Fred Hutch Cancer Center

Prostate Cancer Board Review

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Disclosures

- Paid consultant and/or received Honoria from Sanofi, AstraZeneca, Janssen, Fibrogen, and Pfizer.

- Received research funding to my institution from Novartis, Zenith Epigenetics, Eli Lilly, Bristol Myers Squibb, Merck, Immunomedics, Janssen, AstraZeneca, Pfizer, Hoffmann-La Roche, Tmunity, SignalOne Bio, Epigenetix, Xencor, Incyte and Ambrx, Inc.

Outline

- Background
- Local therapies
- Non-metastatic recurrent prostate cancer
- Metastatic hormone-sensitive prostate cancer
- Metastatic castration-resistant cancer

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Epidemiology

Estimated New Cases

Prostate	299,010	29%
Lung & bronchus	116,310	11%
Colon & rectum	81,540	8%
Urinary bladder	63,070	6%
Melanoma of the skin	59,170	6%
Kidney & renal pelvis	52,380	5%
Non-Hodgkin lymphoma	44,590	4%
Oral cavity & pharynx	41,510	4%
Leukemia	36,450	4%
Pancreas	34,530	3%
All sites	**1,029,080**	

Estimated Deaths

Lung & bronchus	65,790	20%
Prostate	35,250	11%
Colon & rectum	28,700	9%
Pancreas	27,270	8%
Liver & intrahepatic bile duct	19,120	6%
Leukemia	13,640	4%
Esophagus	12,880	4%
Urinary bladder	12,290	4%
Non-Hodgkin lymphoma	11,780	4%
Brain & other nervous system	10,690	3%
All sites	**322,800**	

Siegel, et al. CA Cancer J Clin. 2024

Randomized Screening Trials

- PLCO: No mortality benefit to screening
  - –N >75,000; age 55-74; 7-10 yr f/u
  - –~20% more cancers detected in screened arm
  - –~90% in control group had PSA testing
- ERSPC: 20% reduction in cancer mortality
  - –N > 160,000; age 55-69; 9 years f/u
  - –~70% more cancers detected in screened arm
  - –NNS = 1410; NNT = 48
  - –NNT = 12 in Goteborg series (f/u 14 years)

Andriole, et al. N Engl J Med. 2009 Mar 26;360(13):1310-9
Schroder, et al. N Engl J Med. 2009 Mar 26;360(13):1320-8
Shoag, et al. N Engl J Med. 2016 May 5;374(18):1795-6

Diagnosis and Risk Stratification

- Biopsy indicated:
  - Abnormal DRE
  - Elevated PSA
- Additional testing dependent on risk:
  - Bone scan: T1 and PSA>20, T2 and PSA>10, Gleason ≥8, T3-T4 or symptomatic
  - Pelvic CT or MRI: T3-T4, T1-T2 and >10% chance of lymph node involvement

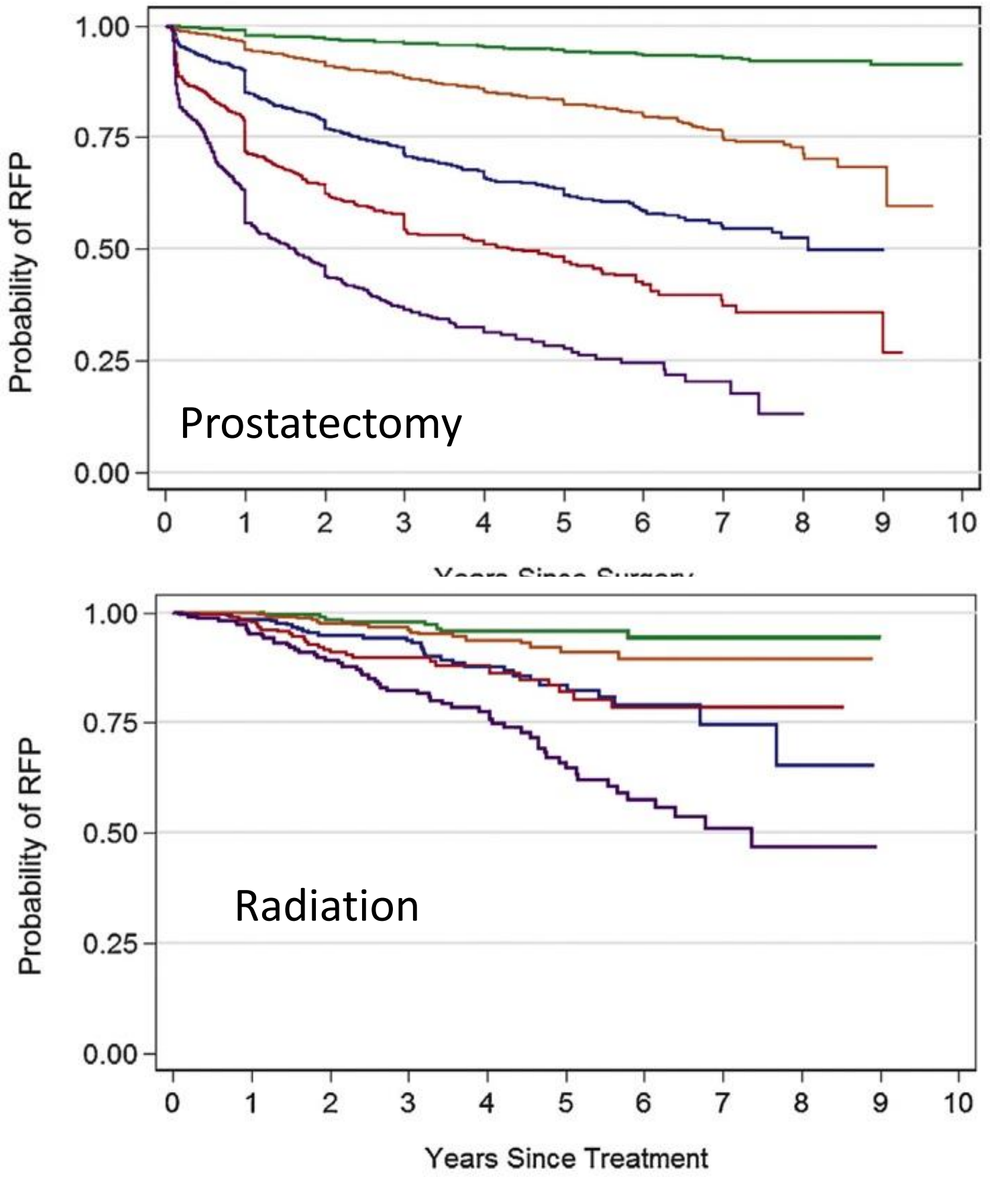
Risk Group	Clinical Features
Very low	T1c Gleason score ≤6 PSA <10 <3 positive biopsy cores ≤50% cancer in each core PSA density <0.15
Low	T1-T2a Gleason ≤6 PSA <10
Intermediate	T2b-T2c or Gleason score 7 or PSA 10-20
High	T3a or Gleason score 8-10 or PSA >20
Very high	T3b-T4

Prostate Cancer NCCN Guidelines

Gleason Grade Group

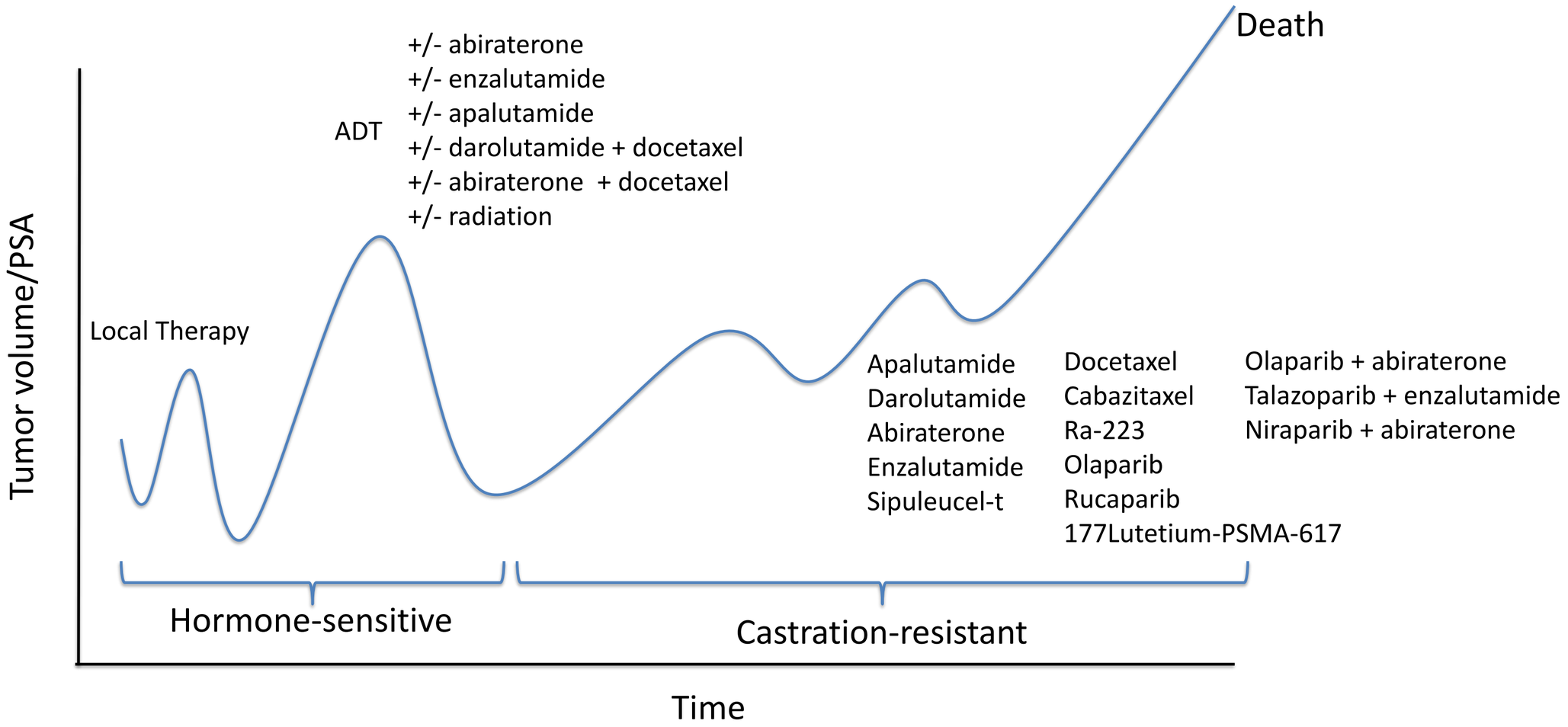
- Included patients treated with radiation (EBRT) or prostatectomy (RP) between 2005 and 2014
  - N=20,845 treated with RP
  - N=5,501 treated with EBRT
- Primary endpoint: Biochemical (i.e. PSA) recurrence

Grade Group	Gleason Pattern
Group 1	Gleason 3+3
Group 2	Gleason 3+4
Group 3	Gleason 4+3
Group 4	Gleason 4+4
Group 5	Gleason 4+5, 5+4 or 5+5



Epstein, et al. Eur Urol. 2016;69(3):428.

Prostate Cancer Disease Continuum



Androgen Deprivation Therapy – Side Effects

- Common: sexual (impotence and decreased libido), hot flashes, fatigue, loss of motivation, gynecomastia, weight gain

- Metabolic: diabetes, hyperlipidemia, osteopenia, cardiovascular disease
  - Check DEXA – if osteopenia or osteoporosis denosumab 60 mg SC q6 months reduces risk of osteoporotic fractures[1]
  - Resistance and Aerobic Exercise can improve muscle mass, physical function and potentially survival
  - Vitamin D 800-1000 IU + Calcium 1000-1200 mg po qd

1. Smith MR et al. NEJM 2009; 361:745

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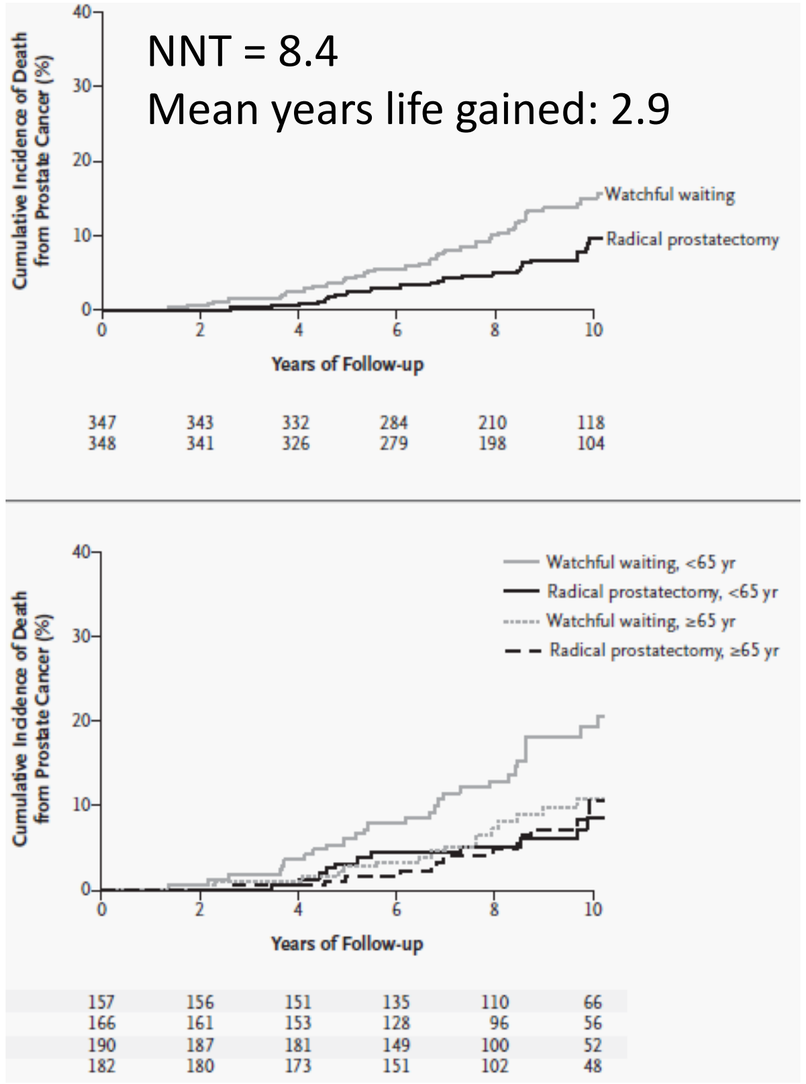
Local Therapy

- SPCG4: Prostatectomy vs. observation
  - T1 or T2 prostate cancer
  - N= 695
  - 64% intermediate/high-risk
  - 23.6 years median follow up
  - Death (RP vs. Observation): 72% vs 84% (P<0.001)
    - NNT = 8.4 to prevent 1 death
  - Benefits most pronounced in those <65 years and with intermediate risk disease
- PIVOT: similar to SPCG4, only 10 year median follow up
  - Death (RP vs. Observation): 47% vs. 49.9% (P=0.22)
- ProtecT: Prostatecomy vs radiation vs observation
  - Similar survival (few patients died) over 10 year median follow up
  - Lower rates of metastatic disease with prostatectomy or radiation (P=0.004)

Bill-Axelson, et al. N Engl J Med. 2014 Mar 6;370(10):932-42
Bill-Axelson, et al. N Engl J Med. 2018 Dec 13;379(24):2319-2329.
Wilt, et al. N Engl J Med. 2012 Jul 19;367(3):203-13Hamdy, et al. N Engl J Med. 2016 Sep 14
Hamdy, et al. N Engl J Med. 2016 Sep 14

Radical Prostatectomy for Localized Prostate Cancer

SPCG4 Trial: Prostatectomy vs. Observation



Bill-Axelson A et al. NEJM 2005; 352:1977-84
Bill-Axelson, et al, NEJM 2018;379:2319-29.

- ADT does not offer benefit prior to surgery
- Adjuvant ADT for lymph node positive[1] and other high risk patients[2] "Investigational"
- Adjuvant XRT for +margins or T3b status[3,4]
- Adjuvant XRT may be advantageous over salvage radiation in men with pN1 or Gleason score 8 to 10 disease[5]

1. Messing EM et al. NEJM 1999; 341:1781
2. Dorff TB et al. JCO 2011;29:2040
3. Thompson IM et al. JAMA 2006; 296:2329 (S8794)
4. Bolla M et al. Lancet 2005; 366:13 (EORTC 22911)
5. Tilki, et al. J Clin Oncol . 2021 Jul 10;39(20):2284-2293.

Radiation for Prostate Cancer

- ADT added to radiation (EBRT) improves survival for higher risk or locally advanced patients[1]
  - 4-6 months (short course) for intermediate risk
  - Neoadjuv + concurrent + adjuvant (2-3 years LHRH) for high risk[2,3]
- ADT + abiraterone +EBRT improves survival in patients with very high risk localized disease[4]
  - Very high risk: Node positive on CT/MRI OR 2+ of the following features: T3/T4, Gleason 8-10, PSA ≥40 ng/ml
- Data suggests radiation may also play a role in managing low volume metastatic disease[5,6]

1. Pilepich MV et al. JCO 1997; 15:1013 (RTOG 8531)
2. Hanks GE et al. JCO 2003; 21:3972 (RTOG 9202)
3. Bolla M et al. Lancet 2002; 360:103 (EORTC)
4. Attard G, et al. Lancet 2022 Jan 29;399(10323):447-460
5. Parker, et al. Lancet. 2018 Dec 1;392(10162):2353-2366.
6. Bossi, et al. ASCO 2023

Prostate Cancer Active Surveillance

- Safe and effective strategy to mitigate overtreatment
- 25% will progress and need treatment
- 25% will select treatment without meeting progression criteria

Center	Toronto[1,2,3]	Johns Hopkins[4,5,6,7]	UCSF[8]	UCSF (newer cohort)[9]	Canary PASS[10]
No. patients	993	1298	321	810	905
Median follow-up (mos)	77	60	43	60	28
Cancer-specific survival	98% (10-y)	99.9% (10-y)	100% (5-y)	-	-
Conversion to treatment	36.5% (10-y)	50% (10-y)	24% (3-y)	40% (5-y)	19% (28-mos)

Adapted from Prostate Cancer NCCN Guidelines v2.2020

1. Klotz, et al. J Clin Oncol. 2015 Jan 20;33(3):272-7.
2. Klotz, et al. J Clin Oncol. 2010 Jan 1;28(1):126-31.
3. Yamamoto, et al. J Urol. 2016 May;195(5):1409-1414.
4. Tosoian, et al. J Clin Oncol. 2015 Oct 20;33(30):3379-85.
5. Carter, et al. J Urol. 2007 Dec;178(6):2359-64
6. Sheridan, et al. J Urol. 2008 Mar;179(3):901-4
7. Tosoian, et al. J Clin Oncol. 2011 Jun 1;29(16):2185-90.
8. Dall'era, et al. Cancer. 2008 Jun 15;112(12):2664-70.
9. Welty, et al. J Urol. 2015 Mar;193(3):807-11.
10. Newcomb, et al. J Urol. 2016 Feb;195(2):313-20.

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Biochemical Recurrence (AKA M0)

- No metastatic disease on imaging
  - Traditionally defined using CT and bone scan
- Definition: PSA >0.2 after RRP, “nadir +2” after XRT
- Salvage radiation is standard of care for biochemical recurrence after surgery
- Natural history can be long
  - Consecutive series from 1981 to 2010
  - N=450 men with biochemical recurrence following prostatectomy
    - >50% with Gleason ≥7
    - Median baseline PSA = 8.5
  - No adjuvant therapy
  - Median metastasis free survival = 10 years

Antonarakis, et al. BJU Int. 2012 Jan;109(1):32-9.

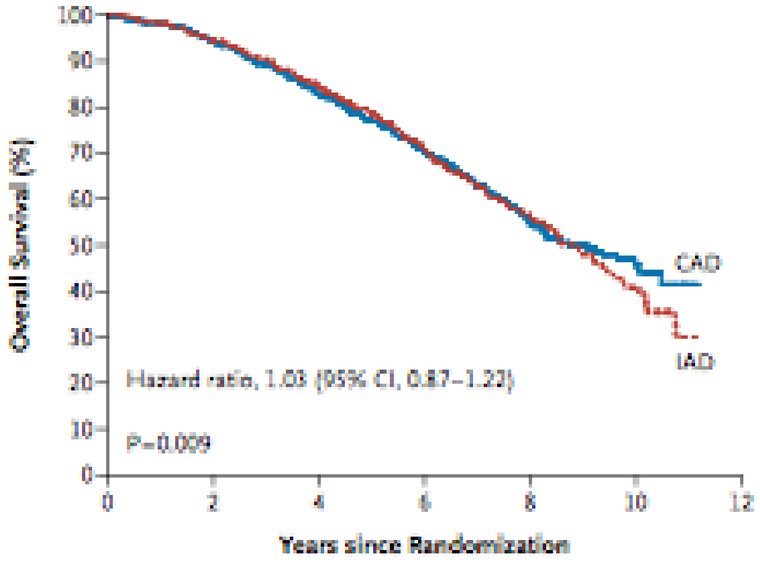
Biochemical Recurrence (AKA M0)

- ADT beneficial when giving salvage radiation for BCR
- GETUG-AFU16[1]
  - 6 months of goserelin with XRT 66 Gy or XRT alone
  - 10 year MFS: 75% (ADT+XRT) vs. 69% (XRT), P=0.0339
- RTOG 9601[2]
  - High dose bicalutamide 150 mg for 24 months with XRT 64.8 Gy or XRT alone
  - HR for OS 0.75 (2-sided p = 0.036).

1. Carrie C. et al Lancet Oncol 2019; 20: 1740–49
2. Shipley WU et al. NEJM 2017; 376:417-28

Intermittent vs. Continuous ADT

PR7 for BCR

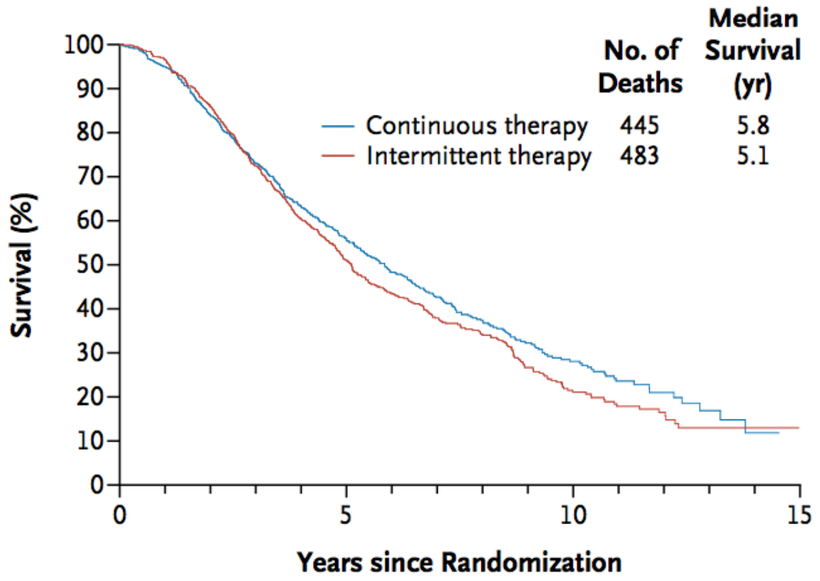


No. at Risk							
CAD	696	652	561	319	125	35	0
IAD	690	651	571	327	140	34	0

No difference in OS

Crook JM et al. N Engl J Med. 2012; 367:895-903.

SWOG 9346 for mHSPC



No. at Risk			
Continuous therapy	765	325	64
Intermittent therapy	770	291	52

Intermittent therapy was not non-inferior to continuous ADT

Hussain M et al. N Engl J Med 2013;368:1314-25.

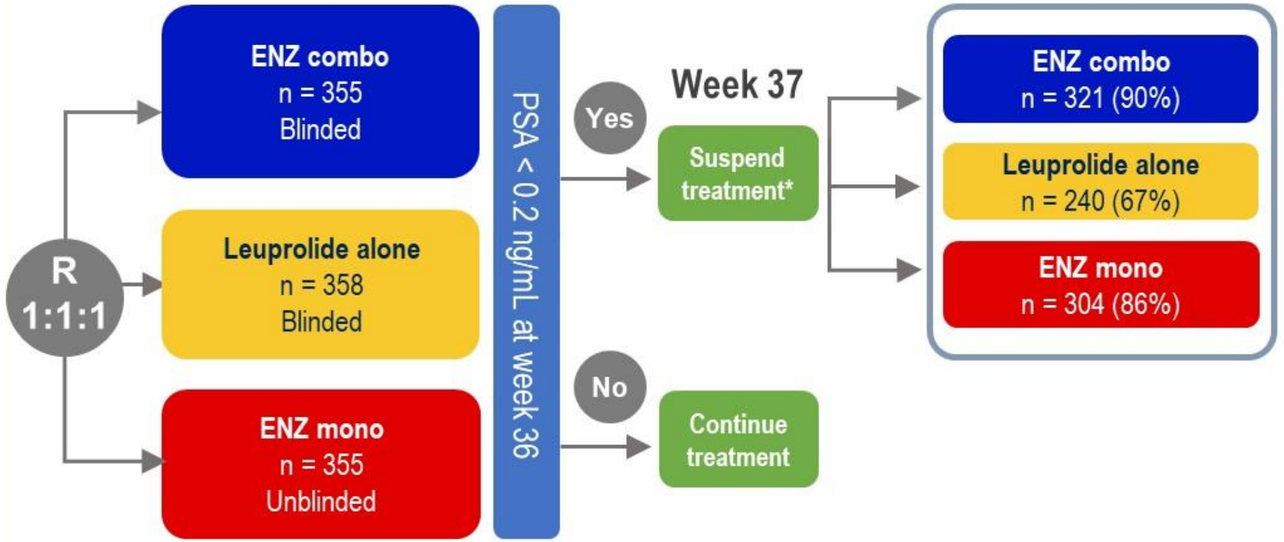
EMBARK

EMBARK

Phase 3 randomized study in patients with high-risk BCR nmHSPC after local therapy **(N = 1068)**

Patient population

- PSA ≥ 1 ng/mL (post-RP)
- PSA ≥ 2 ng/mL above the nadir (post-RT)
- PSADT ≤ 9 months
- T ≥ 150 ng/dL



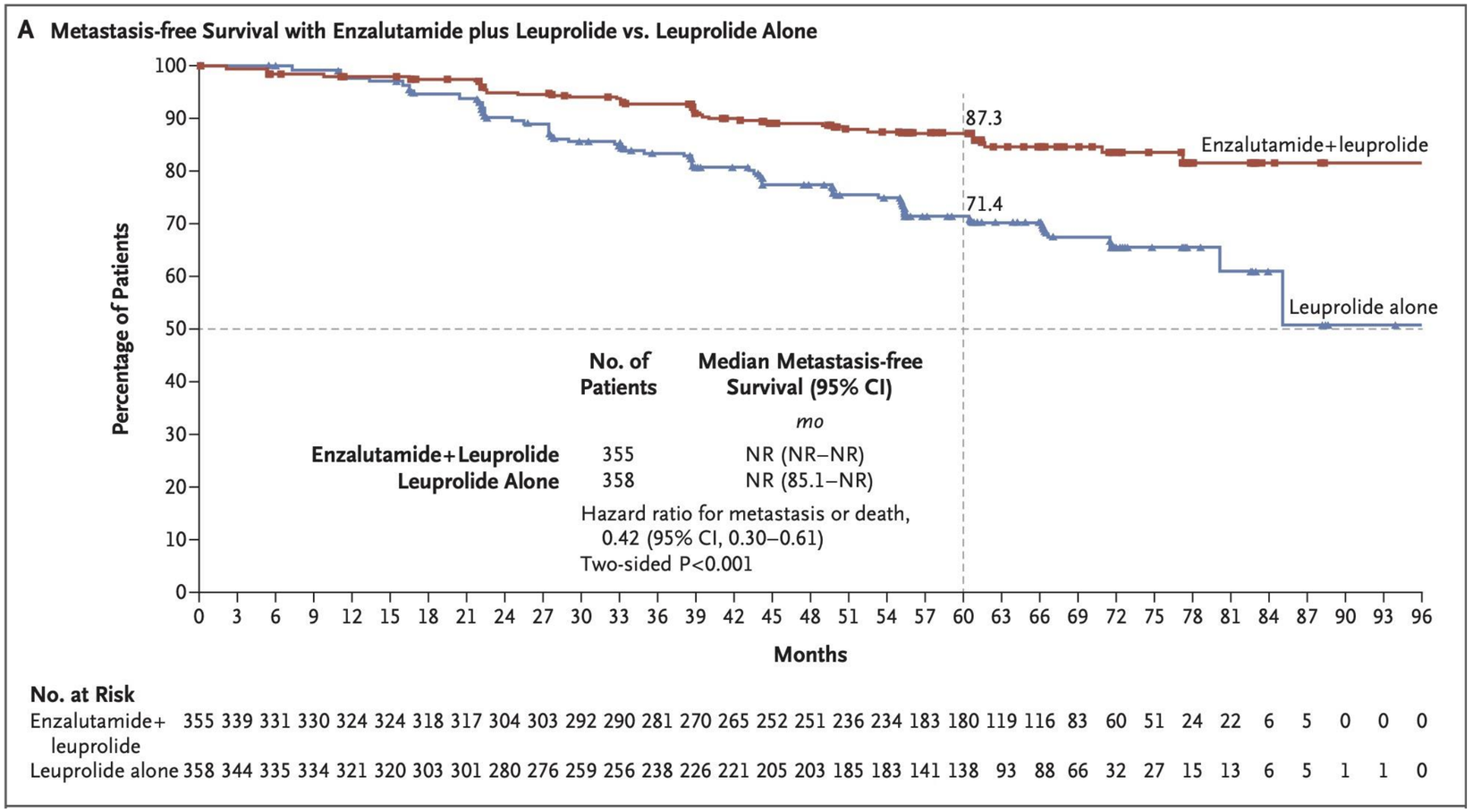
Primary endpoint:
MFS between ENZ combo vs leuprolide alone

Post hoc analysis:
To examine the impact of treatment suspension on HRQoL

***Study drug treatment was suspended, but PSA levels were monitored. Treatment was reinitiated if the PSA increased to ≥2 ng/mL for patients with prior RP or to ≥5 ng/mL for patients without RP**

BCR: biochemical recurrence; ENZ combo: enzalutamide plus leuprolide; ENZ mono: enzalutamide monotherapy; HRQoL: health-related quality of life; MFS: metastasis-free survival; nmHSPC: non-metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen; PSADT: PSA doubling time; R: randomization; RP: radical prostatectomy; RT: radiotherapy; T: testosterone

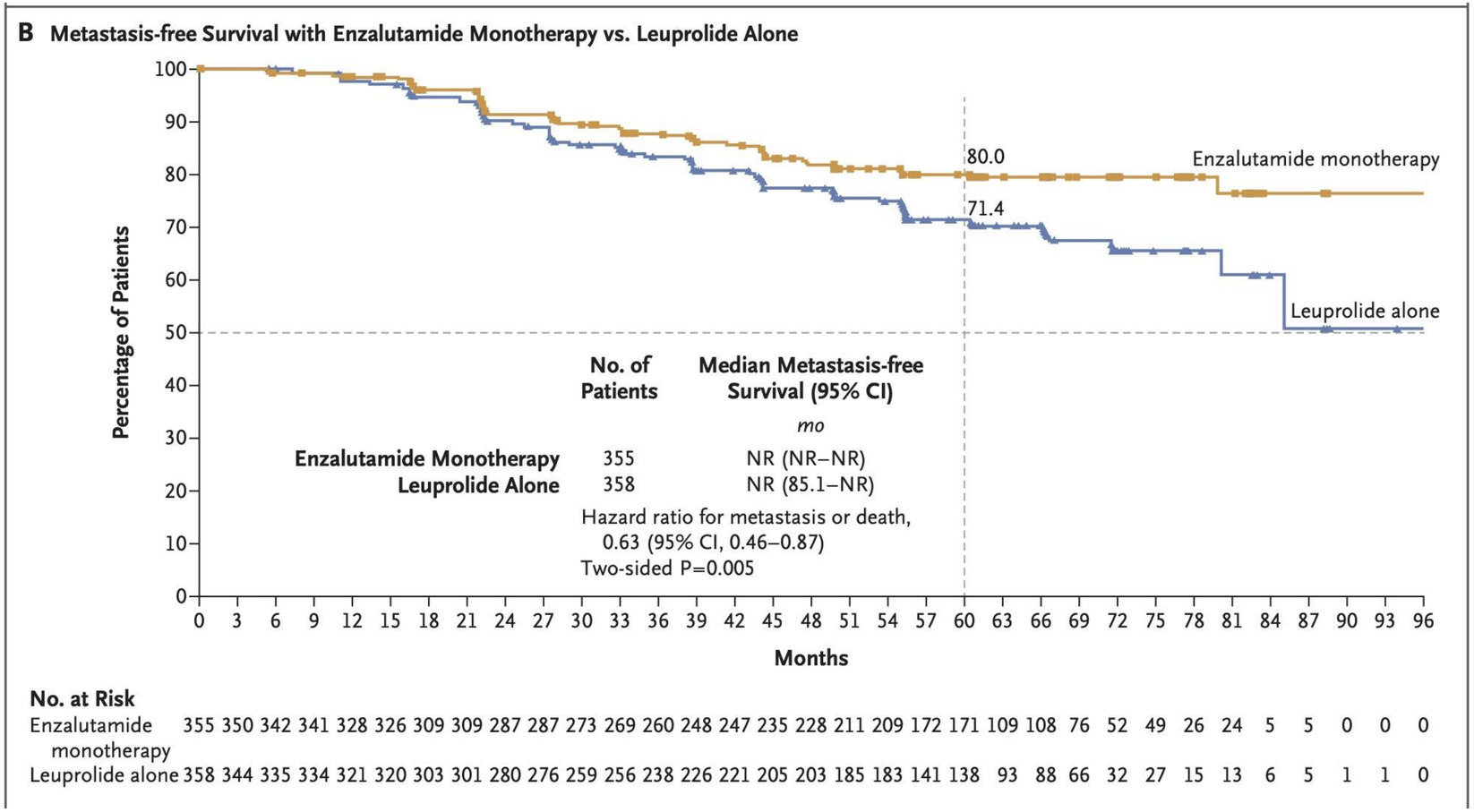
Treatment intensification in BCR prostate cancer: EMBARK



- Median PSADT: 4.6 to 5 mos
- Median PSA: 5.0 to 5.5 ng/ml

Freedland, et al. NEJM 2023

Treatment intensification in BCR prostate cancer: EMBARK



- Median PSADT: 4.6 to 5 mos
- Median PSA: 5.0 to 5.5 ng/ml

Freedland, et al. NEJM 2023

Treatment Related Adverse Events: Meaningful Changes

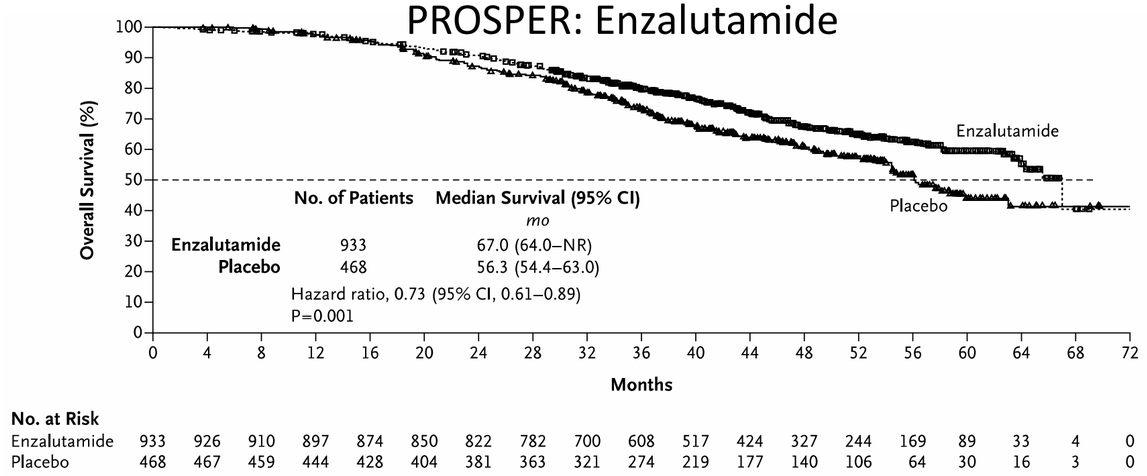
Event	Enzalutamide + Leuprolide (N=353, (%))		Leuprolide Alone (N=354, (%))		Enzalutamide Monotherapy (N=354, (%))	
	Any Grade	Grade≥3	**Any Grade**	Grade≥3	**Any Grade**	Grade≥3
Hot flash	243 (68.8)	2 (0.6)	203 (57.3)	3 (0.8)	77 (**21.8**)	1 (0.3)
Fatigue	151 (**42.8**)	12 (3.4)	116 (32.8)	5 (1.4)	165 (**46.6**)	14 (4)
Nipple Pain	11(3.1)	0	4 (1.1)	0	54 (**15.3**)	0
Gynecomastia	29 (8.2)	0	32 (9)	0	159 (**44.9**)	1 (0.3)
Ischemic heart disease	19 (5.4)	14 (4.0)	20 (5.6)	11 (3.1)	32 (**9.0**)	21 (5.9)
Fracture	65 (**18.4**)	14 (4)	48 (13)	9 (2.5)	39 (11)	7 (2)
Cognitive impairment	53 (**15**)	2 (0.6)	23 (6.5)	2 (0.6)	50 (**14.1**)	0

Freedland SJ, de Almeida Luz M, De Giorgi U, et al. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. *N Engl J Med*. 2023;389(16):1453-1465. https://doi.org/10.1056/NEJMoa2303974. doi: 10.1056/NEJMoa2303974. Sternberg CN, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2020;382(23):2197–2206. doi: 10.1056/NEJMoa2003892

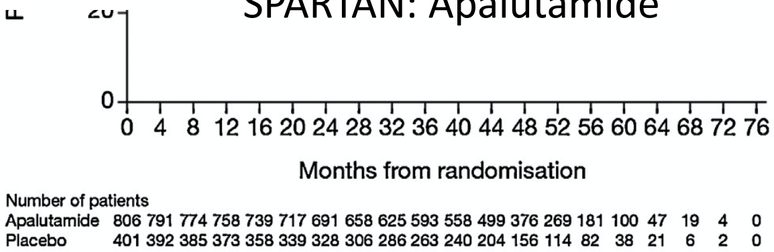
PRESENTED BY: Channing Paller, MD Twitter: @Cpaller

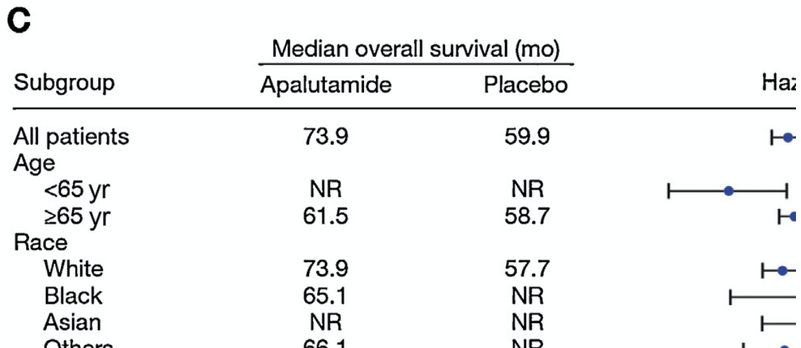
Apalutamide, Darolutamide and Enzalutamide in M0CRPC

PROSPER: Enzalutamide

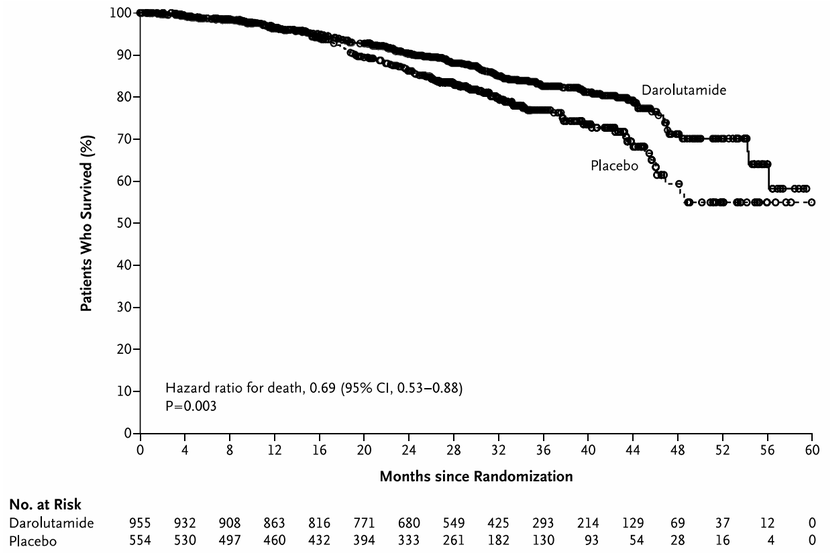


SPARTAN: Apalutamide



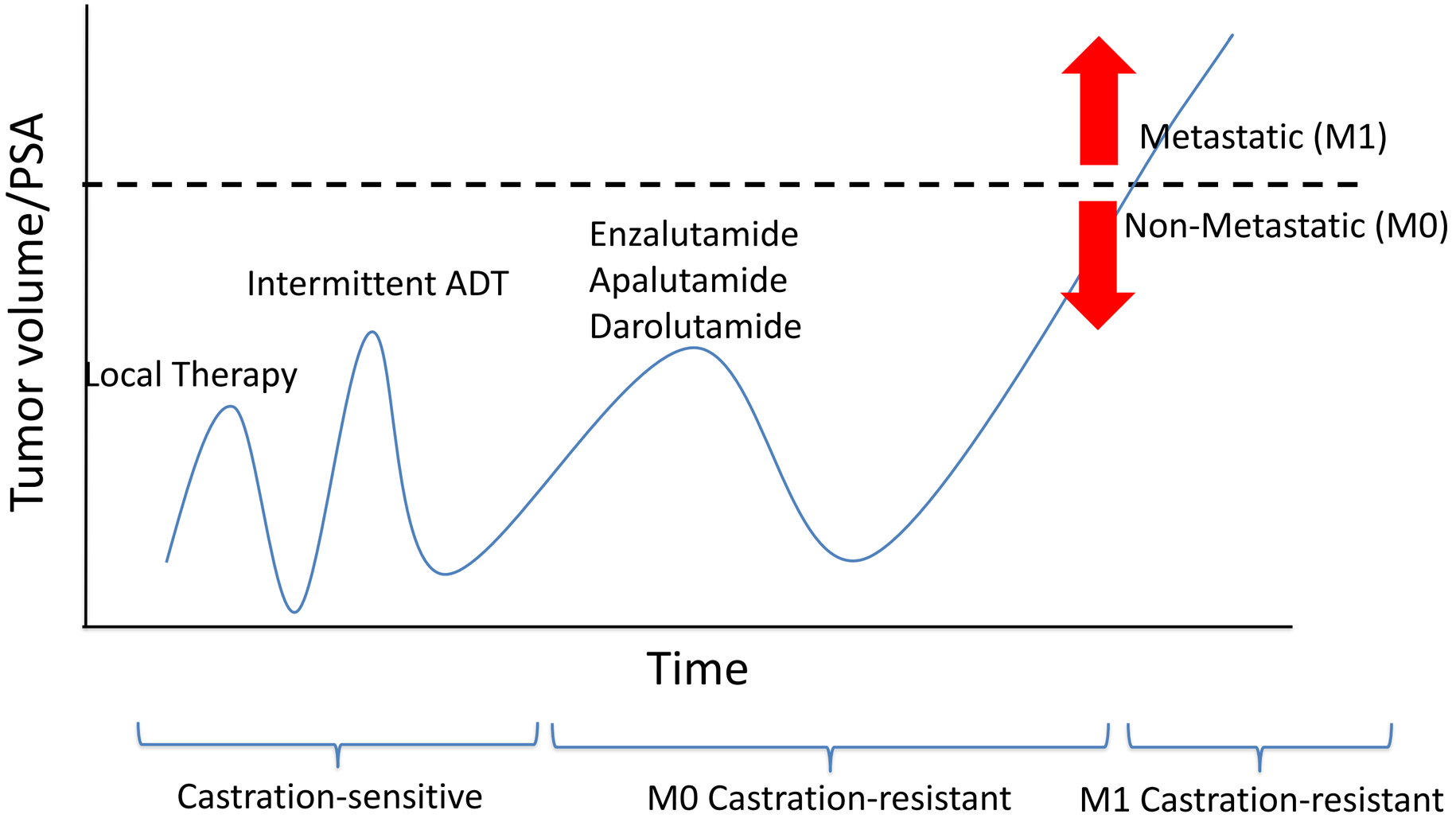


ARAMIS: Darolutamide



Smith MR et al. N Engl J Med 2018; 378:1408-18.
Fizazi, et al. N Engl J Med 2020;383:1040-9
Sternberg, et al. N Engl J Med. 2020 Jun 4;382(23):2197-2206.

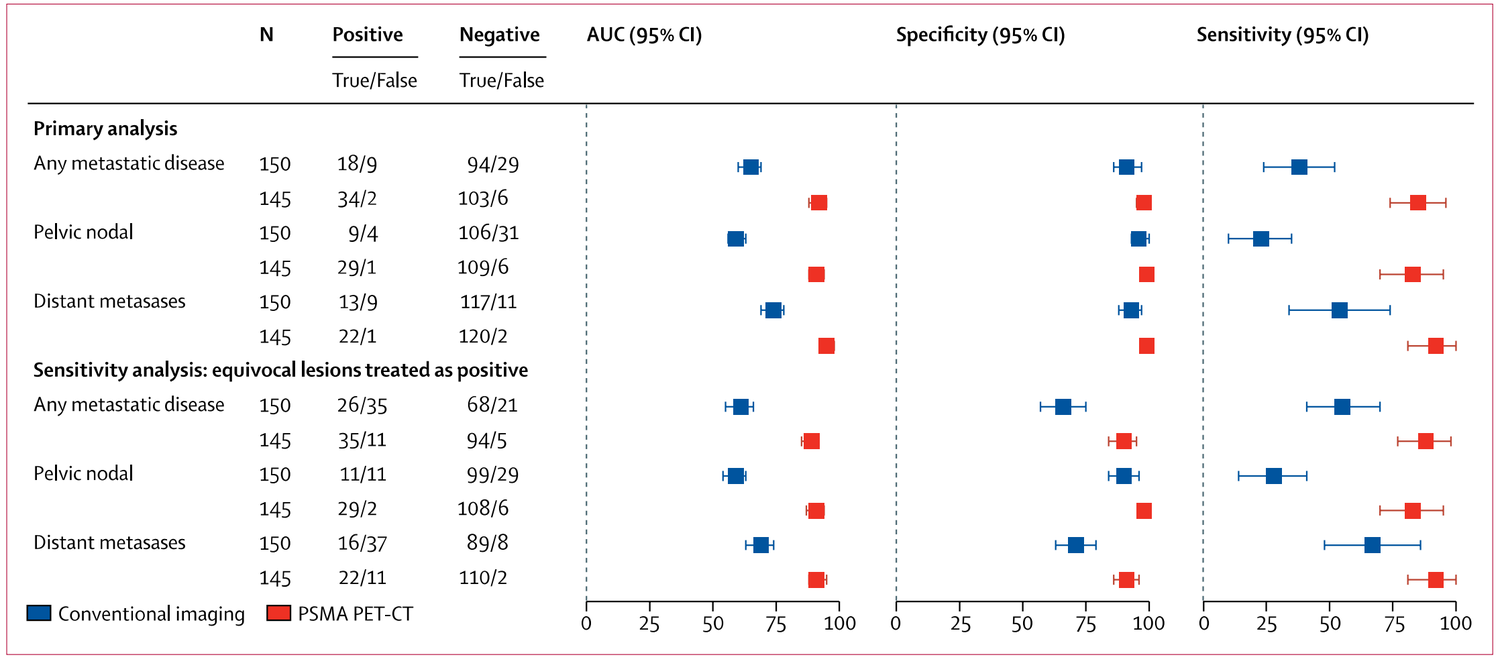
What if we detect metastatic disease earlier?



PSMA PET Imaging

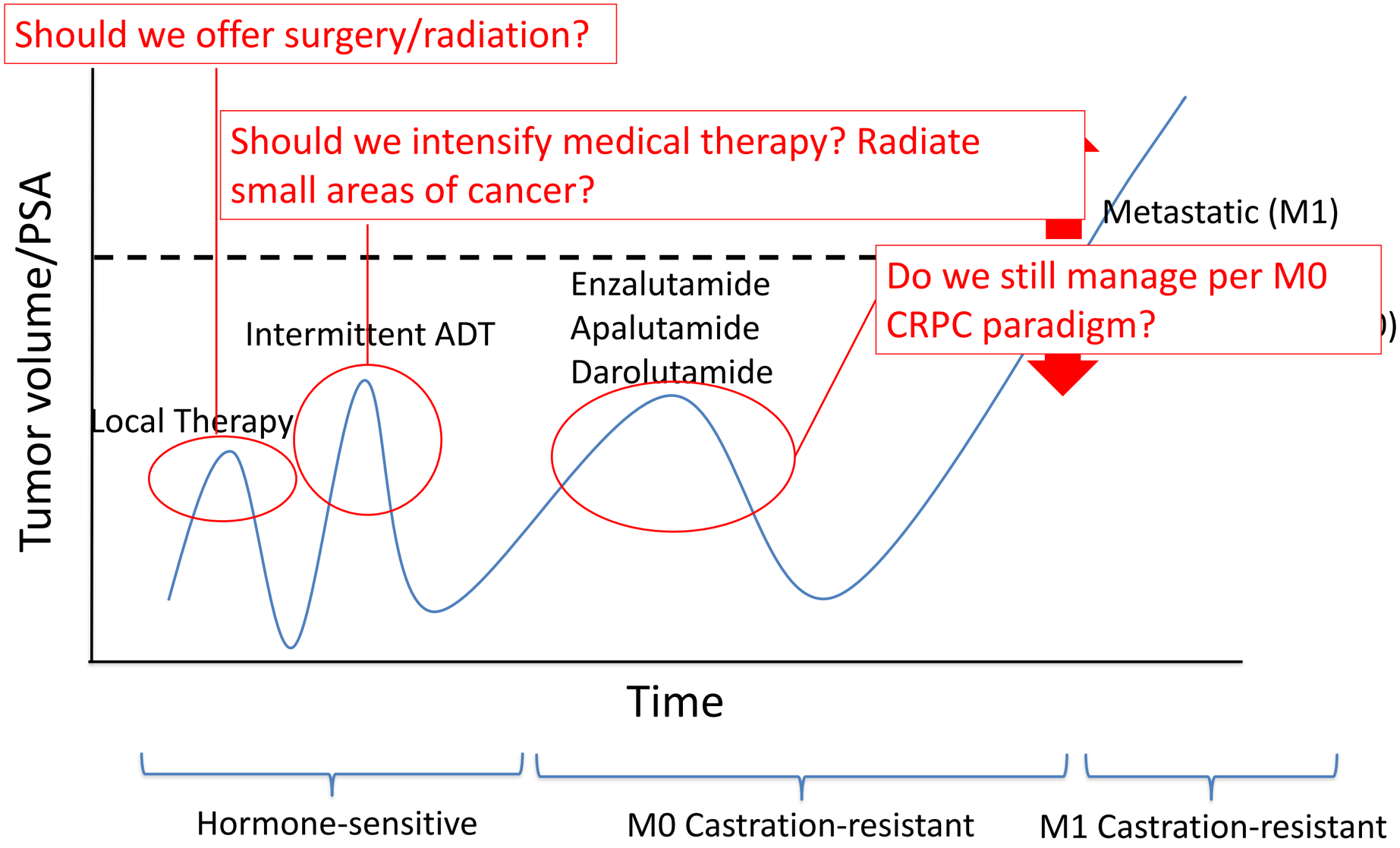
PSMA is a transmembrane carboxypeptidase that is 100-1000x higher expression in cancer compared to normal prostate

PSMA PET has higher AUC for accuracy than conventional imaging: 92% (95% CI: 88-95%) vs. 65% (95% CI: 60-69%)



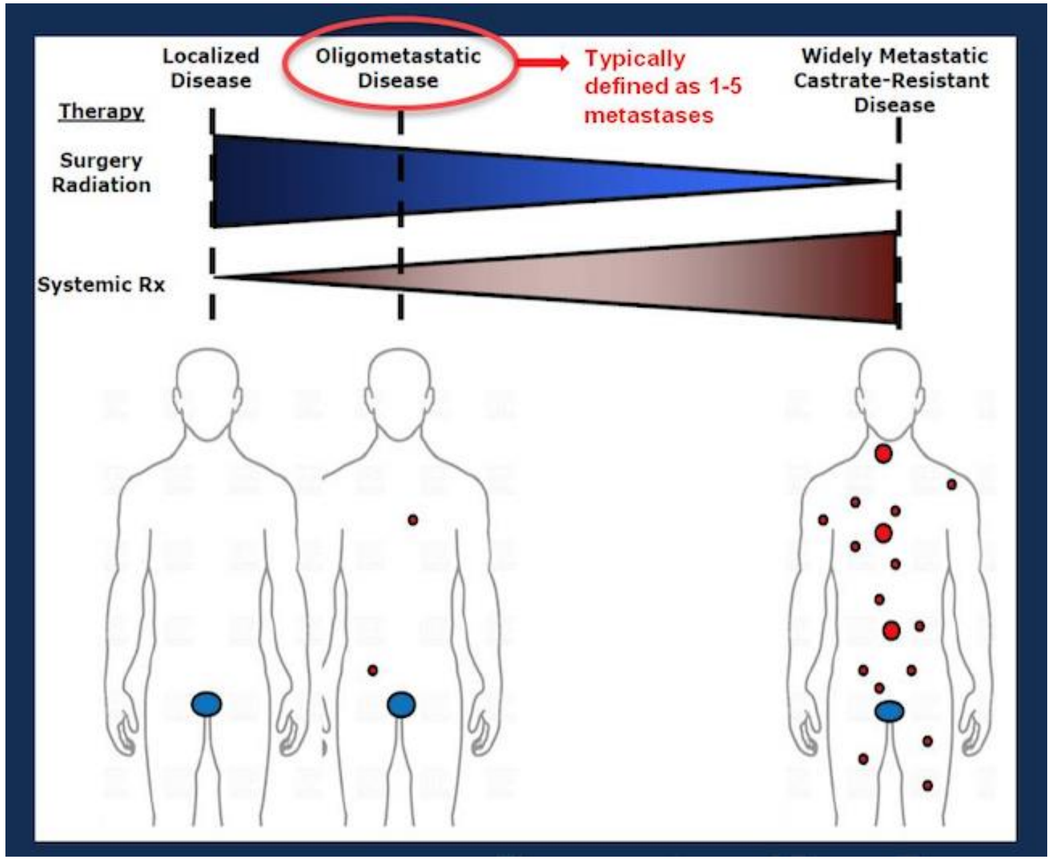
Lawhn-Heath, et al. Radiology 2021; 299:248–260
Eiber et al. J Nucl Med 2015; 56:668–74.
Hofman, et al. Lancet 2020; 395: 1208–16

Best approach for managing low volume metastatic prostate cancer is not clear

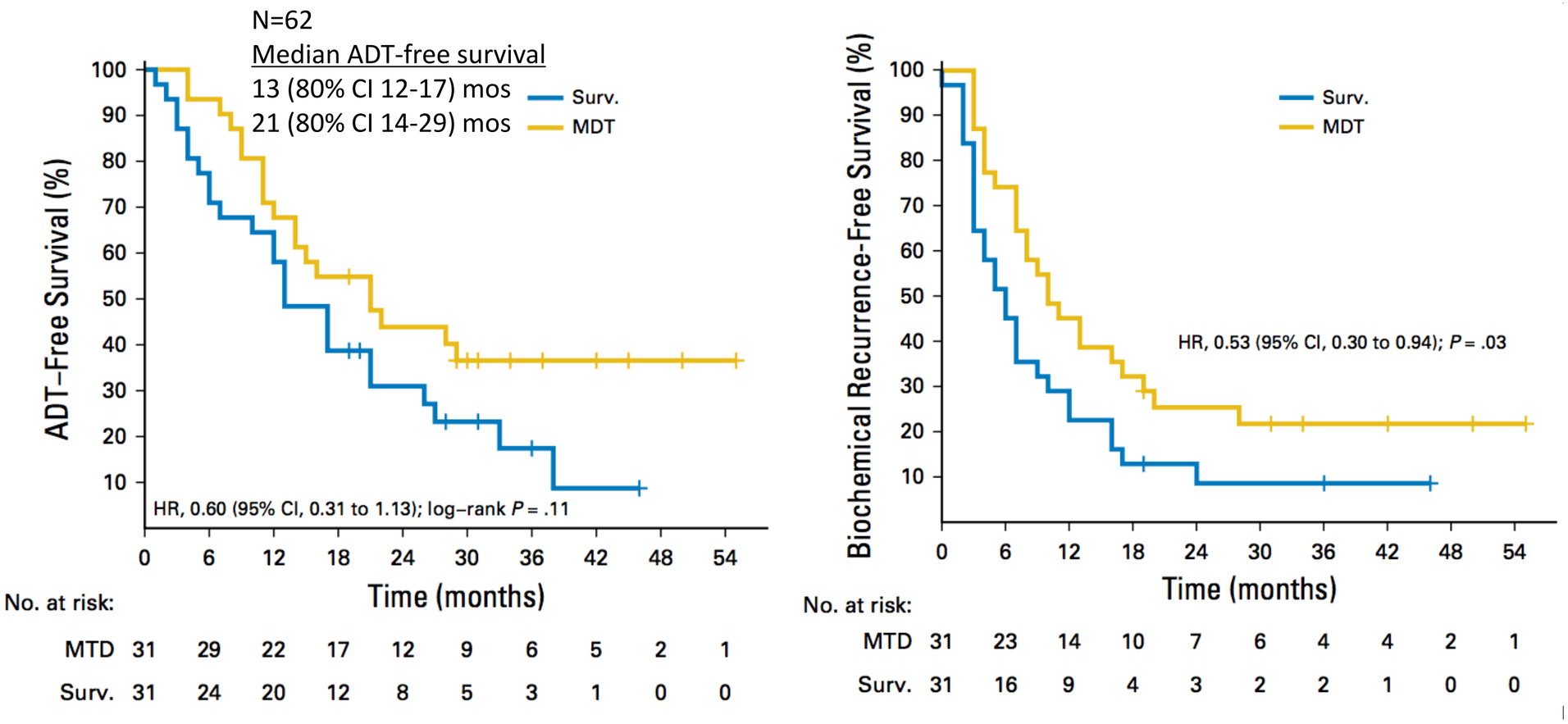


Defining Oligometastatic Disease

- An intermediate state of cancer spread between localized disease and widespread metastases
- Usually defined as 1-3 or 1-5 radiographically-detectable metastatic lesions

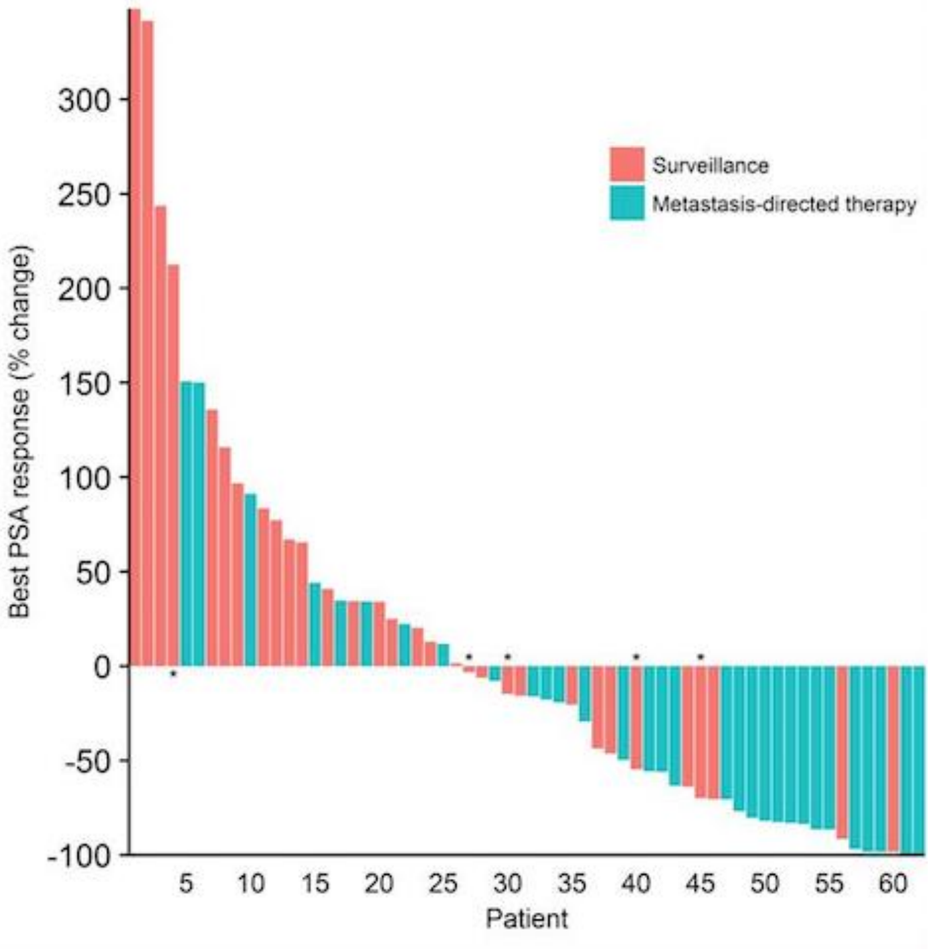


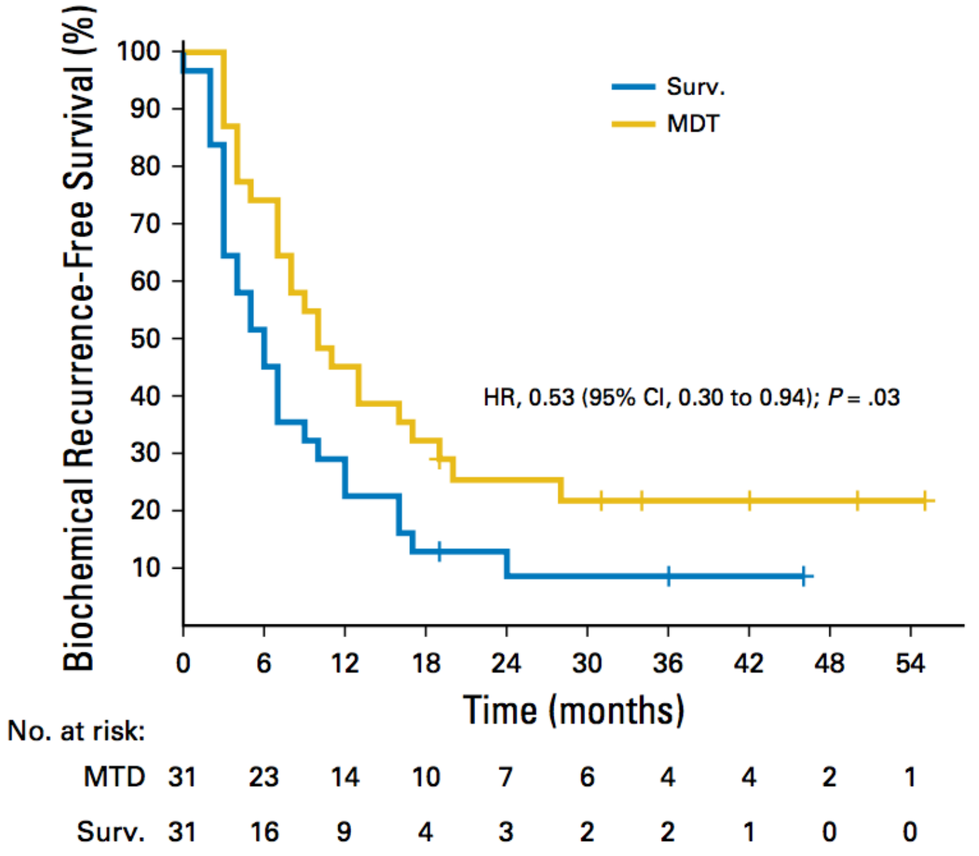
Metastasis-Directed Therapy Identified by Choline PET leads to Improved ADT-free Survival



Ost P et al. J Clin Oncol. 2018; 36:446-53.

PSA and Biochemical Recurrence-Free Survival





Ost P et al. J Clin Oncol. 2018; 36:446-53.

Key Issues to Consider with the Ost Trial

- Was this an objective primary endpoint?
  - Symptomatic progression is questionable
  - Progression using choline PET is not standard
  - Local progression of known metastasis, especially a bone metastasis is not accepted at all in this field
- Both arms observed similar rates of progression to CRPC
- 11/31 (35.4%) patients underwent retreatment with MDT
- How do 35% of patients in surveillance have a PSA decline with no intervention?

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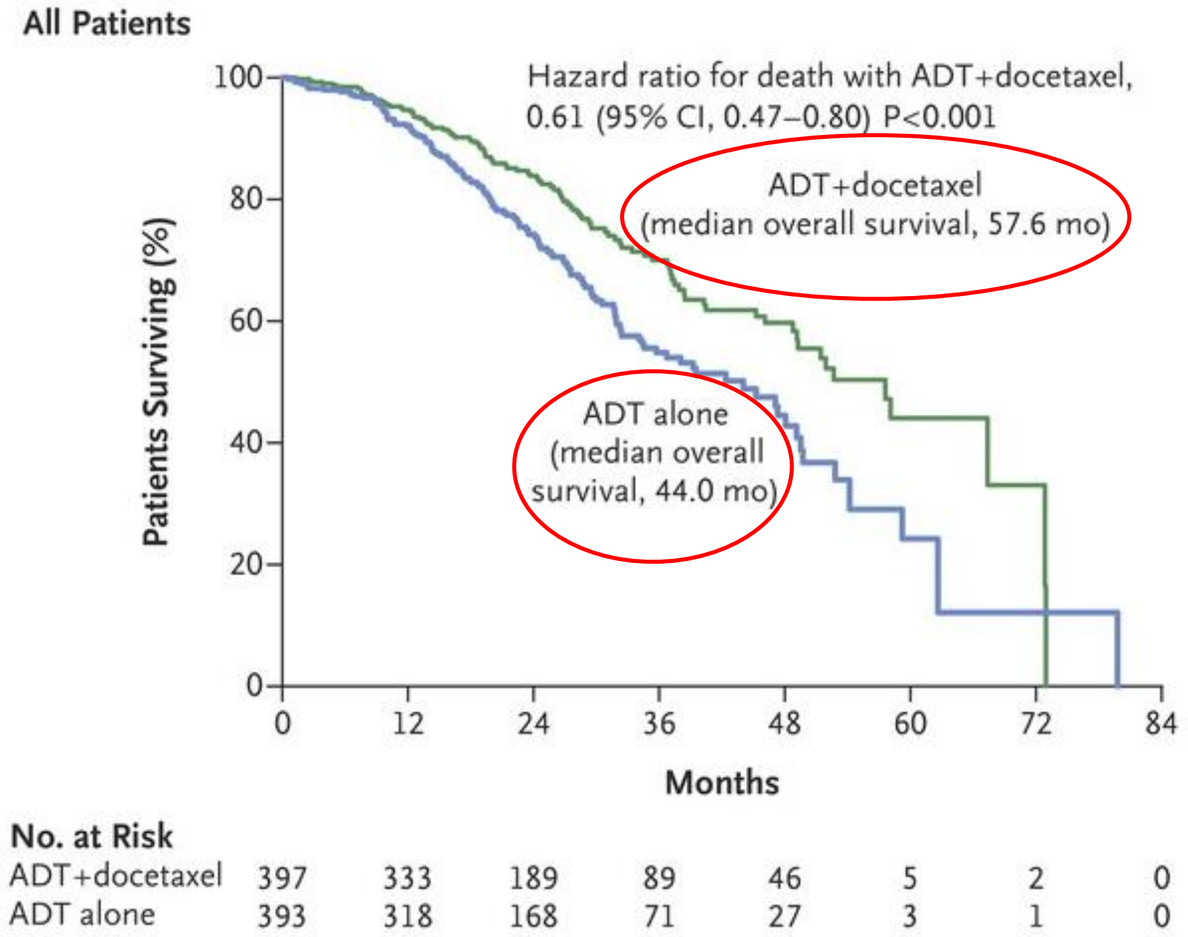
E3805 CHAARTED: ChemoHormonal Therapy vs. Androgen Ablation for Metastatic Prostate Cancer

- N=790 men accrued 07/28/06 - 11/21/12
- Enrollment allowed up to 16 weeks from initiation of ADT

- ADT was initiated a median of 1.1 months prior to enrollment – docetaxel was most certainly layered even later



Sweeney C et al. N Engl J Med 2015; 373:737-46.

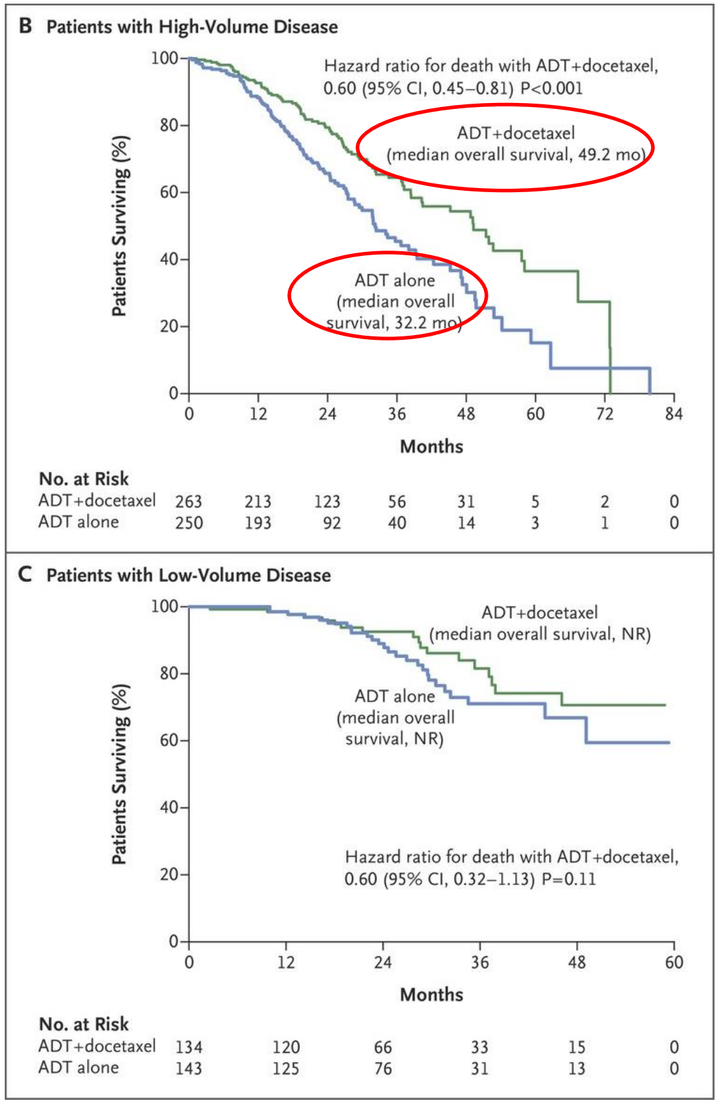
E3805 CHAARTED: ChemoHormonal Therapy vs. Androgen Ablation for Metastatic Prostate Cancer

Overall survival was 17.0 months longer in the combination group in men with high volume disease

≥4 bone lesions *and*
≥1 lesion in any bony structure
beyond the spine/pelvis
OR
visceral disease

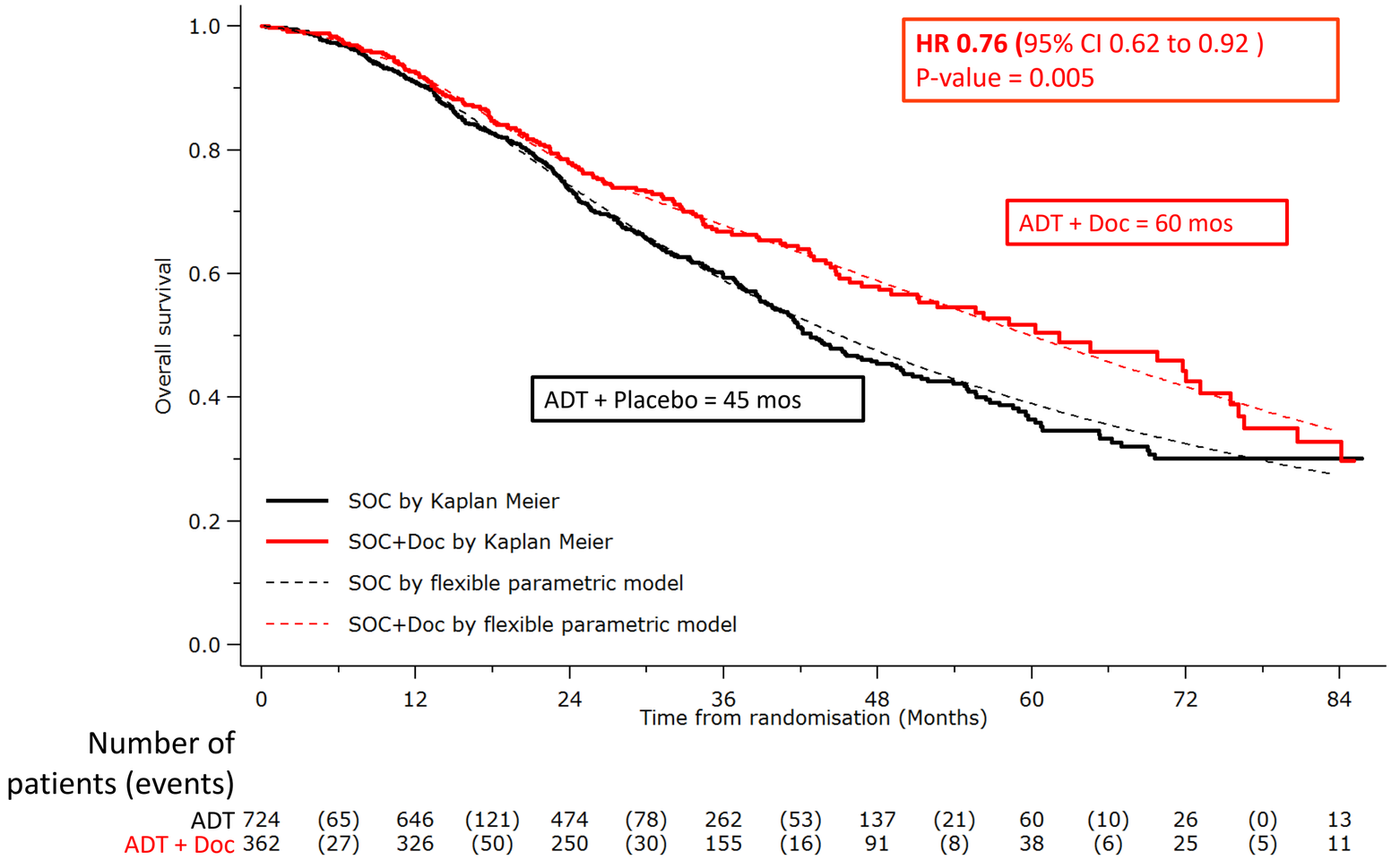
No statistically significant OS was observed between groups in those deemed to have low volume disease (p=0.11)

After a longer follow-up of 54 months, the survival benefit was experienced by only those men who had high volume disease (median 51 months vs. 34 months, HR 0.63, 95% CI 0.50-0.79), and not in those with low volume disease (median 64 months vs. not reached, HR 1.04, 95% CI 0.70-1.55)



Sweeney C et al. N Engl J Med 2015; 373:737-46.

STAMPEDE Overall Survival for Metastatic Patient Population (61% of Trial Population)



Pre-planned subset analysis in patients with metastatic disease

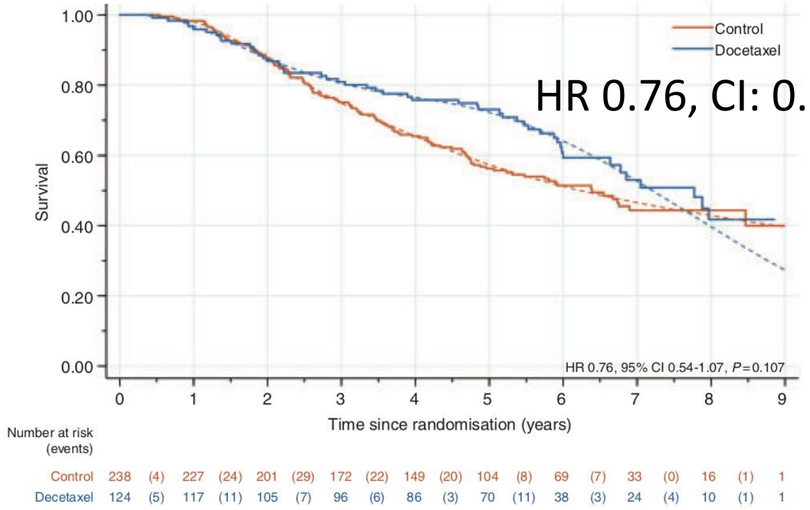
60 months vs. 45 months, HR 0.76, 95% CI 0.62-0.92; p=0.005)

James ND et al. Lancet 2016; 387:1163-77.

Treatment Effect by Metastatic Burden: Docetaxel

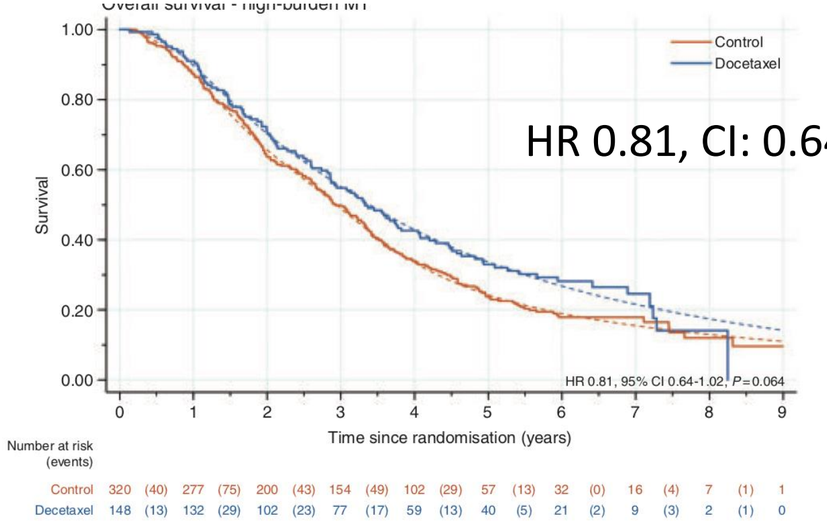
- STAMPEDE: Metastatic burden assessable in 76% of M1 patients
  - Per CHAARTED definition
- No evidence of heterogeneity of docetaxel effect between high vs low metastatic burden subgroups (interaction P = 0.827)
- Underpowered to detect OS benefit in metastatic burden subgroups → no obvious difference in survival
- Significant FFS benefit in both high and low metastatic burden patients

OS: Low metastatic burden



HR 0.76, CI: 0.54-1.07, P=0.107

OS: High metastatic burden



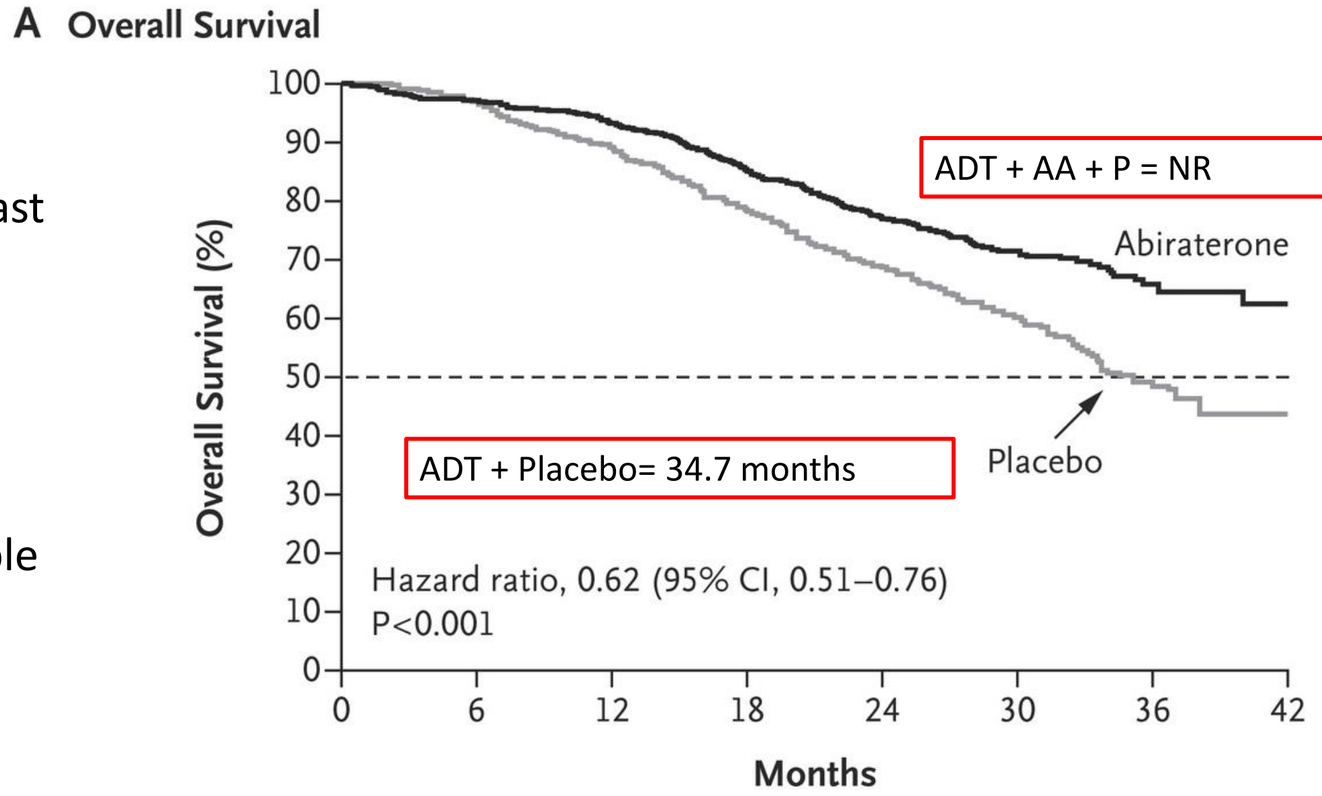
HR 0.81, CI: 0.64-1.02, P=0.064

Clarke NW, et al. Annals Oncol 2019

LATITUDE – Overall Survival with Abiraterone

High risk defined as at least of 2 of 3 criteria:

- Gleason score of 8 or more
- Presence of 3 or more lesions on bone scan
- Presence of measurable visceral lesion



ADT + AA + P = NR

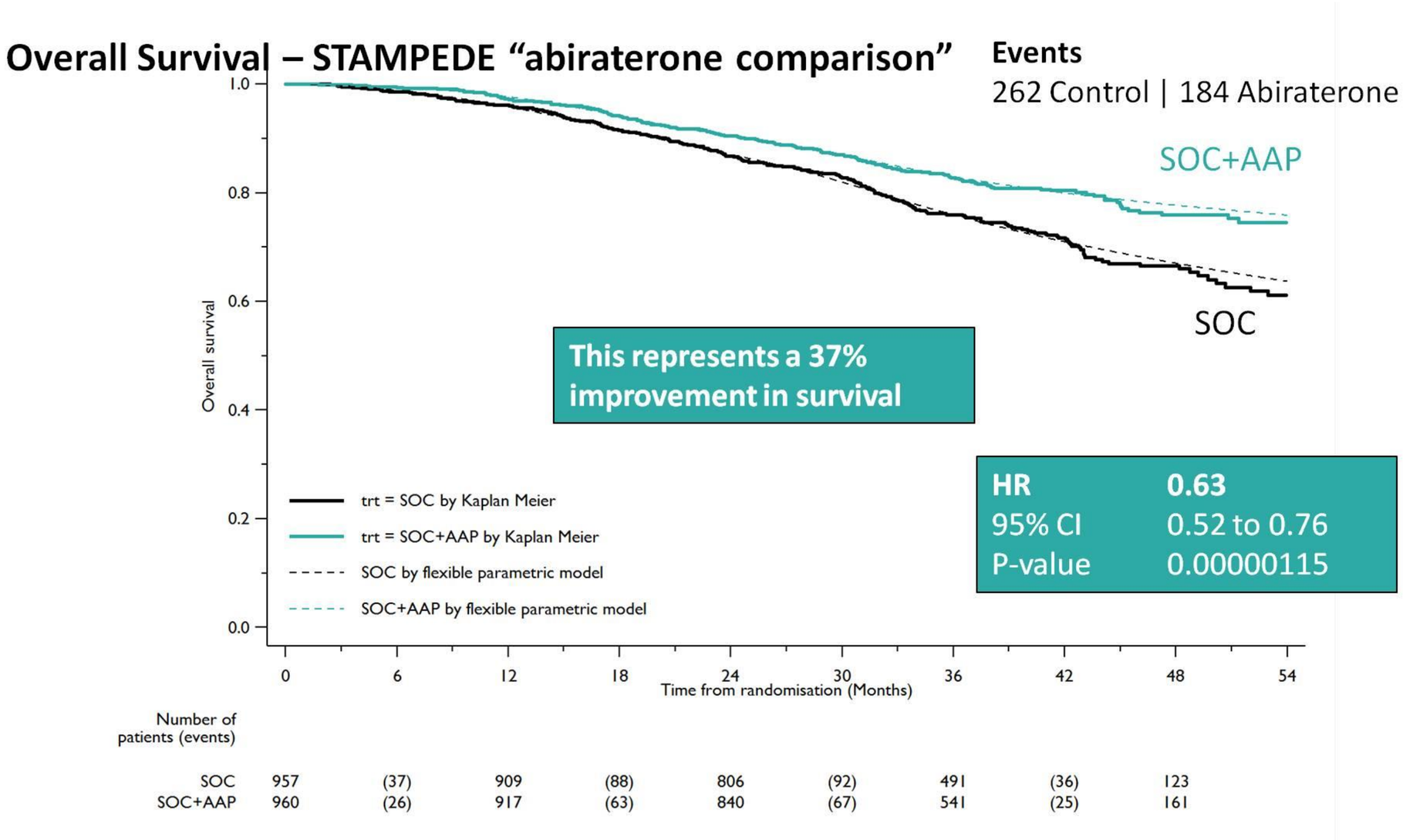
ADT + Placebo= 34.7 months

OS rate at three years:
ADT + AA + P: 66%
ADT + placebos: 49%

Median follow-up: 30.4 months

Fizazi K et al. N Engl J Med 2017; 377:352-60.

STAMPEDE – Overall Survival with Abiraterone

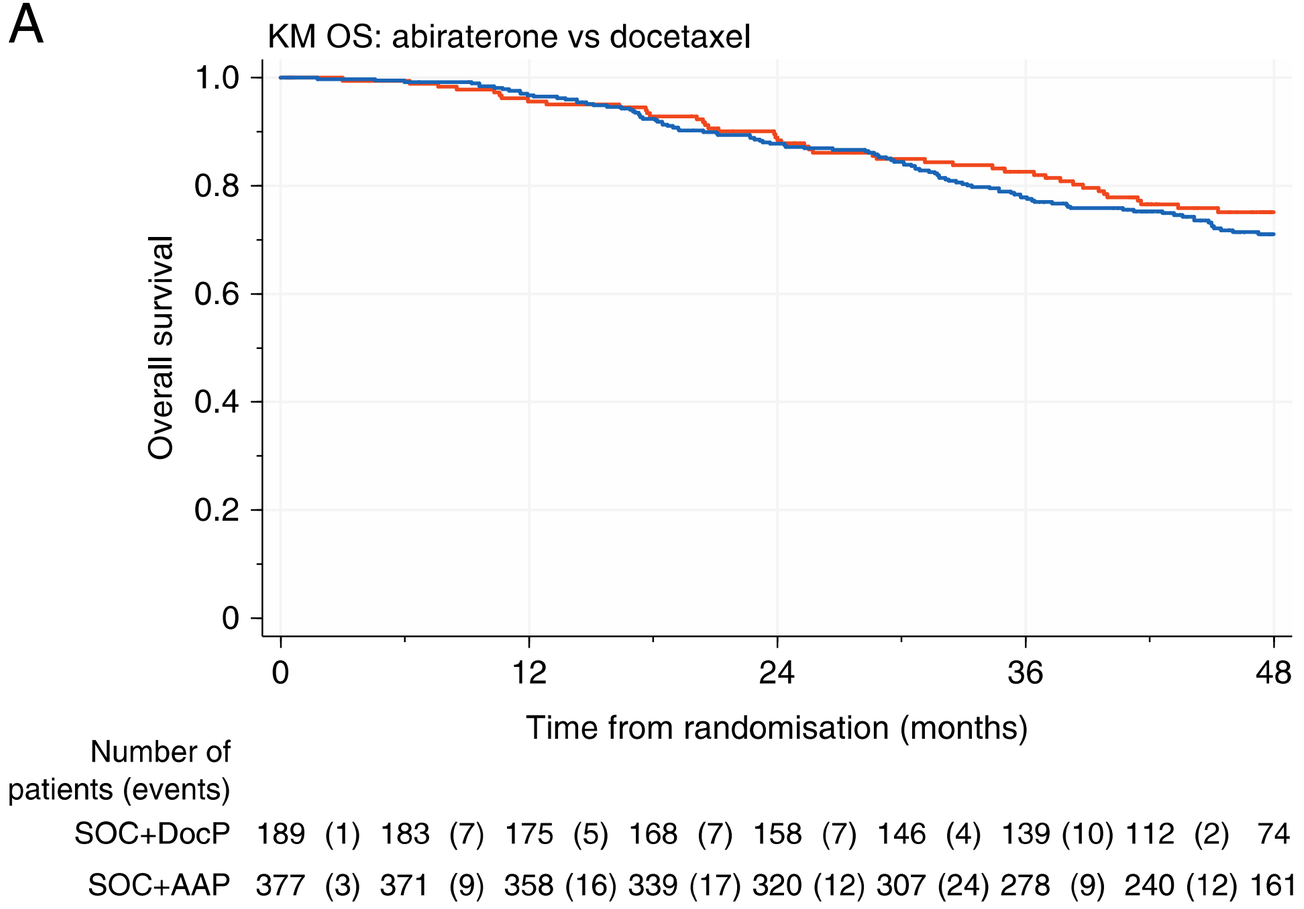


James ND et al. N Engl J Med 2017; 377:338-53.

STAMPEDE – Direct Non-randomized Comparison of Docetaxel with Abiraterone

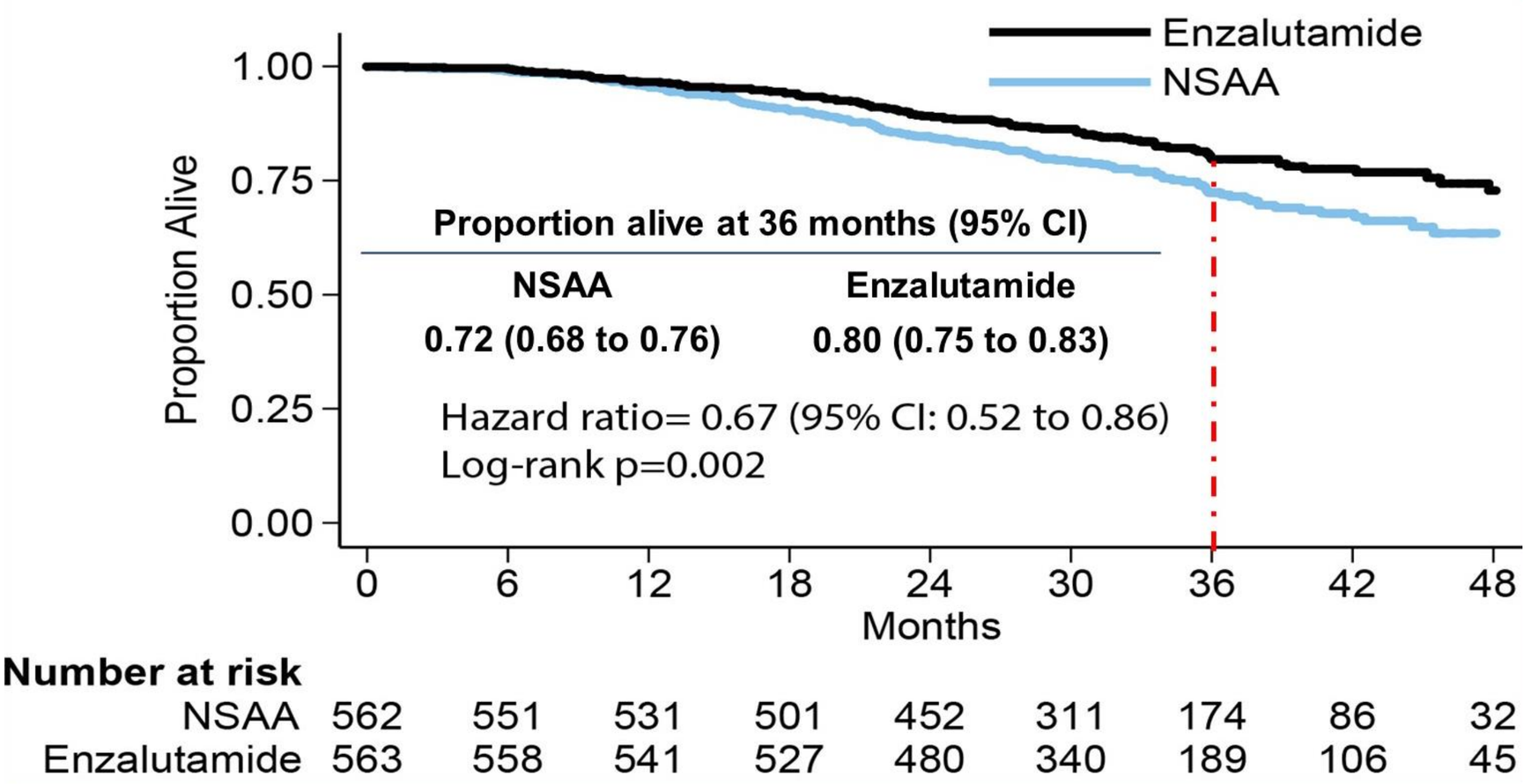
- N=566
- 60% metastatic
- No difference in OS, MFS, cancer-specific survival, or skeletal related events
- PFS (driven by PSA) favored abiraterone

A



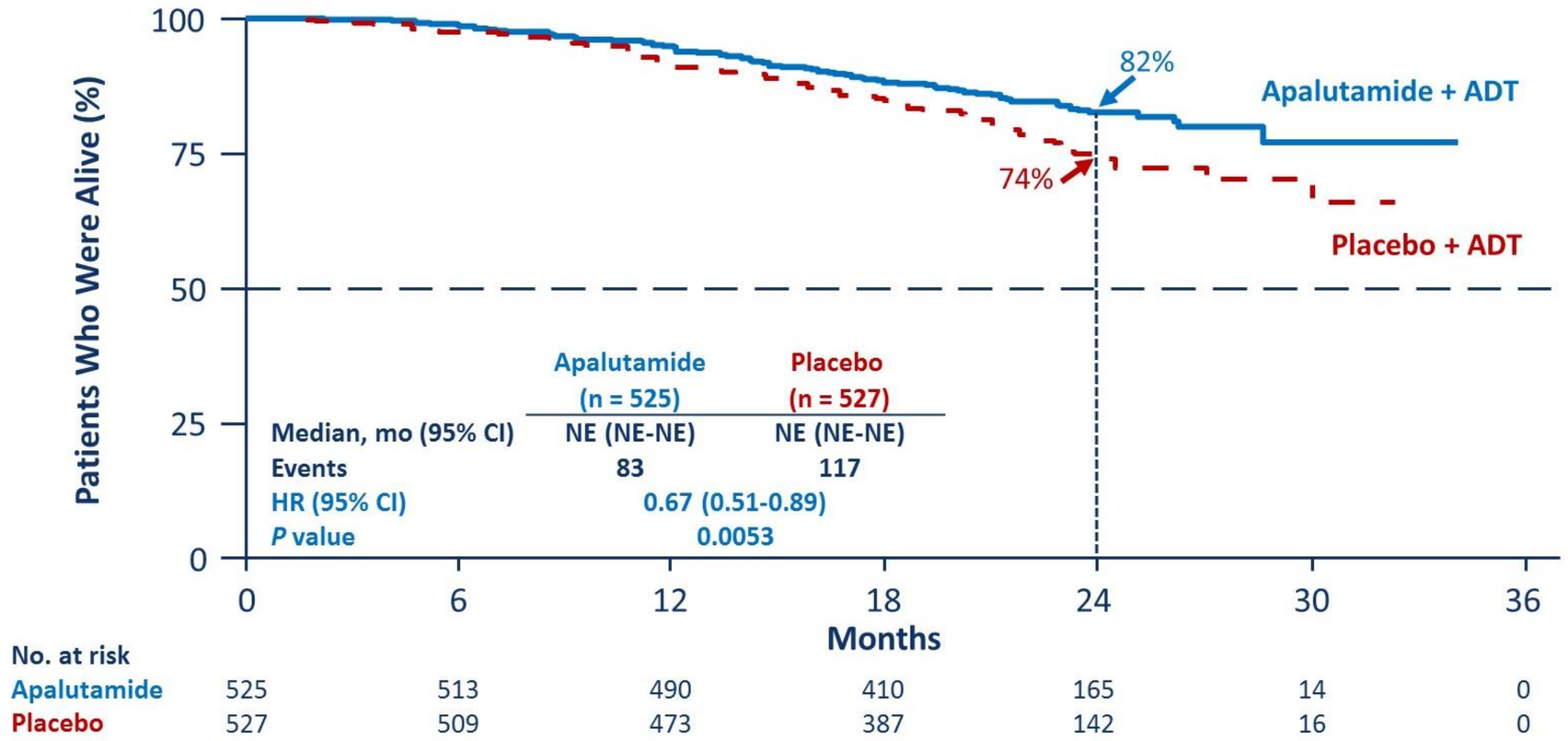
Sydes M et al. Ann Oncol 2018; 29(5):1235–48.

ENZAMET Primary Endpoint: Overall Survival



Davis ID et al. N Engl J Med. Epub June 2, 2019.

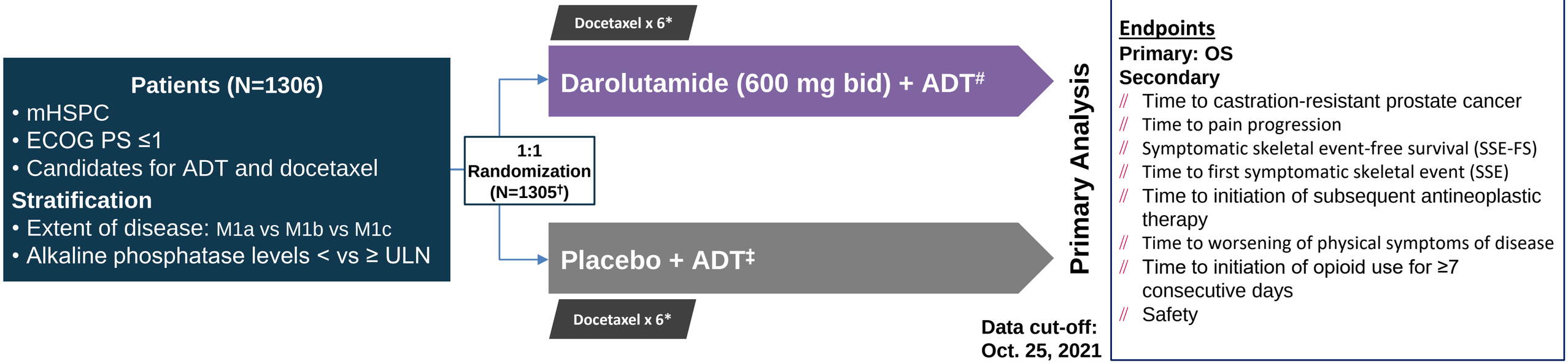
TITAN: Apalutamide in mHSPC



11% of patients received prior docetaxel

Chi KN et al. N Engl J Med. Epub May 31, 2019.

ARASENS Trial Design



*Starting ≤6 weeks after start of study drug at 75 mg/m^2 / 3 weeks, 6 cycles (in combination with prednisone/prednisolone at the discretion of the investigator).
#Investigators' choice (including orchiectomy) starting ≤12 weeks before randomization

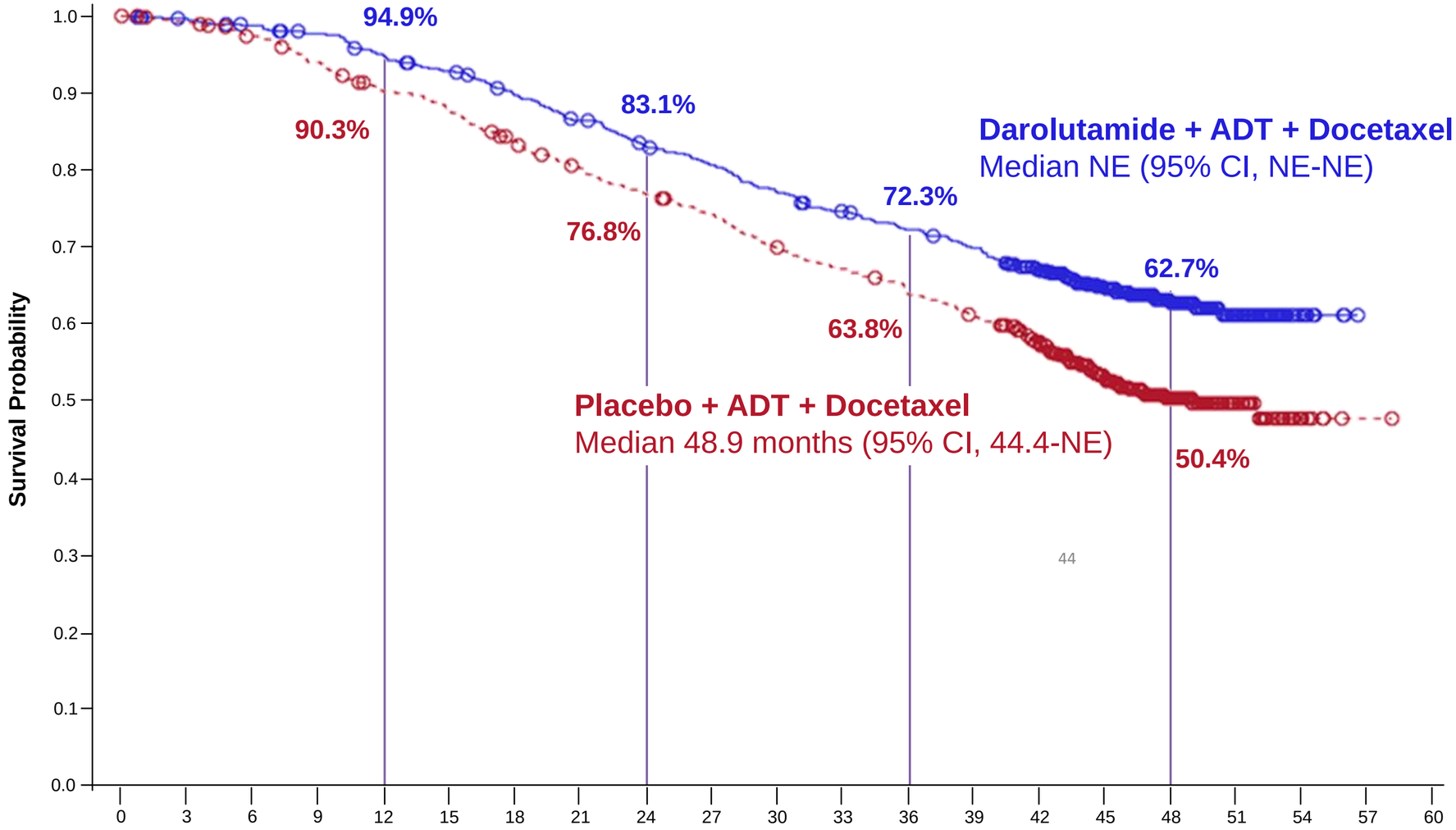
Smith M, et al. *N Engl J Med*. 2022; DOI: 10.1056/NEJMoa2119115.

Key Clinical Characteristics at Baseline

Characteristic	Darolutamide–ADT– Docetaxel (N=651)†	Placebo–ADT– Docetaxel (N=654)†
Gleason score at initial diagnosis — no. (%)‖		
<8	122 (18.7%)	118 (18%)
≥8	505 (77.6%)	516 (78.9%
Data missing	24 (3.7%)	20 (3.1%)
Metastasis stage at initial diagnosis — no. (%)		
M1, distant metastasis	558 (85.7%)	566 (86.5%)
M0, no distant metastasis	86 (13.2%)	82 (12.5%)
MX, distant metastasis not assessed	7 (1.1%)	6 (0.9%)
Metastasis stage at screening — no. (%)		
M1a, nonregional lymph-node metastases only	23 (3.5%)	16 (2.4%)
M1b, bone metastases with or without lymph-node metastases	517 (79.4%)	520 (79.5%)
M1c, visceral metastases with or without lymph-node or bone metastases	111 (17.1%)	118 (18.0%)
Median serum PSA level (range) — ng/ml**	30.3 (0.0–9219.0)	24.2 (0.0–11,947.0)
Median serum ALP level (range) — U/liter**	148 (40–4885)	140 (36–7680)
ALP category — no. (%)**		
<ULN	290 (44.5%)	291 (44.5%)
≥ULN	361 (55.5%)	363 (55.5%)

Smith M, et al. *N Engl J Med*. 2022; DOI: 10.1056/NEJMoa2119115.

ARASENS Overall Survival



Hazard ratio for overall survival, 0.675 (95% CI, 0.568-0.801) *P*<0.001[2]

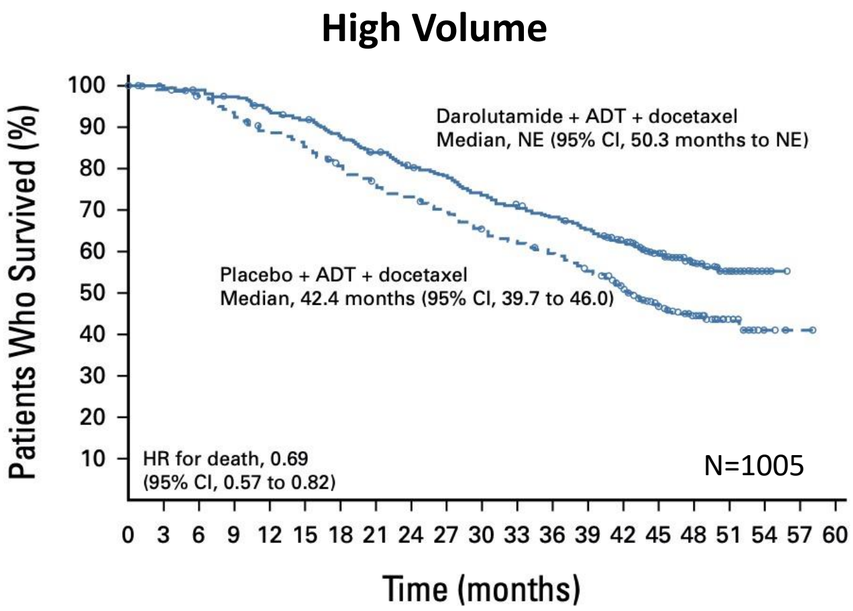
Number of patients at risk

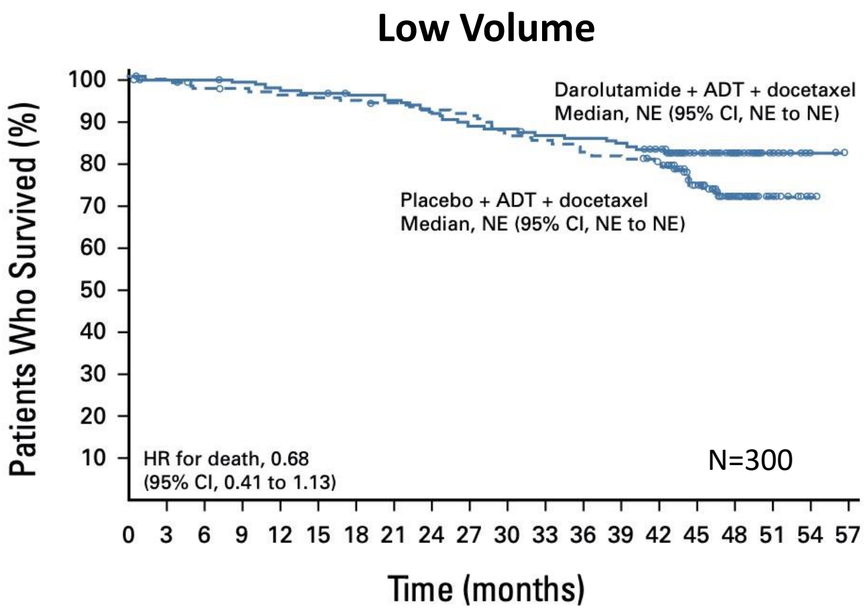
Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

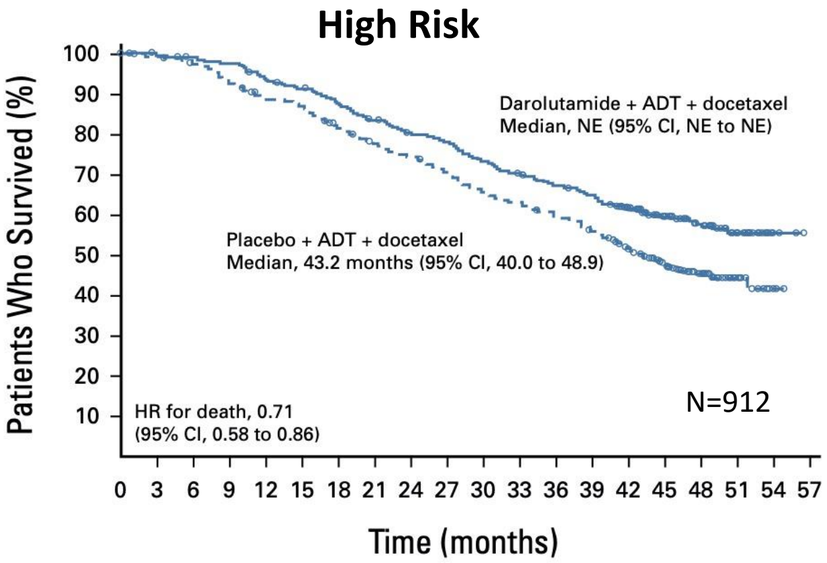
NE, not estimable; CI, confidence interval

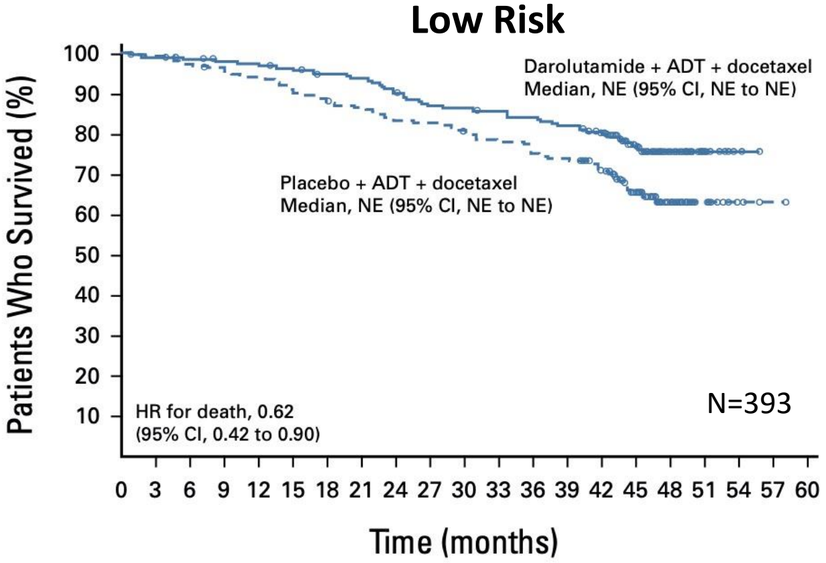
Smith M, et al. *N Engl J Med*. 2022; DOI: 10.1056/NEJMoa2119115.

ARASENS OS by Disease Volume and Risk









Hussain, et al. J Clin Oncol. 2023 Jul 10;41(20):3595-3607.

Adverse Events of Interest

Adverse Event	Darolutamide + ADT + Docetaxel (N=652) No. of patients (%)	Placebo + ADT + Docetaxel (N=650) No. of patients (%)
Events commonly associated with ADT or ARPI therapy		
Fatigue	216 (33.1)	214 (32.9)
Vasodilatation and flushing	133 (20.4)	141 (21.7)
Rash*	108 (16.6)	88 (13.5)
Diabetes mellitus and hyperglycemia	99 (15.2)	93 (14.3)
Hypertension†	89 (13.7)	60 (9.2)
Cardiac disorder	71 (10.9)	76 (11.7)
Cardiac arrhythmia†	52 (8.0)	55 (8.5)
Coronary artery disorder†	19 (2.9)	13 (2.0)
Heart failure†	4 (0.6)	13 (2.0)
Bone fracture‡	49 (7.5)	33 (5.1)
Falls, including accident	43 (6.6)	30 (4.6)
Mental-impairment disorder†	23 (3.5)	15 (2.3)
Weight decreased	22 (3.4)	35 (5.4)
Depressed-mood disorder†	21 (3.2)	24 (3.7)
Breast disorders/gynecomastia†	21 (3.2)	10 (1.5)
Cerebral ischemia	8 (1.2)	8 (1.2)
Seizure	4 (0.6)	1 (0.2)

Incidences of rash and hypertension were higher in the darolutamide arm than in the placebo arm.

Smith M, et al. *N Engl J Med*. 2022;
DOI: 10.1056/NEJMoa2119115.

PEACE-1 Trial Design

PEACE-1: A phase 3 trial with 2x2 factorial design in *de novo* mHSPC patients

Key Eligibility Criteria
- *De novo* mHSPC
- Distant metastatic disease by ≥1 lesion on bone scan and/or CT scan

On-Study Requirement
- Continuous ADT

Permitted
- ADT ≤3 months

Stratification
- ECOG PS (0 vs 1-2)
- Metastatic sites (LN vs bone vs visceral)
- Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
- Docetaxel (yes vs no)

Nov 2013 – Dec 2018

R
1:1:1:1
(n=1173)

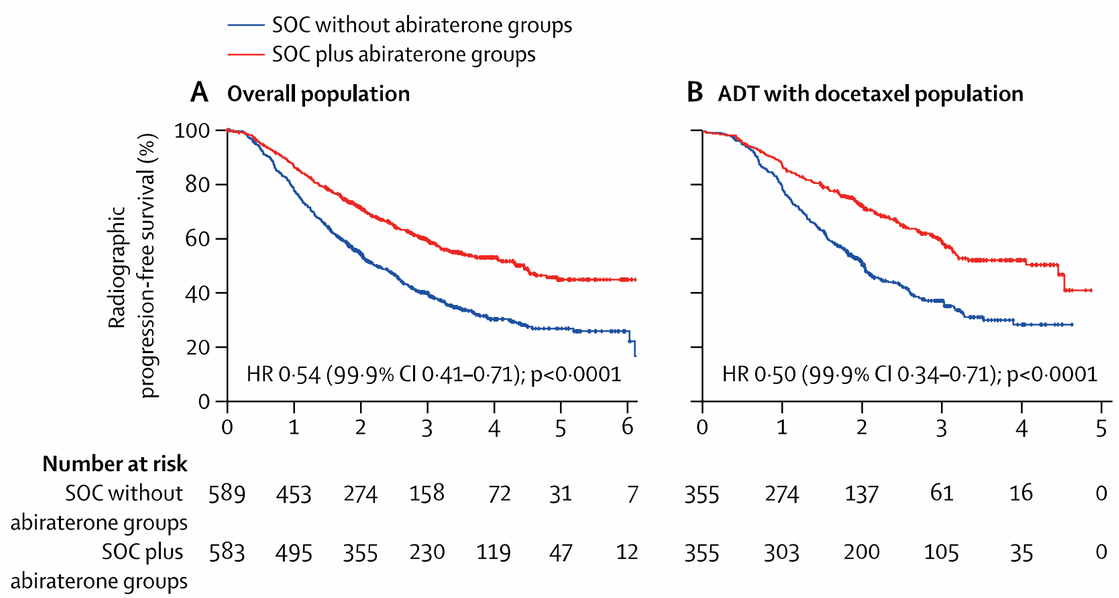
- **SOC (n=296)**
- **SOC + Abiraterone (n=292)**
- **SOC + Radiotherapy (n=293)**
- **SOC + Abiraterone + Radiotherapy (n=292)**

- Co-primary endpoints: rPFS and OS
- Amended midway to allow docetaxel as part of SOC and to revise primary objectives: **i) assess effect of abiraterone in combo with docetaxel**, ii) assess effect of radiation in patients with low metastatic burden
- Sample size increase 916 to 1173

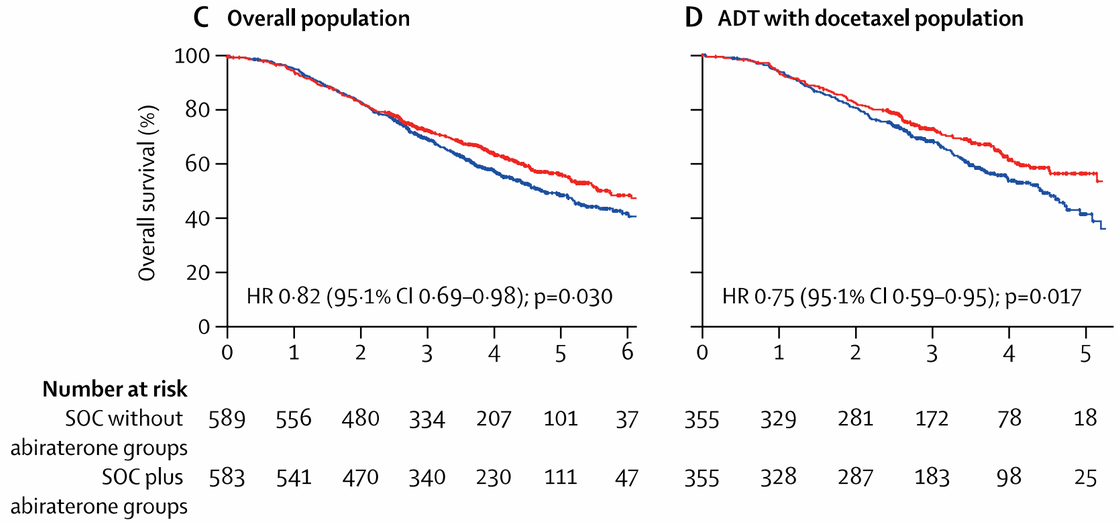
Fizazi K et al. LBA5. ESMO 2021.
Fizazi, et al. Lancet 2022

PEACE-1 Trial – Overall Survival for the Entire Population

PFS



OS



- 60.5% received docetaxel as SOC
- No interaction between abiraterone and radiation → allowed them to evaluate docetaxel vs. abi + docetaxel
- 25% reduction in the risk of death when docetaxel added

Fizazi K et al. LBA5. ESMO 2021.
Fizazi, et al. Lancet 2022

What should we do with mHSPC after all this?

- All patients with metastatic prostate cancer should have some form of treatment intensification
- Adding darolutamide (or abiraterone) to ADT + docetaxel leads to a significant overall survival benefit
  - Additional analyses/follow up needed to define groups that may benefit the most are still needed
- Novel hormonal agent (NHA) still reasonable in those with lower risk prostate cancer or who cannot tolerate chemotherapy

Outline

- Background
- Local therapies
- Non-metastatic recurrent prostate cancer
- Metastatic hormone-sensitive prostate cancer
- Metastatic castration-resistant cancer

Phase 3 Overall Survival Trial Results in mCRPC

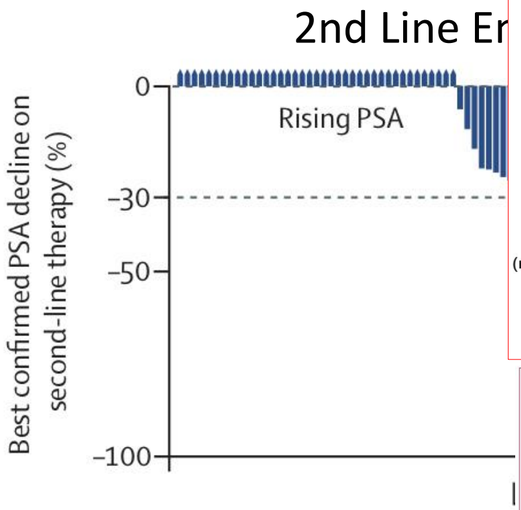
Therapy	Prior Docetaxel	Comparator	HR	*P*
Sipuleucel-T	Mostly No	Placebo	0.775	.032
Docetaxel	No	Mitoxantrone	0.76	.009
Cabazitaxel	Yes	Mitoxantrone	0.70	< .0001
Abiraterone/ Prednisone	No	Prednisone	0.81	.0033
	Yes	Prednisone	0.646	< .0001
Enzalutamide	No	Placebo	0.706	< .001
	Yes	Placebo	0.631	< .001
Radium-223	Slightly over Half	Placebo	0.70	.002
177Lu-PSMA617	Yes	SOC	0.62	<0.001
	No	Abi/Enza	1.16	NS
Olaparib	No	Abi/Enza	0.69	0.02
Rucaparib	No	Abi/Enza/Doce	0.81	NS
Olaparib + abiraterone	No	Abiraterone	0.81	NS
Talazoparib + enzalutamide	No	Enzalutamide	0.89	NS
Niraparib + abiraterone	No	Abiraterone	0.77	NS

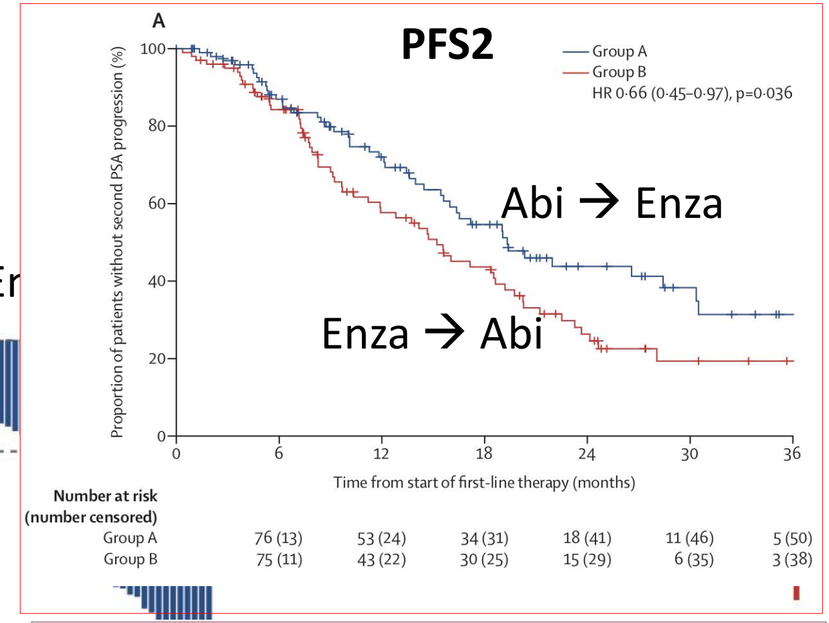
de Bono, et al. NEJM 2011
de Bono, et al. NEJM 2010
Kantoff, et al. NEJM 2010
Tannock, et al. NEJM 2004
Scher, et al. NEJM 2012
Beer, et al. NEJM 2014
Ryan, et al. NEJM 2013
Fizazi, et al. NEJM 2023
Sartor, et al. NEJM 2021
Sartor, et al. ESMO Congress 2023
Parker, et al. NEJM 2013
Hussain, et al. NEJM 2020
Agarwal, et al. Lancet 2023
Chi, et al. JCO 2023
Clarke, et al. NEJM Ev Conn 2022

Phase 2 Abi vs Enza Crossover trial

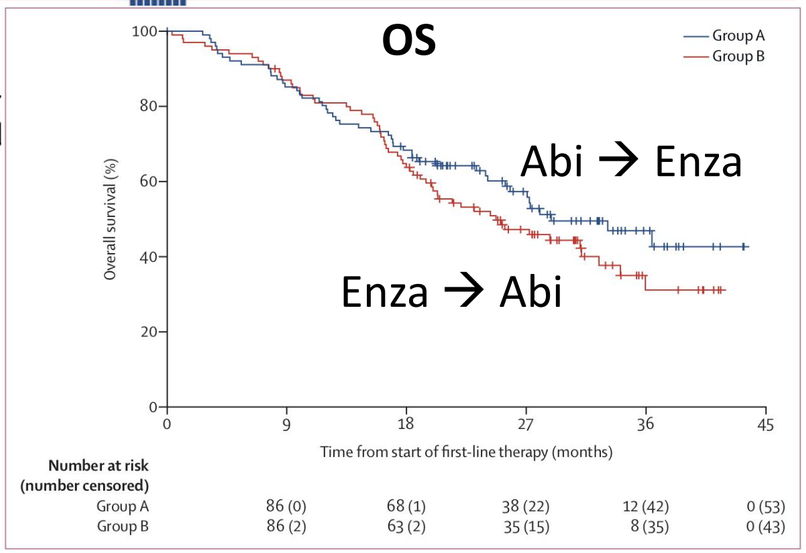
- Enrolled men (N=202) with mCRPC
- Tested: Abi→Enza vs. Enza→Abi
- Co-primary endpoint:
  - PFS2 (time to second PSA progression)
  - PSA response (≥30% PSA decline) on 2nd line treatment

Median PFS2: 19.3 mos vs 15.2 mos, P=0.036





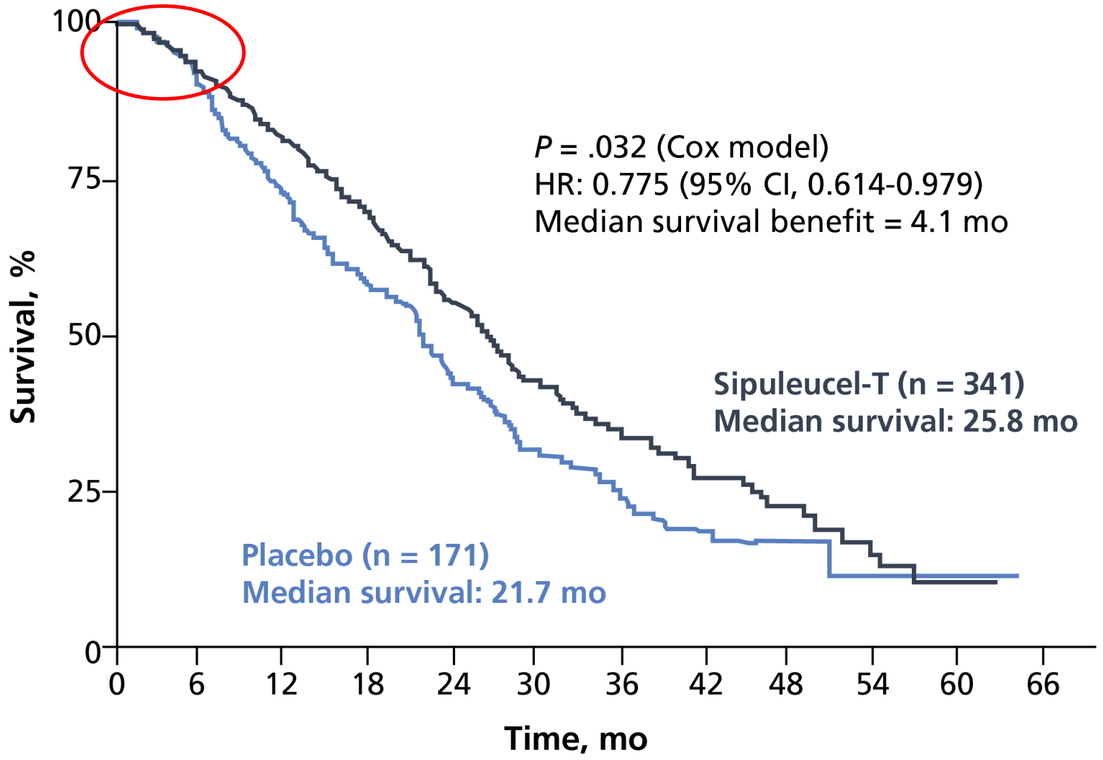
Median OS: 28.8 mos vs 24.7 mos, P=0.23



Khalaf, et al. Lancet Oncology 2019

Sipuleucel-T

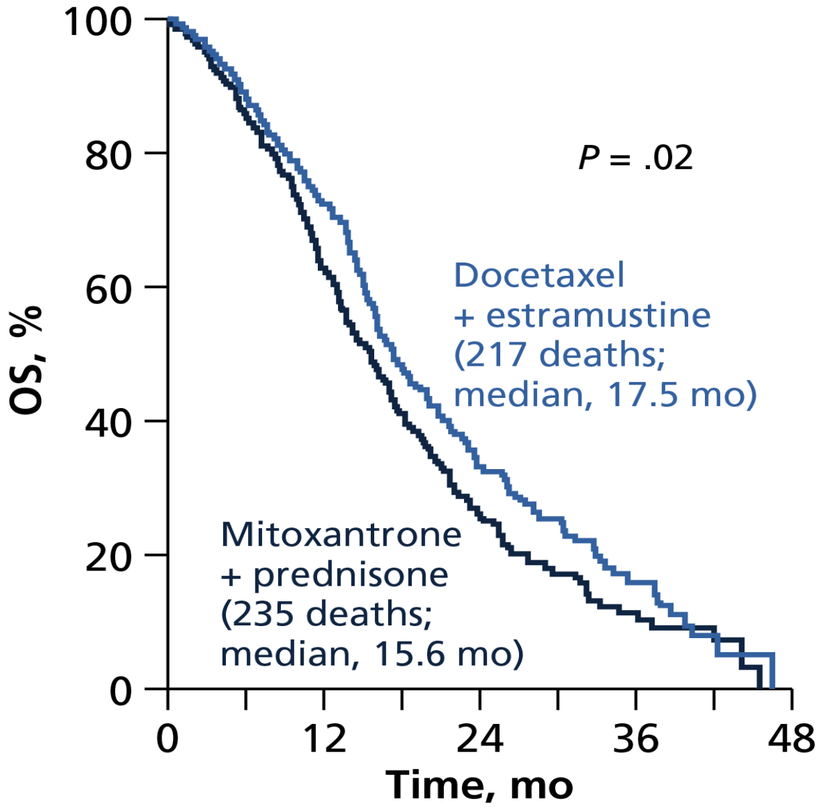
- **Must have asymptomatic metastatic castration-resistant prostate cancer**
- Short window of opportunity
  - Survival curves don't split until the 6-month time point → should have reasonably indolent disease
- Typically, do not see objective responses
  - Only 1-3% with a significant PSA decline
- No improvement in PFS
- Infusion reaction are common and transient



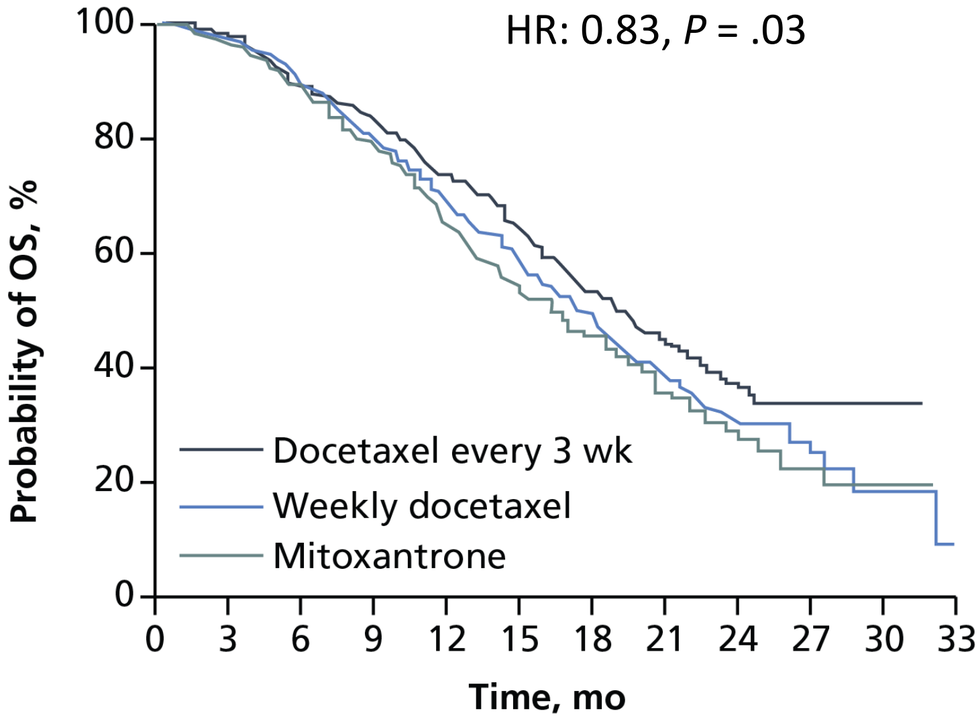
Kantoff PW et al. *N Engl J Med.* 2010; 363:411-22.

Docetaxel – First Drug to Improve OS in mCRPC

SWOG 99-16[1]



TAX-327[2]



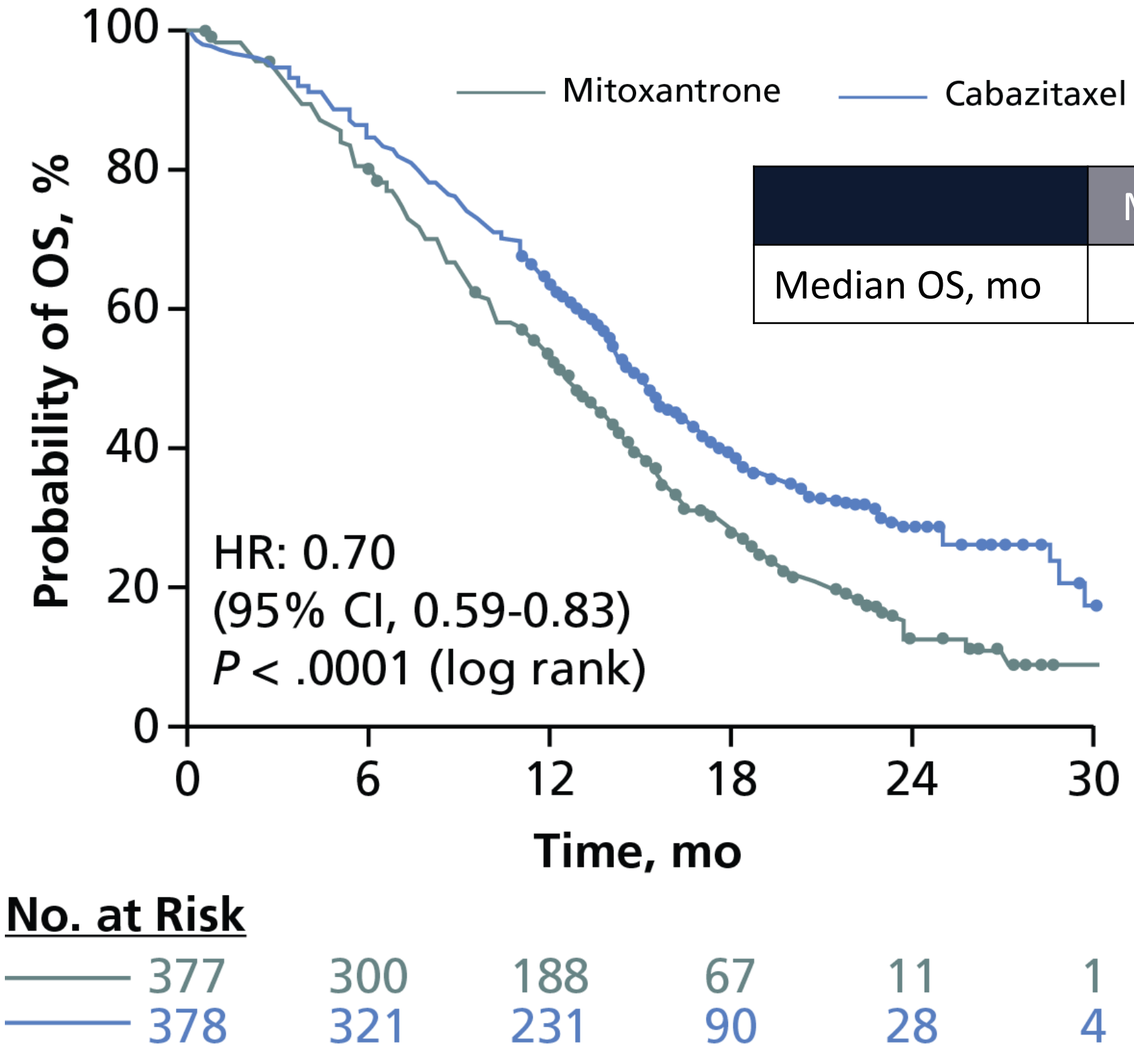
1. Petrylak DP et al. *N Engl J Med.* 2004;351:1513-1520.
2. Tannock IF et al. *N Engl J Med*. 2004;351:1502-1512.

TAX 327: Docetaxel Adverse Events

Table 4. Adverse Events of Any Grade, or of Grade 3 or 4, That Occurred or Worsened during Treatment.

Adverse Event	Docetaxel Every 3 Wk (N=332)	Weekly Docetaxel (N=330)	Mitoxantrone Every 3 Wk (N=335)
		percent	
Grade 3 or 4 anemia	5	5	2
Grade 3 or 4 thrombocytopenia	1	0	1
Grade 3 or 4 neutropenia	32*	2†	22
Febrile neutropenia	3	0	2
Impaired LVEF‡	10†	8†	22
Major decrease	1†	2*	7
Fatigue	53†	49†	35
Grade 3 or 4	5	5	5
Alopecia	65†	50†	13
Nausea, vomiting, or both	42	41	38
Diarrhea	32†	34†	10
Nail changes	30†	37†	7
Sensory neuropathy	30†	24†	7
Anorexia	17	21*	14
Change in taste	18†	24†	7
Stomatitis	20†	17†	8
Myalgia	14	14	13
Dyspnea	15*	14*	9
Tearing	10†	21†	1
Peripheral edema	19†	12†	1
Epistaxis	6	17†	2
≥1 Serious adverse event	26	29	20
Treatment-related death	0.3	0.3	1

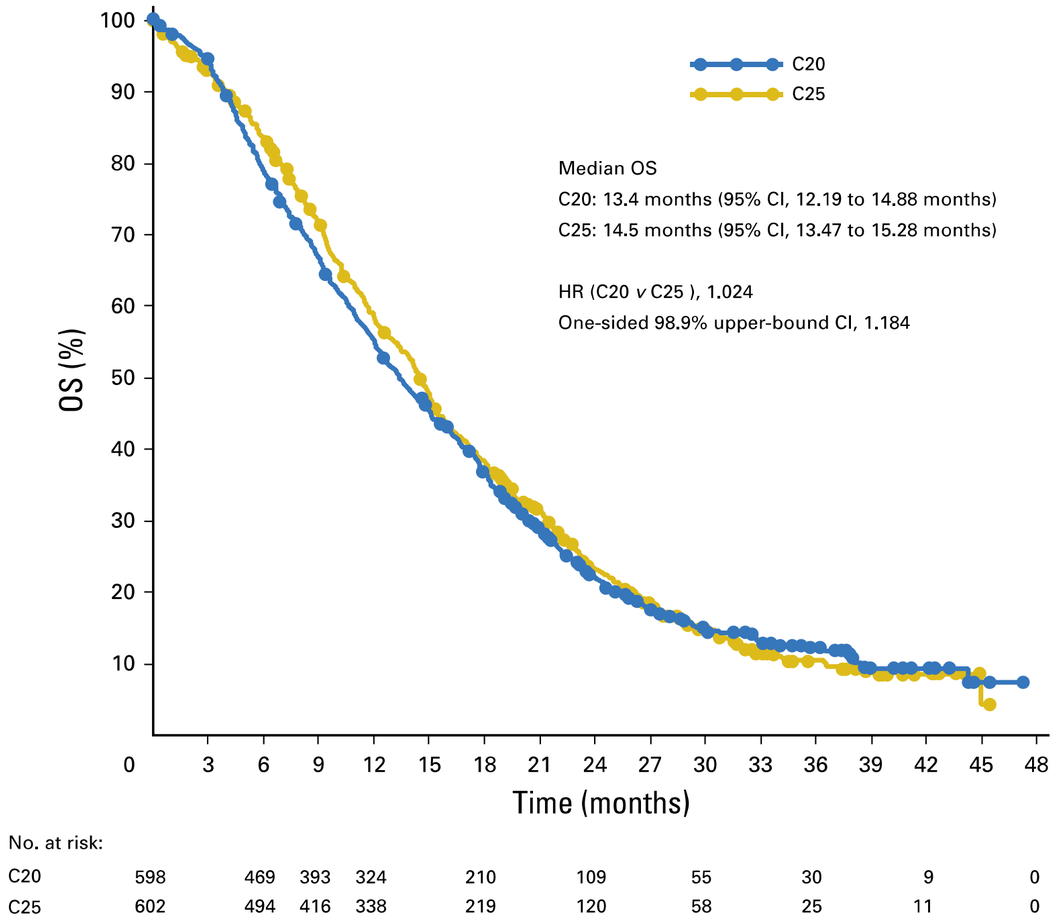
TROPIC Trial: Cabazitaxel after docetaxel

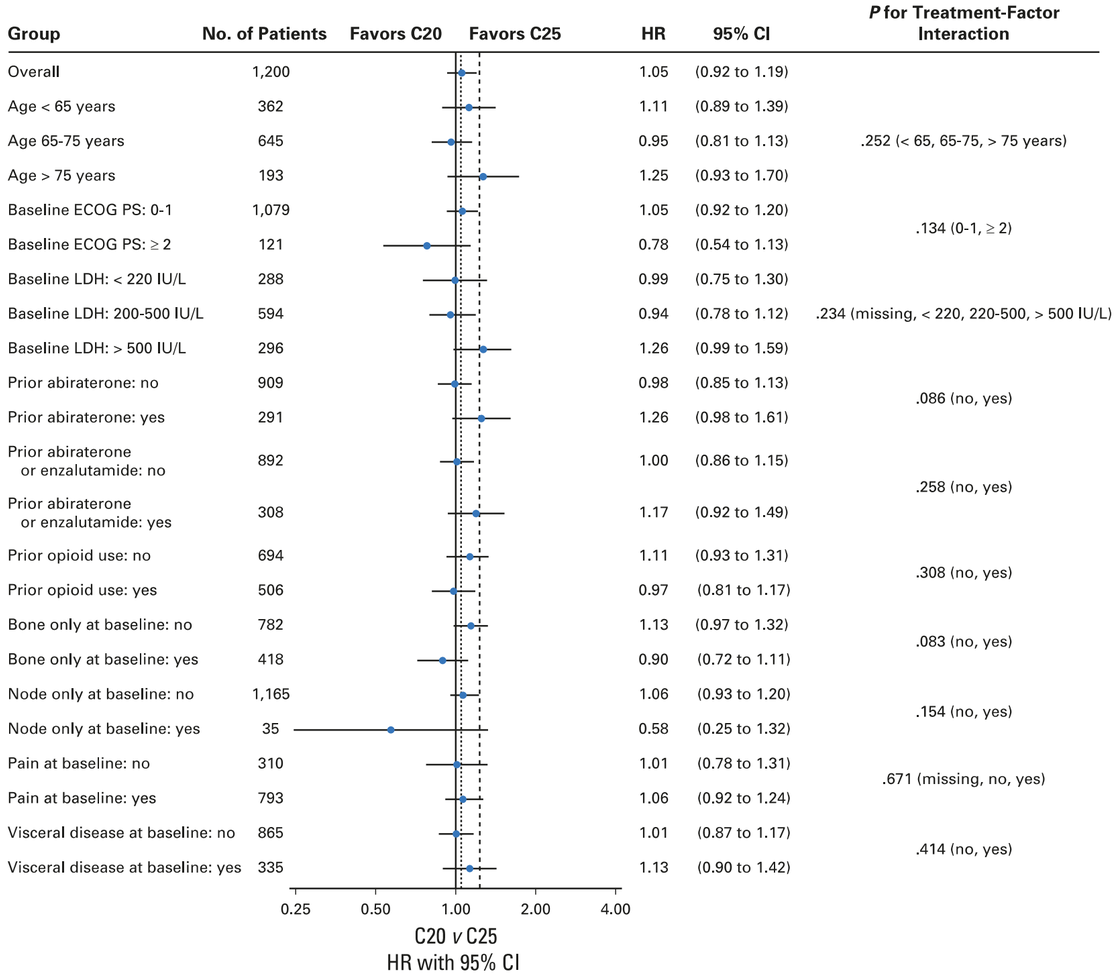


	Mitoxantrone	Cabazitaxel
Median OS, mo	12.7	15.1

De Bono J et al. *Lancet.* 2010; 376:1147-1154.

The PROSELICA Study: low vs high dose cabazitaxel





Eisenberger, et al. J Clin Oncol 35:3198-3206

The PROSELICA Study – Adverse Events

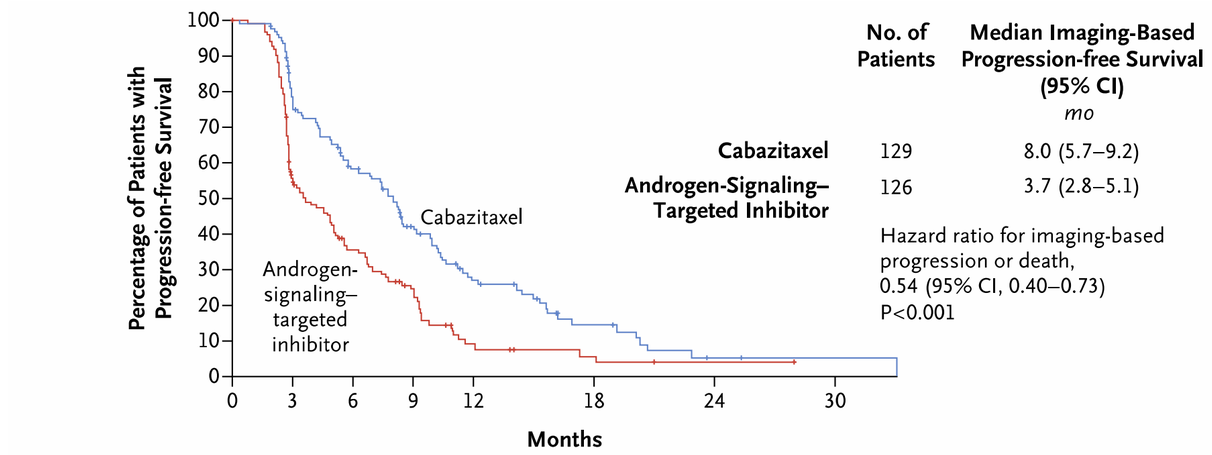
PROSELICA: Treatment-Emergent Adverse Events

Patients, n (%)	CBZ 20 + PRED N = 580	CBZ 25 + PRED N = 595
Any Grade TEAE	529 (91.2)	559 (93.9)
Grade 3–4 TEAE	230 (39.7)	324 (54.5)
Serious TEAE	177 (30.5)	257 (43.2)
TEAE leading to permanent treatment discontinuation	95 (16.4)	116 (19.5)
Most frequent Grade 3–4 TEAEs reported in ≥ 5% pts, n (%)		
Febrile neutropenia	12 (2.1)	55 (9.2)
Hematuria	11 (1.9)	25 (4.2)
Diarrhea	8 (1.4)	24 (4.0)
Fatigue	15 (2.6)	22 (3.7)
Urinary tract infection	10 (1.7)	13 (2.2)
Bone pain	10 (1.7)	13 (2.2)
Asthenia	11 (1.9)	12 (2.0)
Vomiting	7 (1.2)	8 (1.3)
Nausea	4 (0.7)	7 (1.2)

DeBono JS, et al. Presented at: ASCO Annual Meeting; June 3-7, 2016; Chicago, Illinois: abstract 5008.

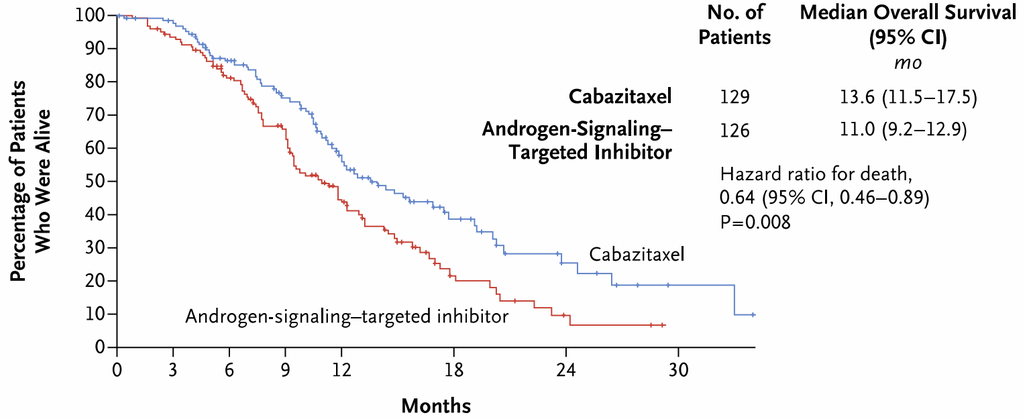
CARD: Cabazitaxel vs. Abiraterone or Enzalutamide in CRPC

- Required to have received ≥3 cycles of docetaxel
- Previously progressed on an NHA
- ~50% of patients progressed on NHA within 6 months of starting



No. at Risk

Cabazitaxel	129	91	64	41	23	9	2	1
Androgen-signaling–targeted inhibitor	126	61	36	22	7	3	1	0



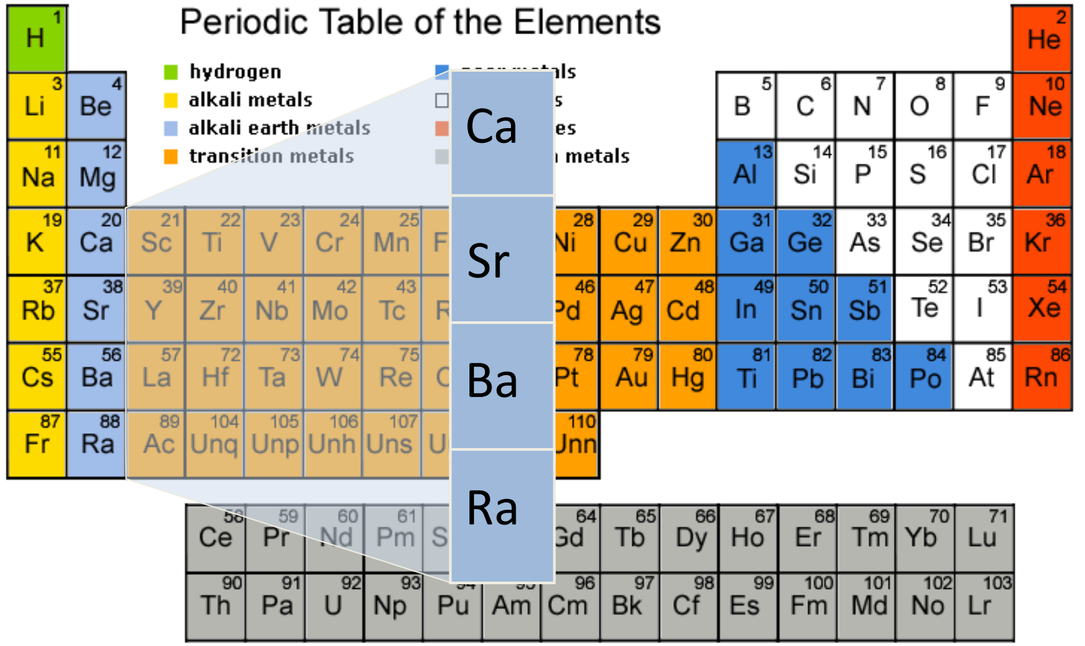
No. at Risk

Cabazitaxel	129	122	96	77	51	21	8	2
Androgen-signaling–targeted inhibitor	126	116	88	64	39	11	3	0

de Wit, et al. n engl j med 381;26

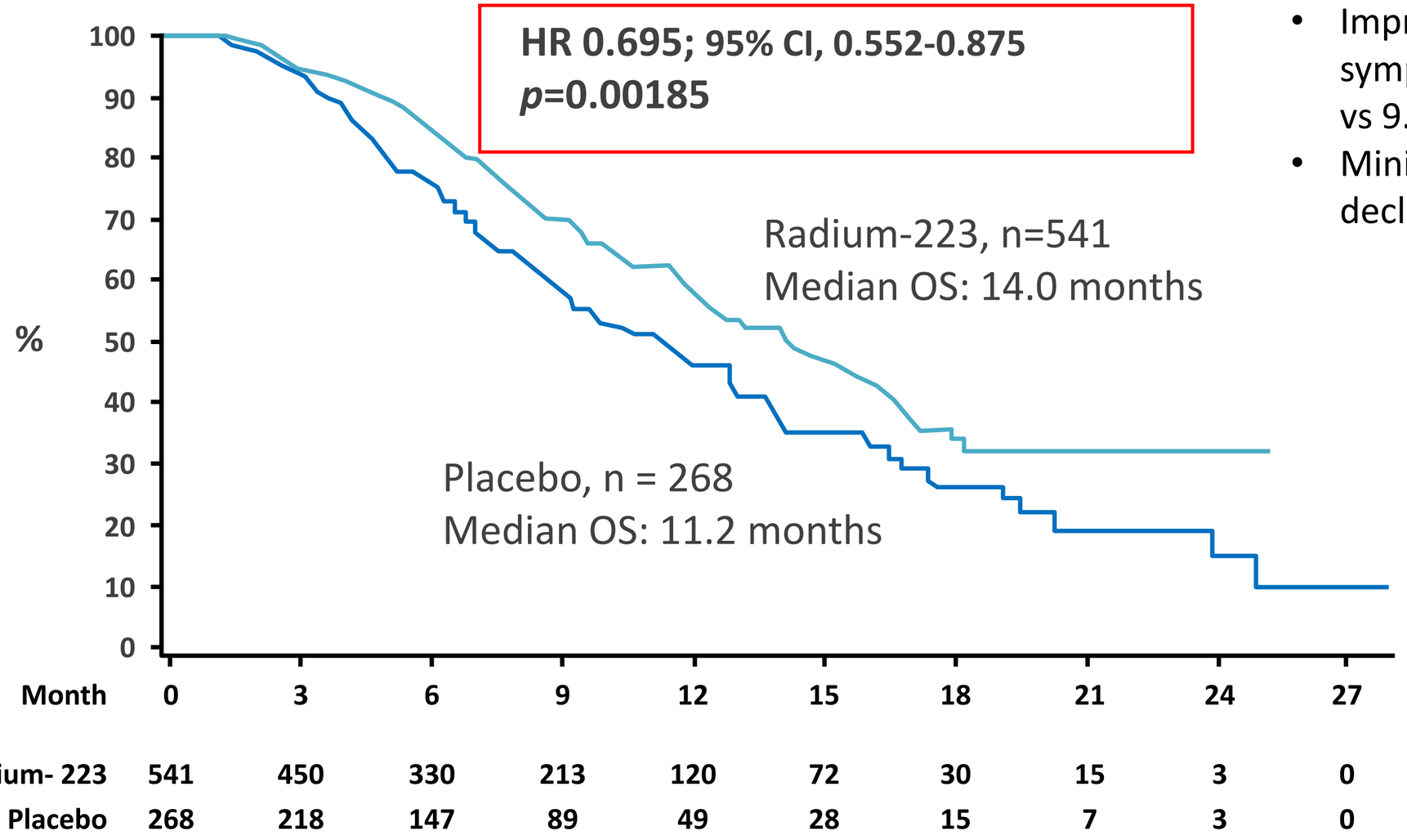
Radium-223 Mechanism of Action

- Radium-223 acts as a calcium mimic
- Alpha-particles induce double-strand DNA breaks in adjacent tumour cells[1]
- Short penetration of alpha emitters (2-10 cell diameters) = highly localized tumour cell killing and minimal damage to surrounding normal tissue
- Radium-223 is excreted by the small intestine



Perez et al. Principles and Practice of Radiation Oncology. 5th ed. Lippincott Williams & Wilkins; 2007:103.

ALSYMPCA Trial Overall Survival Results



Month	0	3	6	9	12	15	18	21	24	27
Radium- 223	541	450	330	213	120	72	30	15	3	0
Placebo	268	218	147	89	49	28	15	7	3	0

- Improvement in time to first symptomatic SRE → Median 15.6 mos vs 9.8 mos, P<0.001
- Minimal effect on PSA → 16% had PSA decline ≥30%

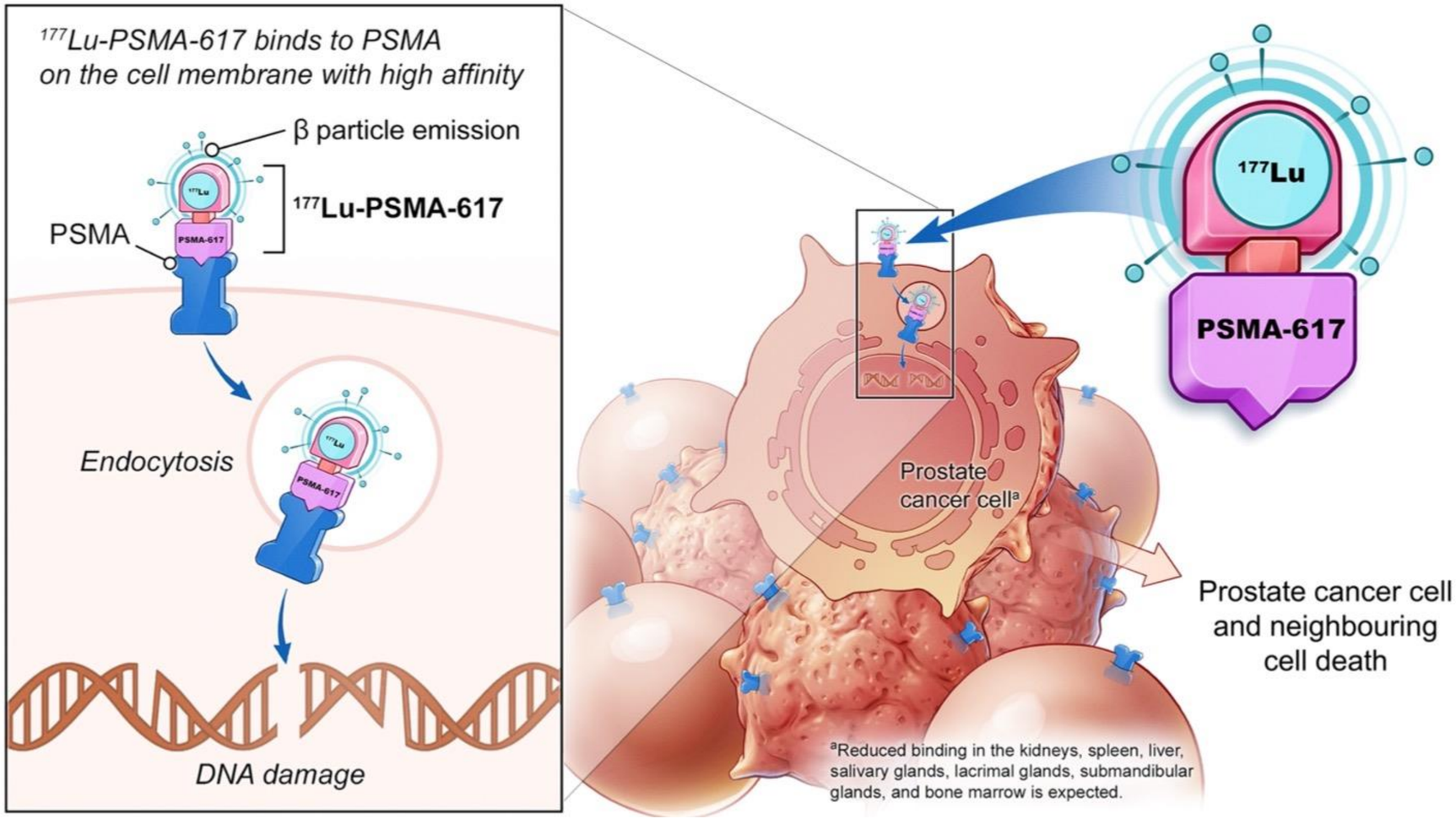
Parker C et al. *N Engl J Med* 2013;369:213-23.

ALSYMPCA: Adverse Events of Interest

	All Grades		Grades 3 or 4	
	Radium-223 (n=509) n (%)	Placebo (n=253) n (%)	Radium-223 (n=509) n (%)	Placebo (n=253) n (%)
Haematologic				
Anemia	136 (27)	69 (27)	54 (11)	29 (12)
Neutropenia	20 (4)	2 (1)	9 (2)	2 (1)
Thrombocytopenia	42 (8)	14 (6)	22 (4)	4 (2)
Non-Haematologic				
Bone pain	217 (43)	147 (58)	89 (18)	59 (23)
Diarrhea	112 (22)	34 (13)	6 (1)	3 (1)
Nausea	174 (34)	80 (32)	8 (2)	4 (2)
Vomiting	88 (17)	32 (13)	10 (2)	6 (2)
Constipation	89 (18)	46 (18)	6 (1)	2 (1)

Parker C et al. *N Engl J Med* 2013;369:213-23.

177-Lutetium-PSMA-617



The VISION Trial

86% met PSMA PET criteria

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

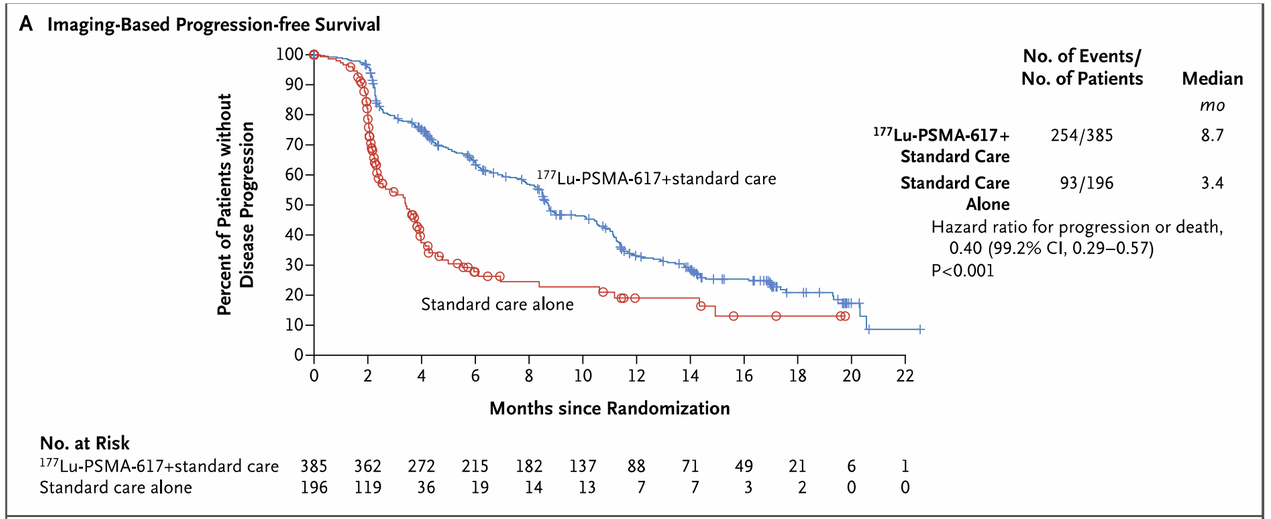
- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)

- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

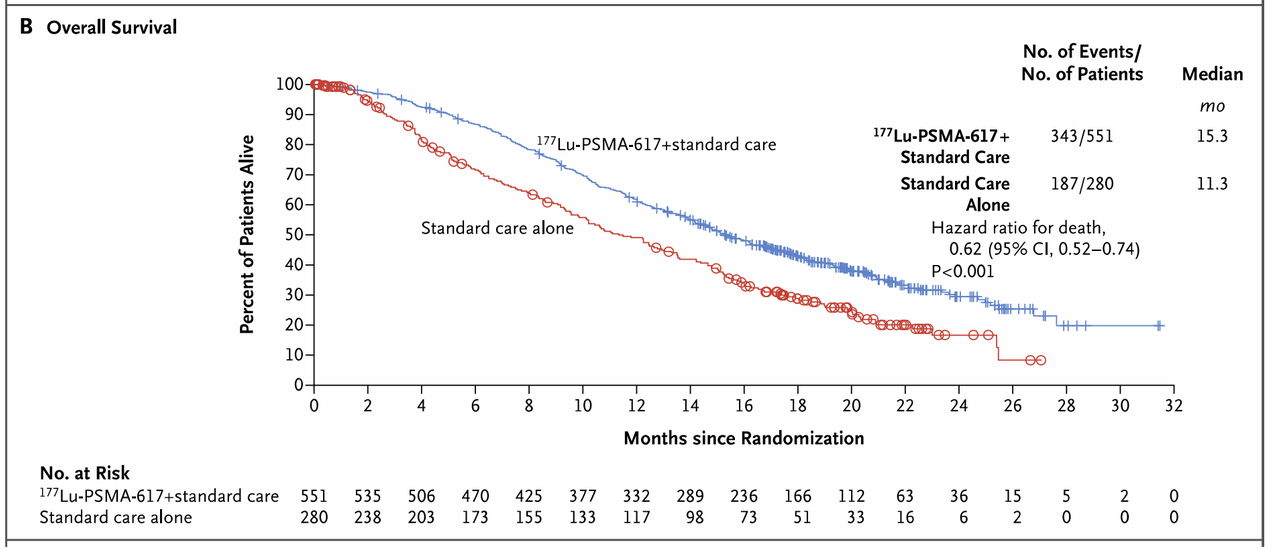
Sartor, O., Et al. N Engl J Med. 2021 Sep 16;385(12):1091-1103.
Morris, et al. ASCO Annual Meeting 2021

Primary Analyses

PFS



OS



Sartor, O., Et al. N Engl J Med. 2021 Sep 16;385(12):1091-1103.
Morris, et al. ASCO Annual Meeting 2021

Adverse Events

Event	[177Lu]Lu-PSMA-617 (n=98)		Cabazitaxel (n=85)		Care Alone (n=205)
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade ≥3
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%)	

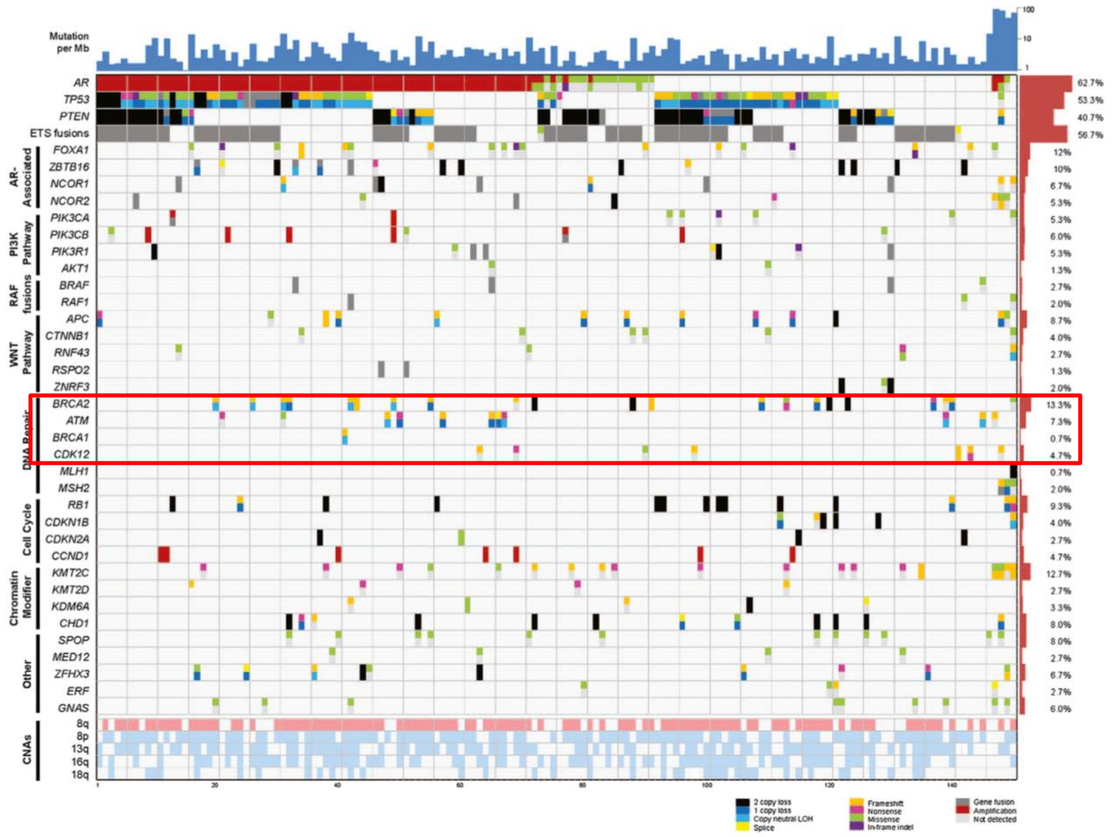
Data are n (%). Events that occurred in at least 10% of participants are shown. 177Lu=Lutetium-177. PSMA=prostate-specific membrane antigen. *Including bone, buttock, chest wall, flank, neck, extremity, tumour pain, or pelvic pain. †Motor or sensory. ‡Febrile neutropenia.

Table 2: **Adverse events**

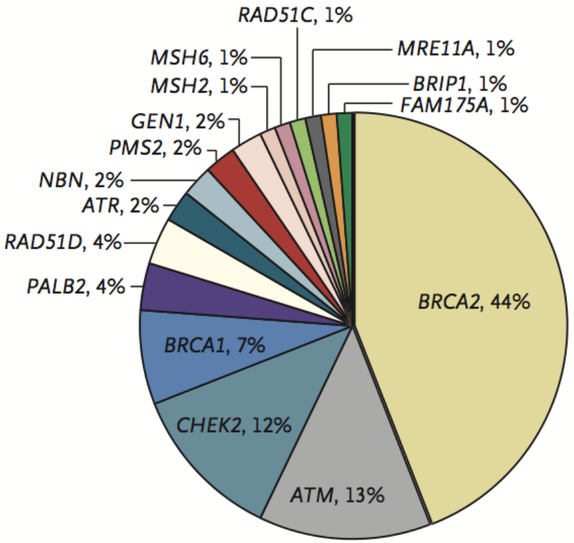
- Fatigue, dry mouth and nausea were most common AEs
  - Mostly grade 1-2
- Fewer Grade 3-4 AE compared to cabazitaxel

Sartor, O., Et al. N Engl J Med. 2021 Sep 16;385(12):1091-1103.
Morris, et al. ASCO Annual Meeting 2021
Hofman, et al. Lancet 2021

DNA Repair Gene Alterations are Common in Metastatic Prostate Cancer



- 23% of metastatic castration-resistant prostate cancers harbor DNA repair alterations



- 11.8% of men with metastatic prostate cancer have a germline alteration in 16 DNA damage repair genes
- Age and family history did not affect mutation frequency
- Germline testing should be considered for all men with high risk localized or metastatic prostate cancer

Robinson D et al. *Cell* 2015; 161:1215-28.

Pritchard CC et al. *N Engl J Med.* July 6,2016.

PARP inhibitors in CRPC

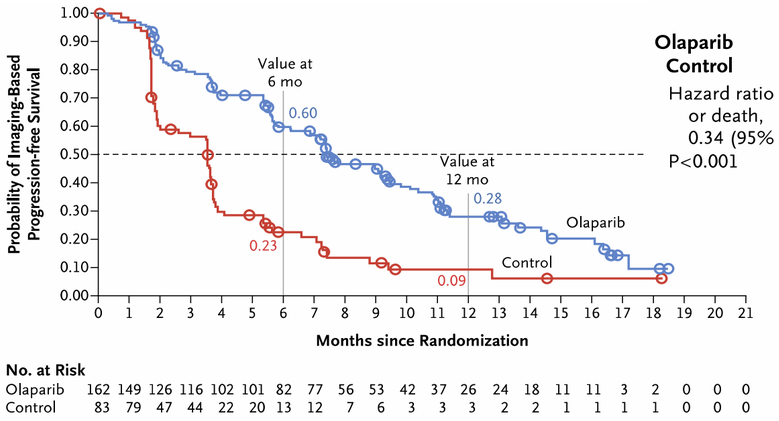
- Olaparib monotherapy[1,2]
  - Approved Pre- or post-taxane chemotherapy
  - *Qualifying mutations: BRCA1/2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* or *RAD54L*
  - *Note: Aside from BRCA1/2, there is limited data on other homologous recombination repair (HRR) genes that might predict response*
- *Rucaparib monotherapy[3]*
  - *Pre-taxane*
  - *Qualifying mutations: BRCA1/2*
- *Talazoparib plus enzalutamide[4]*
  - *Pre-taxane*
  - *Qualifying mutations: BRCA1/2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2,* or *RAD51C*
- *Niraparib plus abiraterone[5]; Olaparib plus abiraterone[6]*
  - *Pre-taxane*
  - *Qualifying mutations: BRCA1/2*

1. de Bono, et al. N Engl J Med 2020;382:2091-102.
2. Hussain, et al. N Engl J Med 2020;383:2345-57.
3. Fizazi, et al. N Engl J Med 2023; 388:719-732
4. Agarwal, et al. Lancet. 2023 Jul 22;402(10398):291-303.
5. Chi, et al. J Clin Oncol. 2023 Jun 20;41(18):3339-3351
6. Clarke, et al. NEJM Evid 2022;1(9)

PROFound: Olaparib vs. abiraterone or enzalutamide

Cohort A: *BRCA 1/2* or *ATM*

PFS



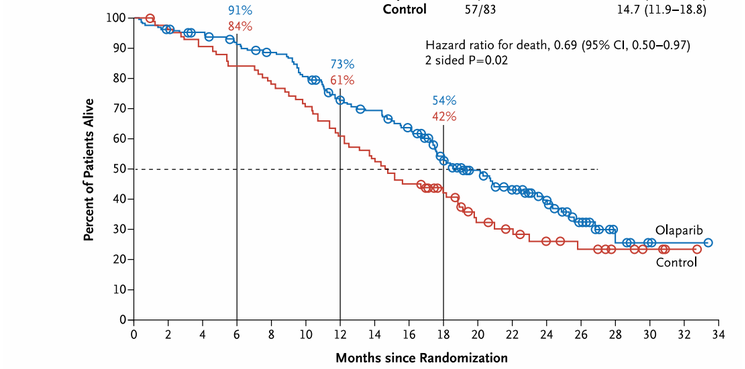
	Median (mo)
Olaparib	7.4
Control	3.6

Hazard ratio for progression or death, 0.34 (95% CI, 0.25–0.47)
P<0.001

No. at Risk

Olaparib	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
Control	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

OS



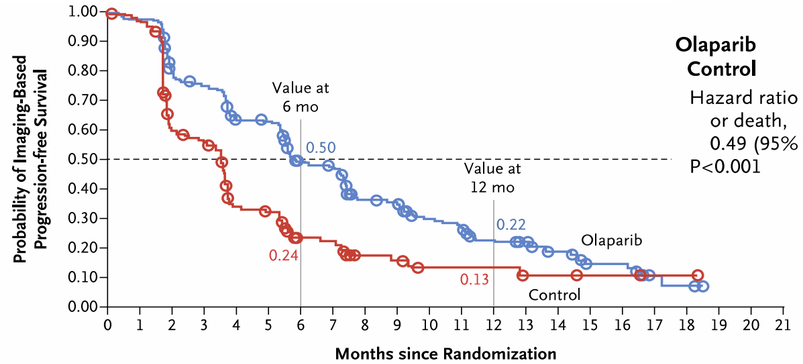
	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI) (mo)
Olaparib	91/162	19.1 (17.4–23.4)
Control	57/83	14.7 (11.9–18.8)

Hazard ratio for death, 0.69 (95% CI, 0.50–0.97)
2 sided P=0.02

No. at risk

Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Control	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

Cohort A + B: Any HR mutation

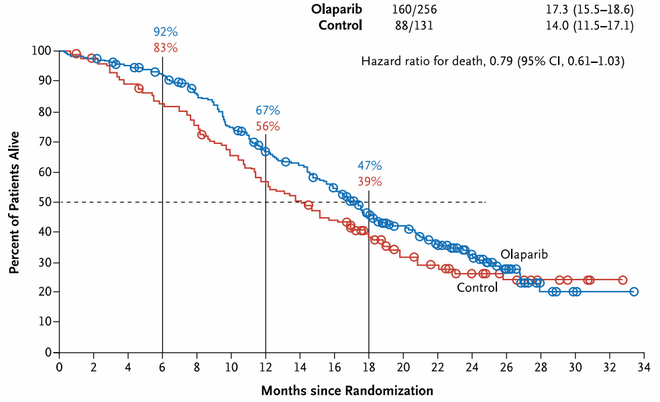


	Median (mo)
Olaparib	5.8
Control	3.5

Hazard ratio for progression or death, 0.49 (95% CI, 0.38–0.63)
P<0.001

No. at Risk

Olaparib	256	239	188	176	145	143	106	100	67	63	48	43	31	28	21	11	11	3	2	0	0	0
Control	131	123	73	67	38	35	20	19	9	8	5	5	5	3	3	2	2	1	1	0	0	0



	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI) (mo)
Olaparib	160/256	17.3 (15.5–18.6)
Control	88/131	14.0 (11.5–17.1)

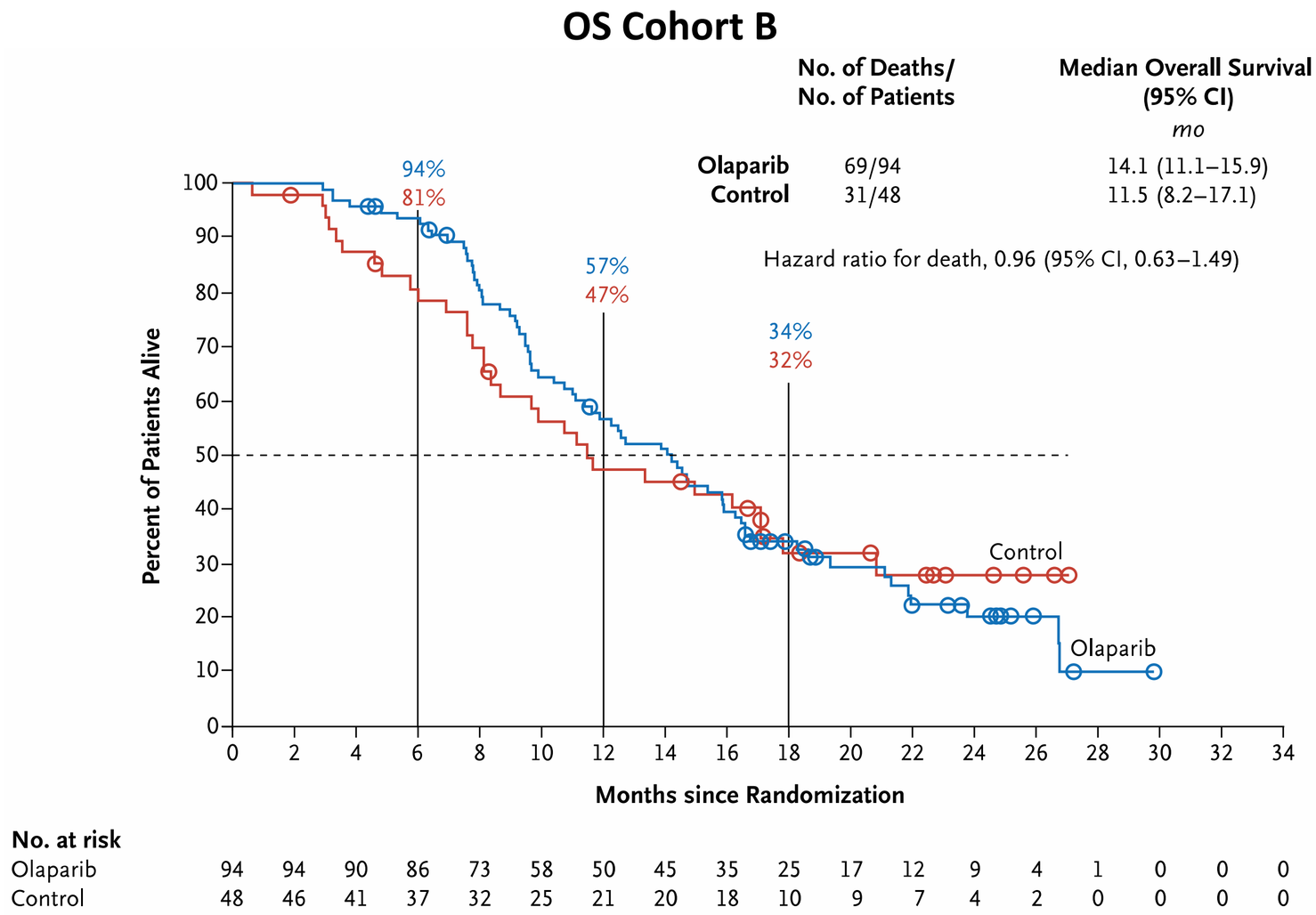
Hazard ratio for death, 0.79 (95% CI, 0.61–1.03)

No. at risk

Olaparib	256	249	240	228	209	182	157	146	126	96	73	56	39	22	7	2	1	0
Control	131	125	115	106	96	83	71	63	55	37	27	22	15	11	6	3	1	0

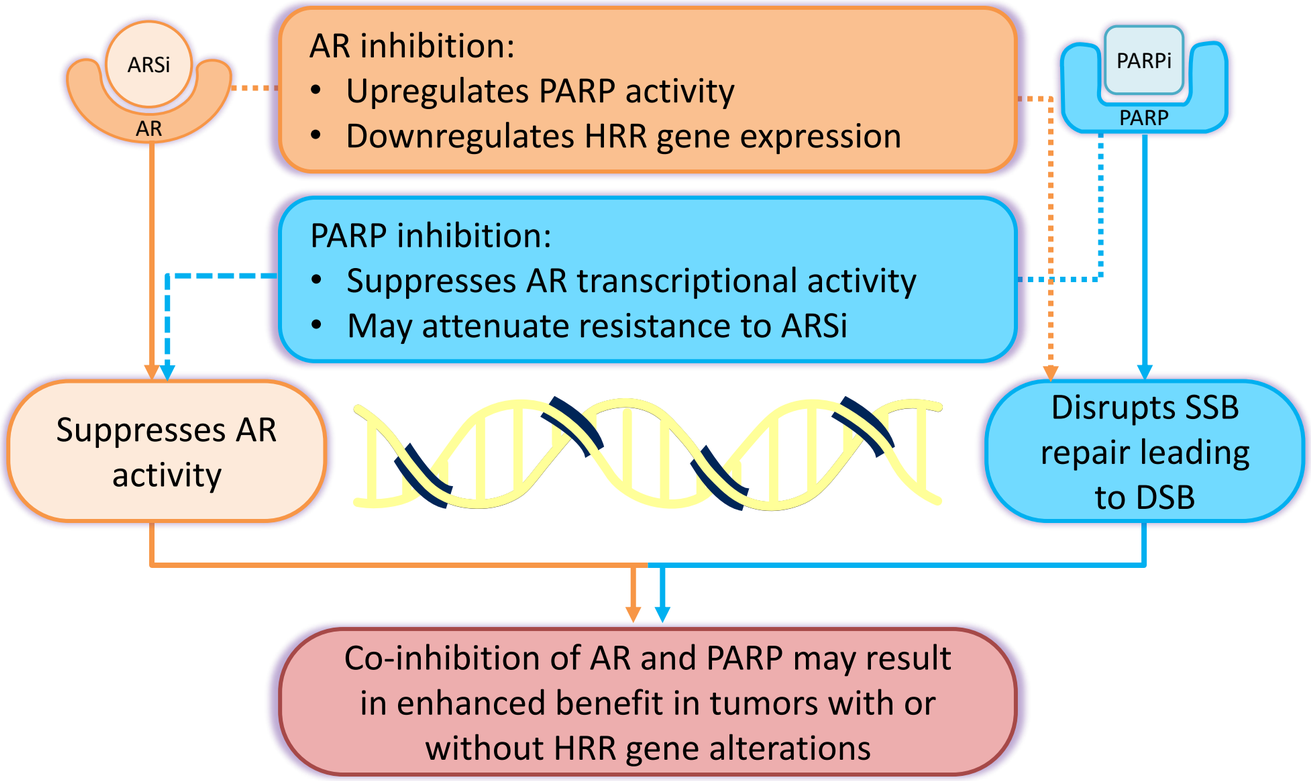
de Bono, et al. N Engl J Med 2020;382:2091-102.
Hussain, et al. N Engl J Med 2020;383:2345-57.

PROFound: Benefit in those without BRCA1/2 alterations is unclear



PARP inhibitor plus AR signaling inhibitors

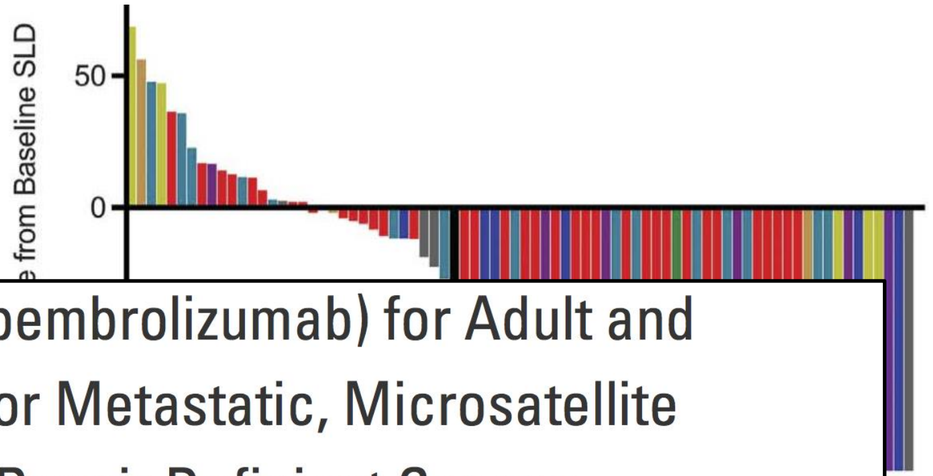
- PFS benefit observed compared to AR signaling inhibitor
  - OS data immature
- Data suggested benefit was primarily in those with HRR mutations → approval only for this group
- These trials mainly enrolled patients exposed to ADT monotherapy
  - Unclear if combos are appropriate in patients progressing on abi/enza
- No data suggesting these combinations are superior to PARP inhibitor monotherapy
- High rates of anemia observed in PARP inhibitor combo studies



1. Agarwal N, et al. *J Clin Oncol*. 2023;41(suppl 6):LBA17
2. Agarwal, et al. Lancet. 2023 Jul 22;402(10398):291-303.
3. Chi, et al. J Clin Oncol. 2023 Jun 20;41(18):3339-3351
4. Clarke, et al. NEJM Evid 2022;1(9)

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3]* Kellie N. Smith,[1,3]* Hao Wang,[3]*
Bjarne R. Bartlett,[2,4]* Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3]

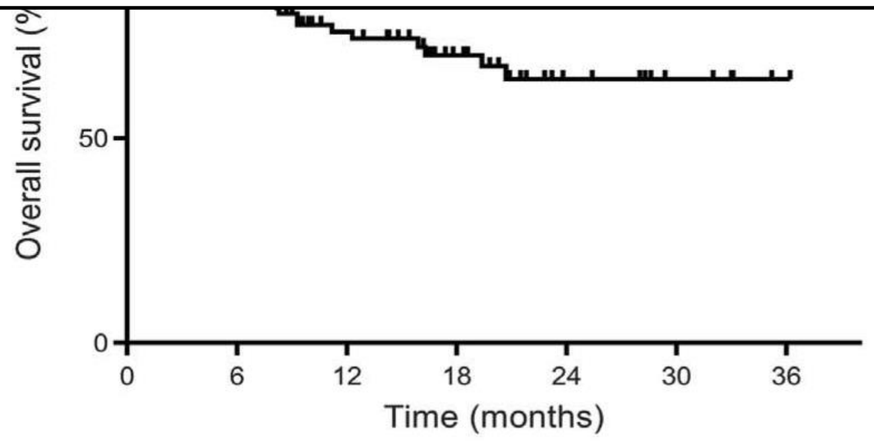


FDA Approves Merck's KEYTRUDA® (pembrolizumab) for Adult and Pediatric Patients with Unresectable or Metastatic, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient Cancer

MAY 23, 2017

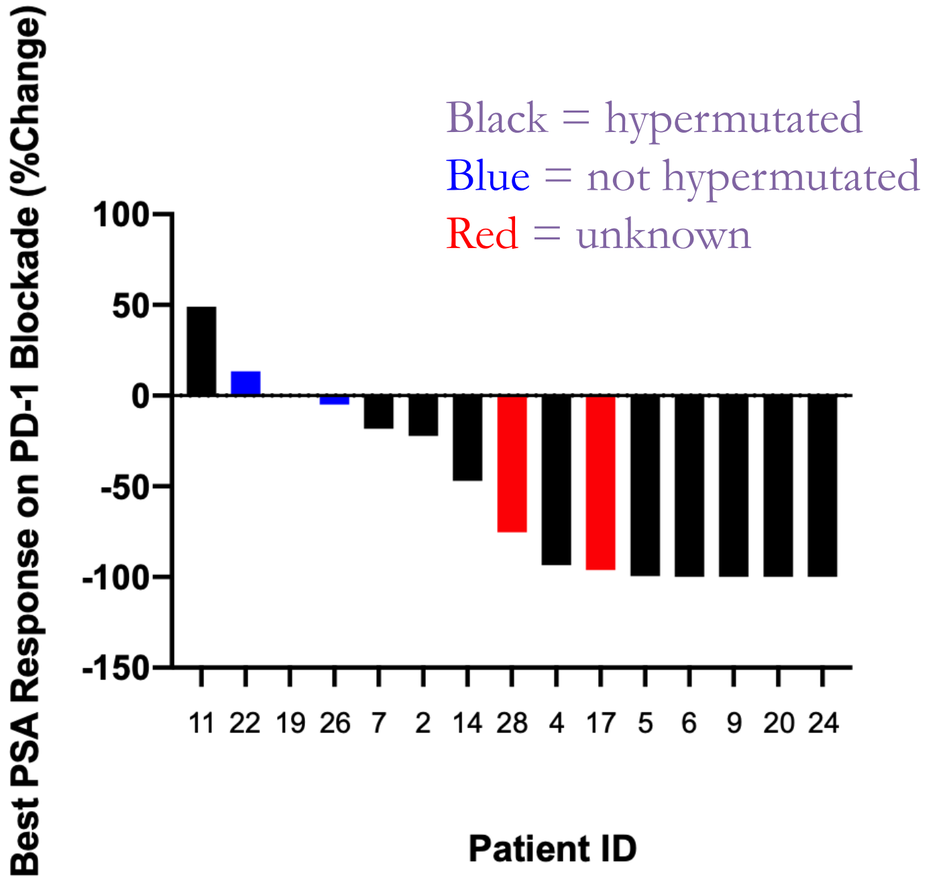
KEYTRUDA Now Approved for Patients with MSI-H or Mismatch Repair Deficient Solid Tumors That Have Progressed Following Prior Treatment and Who Have No Satisfactory Alternative Treatment Options, Which Includes MSI-H or Mismatch Repair Deficient Colorectal Cancer That Has Progressed Following Treatment with a Fluoropyrimidine, Oxaliplatin, and Irinotecan

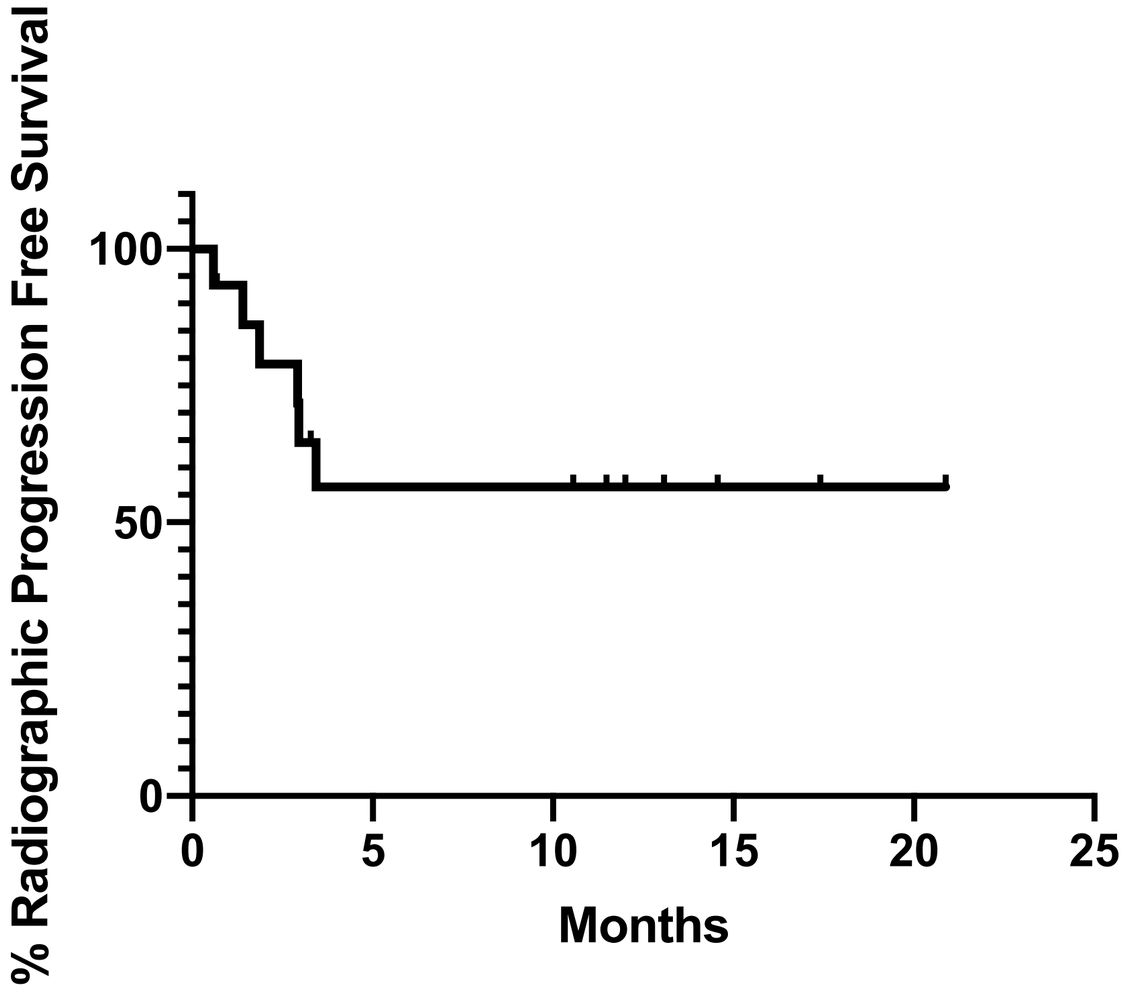
- ~~– Only 2 prostate cancer~~
- MMR deficient/MSI-high
  - – PCR or IHC
  - – 48% with Lynch syndrome
- ORR: 53%
- Median PFS and OS not reached



Le, et al. Science. 2017; 357(6349):409-13

Anti-PD1 Therapy in Prostate Cancer Patients





Graham et al. PlosOne, 2020

Key Take Home Points for the Boards Exam

- Local intervention is appropriate for higher-risk prostate cancer patient in good health
  - ADT + EBRT offers survival benefit over EBRT alone
- Know the side effects of ADT
- Treatment intensification offers survival benefit for new mHSPC
- Apalutamide, darolutamide and enzalutamide offer MFS and OS benefit for M0 CRPC
- Know the mechanisms of action, appropriate disease states and side effects of agents approved for mCRPC
  - Sipuleucel-T, abiraterone, enzalutamide, radium-223, docetaxel, cabazitaxel, Lu-PSMA617, PARP inhibitors
- Pembrolizumab is appropriate for MSI high prostate cancer
- DNA repair alterations occur in ~23% of men with mCRPC (~12% are germline with genetic counseling implications)

Fred Hutch Cancer Center

Thank You.