 inhibition in the adrenal gland
- 5α-reductase inhibition to impair conversion of T to DHT



Inhibiting androgen signaling in castration sensitive prostate cancer: hormonal manipulation beyond castration therapy



abiraterone

enzalutamide
apalutamide
(darolutamide)

Inhibition of CYP17 (17a-hydroxylase / 17,20-lyase) to impair androgen synthesis: abiraterone acetate

Acquired *de novo* androgen synthesis by the testis and extra-gonadal sources in mCRPC

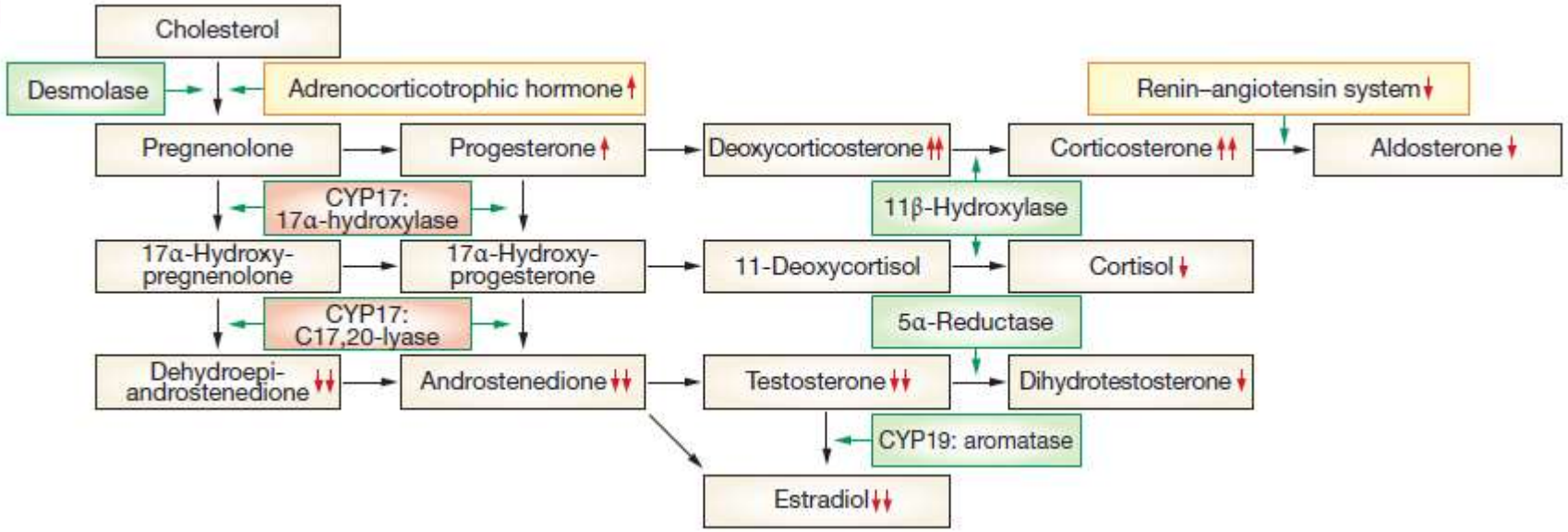


Figure from Reid AHM, et al. (2009) Nat Clin Pract Urol;5:610-20

- Abiraterone acetate: Irreversible inhibitor of CYP17 (17α-hydroxylase / 17,20-lyase)
- Predominant toxicities from mineralocorticoid excess due to loss of negative feedback on ACTH: hypertension, hypokalemia, edema
- Prednisone is co-administered with abiraterone acetate to suppress symptoms of secondary hyperaldosteronism

Abiraterone for castration-sensitive prostate cancer

- LATITUDE Phase III Trial: Randomized, double-blind, placebo-controlled phase III trial *(Fizazi K et al (2017) NEJM; Fizazi K et al (2019) The Lancet Oncology)*
- 1199 patients with high-risk metastatic, castration-sensitive prostate cancer with high-risk factors
- Orchiectomy or GnRH analogue + abiraterone 1000 mg daily + prednisone 5 mg daily OR + placebos
  - Median OS: 53.3 mos vs 36.5 mos (HR 0.66; 95% CI 056-0.78, p< 0.0001)
  - Improvement in all secondary endpoints with abiraterone (time until pain progression, next subsequent prostate cancer therapy, initiation of chemotherapy, PSA progression)

- STAMPEDE Multigroup, Multistage TRIAL *(James ND et al 2017 NEJM)*
- 1917 patients; 52% metastatic, 20% node-positive/indeterminate, 28% node-negative
- Randomized to ADT $\geq$ 2 years +/- abiraterone 1000 mg daily + prednisolone 5 mg daily
- Median f/u 40 mos: OS HR 0.63 (95% CI 0.52-0.76, P<0.001), Failure-Free Survival HR 0.29 (95% CI 0.25-0.34, P<0.001)

- PEACE-1 Phase III Trial *(Fizazi K et al 2022 Lancet. 399(10336):1695-1707)*
- Randomized, open-label, phase 3 trial with 2x2 factorial design
- 1:1:1:1 randomization (n=1173): SOC (ADT or ADT + docetaxel, n=296; SOC + RT, n=293; SOC + abiraterone, n=292; SOC + RT + abiraterone, n=291) – trial amended to allow docetaxel, and subsequently to make it mandatory once abiraterone had been shown to improve OS
- Abiraterone associated with improved rPFS and OS in the overall population (HR 0.54 and 0.82) and for those receiving docetaxel (HR 0.50 and 0.75)

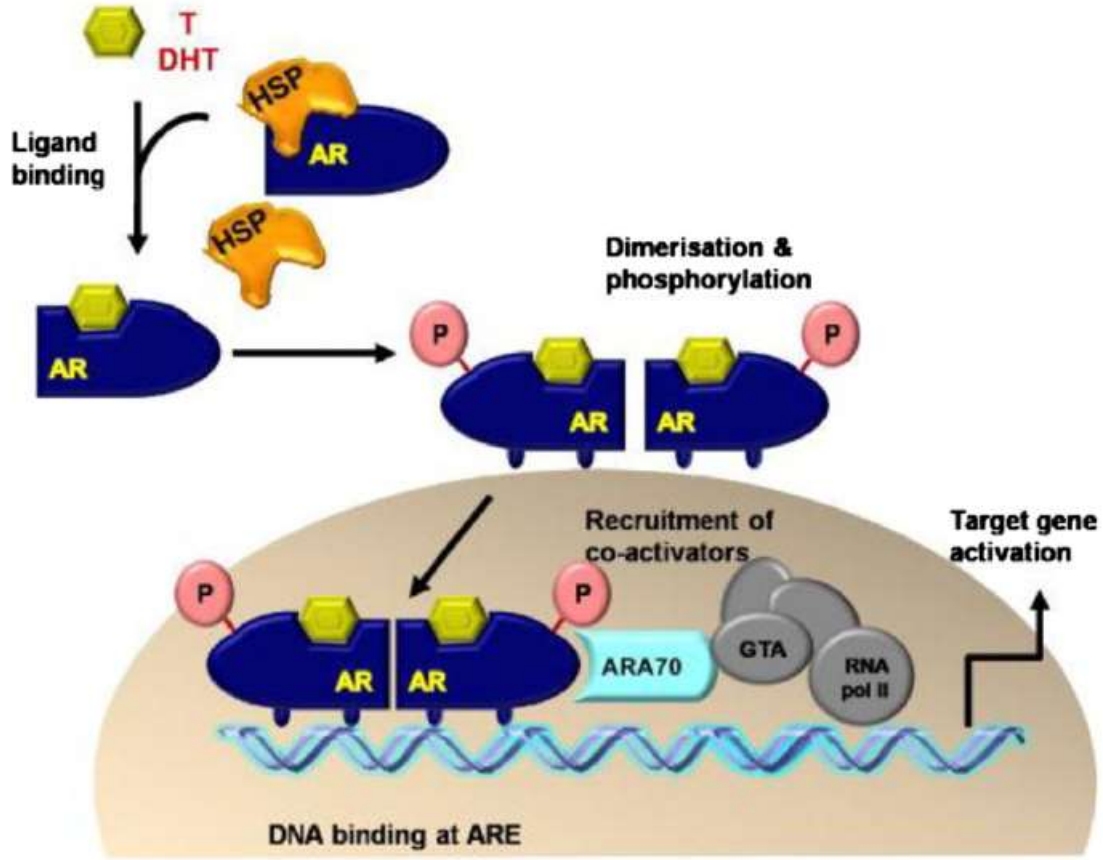
Abiraterone acetate improves overall survival (OS) for men with mCRPC

- Pre-docetaxel trial:
  - Randomized, double-blind, phase III study of abiraterone 1000 mg daily + prednisone 5 mg bid vs placebo + prednisone
  - 546 vs 542 subjects
  - Co-Primary endpoints:
    - Radiographic PFS
    - OS
  - Median PFS 16.5 vs 8.3 months, HR 0.53, P<0.001
  - Median OS 35.3 mos vs 30.1 mos, HR 0.79

- Post-docetaxel trial:
  - Randomized, placebo-controlled phase III study compared abiraterone acetate 1000 mg daily + prednisone 5 mg bid to placebo + prednisone 5 mg bid
  - 2:1 (779 vs 398)
  - Primary endpoint: OS
  - Improved OS of 14.8 vs 10.9 mos (HR 0.65, P < 0.001) with median f/u of 12.8 mos

de Bono JS, et al. NEJM 2011; 364:1995-2005.
Ryan CJ, et al. NEJM 2013; 368:138-148

Androgen receptor signaling: therapeutic role for androgen receptor (AR) antagonists



"The presence of testosterone (T) or dihydrotestosterone (DHT) causes dissociation of HSP, dimerization, and phosphorylation (P) of the AR and translocation to the nucleus where the AR binds to an ARE, causing recruitment of DNA transcriptional machinery and gene transcription."

Friedlander TW and Ryan CJ. Urol Clin N Am 2012; 39:453-464.

Androgen receptor antagonists enzalutamide, apalutamide, darolutamide improve survival in patients with metastatic castration sensitive prostate cancer

ENZAMET	ARCHES	TITAN	ARANSENS
Open-label, randomized phase III trial of testosterone suppression + enzalutamide or a "standard nonsteroidal antiandrogen" (bicalutamide, nilutamide, or flutamide)	Randomized, double-blind, phase III trial of ADT + enzalutamide or placebo	Randomized, double-blind, phase III trial of apalutamide vs placebo added to ADT	Randomized, phase III, placebo-controlled trial of ADT + docetaxel + darolutamide vs + ADT + docetaxel + placebo
1125 randomized 1:1, 52% high volume disease	1150 randomized 1:1; 63.2% high volume disease	1053 randomized 1:1; 62.7% high volume disease	1306 randomized 1:1;
After 88 were enrolled, protocol revised to permit concurrent docetaxel – 15.8% received	17.8% received prior docetaxel	10.7% received prior docetaxel	86.1% primary metastatic disease, 17.5% visceral metastases
Primary endpoint: overall survival (OS)	Primary endpoint: radiographic progression free survival (rPFS)	Co-Primary endpoints: OS and radiographic PFS	Primary endpoint: OS
Median overall survival was not reached (hazard ratio 0·70 [95% CI 0·58–0·84]; p<0·0001), with 5-year overall survival of 57% (0·53–0·61) in the control group and 67% (0·63–0·70) in the enzalutamide group.	Final analysis (crossover allowed after unblinding): median f/u 44.6 mos; 71% alive vs 57% alive (HR 0.66; 95% CI 0.53-0.81; P < 0.0001)	Final analysis (crossover allowed at unblinding): Median f/u 44.0 mos; median OS not reached vs 52.2 mos (HR 0.65; 95% CI 0.53-0.79, P < 0.0001)	Improvement in OS primary endpoint with darolutamide: 32.5% reduction in risk of death (HR 0.68, 95% CI 0.57-0.80, P<0.001)
Davis ID, et al. N Engl J Med 2019; 381:121-131 Sweeney CJ, et al. The Lancet 2023 Oncol,24(4):323-334	Armstrong AJ, et al. J Clin Oncol 2019; 37:2974-2986 Armstrong AJ, et al J Clin Oncol. 2022; 40(15): 1616–1622.	Chi KN, et al. 2019 NEJM, 381(1):13-24 Chi KN, et al. 2021 JCO, 39(20):2294-2303	Smith MR, et al. N Engl J Med 2022; 386:1132-1142

Apalutamide, enzalutamide, and darolutamide associated with improved metastasis-free survival and overall survival in patients with M0 CRPC

Apalutamide: SPARTAN TRIAL *(Smith MR et al. N Engl J Med. 2018 Apr 12;378(15):1408-18)*

- Median metastasis-free survival 40.5 months vs 16.2 months in the placebo group (HR, 0.28; 95% CI, 0.23 to 0.35; P<0.001)
- Adverse events at a higher rate with apalutamide than with placebo: rash (23.8% vs. 5.5%), hypothyroidism (8.1% vs. 2.0%), and fracture (11.7% vs. 6.5%)

Enzalutamide: PROSPER TRIAL *(Hussain M et al. 2018 NEJM 378(26):2465-74)*

- Primary endpoint: metastasis free survival 36.6 months vs 14.7 months (HR 0.29, 95% CI 0.24-0.35; P<0.001)
- Time to PSA progression 37.2 vs 3.9 months (HR0.07, P<0.001)

Darolutamide: ARAMIS Trial *(Fizazi K., et al. 2019 NEJM, 380(13):1235-46)*

- Median metastasis-free survival 40.4 months vs 18.4 months in favor of darolutamide (HR 0.41, 95% CI 0.34-0.50, P<0.001)
- Similar AEs to placebo
- Notably, darolutamide was not associated with increased incidence of falls, fractures, cognitive disorder, or hypertension compared to placebo

Enzalutamide for mCRPC

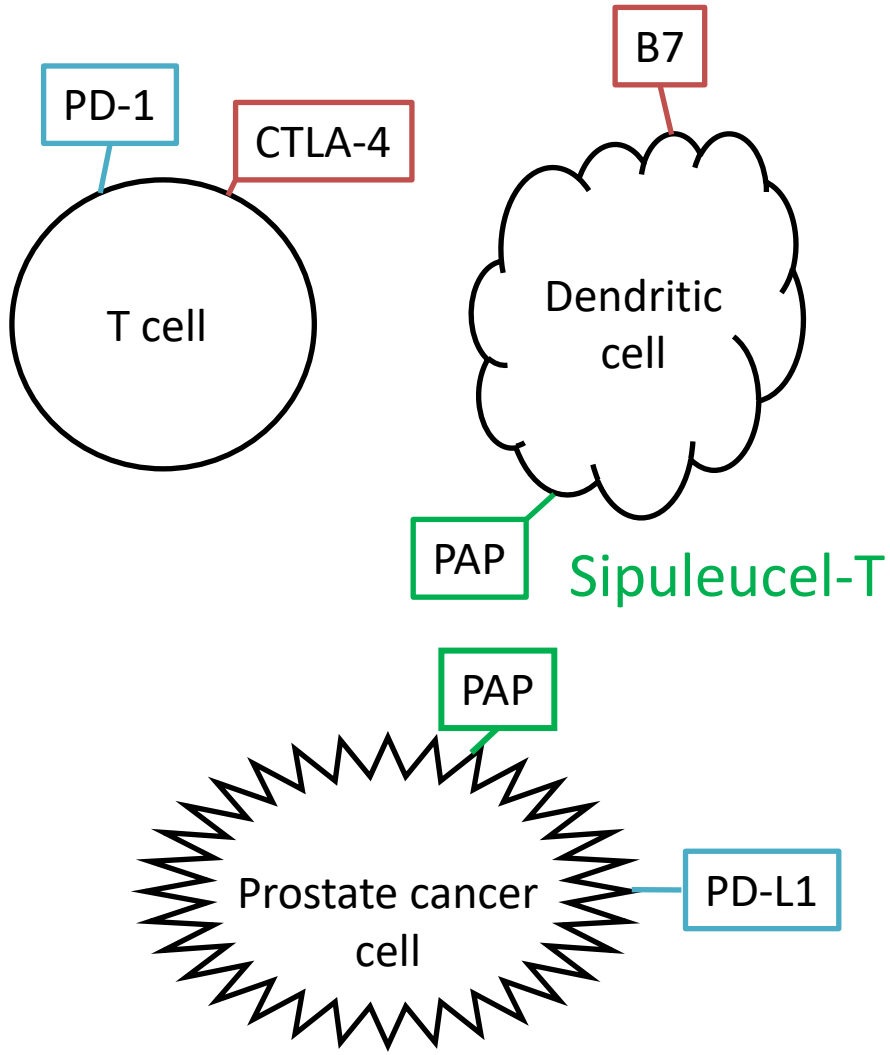
- AFFIRM (post-docetaxel):
  - Enzalutamide 160 mg daily (800) vs placebo (399)
  - Median OS: 18.4 vs 13.6 mos (HR 0.63, P<0.001)

- PREVAIL (pre-docetaxel):
  - 1,717 men were randomized 1:1 to enzalutamide vs placebo
  - OS and rPFS were co-primary endpoints
  - 81% reduction in rPFS (65% vs 14%, HR 0.19, P<0.001) and 29% reduction in risk of death (72% vs 63% survival, HR 0.71, 95% CI 0.60-0.84, P<0.001) with enzalutamide treatment

Scher HI, et al. NEJM 2012; 367:1187-1197.
Beer TM, et al. NEJM 2014; 371:424-433.

Immunotherapy for CRPC

- Immune escape is a hallmark of cancer
- Increased activity of immunosuppressive T regulatory cells (Treg), myeloid-derived suppressor cells (MDSC)
- Upregulation of T-cell inhibitory checkpoint pathways (CTLA-4, PD-1)
- Impaired tumor antigen presentation by antigen presenting cells (APCs)
- Prostate-cancer specific antigens are non-essential: attractive therapeutic targets

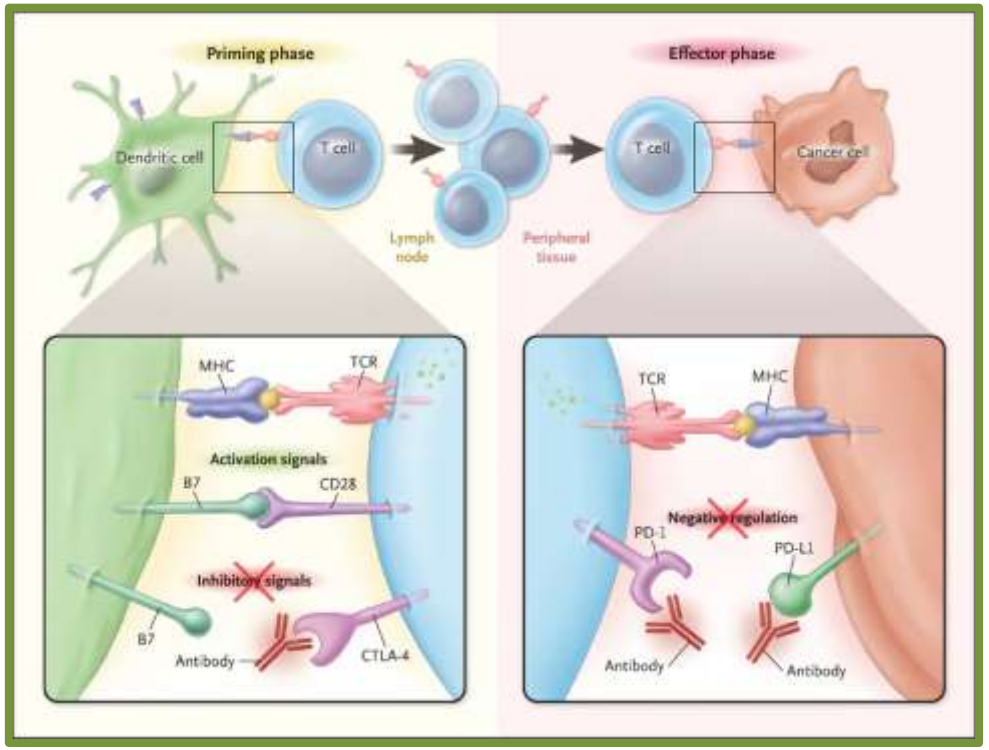


Sipuleucel-T for metastatic CRPC

- Active cellular immunotherapy approved for treatment of asymptomatic or minimally symptomatic men with mCRPC
- CD45+ APCs collected by leukapheresis and pulsed with fusion construct of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF) called PA2024
- 3 leukapheresis procedures each separated by 2 weeks, with reinfusion of sipuleucel-T 3 days after each leukapheresis

Sonpadve G and Kantoff PW. Urol Clin N Am 2012; 39:465-481.
Kantoff PW, et al. NEJM 2010; 363:411-422.

Microsatellite instability mismatch repair deficiency and immune checkpoint inhibitor therapy for solid tumors including prostate cancer

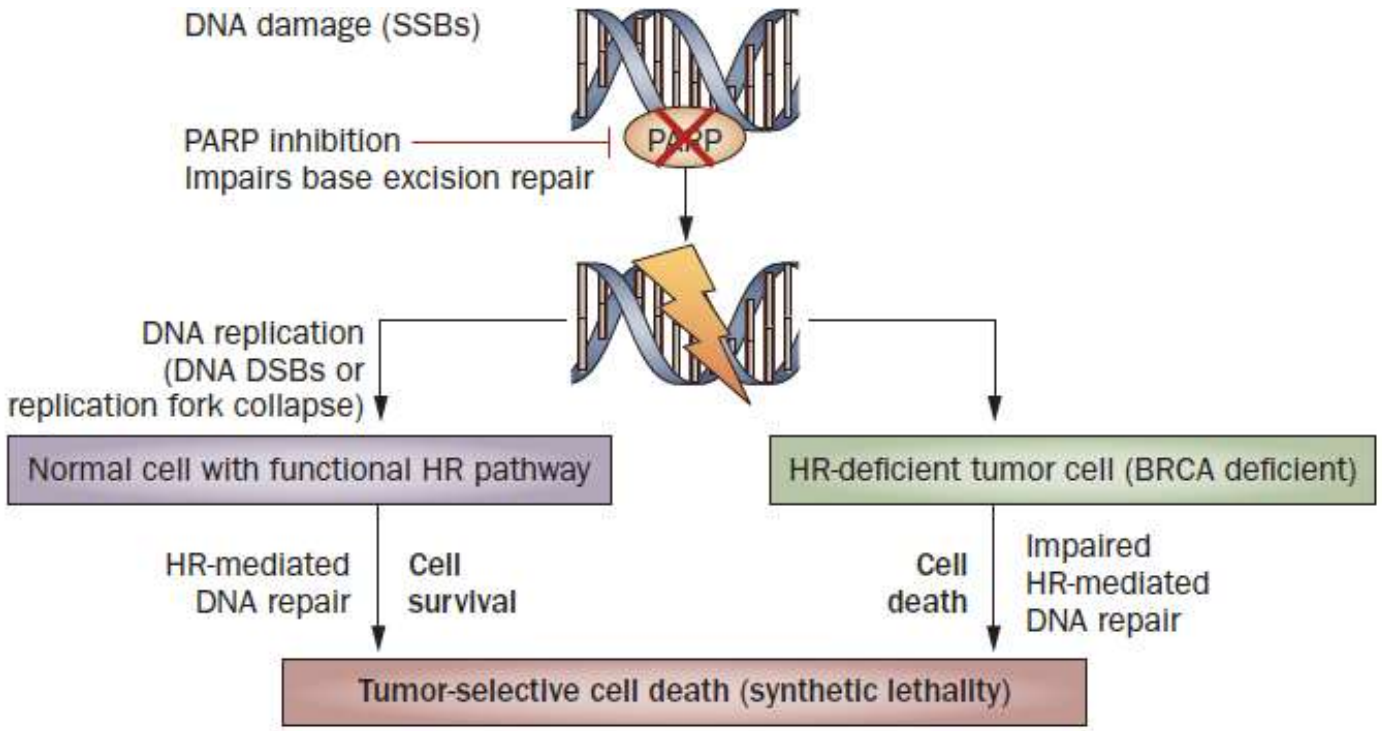


Ribas A. N Engl J Med 2012;366:2517.

- **Incidence of MSI-H / dMMR prostate cancer is low**
- MSKCC case series of 1033 prostate cancer patients: 3.1% MSI-H/dMMR (Abida W et al, JAMA Oncol. 2019;5(4):471-478.)
- **Pembrolizumab:**
- FDA approved for “Microsatellite Instability-High or Mismatch Repair Deficient Cancer □ for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options”
- Approval based on results from 5 MSI-H trials (KEYNOTE-016, -164, 012, 028, -158) that enrolled 149 patients with MSI-H or dMMR cancers
- ORR: 39.6% (95% CI 31.7, 47.9)
- CR 7.4%, PR 32.2%
- **Prostate cancer: N = 2 (PR, PR)**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s096lbl.pdf. Accessed Feb 29, 2024

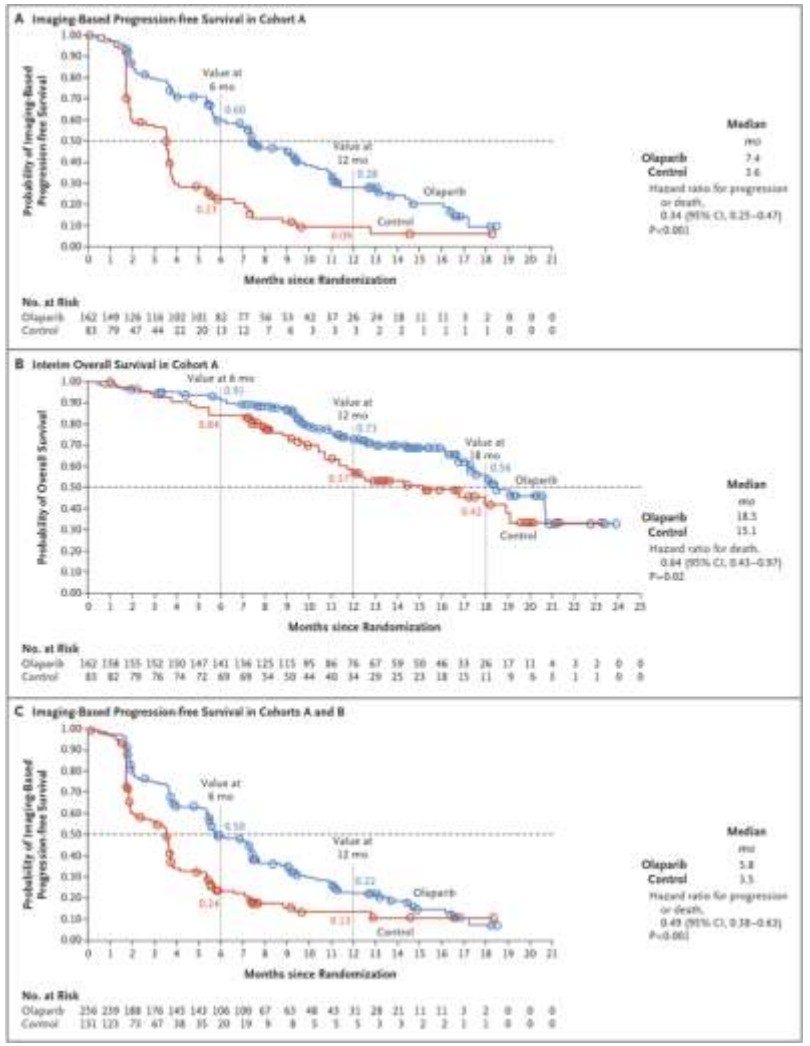
Synthetic lethality of PARP inhibition and homologous recombination (HR) deficiency



Banerjee, S. *et al. Nat. Rev. Clin. Oncol.* 7, 508–519 (2010); published online 10 August 2010; doi:10.1038/nrclinonc.2010.116

Olaparib for treatment of mCRPC with HRD following progression on enzalutamide or abiraterone

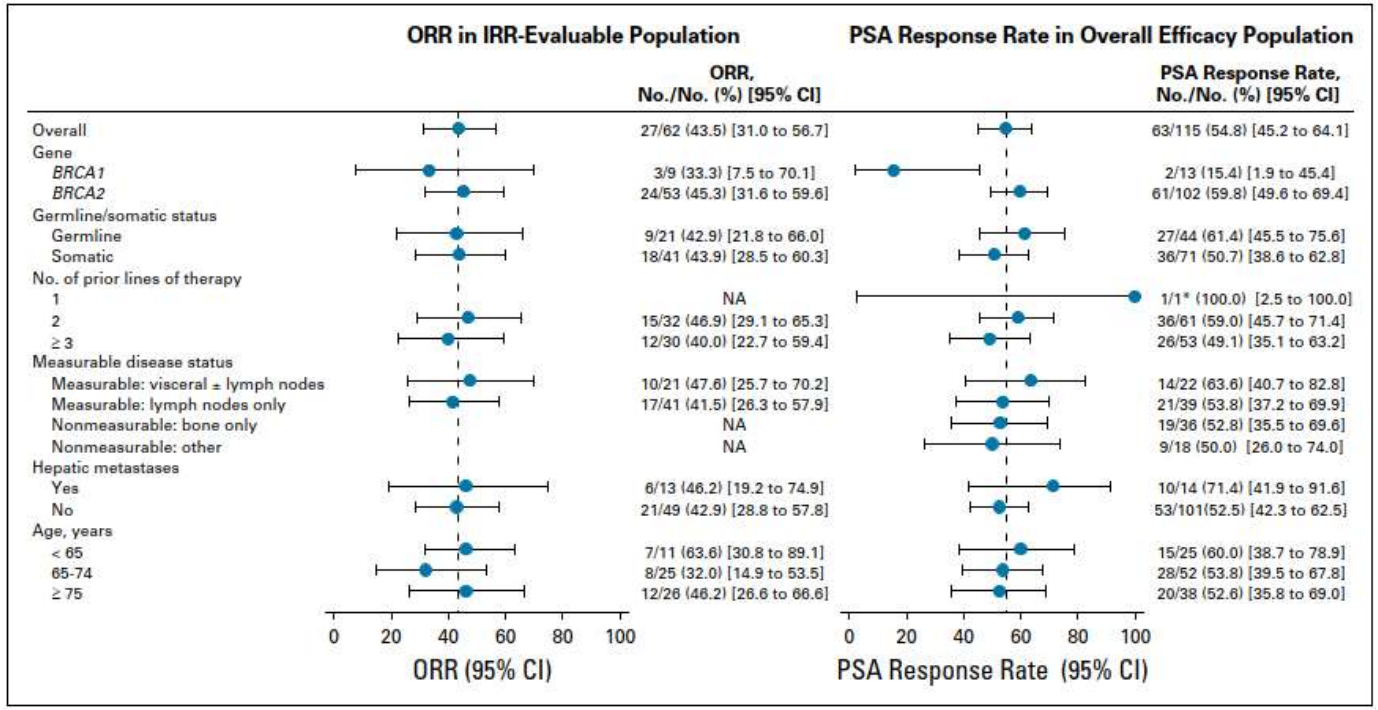
- PROfound: randomized, open-label phase III trial
- mCRPC with progression on abiraterone or enzalutamide
- HHR gene alterations
- Cohort A (245 patients): *BRCA1*, *BRCA2*, *ATM*
- Cohort B (142 patients): *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*
- 2:1 olaparib vs physician's choice of enzalutamide or abiraterone; crossover permitted
- Primary endpoint: radiographic PFS in cohort A
- Anemia, nausea, fatigue / asthenia the most frequent AE s associated with olaparib
- FoundationOne CDx and BRACAnalysis CDx approved as companion diagnostic devices



de Bono J, et al. 2020 NEJM, 382:2091-2102

Rucaparib: FDA accelerated approval for mCRPC patients with deleterious *BRCA* mutation following treatment with androgen signaling inhibitor and taxane-based chemotherapy

- **TRITON2 phase II clinical trial**
- germline or somatic alteration in 1 of 15 prespecified HRR genes, including *BRCA1/2*
- 115 patients with BRCA alteration



Abida W et al. JCO 2020, 38:3763-3772

PARP inhibitor + Androgen Receptor Pathway Inhibitor (ARPi) Phase III trials in mCRPC

	PROpel	TALAPRO-2	MAGNITUDE
Randomization	olaparib + abiraterone (n = 399; HRRm n = 111) vs placebo + abiraterone (n = 397; HHRm = 115)	talazoparib + enzalutamide (n 402; HRRm n = 85) vs placebo + enzalutamide (n 403; HHRm = 84)	niraparib + abiraterone (n 335; HHRm n = 212) vs placebo +abiraterone (n 335; HHRm n = 211); HRR neg halted at futility
Dosing	olaparib 300 mg bid + abi 1000 mg bid + pred 5 mg bid	talazoparib 0.5 mg qd + enzalutamide 160 mg qd	niraparib 200 mg qd + abiraterone 1000 mg qd + pred 10 mg qd
HRR-deficient genes	ATM, BRCA1, BRCA2, BARD1, BRP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51D, RAD54L	ATM, BRCA1, BRCA2, CHEK2, FANCL, MLH1, MRE11A, NBN, PALB2, RAD51C	ATM, BRCA1, BRCA2, BRP1, CDK12, CHEK2, FANCA, HDAC2, PALB2
Prior therapies	Prior docetaxel pre-mCRPC No prior abiraterone Prior ARPi for pre-mCRPC if stopped ≥12 mos prior	Prior docetaxel pre-CRPC Prior abiraterone pre-CRPC No prior rx for M0CRPC or mCRPC	≤4 mos prior abiraterone for mCRPC Prior apalutamide, darolutamide, enzalutamide, taxane for non-mCRPC allowed
Prior ARPi %	0.15%	6.2%	3.0%
Prior docetaxel %	24.4%	22.2%	19.3%
References	Clarke NW et al., NEJM Evid 2022; 1 (9)	Aggarwal N et al., Lancet 2023; 402: 291–303	Chi KN et al., J Clin Oncol 41:3339-3351.

Kanesvaran R. Relative Efficacy of Androgen Receptor Targeting Plus PARP Inhibition. ASCO Genitourinary Cancers Symposium 2024. January 25, 2024.

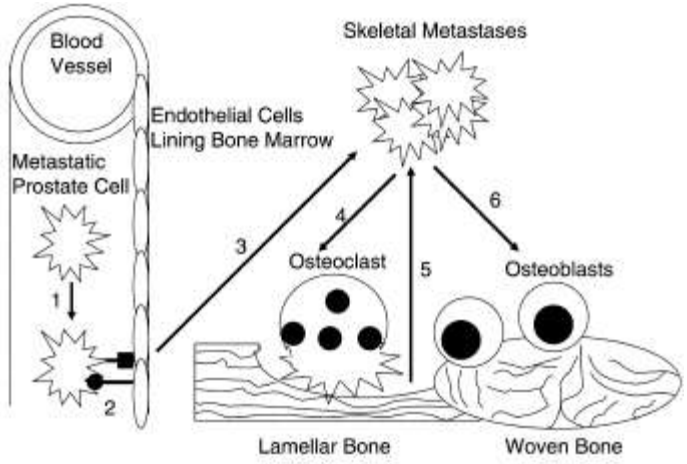
PARP inhibitor + Androgen Receptor Pathway Inhibitor (ARPi) Phase III trials in mCRPC

	PROpel	TALAPRO-2	MAGNITUDE
Randomization	olaparib + abiraterone (n = 399; HRRm n = 111) vs placebo + abiraterone (n = 397; HHRm = 115)	talazoparib + enzalutamide (n 402; HRRm n = 85) vs placebo + enzalutamide (n 403; HHRm = 84)	niraparib + abiraterone (n 335; HHRm n = 212) vs placebo +abiraterone (n 335; HHRm n = 211); HRR neg halted at futility
Dosing	olaparib 300 mg bid + abi 1000 mg bid + pred 5 mg bid	talazoparib 0.5 mg qd + enzalutamide 160 mg qd	niraparib 200 mg qd + abiraterone 1000 mg qd + pred 10 mg qd
Primary endpoint	rPFS (investigator assessed) in unselected patients	rPFS (BICR) in patients with DDR and unselected patients	Cohorts 1+3: rPFS (BICR) Cohort 1: HHRm Cohort 2: No HHRm Cohort 3: fixed dose open label
HRR mutated	mPFS: NR vs 13.9 mos (HR 0.50) mOS: NR vs 28.5 mos (HR 0.66)	mPFS: 27.9 vs 16.4 mos (HR 0.46) mOS: NR vs 33.7 mos (HR 0.69)	mPFS :16.5 vs 13.7 mos (HR 0.73) mOS: 29.3 vs 32.2 mos (HR 1.01)
Non-HRR mutated	mPFS: 24.1 vs 19.0 mos (HR 0.76) mOS 42.1 vs 38.9 mos (HR 0.89)	mPFS: NR vs 22.5 mos (HR 0.70) mOS: NR vs 38.7 mos (HR 0.93)	mPFS: NR vs NR (HR 1.09)
BRCA mutated	mPFS: NR vs 8.4 mos (HR 0.23) mOS: NR vs 23.0 mos (HR 0.29)	mPFS: NR vs NR (HR 0.23) mOS: NR vs NR (HR 0.61)	mPFS: 16.6 vs 10.9 mos (HR 0.53) mOS: 30.4 vs 28.6 mos (HR 0.79)
Non-BRCA mutated	mPFS: 24.1 vs 19.0 mos (HR 0.76) mOS: 39.6 vs 38.0 mos (HR 0.91)	mPFS: NR vs NR (HR 0.66)	
FDA Approvals in mCRPC patients	BRCA-mutated	HRR-mutated	BRCA-mutated
References	Clarke NW et al., NEJM Evid 2022; 1 (9)	Aggarwal N et al., Lancet 2023; 402: 291–303	Chi KN et al., J Clin Oncol 41:3339-3351.

Kanesvaran R. Relative Efficacy of Androgen Receptor Targeting Plus PARP Inhibition. ASCO Genitourinary Cancers Symposium 2024. January 25, 2024.

Prostate cancer bone tropism and bone-targeted therapies

- ~ 90% of patients with metastatic prostate cancer develop bone metastases
- Zoldedronic acid (bisphosphonate) and denosumab (RANKL inhibitor) approved in mCRPC to reduce SREs
- Strontium-89 and samarium-153 lexidronam (beta-emitters) approved to provide palliation for painful bone metastases



Model of cross-talk between prostate cancer and bone microenvironment: a "vicious cycle" where CaP cells stimulate osteoclasts to break down bone, releasing growth factors that support proliferation of CaP, which releases factors supporting osteoblast proliferation/survival.

Pal SK, Lewis B, and Sartor O. (2012) Urol Clin N Am; 39:583-91.
Keller ET, et al. (2001) Cancer Metast Rev; 333-49.

Radium-223 dichloride preferentially targets osteoblastic metastases

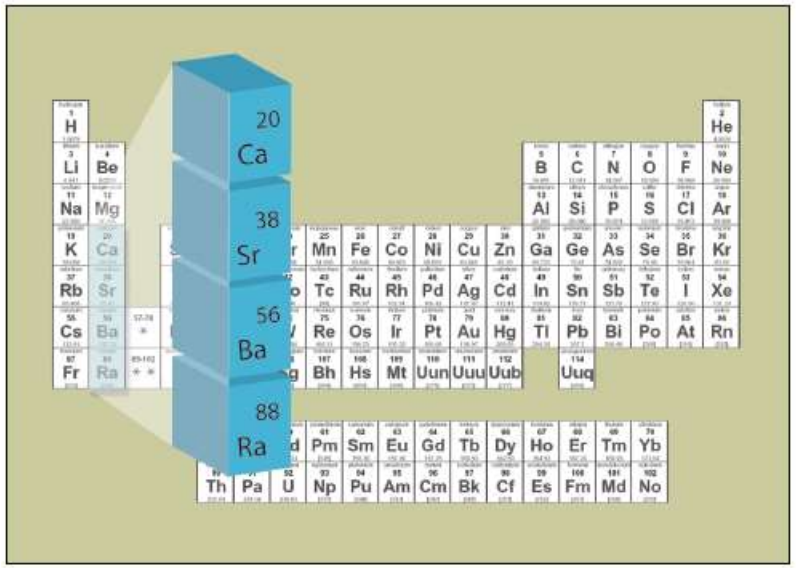
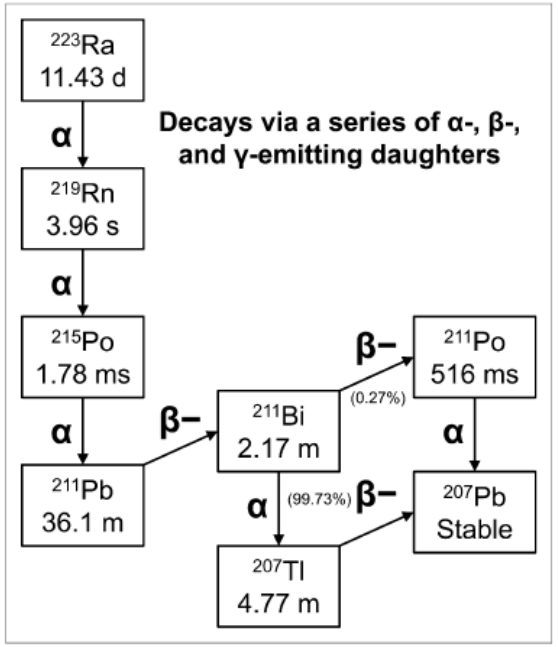
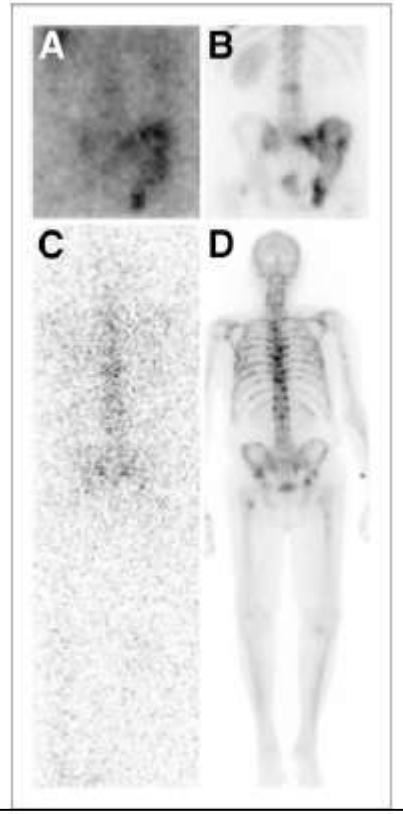


Figure 1: Radium-223 Physical Properties—Position of the alkaline earth metal, radium, in the periodic table. It has four natural isotopes of atomic weight: 228, 226, 224, and 223.





Imaging Radium-223

- Bone-targeted α-emitter
- Effective at inducing DNA double-strand breaks
- Emission over a short (microns) path-length vs. β-radiation (millimeters)
- Calcium mimic with preferential uptake in osteoblastic metastases vs. normal bone

Cheetham PJ and DP Petrylak (2012) Oncology; epub.
Pandit-Taskar N, et al. (2014) J Nucl Med; 55:268-74.

Bone-targeted therapies: radium-223 chloride

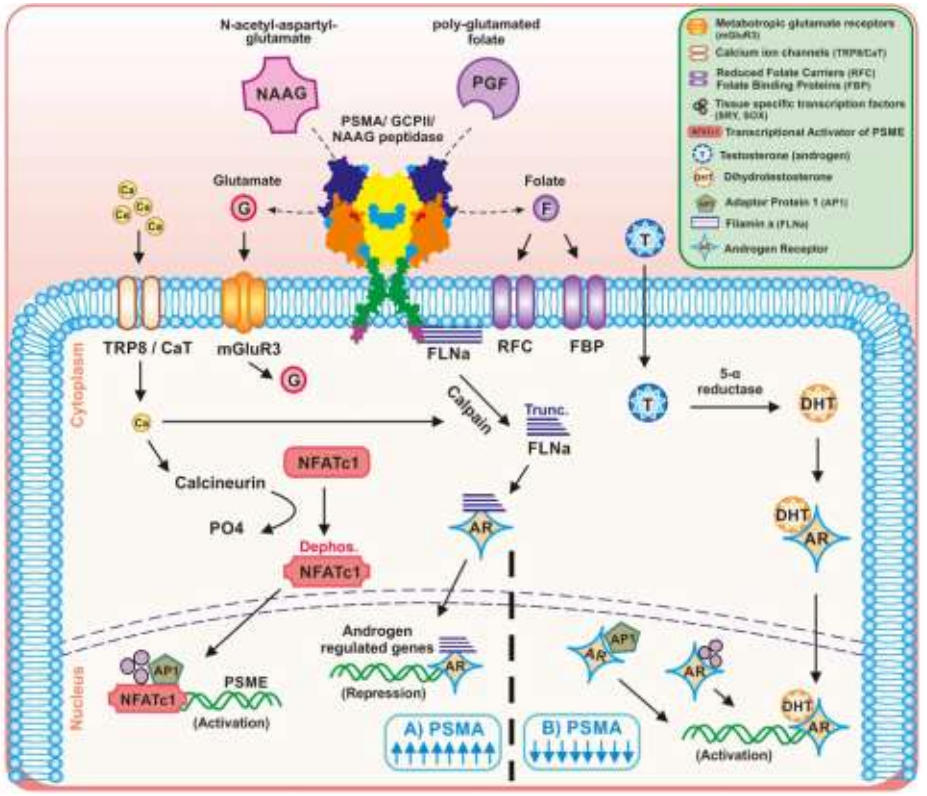
- ALSYMPCA:
- Randomized phase III study of patients with mCRPC previously treated with, unfit for, or refusing docetaxel
- Symptomatic CRPC with ≥ 2 bone lesions with no visceral metastases or bulky (>3 cm) lymph nodes
- 921 patients randomized 2:1 to Ra-223 vs placebo
- 6 injections 50 kBq/kg IV q 4 wks vs placebo
- Median OS: 14.9 vs 11.3 mos, HR 0.70, 95% CI 0.58-0.83, P<0.001
- Prolonged time to 1st SRE: 15.6 vs 9.8 mos, HR 0.66, 95% CI 0.52-0.83, P<0.001
- Low rates of Ra-223-associated myelosuppression
- Three-year safety follow up:
  - 98/600 (16%) radium-223 and 68/301 (23%) placebo patients experienced grade 5 TEAEs
  - No AML, MDS, or new primary bone cancer
  - One radium-223 patient had aplastic anemia 16 mo after the last injection.

Parker C, et al. NEJM 2013; 369:213-223. Parker CC, et al. Eur Urol, 2018, 73(3):427-435

PSMA-TARGETED RADIOLIGAND THERAPY

Prostate Specific Membrane Antigen (PSMA)

- PSMA, aka glutamate carboxypeptidase II (GCPII), is a transmembrane glycoprotein
- Involved in glutamate and folate metabolism
- Highest expression in prostate tissue
- Also present in kidney, small intestine, glial cells (supporting cells in the nervous system), and salivary glands
- Also expressed in tumor neovasculature

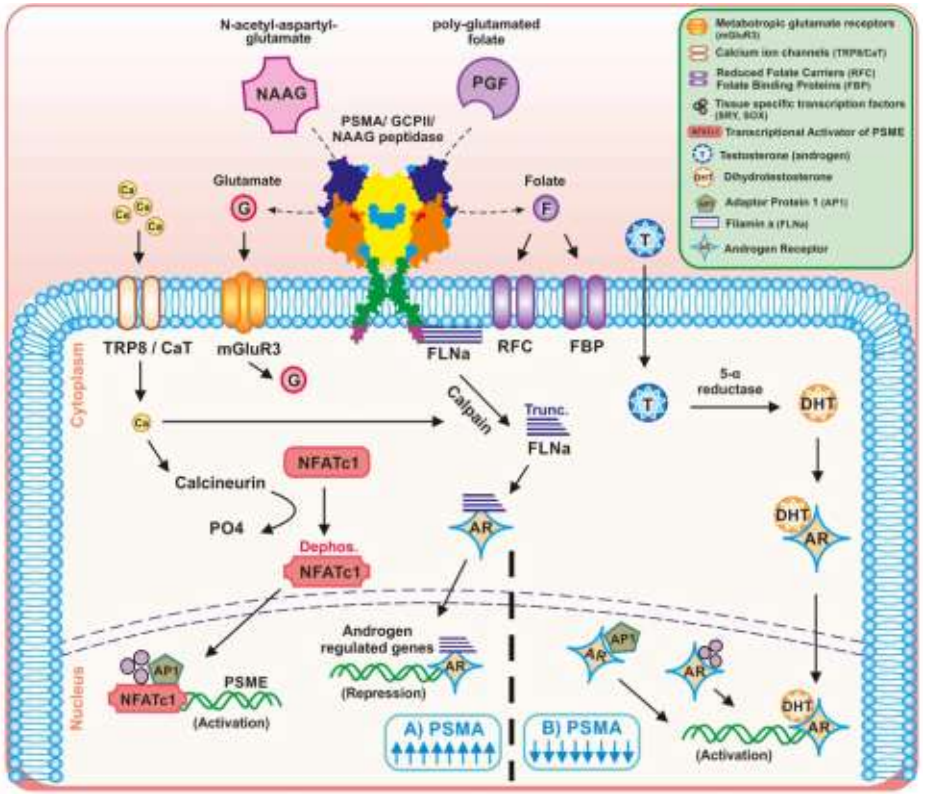


From Evans JC et al. (2016) Br J Pharmacol, 173:3041-3079

Teo MY and Morris MJ. 2016 Cancer J; 22(5):347-352.
Evans JC et al. (2016) Br J Pharmacol, 173:3041-3079
Cimadamore A et al (2018) Frontiers in Oncology

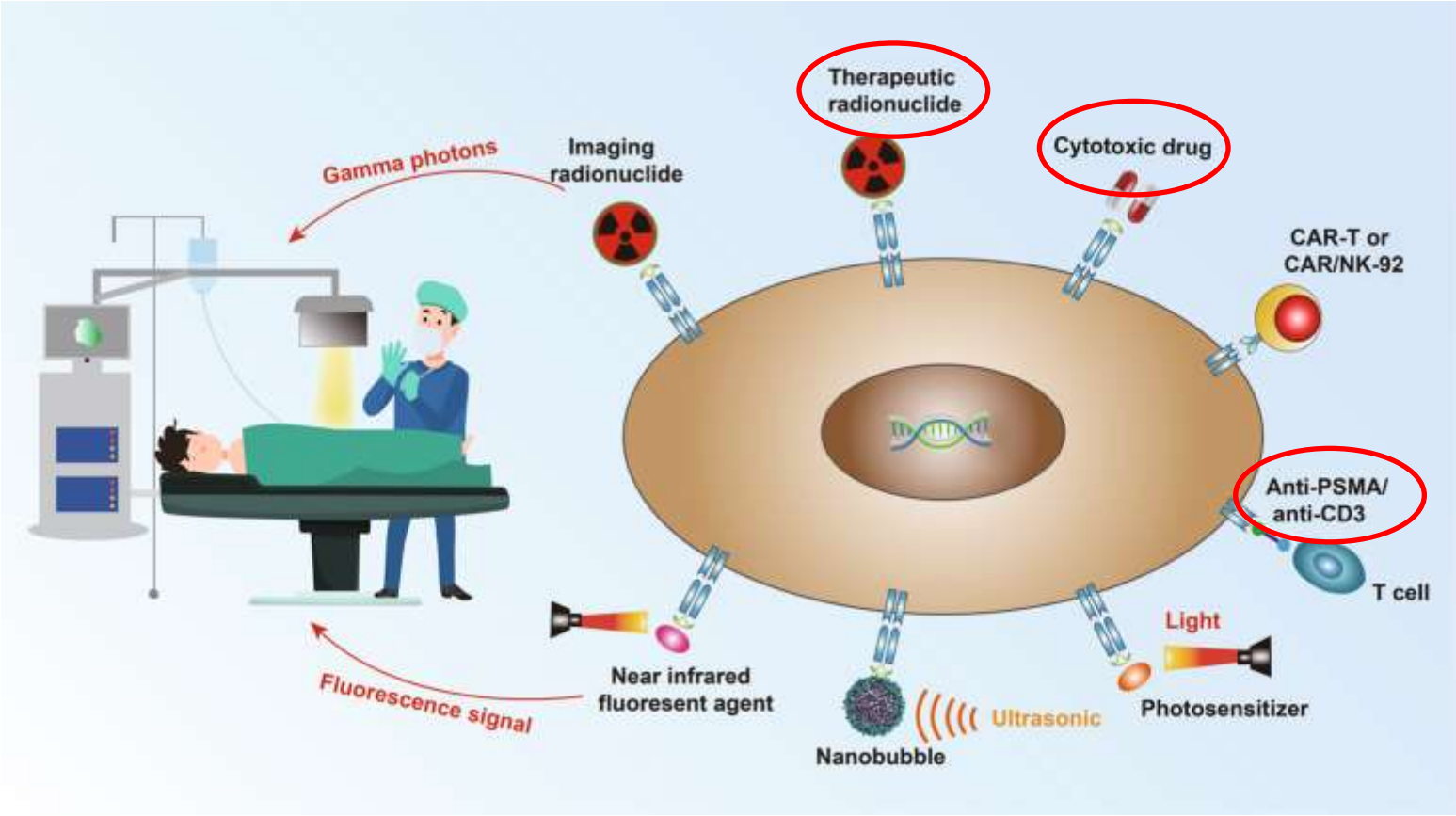
PSMA

- 100-1000 times overexpressed in prostate cancer
- Correlation between PSMA and serum PSA
- PSMA expression increases with androgen deprivation therapy
- PSMA can be internalized – can take advantage of this feature for therapy



Evans JC et al. (2016) Br J Pharmacol, 173:3041-3079.

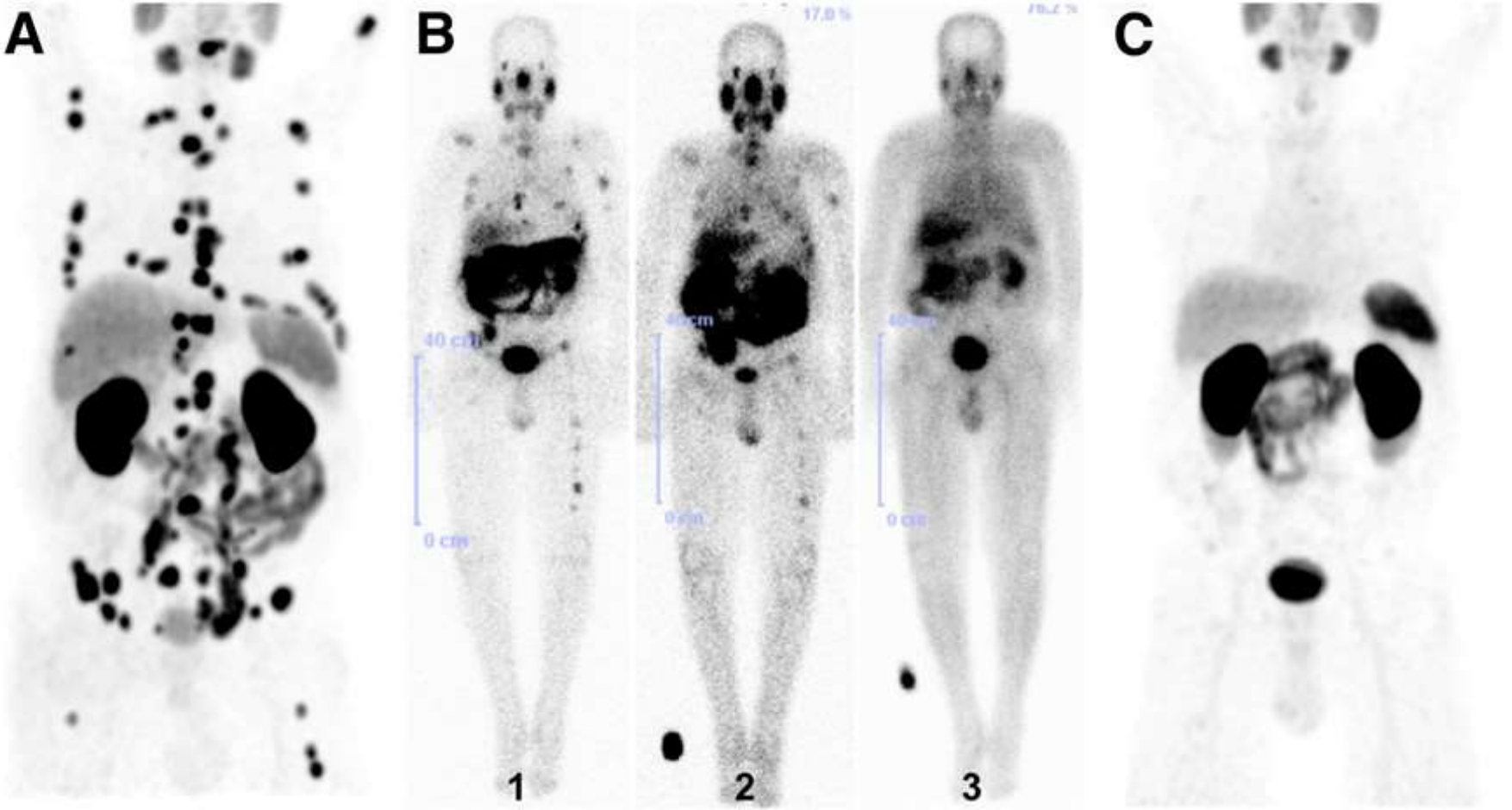
PSMA as a potential target for imaging and treating prostate cancer



Wang F et al., 2021, Prostate Cancer and Prostatic Diseases, https://doi.org/10.1038/s41391-021-00394-5

Courtesy of R. Subramaniam

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



^{68}Ga PSMA PET/CT Baseline	SPECT During ^{177}Lu-PSMA Therapy	^{68}Ga PSMA PET/CT Post Therapy

^{177}Lu-PSMA-617

- More than 20 retrospective / compassionate use studies and a prospective phase II study showed activity (decreased PSA and pain) from treatment of patients with prostate cancer with ^{177}Lu-PSMA radioligand therapy (von Eyben FE et al Eur J Nuc Med and Mol Imag 2018; 45:496-508; Hofman MS et al, Lancet Oncol 2018 19:825-833).

^{177}Lu-PSMA-617

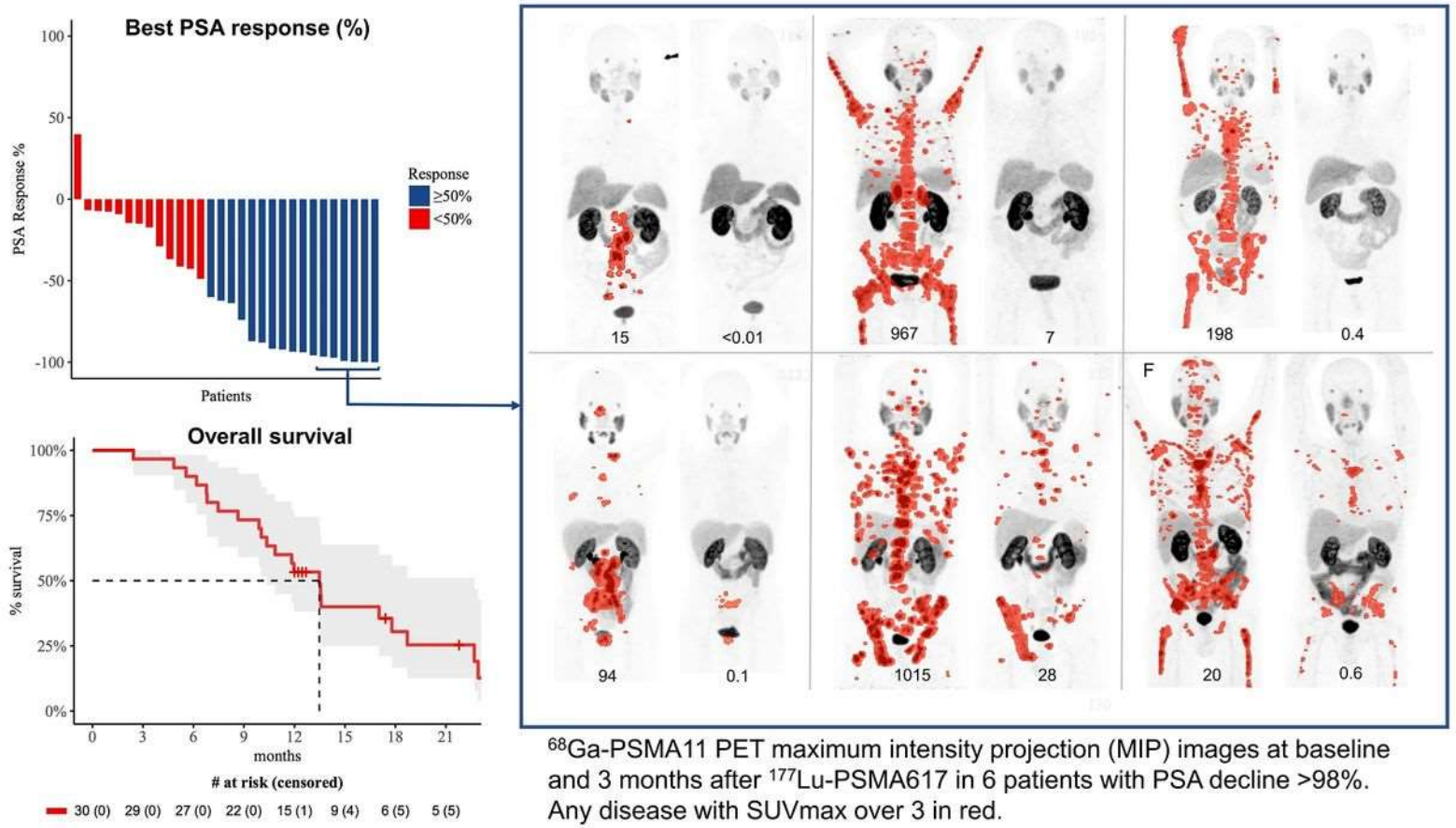
- Compassionate access protocol in Germany
- 54 subjects in 2 investigational groups of pre-treated CRPC patients with PSMA-expressing tumors by PSMA imaging (PSMA PET/CT with 68Ga-PSMA-11 or 99m-PSMA-SPECT/CT)
- Group 1: 30 subjects
  - 13 (43.3%) with > 50% PSA decline
  - 11 received $\geq$ 3 cycles (8 week intervals)
  - 10/11 with radiographic responses
- Group 2: 24 subjects
  - 47.6% with > 50% PSA decline
  - 22/24 received 2 cycles; 60% with > 50% PSA decline

Kratochwil C et al. 2016 J Nuc Med; 57(8):1170-1176.
Ahmadzadehfar H et al. 2016 Oncotarget; 7:12477-12488.
Teo MY and Morris MJ. 2016 Cancer J; 22(5):347-352.

Prospective phase II trial of ^{177}Lu-PSMA

- “30 patients with PSMA-avid mCRPC who had failed standard therapies received up to 4 cycles of Lu PSMA every 6 weeks”
- Had to have detectable disease by PSMA PET-CT
- Excluded if they had tumors that were FDG-PET avid but not detected by PSMA PET
- 83% progressed after abiraterone and/or enzalutamide
- 87% progressed after chemotherapy

Hofman M et al (2018) J Nucl Med vol. 59 no. supplement 1 531



^{68}Ga-PSMA11 PET maximum intensity projection (MIP) images at baseline and 3 months after ^{177}Lu-PSMA617 in 6 patients with PSA decline >98%. Any disease with SUVmax over 3 in red.

Michael Hofman et al. J Nucl Med 2018;59:531

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

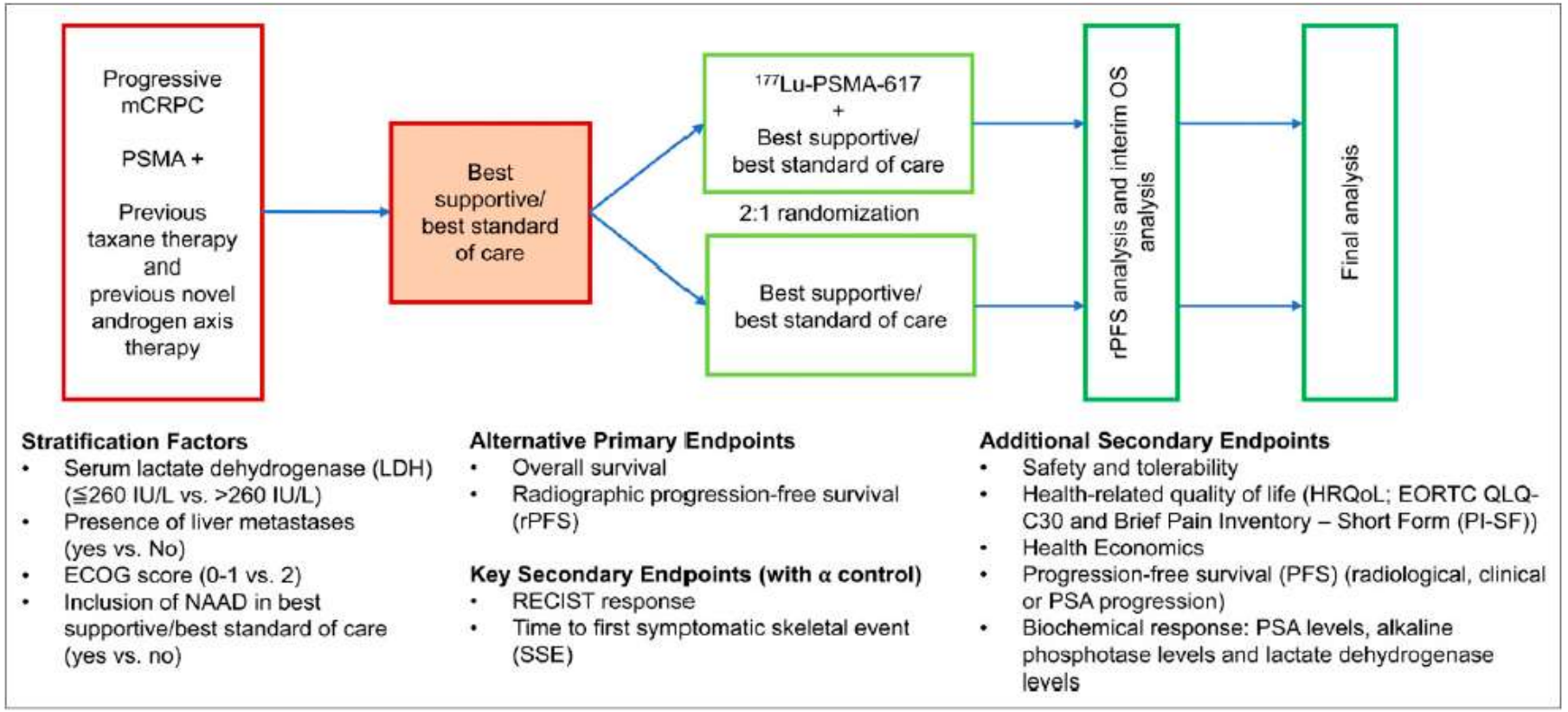
Sartor O et al , N Engl J Med 2021;385:1091-103.

VISION TRIAL: DESIGN

- Randomized phase III trial
- Enrolled patients with metastatic castration resistant prostate cancer previously treated with at least one androgen-receptor-pathway inhibitor (eg: abiraterone, enzalutamide, apalutamide, darolutamide) and 1 or 2 taxane chemotherapy regimens (docetaxel, cabazitaxel)
- Randomized 2:1 to treatment with protocol-permitted* standard of care with or without ^{177}Lu-PSMA-617 administered every 6 weeks for 4 to 6 cycles
- * not chemotherapy, immunotherapy, radium-223, or investigational therapies

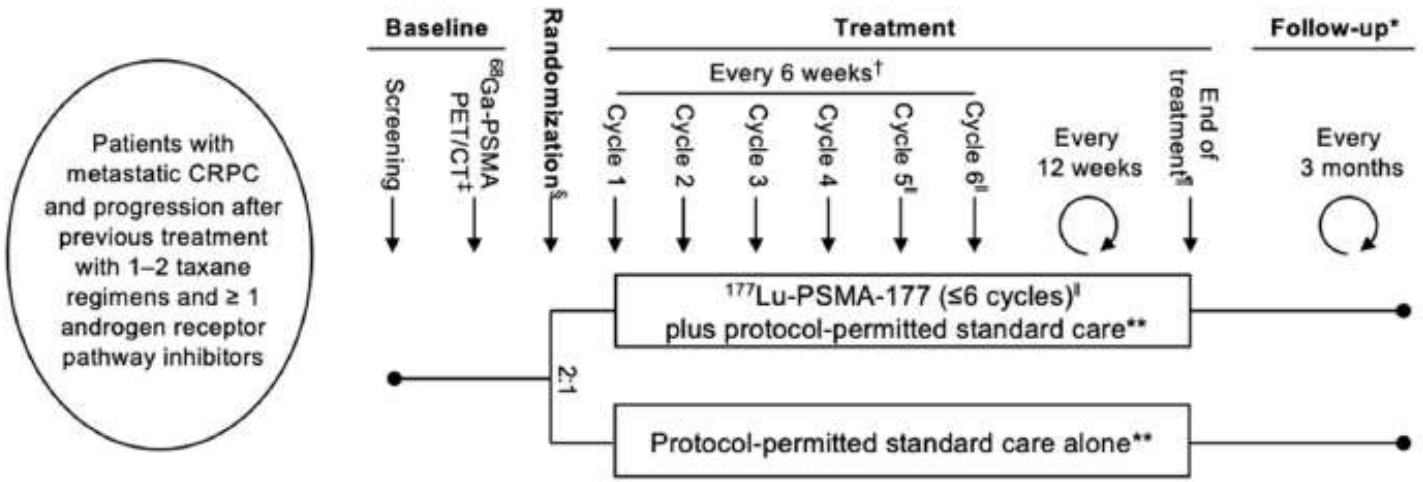
Sartor O et al , N Engl J Med 2021;385:1091-103.

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF 177LU-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)



Rahbar K et al. (2019) J Nucl Med 60:1504-1506.

VISION TRIAL: Schema



Sartor O et al , N Engl J Med 2021;385:1091-103.

VISION TRIAL: PSMA-PET ELIGIBILITY

- PSMA-positive mCRPC as per 68Ga-PSMA PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. (Fendler WP, et al., Eur J Nucl Med Mol Imaging 2017; 44: 1014-24)
- “at least one PSMA-positive metastatic lesion and no PSMA-negative lesions that would be excluded according to the protocol criteria”
- gallium-68 (68Ga)–labeled PSMA-11 (68Ga-PSMA-11) PET–CT imaging at baseline
- PSMA-positive lesions: “68Ga-PSMA-11 uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system”
- PSMA-negative lesions: “PSMA uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis. Patients with any PSMA-negative metastatic lesion meeting these criteria were ineligible.”

Sartor O et al , N Engl J Med 2021;385:1091-103.

VISION TRIAL: OUTCOMES TESTED

- Primary endpoints: imaging-based progression-free survival and overall survival
- Secondary endpoints: objective response , disease control, and time to symptomatic skeletal events

Sartor O et al , N Engl J Med 2021;385:1091-103.

Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate cancer: VISION

- Screened 1179 potentially eligible patients
- Randomized 831 patients
- Median follow-up 20.9 months
- Adding ^{177}Lu-PSMA-617 to standard of care increased the imaging-based progression free survival (median, 8.7 vs. 3.4 months; hazard ratio for progression or death, 0.40; 99.2% confidence interval [CI], 0.29 to 0.57; P<0.001) and overall survival (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; P<0.001)
- All key secondary endpoints favored adding ^{177}Lu-PSMA-671
- There were more grade $\geq$ 3 adverse events with 177Lu-PSMA-617 than without (52.7% vs 38.0%), including more fatigue, decreased blood counts, decreased appetite, and nausea, but these did not decrease quality of life

Sartor O et al , N Engl J Med 2021;385:1091-103.

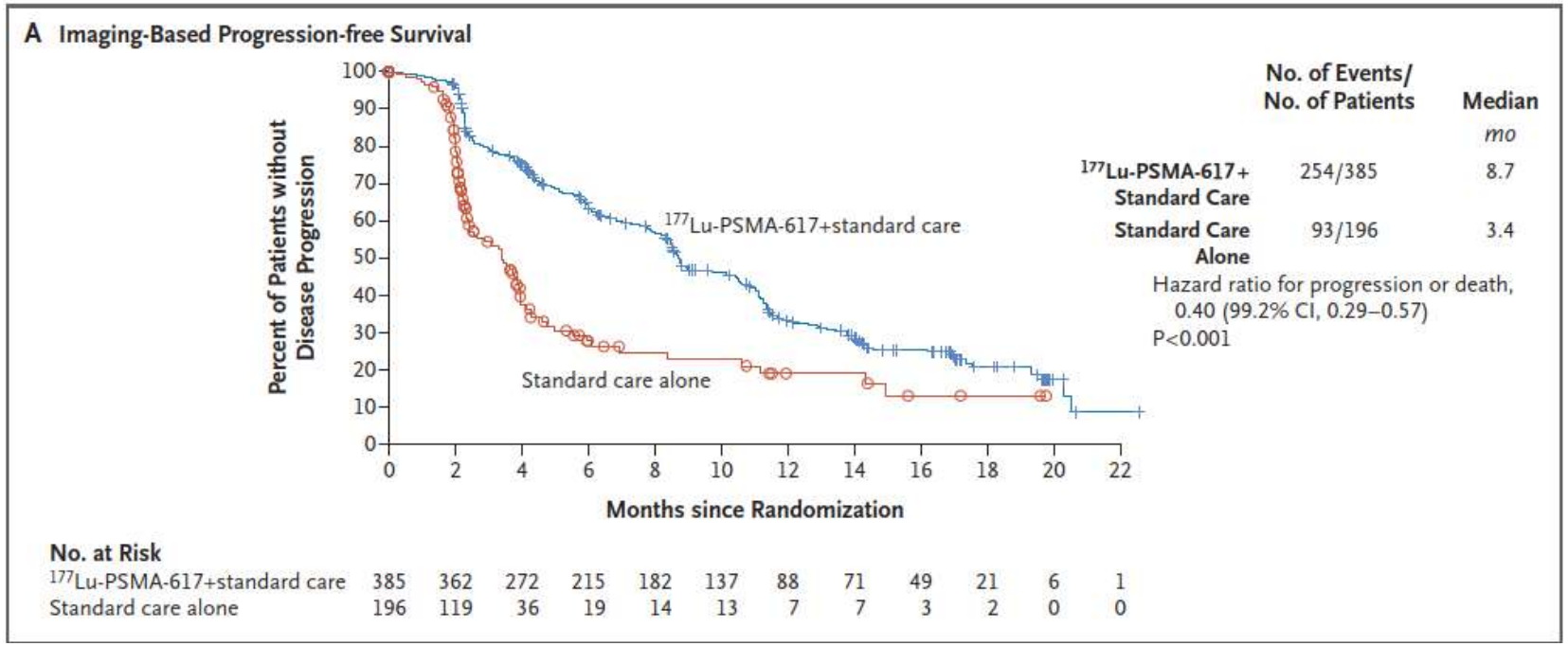
VISION TRIAL: Patient Characteristics

Table 1. Characteristics of the Patients at Baseline, According to Analysis Set.*

Characteristic	Analysis Set for Imaging-Based Progression-free Survival (N=581)		All Patients Who Underwent Randomization (N=831)	
	^{177}Lu-PSMA-617 plus Standard Care (N=385)	Standard Care Alone (N=196)	^{177}Lu-PSMA-617 plus Standard Care (N=551)	Standard Care Alone (N=280)
Median age (range) — yr	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
ECOG performance-status score of 0 or 1 — no. (%)†	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
Site of disease — no. (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Bone	351 (91.2)	179 (91.3)	504 (91.5)	256 (91.4)
Median PSA level (range) — ng/ml	93.2 (0–6988)	90.7 (0–6600)	77.5 (0–6988)	74.6 (0–8995)
Median alkaline phosphatase level (range) — IU/liter‡	108.0 (26–2524)	96.0 (34–1355)	105.0 (17–2524)	94.5 (28–1355)
Median LDH (range) — IU/liter‡	230.5 (119–5387)	232.0 (105–2693)	221.0 (88–5387)	224.0 (105–2693)
Median time since diagnosis (range) — yr	7.3 (0.9–28.9)	7.0 (0.7–26.2)	7.4 (0.9–28.9)	7.4 (0.7–26.2)
Gleason score at diagnosis — no. (%)§				
8–10	226 (58.7)	118 (60.2)	324 (58.8)	170 (60.7)
Unknown	28 (7.3)	19 (9.7)	42 (7.6)	24 (8.6)
Previous prostatectomy — no. (%)¶	159 (41.3)	82 (41.8)	240 (43.6)	130 (46.4)
Previous androgen-receptor–pathway inhibitor — no. (%)‖				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy — no. (%)**				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)

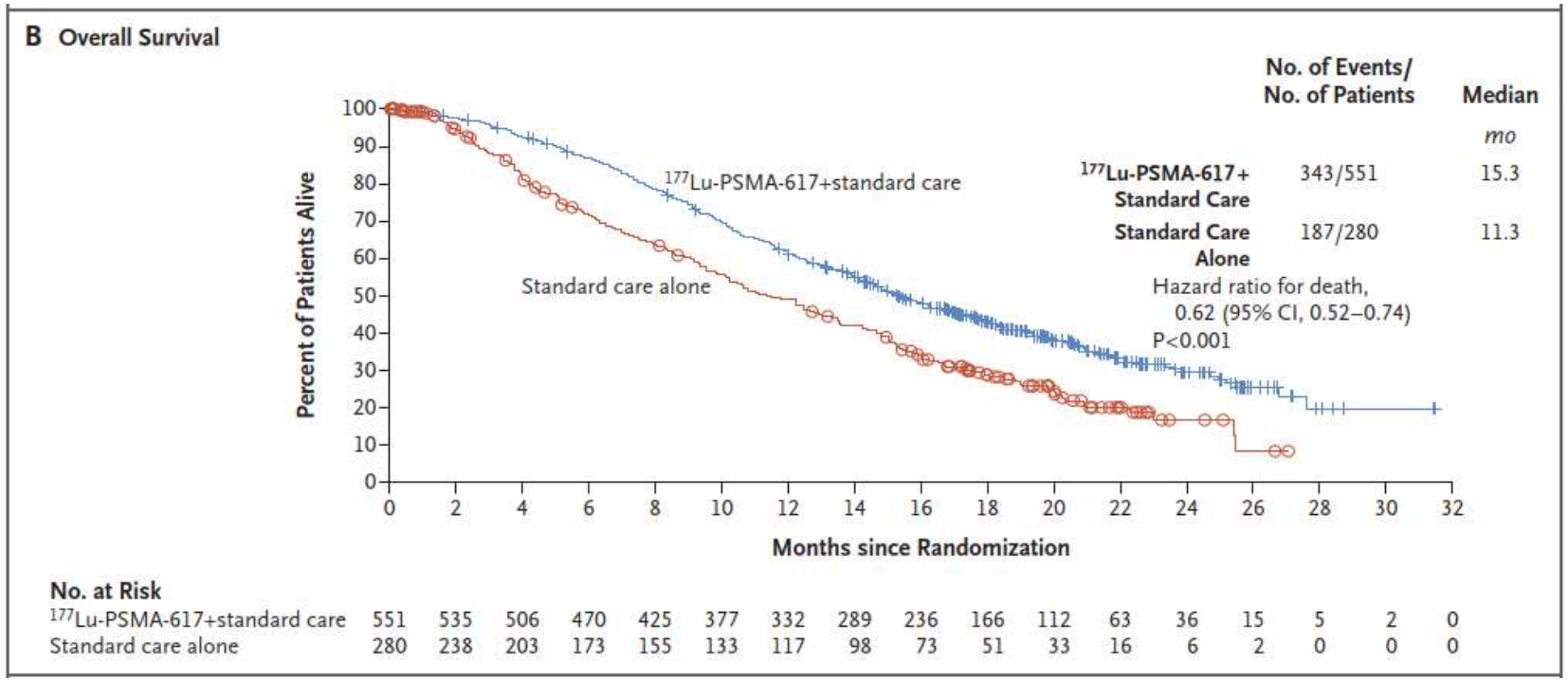
Sartor O et al , N Engl J Med 2021;385:1091-103.

VISION TRIAL: ^{177}Lu-PSMA-617 improves progression-free survival



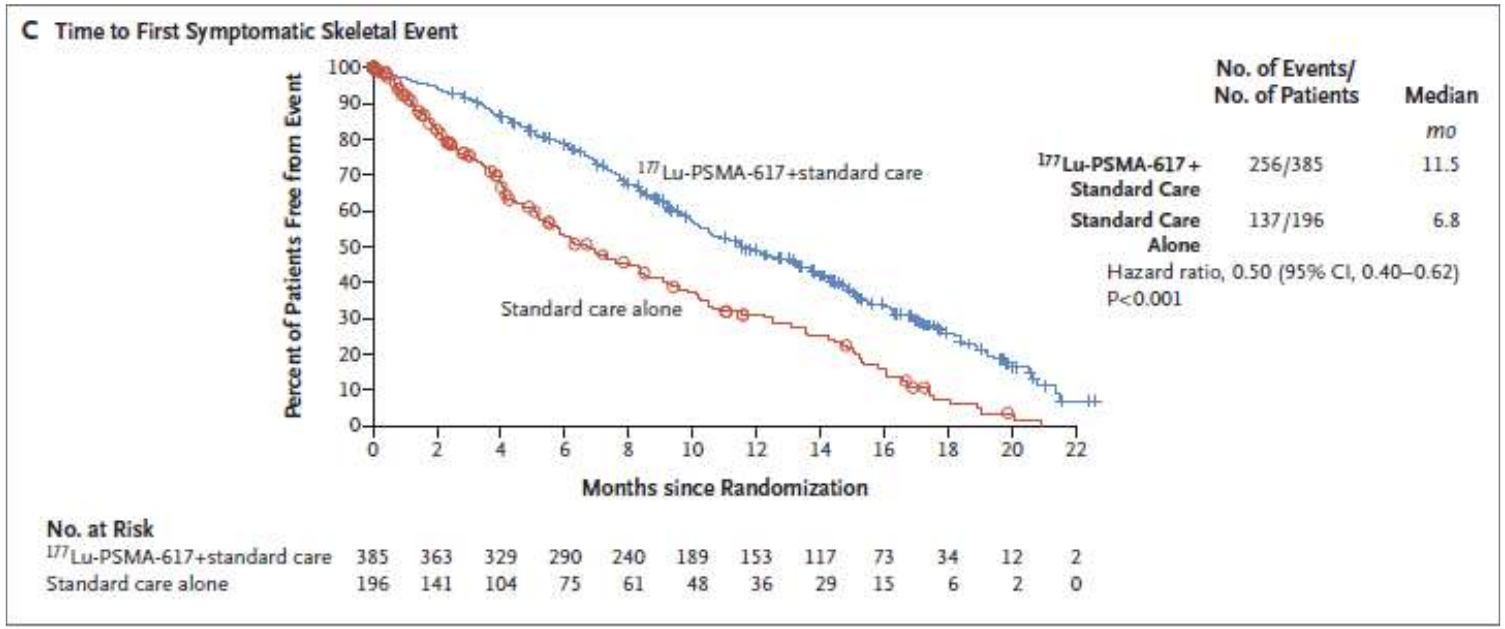
Sartor O et al , N Engl J Med 2021;385:1091-103.

VISION TRIAL: ^{177}Lu-PSMA-617 improves overall survival



Sartor O et al , N Engl J Med 2021;385:1091-103.

VISION TRIAL: ^{177}Lu-PSMA-617 improves time to first symptomatic skeletal event



Sartor O et al , N Engl J Med 2021;385:1091-103.

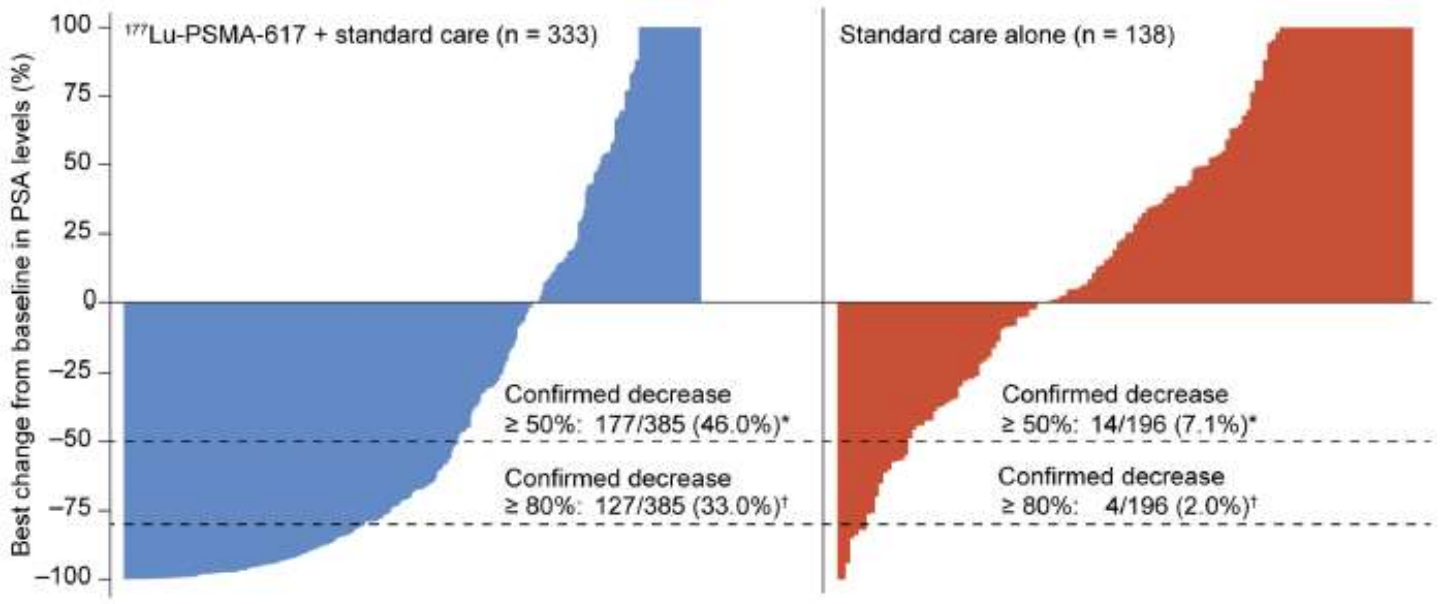
VISION TRIAL: Adverse Events

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)
Adverse event that led to reduction in ^{177}Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
Adverse event that led to interruption of ^{177}Lu-PSMA-617†	85 (16.1)	42 (7.9)	NA	NA
Adverse event that led to discontinuation of ^{177}Lu-PSMA-617†	63 (11.9)	37 (7.0)	NA	NA
Adverse event that led to death‡	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

Sartor O et al , N Engl J Med 2021;385:1091-103.

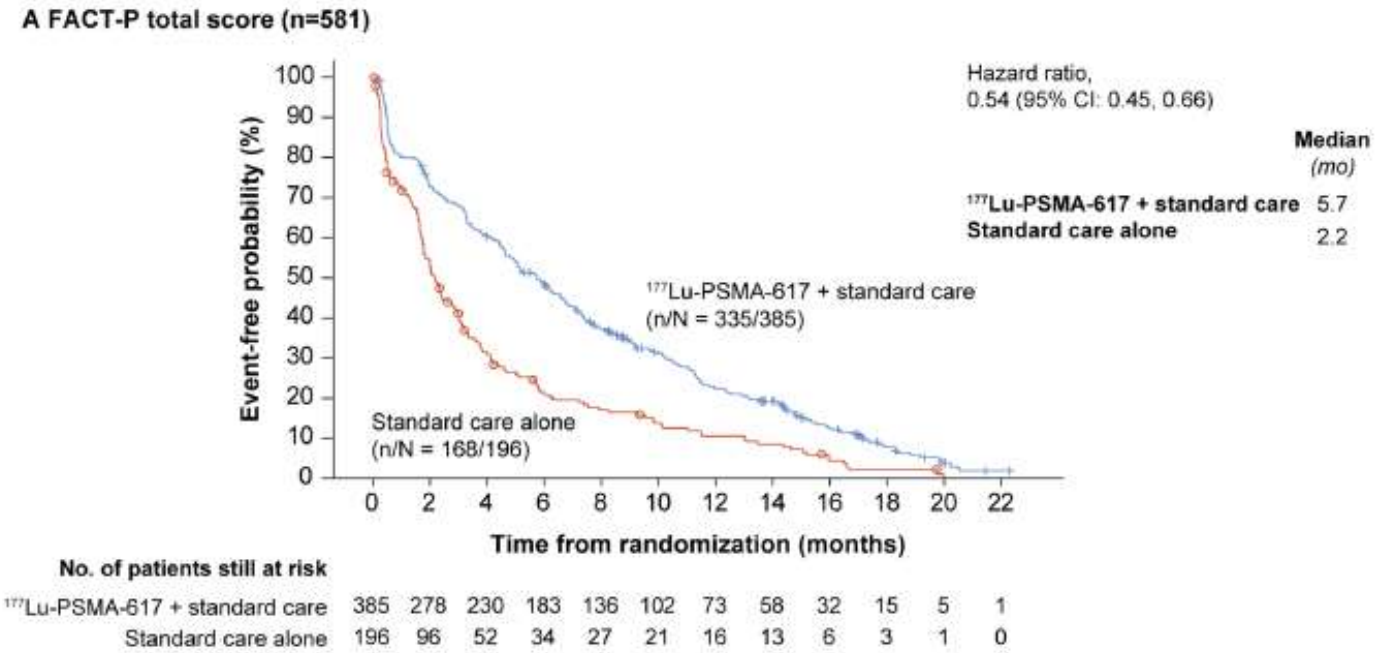
VISION TRIAL: PSA response



*Odds ratio, 11.19 (95% CI: 6.25, 20.04)
†Odds ratio, 23.62 (95% CI: 8.57, 65.11)

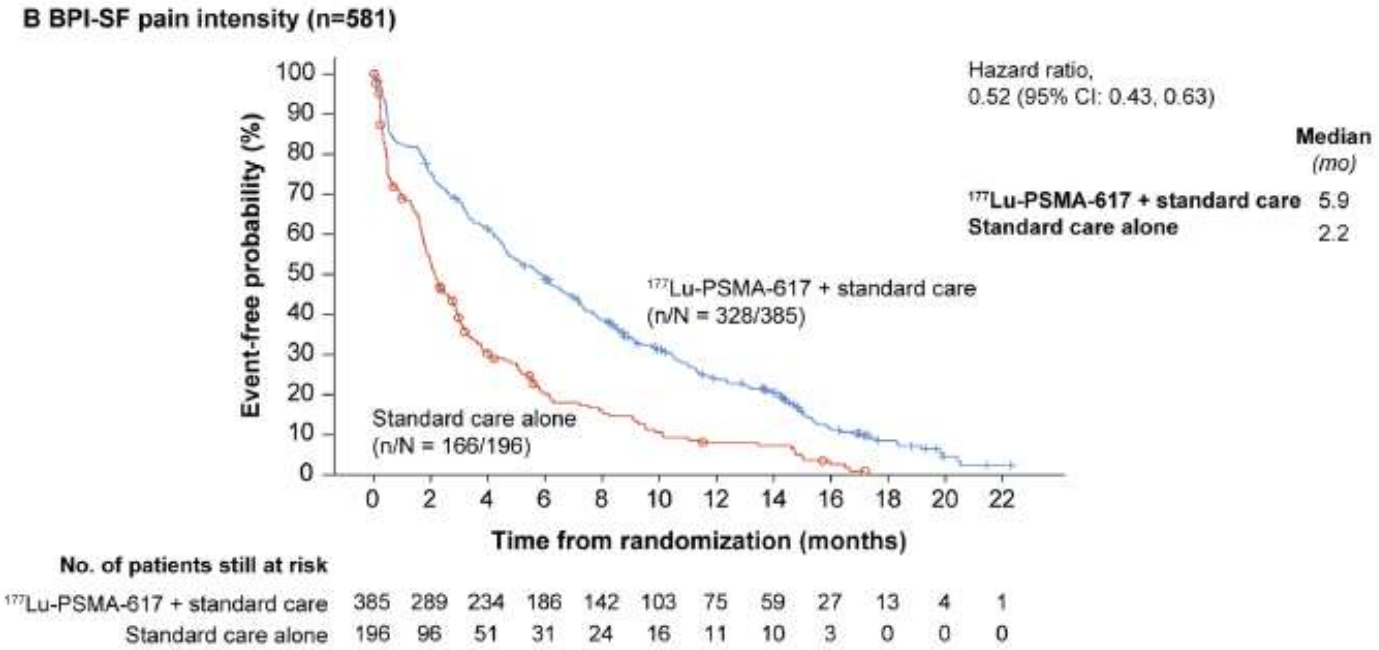
Sartor O et al , N Engl J Med 2021;385:1091-103.

VISION TRIAL: health-related QoL



Sartor O et al , N Engl J Med 2021;385:1091-103.

VISION TRIAL: pain



Sartor O et al , N Engl J Med 2021;385:1091-103.

[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

- Screened 291 potentially eligible patients for whom cabazitaxel was the next appropriate standard of care therapy
- PET eligibility: [^{68}Ga]Ga-PSMA-11 and [^{18}F] (FDG) PET-CT scans showing PSMA-positive disease and “no sites of metastatic disease with discordant FDG-positive and PSMA-negative findings”
- Randomized to receive [^{177}Lu]Lu-PSMA-617 (6·0–8·5 GBq iv q 6 wk x 6) or cabazitaxel (20 mg/m^2 iv q 3 weeks x 10).
- Randomized 200 patients – 98/99 received [^{177}Lu]Lu-PSMA-617, 85/101 received cabazitaxel
- Primary endpoint: PSA50 response from baseline

Hofman MS, et al. Lancet 2021; 397: 797–804

[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

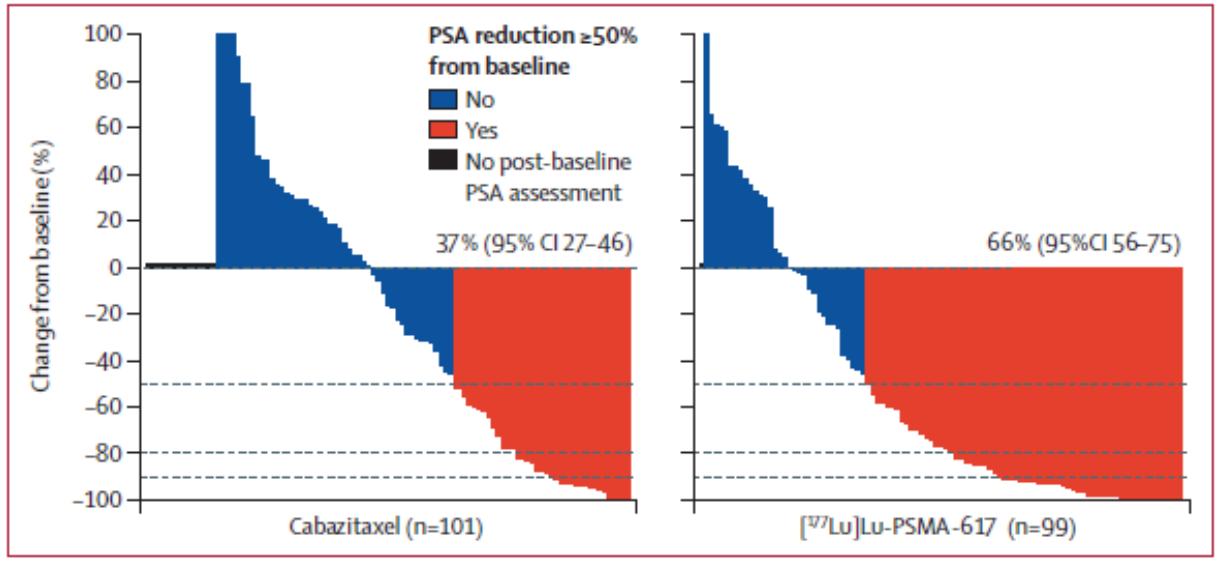


Figure 2: PSA response

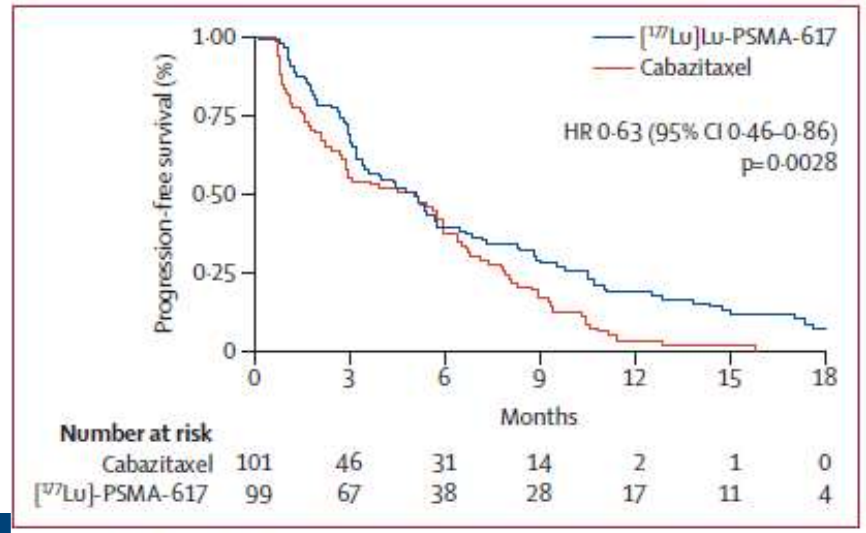


Figure 3: Radiographic or PSA progression-free survival

	[^{177}Lu]Lu-PSMA-617 (n=98)		Cabazitaxel (n=85)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Fatigue	69 (70%)	5 (5%)	61 (72%)	3 (4%)
Pain*	60 (61%)	11 (11%)	52 (61%)	4 (5%)
Dry mouth	59 (60%)	0	18 (21%)	0
Diarrhoea	18 (18%)	1 (1%)	44 (52%)	4 (5%)
Nausea	39 (40%)	1 (1%)	29 (34%)	0
Thrombocytopenia	18 (18%)	11 (11%)	4 (5%)	0
Dry eyes	29 (30%)	0	3 (4%)	0
Anaemia	19 (19%)	8 (8%)	11 (13%)	7 (8%)
Neuropathy†	10 (10%)	0	22 (26%)	1 (1%)
Dysgeusia	12 (12%)	0	23 (27%)	0
Haematuria	3 (3%)	1 (1%)	12 (14%)	5 (6%)
Neutropenia‡	7 (7%)	4 (4%)	4 (5%)	11 (13%)
Insomnia	9 (9%)	0	12 (14%)	1 (1%)
Vomiting	12 (12%)	1 (1%)	10 (12%)	2 (2%)
Dizziness	4 (4%)	0	11 (13%)	0
Leukopenia	10 (10%)	1 (1%)	5 (6%)	1 (1%)
Any adverse event	53 (54%)	32 (33%)	34 (40%)	45 (53%)

Data are n (%). Events that occurred in at least 10% of participants are shown. ^{177}Lu=Lutetium-177. PSMA=prostate-specific membrane antigen. *Including bone, buttock, chest wall, flank, neck, extremity, tumour pain, or pelvic pain. †Motor or sensory. ‡Febrile neutropenia.

Table 2: Adverse events

Hofman MS, et al. Lancet 2021; 397: 797–804

Overall survival with [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in metastatic castration-resistant prostate cancer (TheraP): secondary outcomes of a randomised, open-label, phase 2 trial

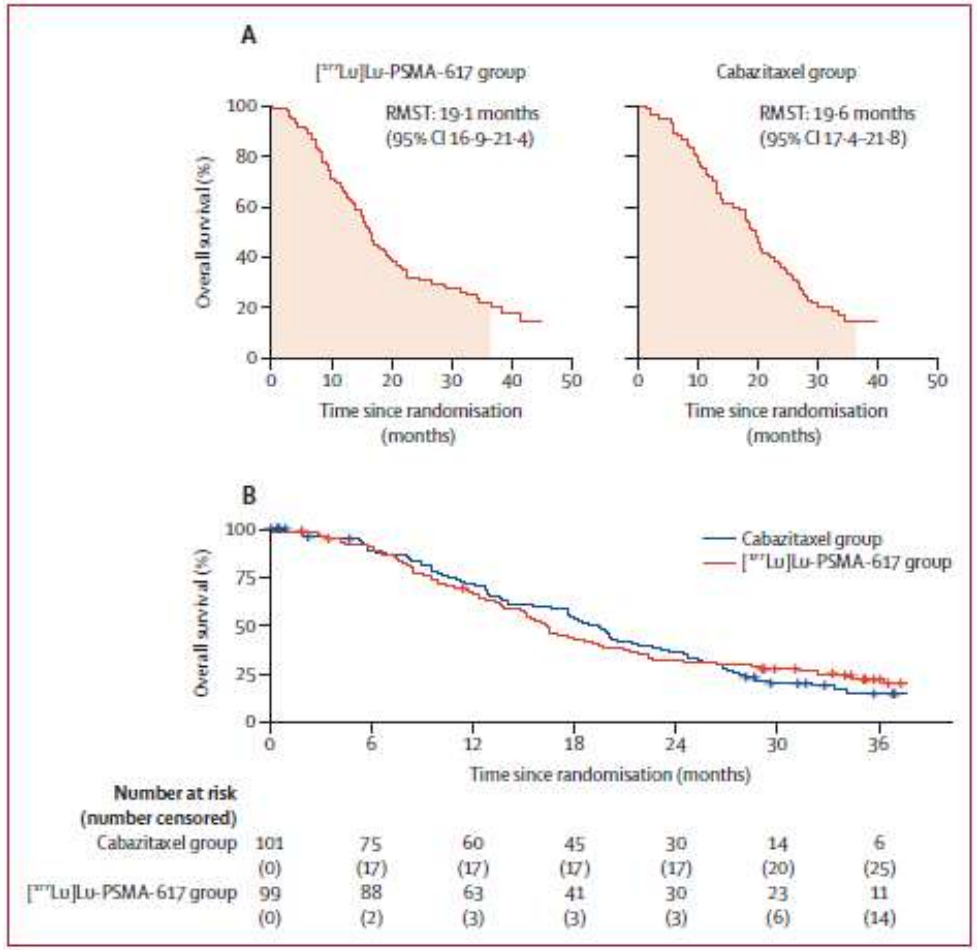


Figure 2: Overall survival

Hofman MS, et al. *Lancet Oncol* 2024; 25: 99–107

PSMA PET selection criteria for treatment with lutetium Lu 177 vipivotide tetraxetan

- “Select patients with previously treated mCRPC for treatment with PLUVICTO using LOCAMETZ or another approved PSMA-11 imaging agent based on PSMA expression in tumors.” (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215833s000lbl.pdf Accessed April 11, 2024.)
- PSMA-positive mCRPC as per 68Ga-PSMA PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. (Fendler WP, et al., Eur J Nucl Med Mol Imaging 2017; 44: 1014-24)
- “at least one PSMA-positive metastatic lesion and no PSMA-negative lesions that would be excluded according to the protocol criteria”
- gallium-68 (68Ga)–labeled PSMA-11 (68Ga-PSMA-11) PET–CT imaging at baseline
- PSMA-positive lesions: “68Ga-PSMA-11 uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system”
- PSMA-negative lesions: “PSMA uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis. Patients with any PSMA-negative metastatic lesion meeting these criteria were ineligible.”

Sartor O et al , N Engl J Med 2021;385:1091-103.

Proposed frameworks for the assessment of response to systemic therapy using PSMA-directed imaging

- **PPP**: PSMA PET Progression Criteria (Fanti S, Hadaschik B, and Herrmann K. Journal of Nuclear Medicine, 2020, 61(5):678-682) – expert recommendation
- **RECIP**: response evaluation criteria in prostate-specific membrane antigen (PSMA) PET/CT (Gafita A., et al, J Nucl Med 2022; 63:1651–1658) – expert recommendation and validation by overall survival in patients undergoing ^{177}Lu-PSMA RLT

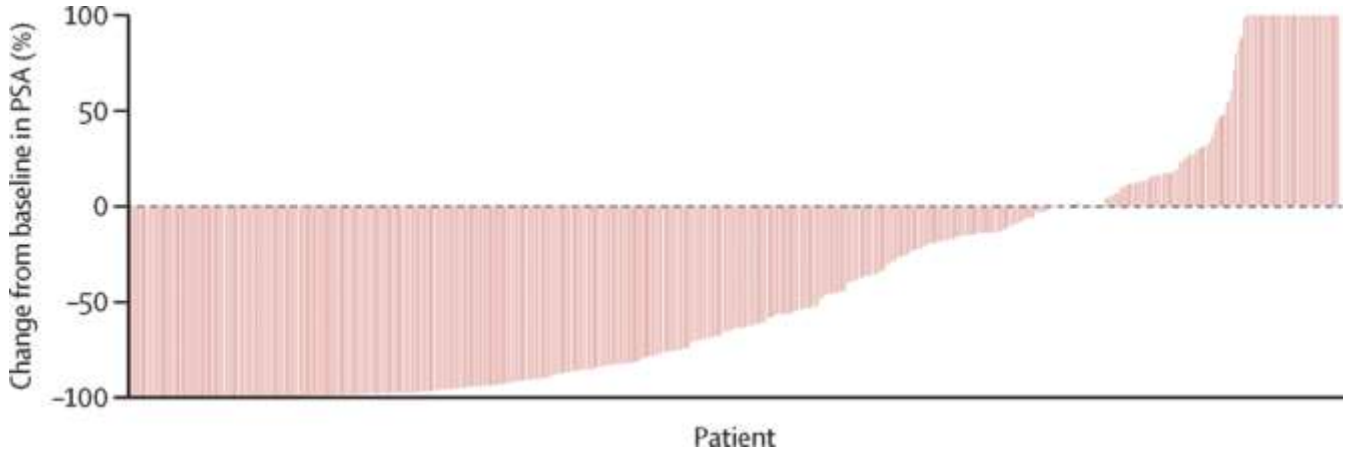
Criteria	Definition
PPP [80]	
Progressive disease	(a) Appearance of ≥ 2 new PSMA-positive distant lesions or (b) Appearance of 1 new PSMA-positive distant lesion plus consistent clinical and/or laboratory data (including changes in serum PSA, lactate dehydrogenase, alkaline phosphatase levels, or ECOG score) or (c) Increase in size or PSMA uptake of ≥ 1 existing lesions by 30% plus consistent clinical and/or laboratory data
RECIP 1.0 [79]	
Complete response	Absence of any PSMA uptake on follow-up PET scan
Partial response	≥ 30% decrease in PSMA-VOL without appearance of new lesions
Progressive disease	≥ 20% increase in PSMA-VOL with appearance of new lesions
Stable disease	Does not meet the above criteria

PSMA-VOL, PSMA-ligand PET derived tumor volume

Fendler W., et al. "PSMA PET/CT: joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0" European Journal of Nuclear Medicine and Molecular Imaging (2023) 50:1466–1486

Is PSMA-targeted alpha therapy next? Second Attendance Verification Codes: **4551**

- WARMTH Act: multi-center, retrospective study of Actinium-225 (^{225}Ac-PSMA RLT in 488 patients with mCRPC who received ≥ 1 cycle at 8 MBq *(Sathekge MM et al, Lancet Oncol 2024; 25: 175–83)*
- mOS 15.5 months, mPFS 7.9 months



- Potential alpha therapies: actinium-225, astatine-211, thorium-227 *(De Vincentis G et al, Annals of Oncology 2019; 30:1728-1739)*