

MSKCC Hematology/Oncology Board Review: Prostate Cancer

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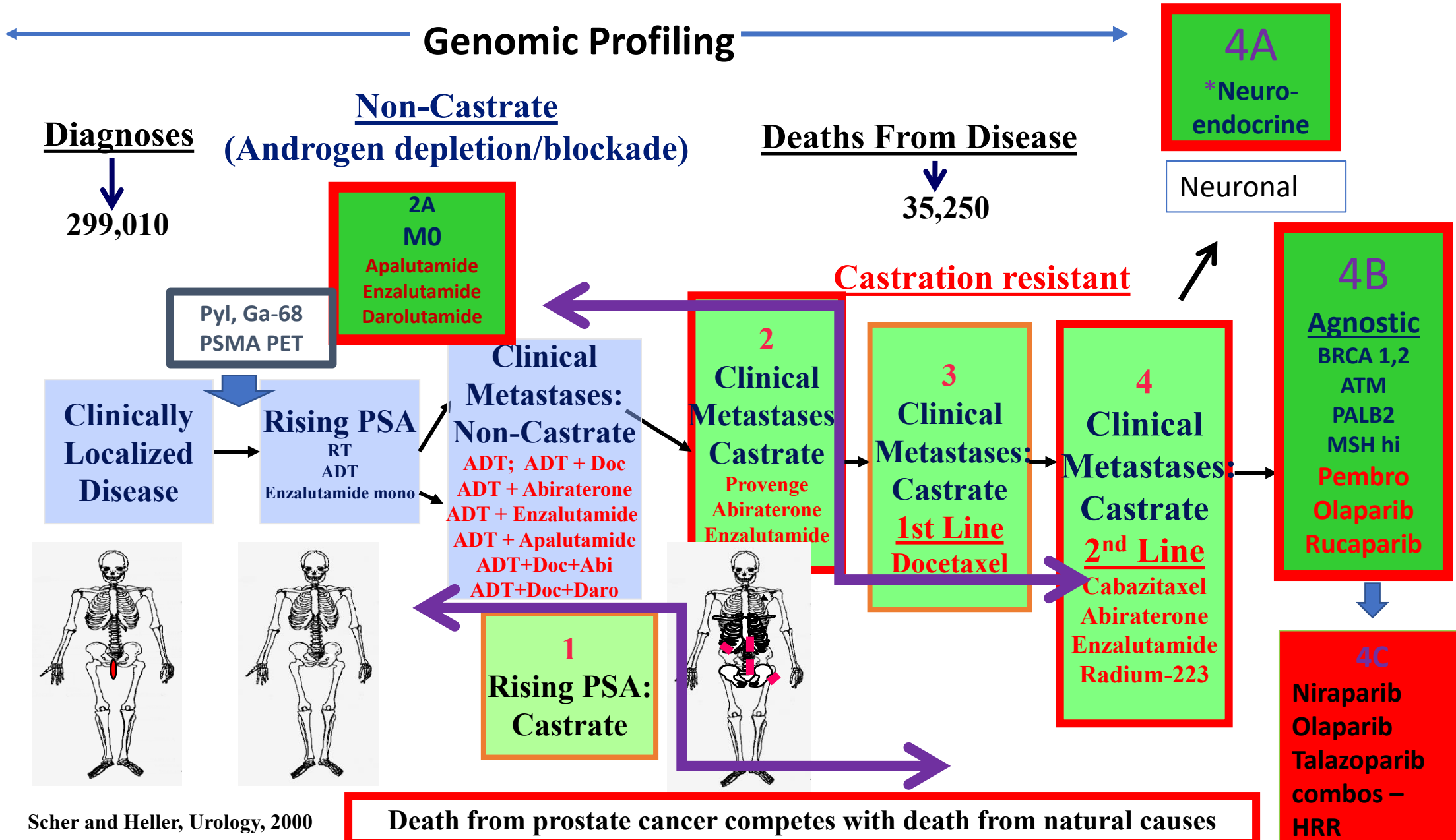


Memorial Sloan Kettering
Cancer Center

To know...

- Importance of FH, de novo metastatic disease and genomic profiling
- Indications for active surveillance
- When to start ADT/ARSI versus SOC chemotherapy; intensification
- Role of radiation in both primary and salvage setting
- Role of PARP inhibitors – BRCA; PARP combos
- Role of ICI for MSI^{hi}
- Role of PSMA PET imaging
- Lutetium-PSMA as new SOC

Prostate Cancer Treatment Landscape 2024



Newly Diagnosed Prostate Cancer...

- Importance of family history – son at 2-fold ↑ risk; but if father, grandfather, uncle, brother – risk ↑ 8x
- High-risk inherited genetic factors (BRCA 1/2, Lynch Syndrome) in 5-10% of prostate cases – 2-6x risk increase in BRCA2 vs BRCA1
- Germline mutations: ATM, CHEK2, PALB2, MLH1, MSH2, MSH6, PMS2 (Lynch)
- HOXB**+ c/w significant family history
- **NCCN guidelines** for undergoing germline testing/genomic profiling:
 - ☐ men with +FH or “suspicious” FH: Ashkenazi ancestry
 - ☐ high risk, very high risk, regional cancers, regardless of FH
 - ☐ metastatic prostate cancer regardless of FH
 - ☐ intraductal* or cribriform histology in intermed risk

*Porter, et al. Eur Urol, 2017; **Ewing CM, et al, NEJM, 2012

Familial Prostate Cancer Genes...

- Loci at chromosome 17q21; 8q24
- HOXB13 mutations – rare susceptibility genes – 20-fold risk
- Limited data in germline mutations in ATM, PALB2 and CHEK2 regarding increased risk of prostate cancer
- MMR genes – cumulate risk at 6.3% at age 60; 30% at age 80
- DDR (DNA damage repair) mutations – occur in 11.8%
- **Advanced prostate cancer:** consider tumor testing for homologous recombination repair gene mutations (HRRm) or microsatellite instability (MSI)^{high} or mismatch repair deficiency (dMMR)

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

SOMATIC TUMOR TESTING

- Pre-test Considerations

- At present, tumor molecular and biomarker analysis may be used for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, early use of platinum chemotherapy, and eligibility for clinical trials. Clinical trials may include established and/or candidate molecular biomarkers for eligibility.
- Tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making.
- Patients should be informed that tumor molecular analysis by DNA sequencing has the potential to uncover germline findings. Confirmatory germline testing may be recommended [see Post-test Considerations, below, and see Tumor Testing: Potential Implications for Germline Testing in the Principles of Cancer Risk Assessment and Counseling (EVAL-A) in the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#)]

- Testing

- Tumor testing for alterations in homologous recombination DNA repair genes, such as *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12*, is recommended in patients with metastatic prostate cancer. This testing can be considered in patients with regional prostate cancer.
- Tumor testing for MSI-H or dMMR is recommended in patients with metastatic castration-resistant prostate cancer and may be considered in patients with regional or castration-sensitive metastatic prostate cancer.
- TMB testing may be considered in patients with metastatic castration-resistant prostate cancer.

- Tumor Specimen and Assay Considerations

- The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. When unsafe or unfeasible, plasma circulating tumor (ctDNA) assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield.
- Caution is needed when interpreting ctDNA-only evaluation due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP), which can result in a false-positive biomarker signal.
- DNA analysis for MSI and immunohistochemistry for MMR are different assays measuring different biological effects caused by dMMR function. If MSI is used, testing using an a next-generation sequencing assay validated for prostate cancer is preferred.

- Post-test Considerations

- Post-test genetic counseling is recommended if pathogenic/likely pathogenic variant (mutation) identified in any gene that has clinical implications if also identified in germline (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *PMS2*).
- Post-test genetic counseling to assess for the possibility of Lynch syndrome is recommended if MSI-H or dMMR is found.

To biopsy or not to biopsy?....we really should

- Metastatic bx for histologic and molecular evaluation
- When bx unsafe could consider plasma ctDNA at time of BCR +/- POD
- Caution needed when interpreting ctDNA-only evaluation due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP) - results in false positive signal
- DNA analysis for MSI and IHC for MMR measure different biologic effects caused by dMMR function
- If MSI is used, testing using a NGS assay validated for prostate cancer is preferred
- Genetic counseling if germline variants of uncertain significance are found

Can we prevent prostate cancer?

- **Prostate Cancer Prevention Trial (PCPT)** - Tested hypothesis; could finasteride, provided to a lower risk, general population of men over a course of 7 yrs, ↓risk of pc?
- Finasteride ↓ the risk of pc by 30%; the agent appears to have no to minimal effect on high-grade disease.
- High-grade pc - more common in the finasteride group c/w placebo group; after 18 years of follow-up, **NO** significant between-group difference in rates of OS or survival after the diagnosis of prostate cancer.
- **Prostate Cancer Prevention with Vitamin E/ Selenium “SELECT Trial”**
- Selenium supplementation has **no** effect on prostate cancer risk.
- Vitamin E supplementation significantly increases the risk of prostate cancer by 17%.

Are all men candidates for active surveillance?

- Prostate cancer – heterogenous disease
- heterogeneity across the low-risk group
- factors that may be associated with ↑probability of higher grade behavior: high PSA density, high number of positive cores (eg, ≥ 3), high percentage of core involvement, high genomic risk (from tissue-based molecular tumor analysis), and/or a known BRCA2 germline mutation.
- In some cases, upfront treatment with radical prostatectomy or prostate RT may be preferred based on shared decision-making with the pt.

Localized disease

- Consider life expectancy: 10 yrs, 10-20 yrs or >10 yrs
- **Options:** active surveillance, EBRT or brachytherapy, RRP
- **Active surveillance:** include mpMRI yearly; PSA q6 mo, DRE/Bx q12 mo
- **Active interventions:** If >10 yrs: **RRP** → undetectable PSA,
• or **EBRT** or **brachytx** → PSA nadir is lowest value reached after tx
- Post RRP Decipher molecular assay to inform on adjuvant treatment if **adverse features** are found, ie...
- Post RRP adverse features: positive margin(s), SVI, ECE, detectable PSA
- Post RT failure is PSA increase by 2ng/dl or more above the nadir PSA



INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE^g

Risk Group	Clinical/Pathologic Features See Staging (ST-1)			Additional Evaluation ^{h,i}	Initial Therapy
Very low ^f	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core^g • PSA density <0.15 ng/mL/g			• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	watch
Low ^f	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL			• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	watch
Intermediate ^f	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▶ cT2b–cT2c ▶ Grade Group 2 or 3 ▶ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)^g	• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	Watch/ RT/RRP
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)^g	Bone and soft tissue imaging ^{j,k} • If regional or distant metastases are found, see PROS-8 or PROS-12	ADT/RT +/- brachy +/- ARSI
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			Bone and soft tissue imaging ^{j,k} • If regional or distant metastases are found, see PROS-8 or PROS-12	ADT/RT+ brachy + ARSI
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			Bone and soft tissue imaging ^{j,k} • If regional or distant metastases are found, see PROS-8 or PROS-12	ADT/RT + brachy + ARSI

High Risk Localized-External Beam Radiation + ADT (optimal duration of ADT) either by features of Gleason group 4, 5; PSA >20, bulky gland

- 36 months ADT > no ADT
 - Bolla et al NEJM 1997
- 36 months ADT > 6 months of ADT
 - Bolla et al NEJM 2009
- 18 months ADT > 6 months of ADT
 - Denham et al Lancet Onc 2019
- 36 months = 18 months (91% vs 86% 5 year OS NS)
 - Nabid et al Eur Urol 2018
- **XRT + 24 months likely the standard**

Are we speaking the same language?

The jargon is changing...

- The term "castration-naïve sensitive" is used to define pts who have not been treated with ADT and those who are not on ADT at the time of progression.
- NCCN Prostate Cancer Panel uses the term "castration-naïve sensitive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.
- **High-volume** disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column.
- Pts with **low-volume** disease have less certain benefit from early treatment with docetaxel combined with ADT.

How to treat scenarios...

Local (N0M0)

- neoadjuvant ADT for RRP - **discouraged** outside of a clinical trial
- ADT before, during and/or after RT [neoadjuvant, concurrent, adjuvant] prolongs survival
- Anti-androgens added; no prospective data

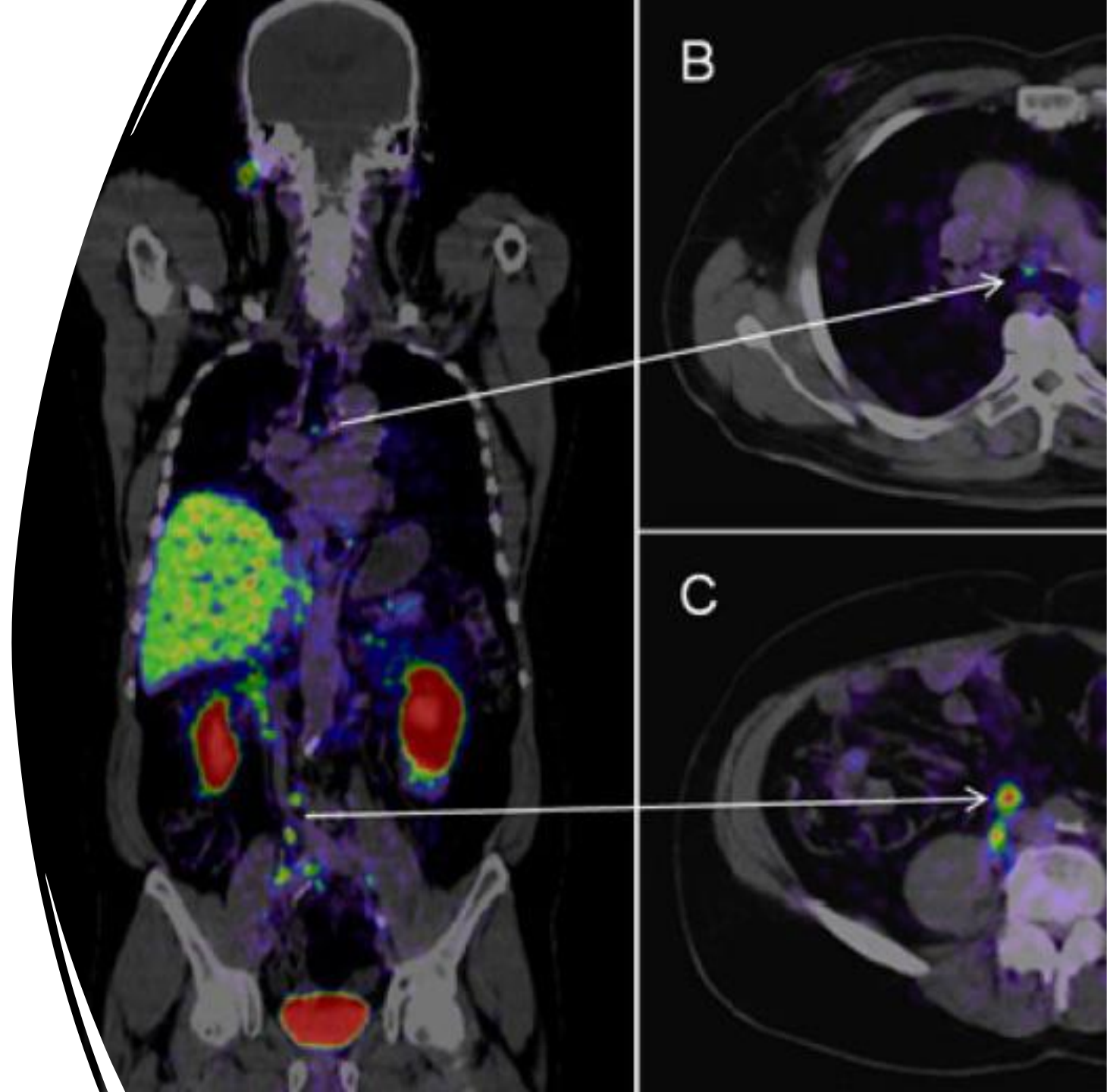
Regional (N1M0)

- ADT before, during and/or after RT [neoadjuvant, concurrent, adjuvant] with
*abiraterone/prednisone

* Consider for up to 2 years

Impact of ^{18}F PSMA/ ^{18}Ga PSMA PET imaging...

- Now “essential” to pre/post prostatectomy evaluations
- Approved in the high risk pre-prostatectomy patient
- Approved for biochemical risk post prostatectomy
- Approved in the de novo state to clarify bone lesions



NCCN: footnote

- because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective, front-line imaging tool for these patients."

New SOC use...

- F-18 piflufolastat PSMA or Ga-68 PSMA-11 PET/CT or PET/MRI can be considered as an **alternative** to standard imaging of bone and soft tissue for initial staging, the detection of biochemically recurrent disease, and as workup for progression with bone scan plus CT or MRI for the evaluation of bone, pelvis, and abdomen.
- PSMA imaging should be done **before** initiation of ADT because ADT may affect detection sensitivity

How to treat scenarios...

s/p RRP (pN1+) disease	Biochemical relapse s/p RRP or RT
• Immediate and continuous ADT post RRP – significantly improved OS c/w men treated with delayed ADT • EBRT added	• No right answer – 15 yr good prognosis • Treatment dictated by <u>PSADT</u>, patient anxiety, potential treatment-associate side effects • Adj RT for rising PSA, +ECE, +anastomotic recurrence, positive margins • *SWOG 8794 – randomize to either adjuv eRBT – followed by 12.6 years. • Reduced risk of PSA relapse and disease relapse. blf SV+ post RRP; adj RT improved 10-year biochemical FFS c/w observation (36% vs 12%; P = 0.001) • Ph II: intermittent ADT not inferior to continuous ADT regarding OS, QOL improved with intermittent. Unplanned subset analysis showed that men with Grade Group 4/5 in continuous arm had a median OS: 14 months long (8 yr) c/w intermittent arm (6.8 ys)

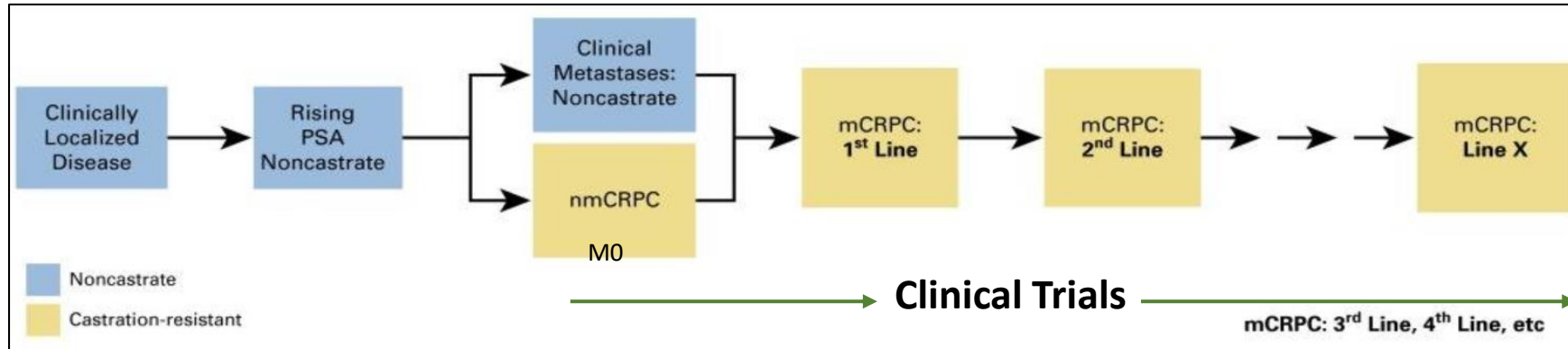
Adjuvant Therapy...

- Adjuvant radiation, ie radiation post RRP in “**high risk**” patients
 - Three studies demonstrating PFS benefit
 - One study (SWOG) showed OS benefit
 - Adjuvant versus early salvage still controversial
 - **Prefer early salvage in most cases to avoid overtreatment**
- Adjuvant or neoadjuvant chemotherapy
 - 4 studies-2 negative, 2 marginal benefit
 - **Not standard**
- Neoadjuvant or adjuvant ADT after RP
 - **No proven benefit**

Options for RT based on tumor volume...

- Radiation to the prostate - option in low-volume metastatic burden castration-naïve sensitive metastatic disease, without contraindications to radiotherapy (ulcerative colitis).
- ADT - required unless medically contraindicated. **Low metastatic burden is defined as either non-regional, lymph-node-only disease OR <4 bone metastases and without visceral/other metastases.**
- Metastases defined only by PET imaging should ***not*** be used to exclude a pt from treatment of the primary tumor. This is based on the STAMPEDE phase 3 randomized trial, which randomized >2000 pts to standard systemic therapy +/- RT to the primary.
- Overall cohort had a significant improvement from the addition of RT to the primary in failure-free survival, but not OS.
- The prespecified low-volume subset had a significant improvement in both failure-free survival and overall survival. A meta-analysis with two other studies confirmed this benefit for primary RT to the primary tumor in lower volume disease
- **New area of ongoing research is in pts with oligometastatic disease; feasible yet controversial regarding types of radiation, dosimetry, timing and EOD**

How to treat in a sea of plenty...



Hormone Sensitive

Local/Loco-regional Disease	Biochemical Recurrence	de novo Metastatic
• Active surveillance • Surgery • Radiation +/- ADT STAMPEDE (abi x2 years) • Role of PSMA PET imaging* - FDA Approved	• ADT (oral and im) • Active surveillance • Enzalutamide (EMBARK)	• Docetaxel (2015) CHAARTED (OS) STAMPEDE (OS) • Abiraterone (2017) LATITUDE (OS) STAMPEDE (OS) • Enzalutamide (2019) ARCHES (mPFS) ENZAMET (OS) • Apalutamide(2019) TITAN (mPFS, OS) • Doc + Abi (2022) LATITUDE (rPFS, OS) • Doc + Daro (2022) Arasens (rPFS, OS)

Castration-Resistant

Non-Metastatic CRPC (M0)	Metastatic CRPC	Metastatic CRPC Post-Docetaxel
• Apalutamide (2018) SPARTAN (MFS, OS) • Enzalutamide (2018) PROSPER (MFS, OS) • Darolutamide (2019) ARAMIS (MFS, OS)	• Docetaxel • Sipuleucel-T • Abiraterone • Enzalutamide • Radium 223	• Cabazitaxel • Abiraterone • Enzalutamide • Radium 223 • PARP Inhibitors • CPI • Lutetium-PSMA • PARP combos

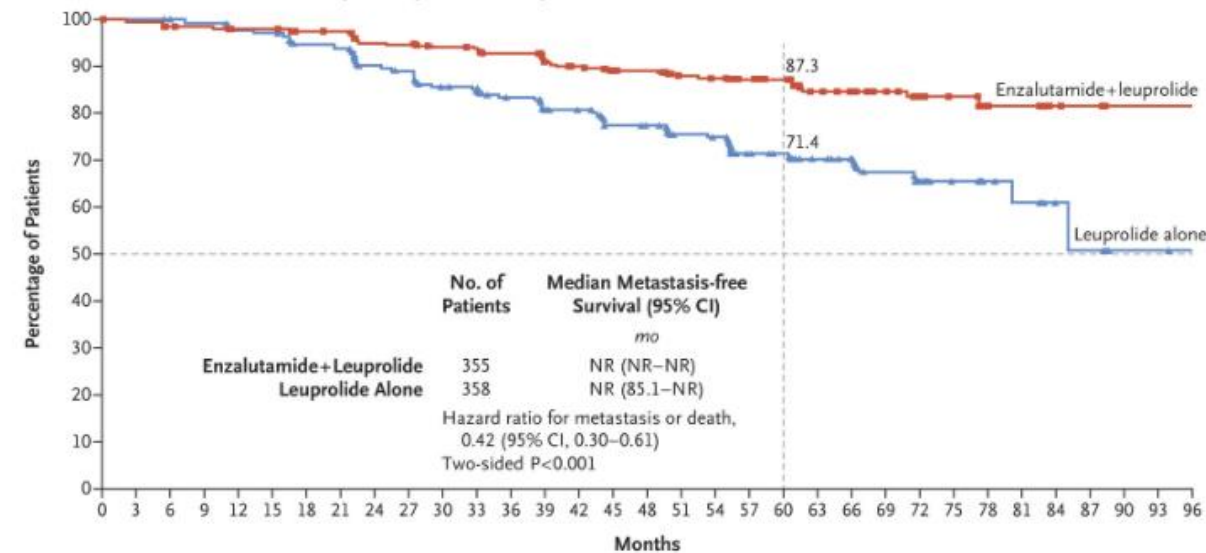
Treating pts with biochemical relapse s/p RRP or RT or both...

- If s/p RT with rising PSA, consideration to focal therapy in areas that were outside the original RT field, ie, node
- Could consider using proton beam RT if node is close to prior RT field or received suboptimal RT previously
- Consider brachytherapy in a recurrent seminal vesicle
- Less enthusiasm for salvage RRP post RT
- If RRP followed by RT, usually standard ADT, consider relugolix
- Now new indication for monotherapy with Enzalutamide

EMBARK... Freedland, NEJM 2023

- phase 3 trial, pts with high-risk biochemical recurrence and PSADT 9 months or less.
- Pts randomly assigned, in a 1:1:1 ratio, to enzalutamide (160 mg) daily + ADT q12 weeks (combination group), placebo + ADT (leuprolide-alone group), or enzalutamide monotherapy (monotherapy group).
- 1^o endpoint- MFS assessed by BICR in the combination group as compared with the leuprolide-alone group.
- 2^o endpoint - MFS in monotherapy group c/w the leuprolide-alone group.
- Other secondary endpoints were patient-reported outcomes and safety.

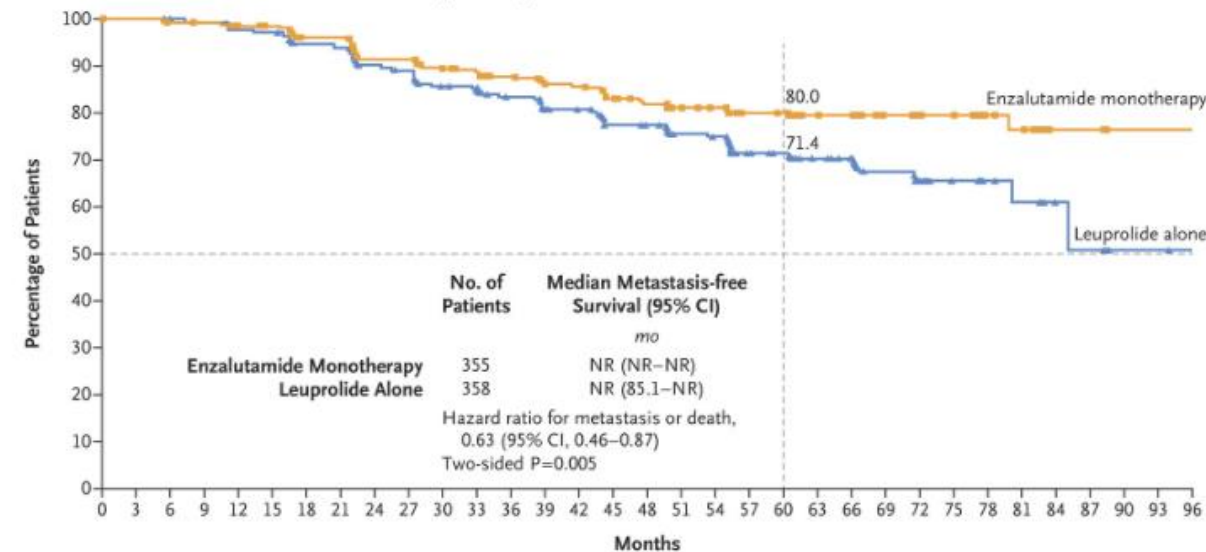
A Metastasis-free Survival with Enzalutamide plus Leuprolide vs. Leuprolide Alone



No. at Risk

Enzalutamide+leuprolide	355	339	331	330	324	324	318	317	304	303	292	290	281	270	265	252	251	236	234	183	180	119	116	83	60	51	24	22	6	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

B Metastasis-free Survival with Enzalutamide Monotherapy vs. Leuprolide Alone



No. at Risk

Enzalutamide monotherapy	355	350	342	341	328	326	309	309	287	287	273	269	260	248	247	235	228	211	209	172	171	109	108	76	52	49	26	24	5	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

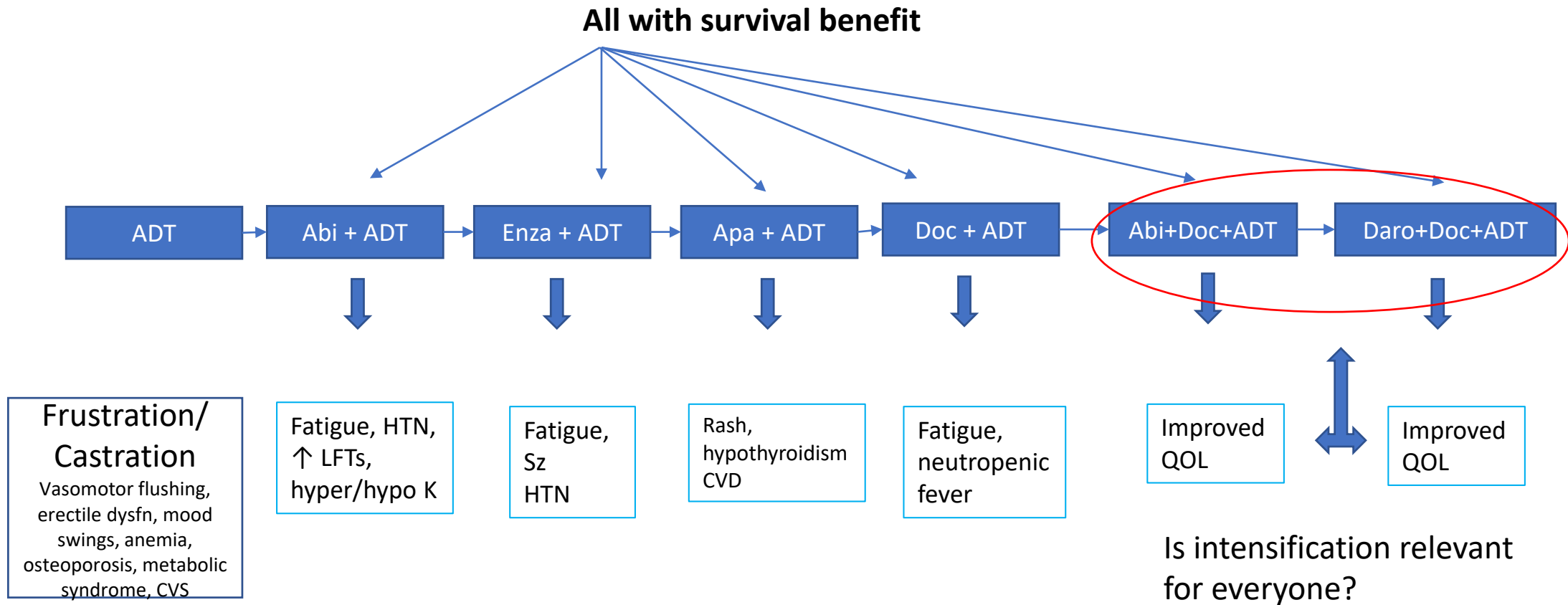
Kaplan–Meier curves for metastasis-free survival, defined as the time from randomization to the date of earliest evidence of imaging-based progression or death from any cause, in the combination group as compared with the leuprolide-alone group (Panel A); and in the monotherapy group as compared with the leuprolide-alone group (Panel B)

Median follow-up was 60.7 months in the combination group, 60.6 months in the leuprolide-alone group, and 60.7 months in the monotherapy group.

De novo non-castrate metastatic disease (M1)

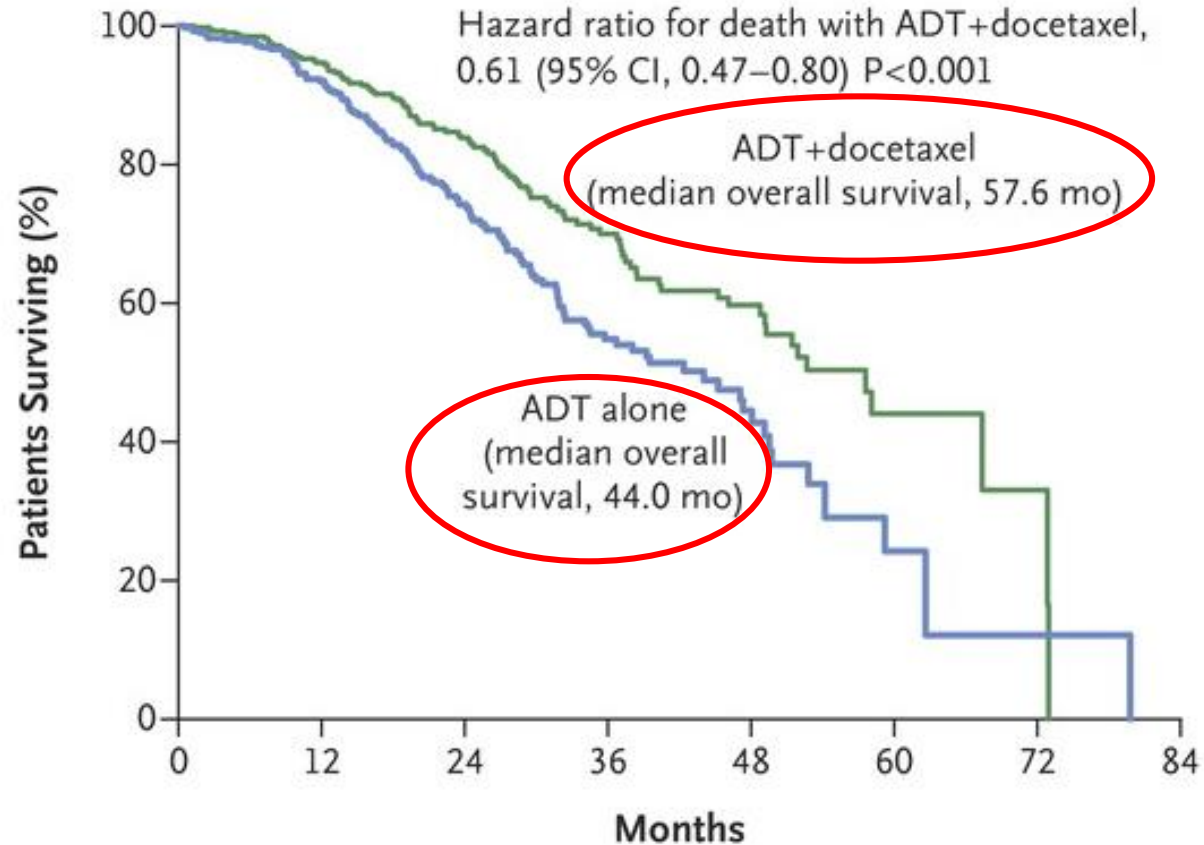
- ADT
- ADT + docetaxel (CHAARTED)
- ADT + abiraterone
- ADT + enzalutamide
- ADT + apalutamide
- PEACE-1 – Abiraterone Plus Androgen-Deprivation Therapy and Docetaxel Fizazi, et al. Lancet Oncol 2022
- ARASENS – Darolutamide Plus Androgen-Deprivation Therapy and Docetaxel Smith, et al, NEJM 2022

de Novo metastatic Hormone Sensitive Prostate Cancer



ECOG 3805 CHAARTED: ChemoHormonal Therapy vs. Androgen Ablation for Extensive Disease in Metastatic Prostate Cancer

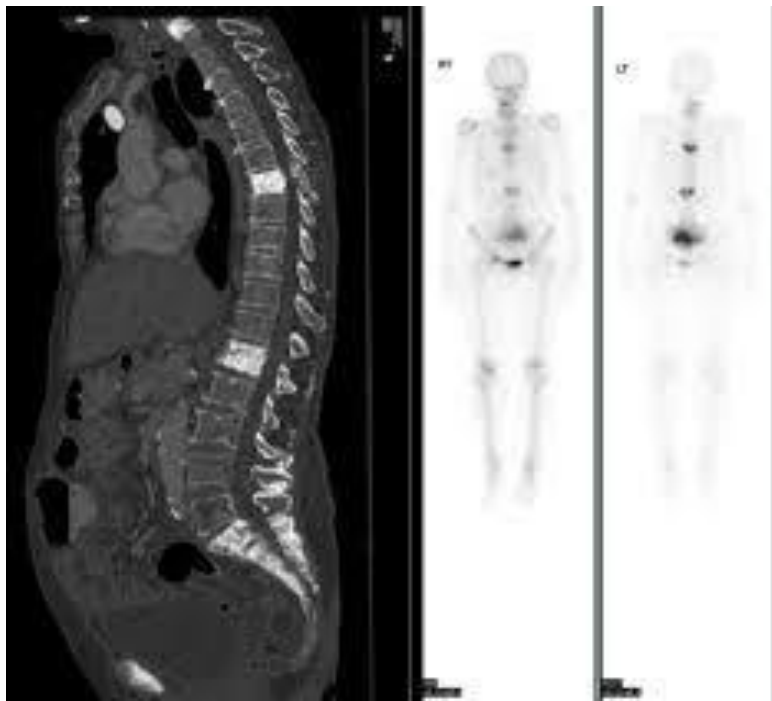
All Patients



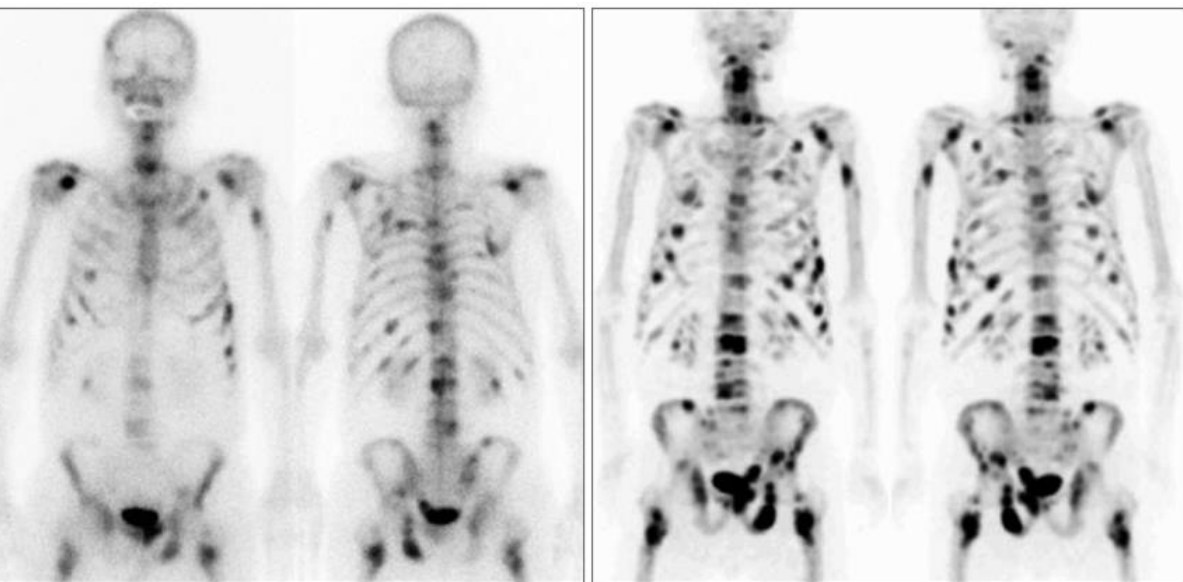
No. at Risk

ADT+docetaxel	397	333	189	89	46	5	2	0
ADT alone	393	318	168	71	27	3	1	0

A

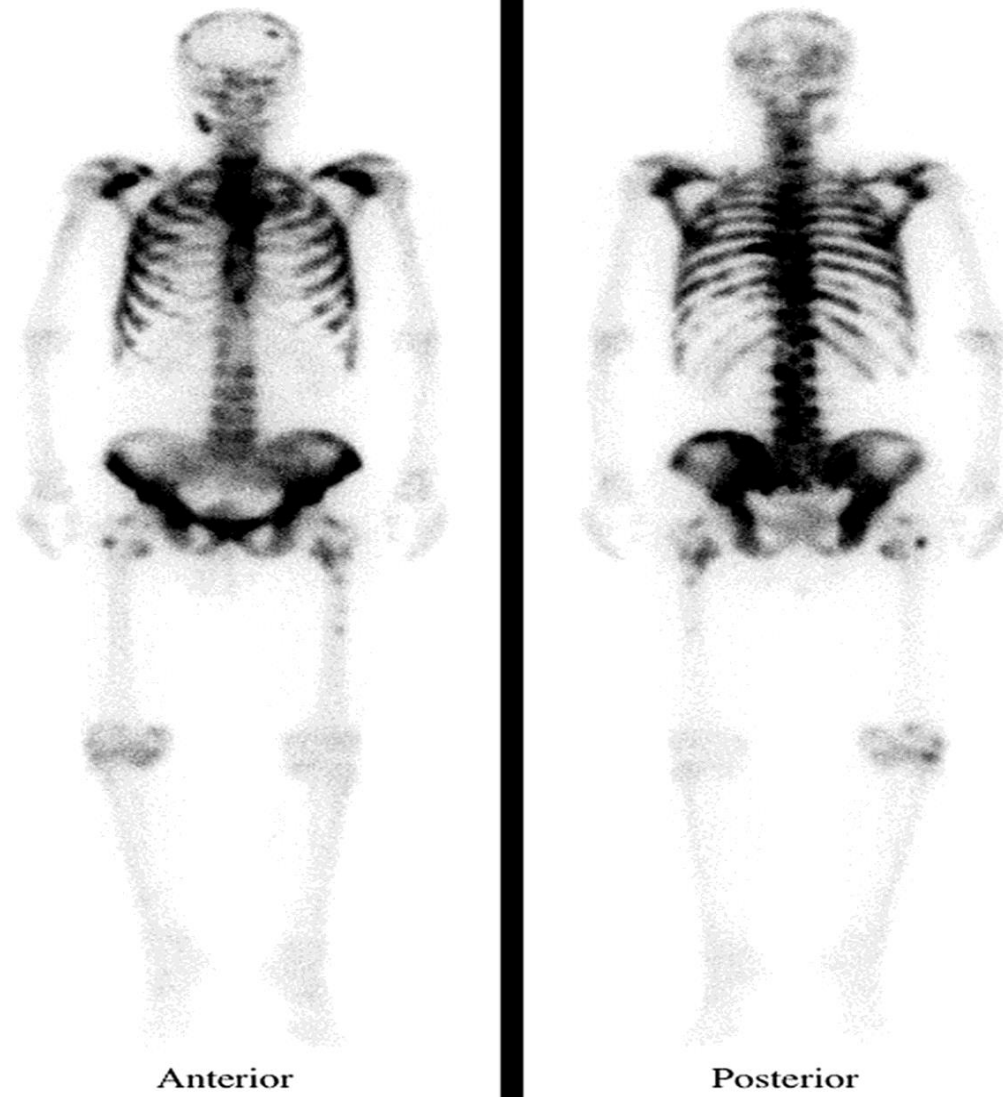


B



B

Metastatic Prostate cancer – but to what degree?



C

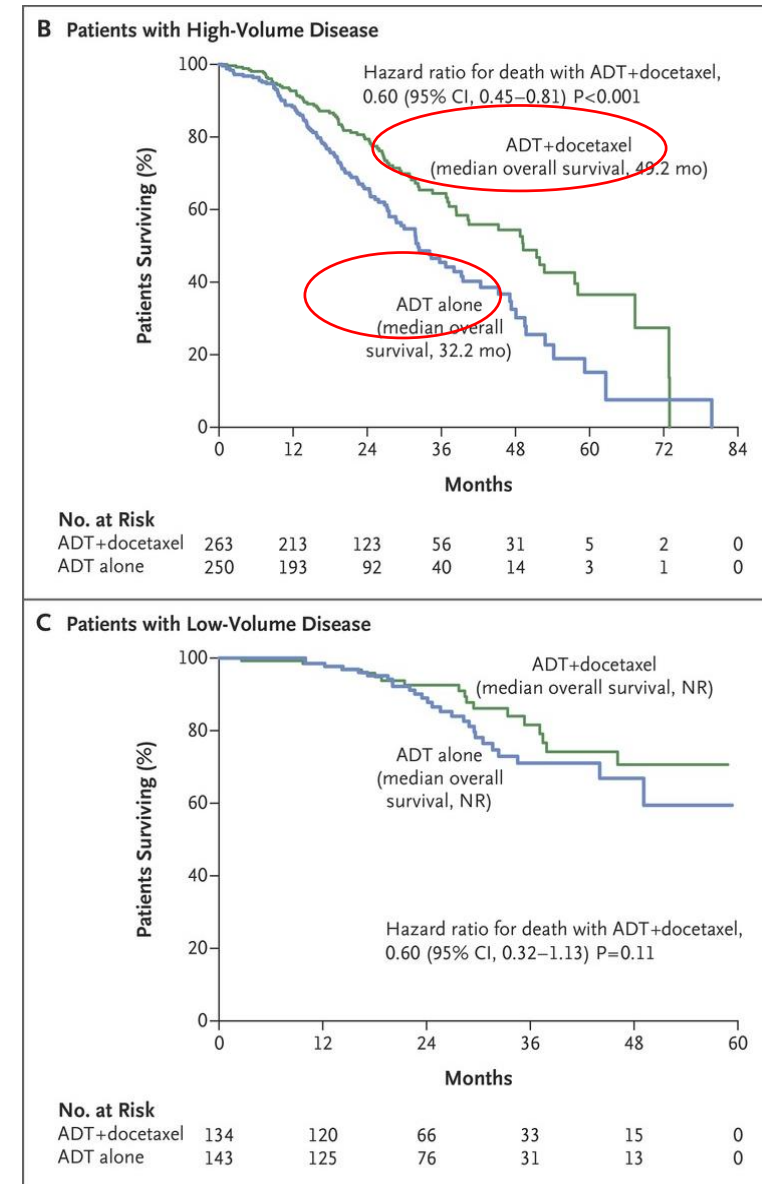
ECOG 3805 CHAARTED: ChemoHormonal Therapy vs. Androgen Ablation for Extensive Disease in Metastatic Prostate Cancer

Overall survival was 17.0 months longer in the combination group in men with high volume disease; increase from 32.2 mo with ADT alone to 49.2 mo with ADT + doc

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

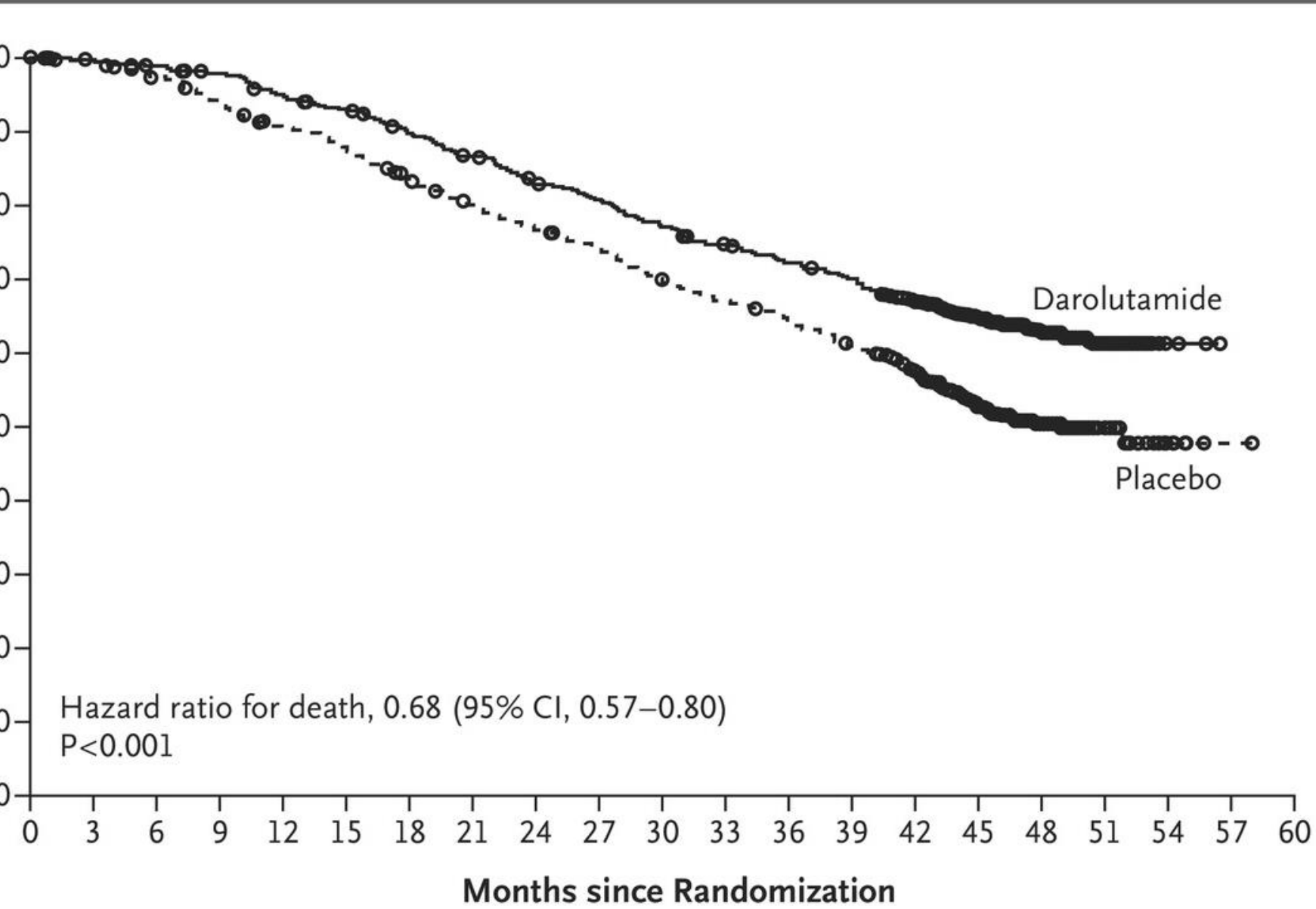
No statistically significant OS was observed between groups in those deemed to have low volume disease (p=0.11)

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)



Can dose-intensification improve outcome?

- ADT + docetaxel + abiraterone
- ADT + docetaxel + darolutamide



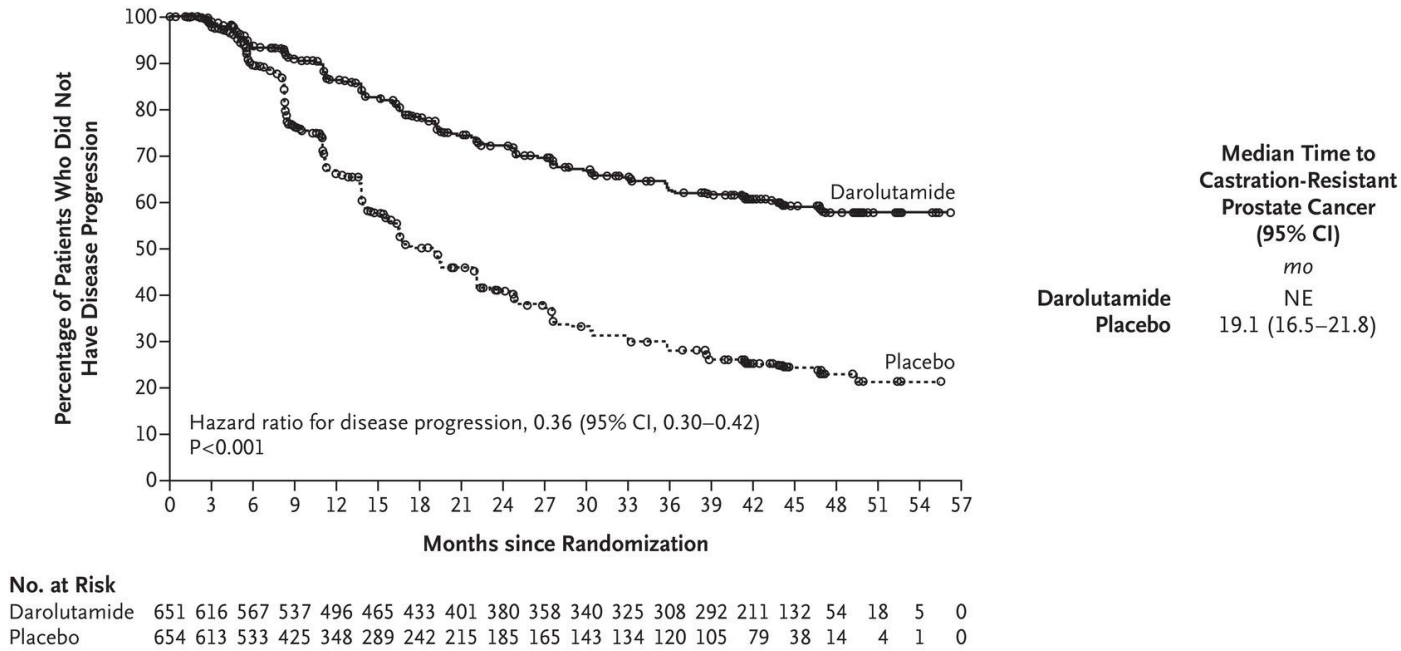
Kaplan-Meier estimates of Overall survival.

	Median Survival (95% CI)
Darolutamide	48.9 (44.4–NE)
Placebo	32.3 (28.8–36.8)

Significant reduction in risk of death by 32.3% (HR 0.68; 95% CI .57-0.8)

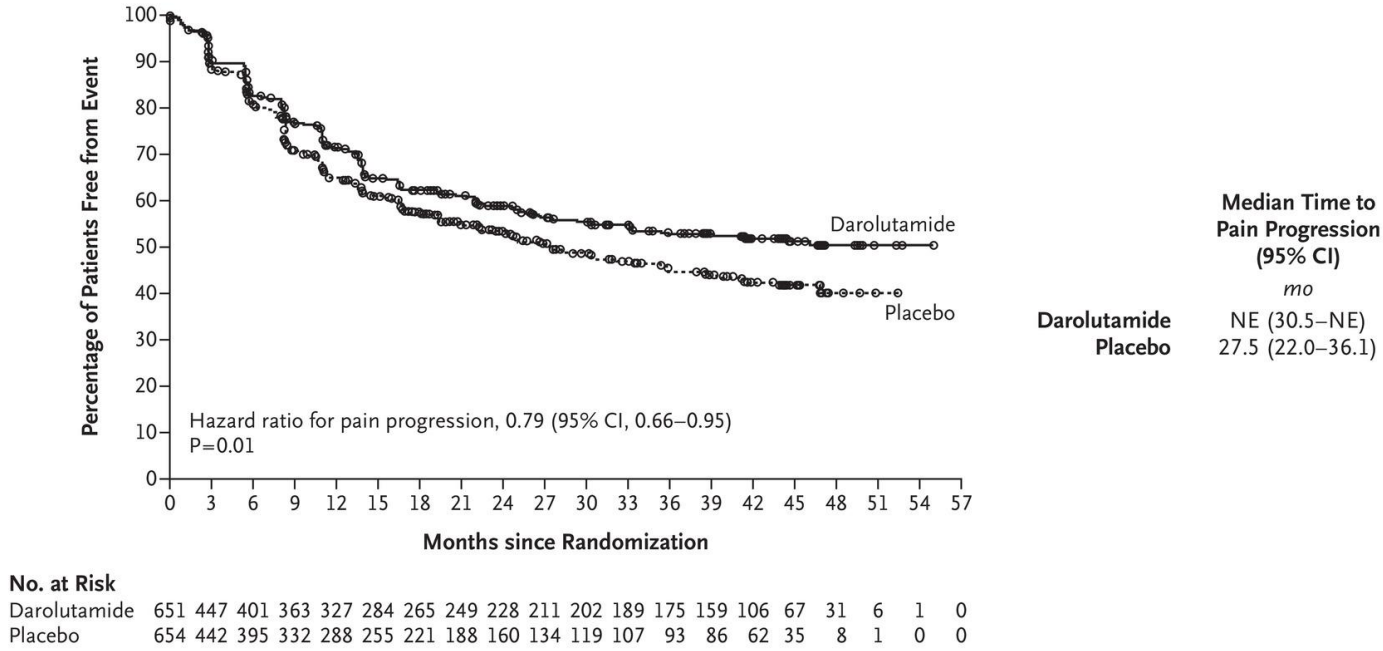
651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

A Time to Castration-Resistant Prostate Cancer

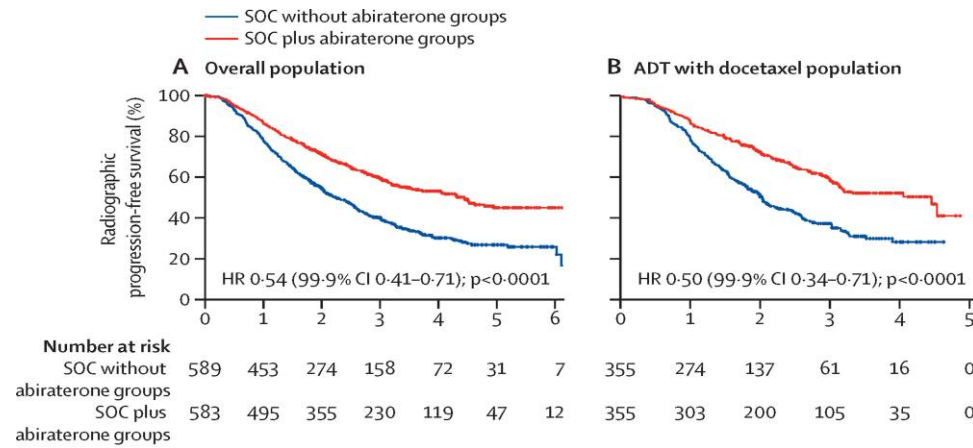


Panel A shows the time to castration-resistant prostate cancer; **Panel B** shows the time to pain progression. The Kaplan–Meier method was used to estimate the time to events; data were censored at the date of the patients’ last assessment for that end point.

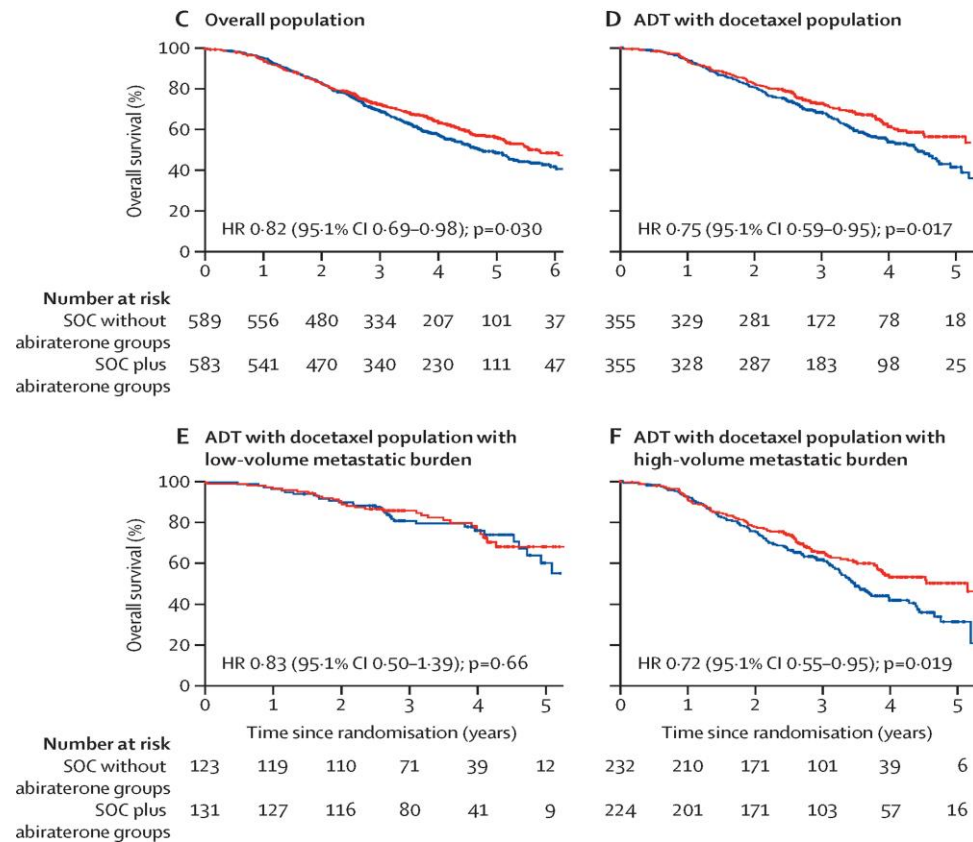
B Time to Pain Progression



rFPS →



OS →



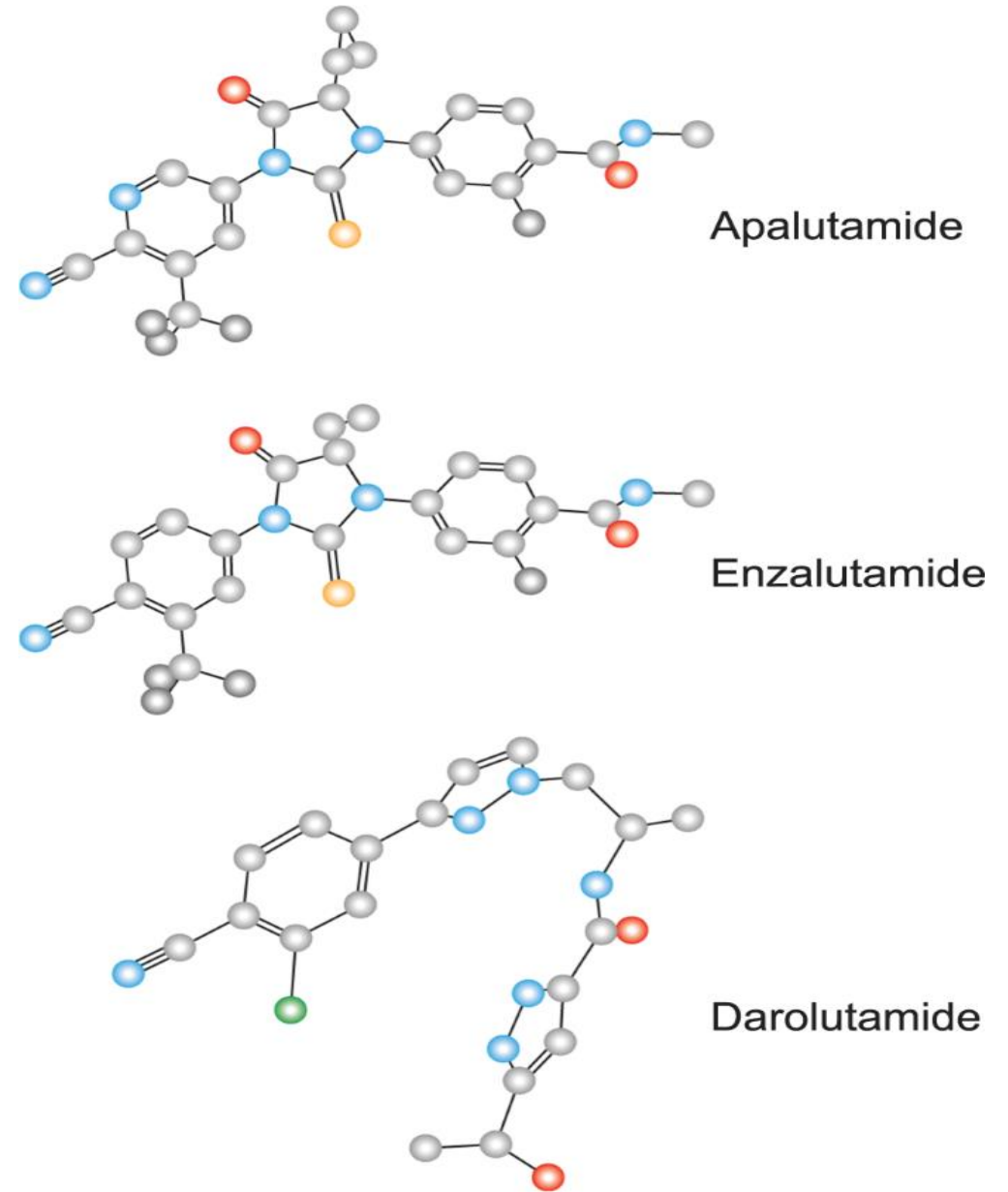
Kaplan-Meier estimates of radiographic progression-free survival and overall survival in the overall population and ADT with docetaxel population. Time-to-event curves are presented for radiographic progression-free survival (A) and overall survival (C) in the overall population, radiographic progression-free survival (B) and overall survival (D) in the ADT with docetaxel population, and overall survival in the ADT with docetaxel population in patients with low-volume metastatic burden (E) and high-volume metastatic burden (F). SOC in the overall population was ADT with or without docetaxel. SOC in the ADT with docetaxel population was ADT with docetaxel. ADT=androgen deprivation therapy. SOC=standard of care (with or without radiotherapy).

MO hormone resistant disease

Same drugs, different clinical state

Treatment of M0 Castration-Resistant Prostate Cancer

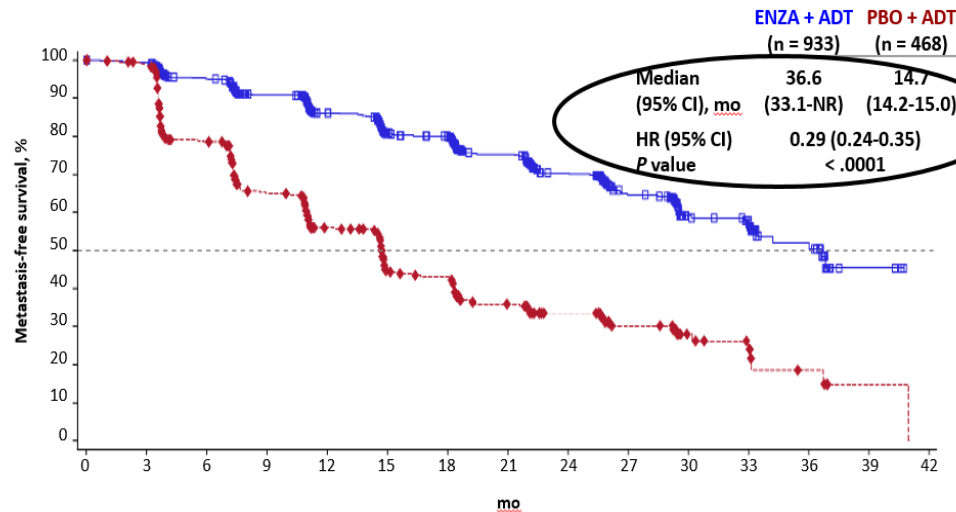
- Three choices: Enzalutamide, apalutamide, darolutamide
- Choice depends on co-morbidities, drug interactions, side effect profile
- Unclear if pts are truly M0; progressive use of PSMA PET imaging may ablate the M0 state
- M0 may not exist and may be a transient state proceeding rapidly to metastatic state.



Enzalutamide in Mo mCRPC – “Prosper”

Median time to MFS

Hussain, et al, NEJM 2018

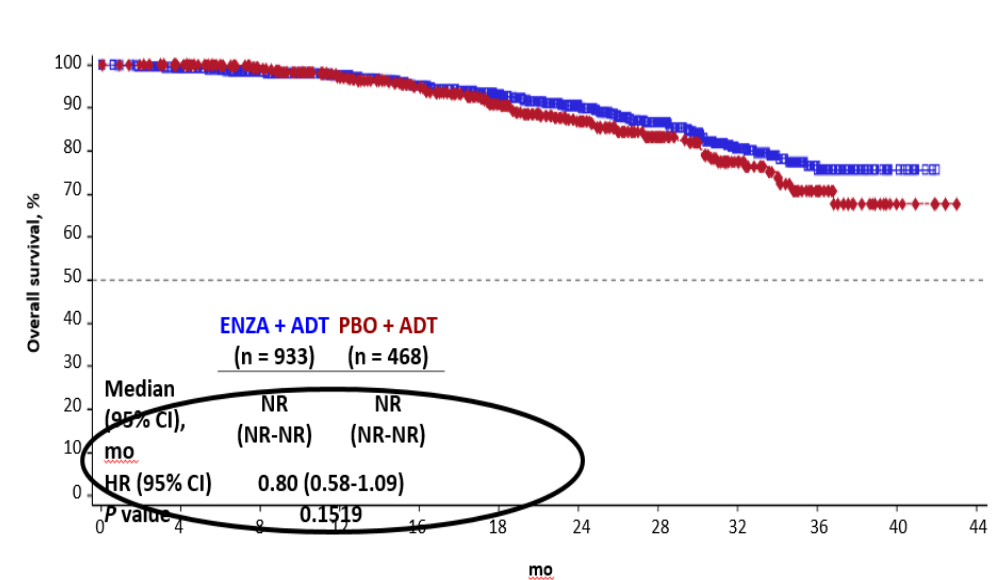


- Median time to MFS was ~ 22 months longer with enzalutamide than with placebo (71% reduction in relative risk of radiographic progression or death)

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; PBO, placebo.

Overall Survival

Hussain, et al, NEJM 2018



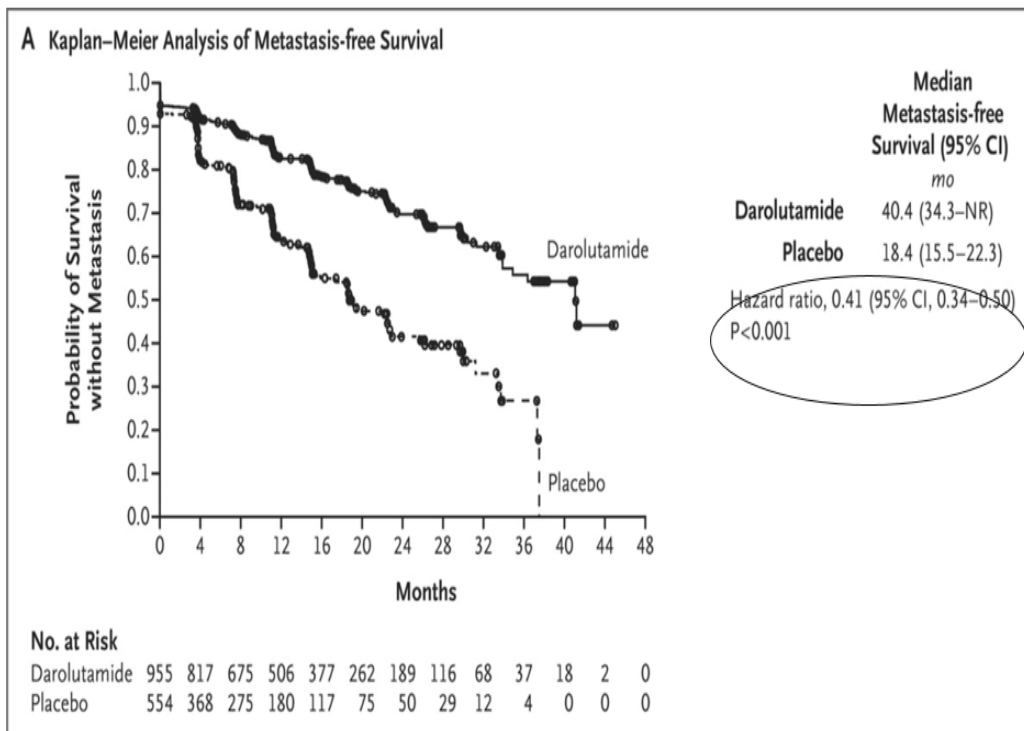
- There was a 20% reduction in the relative risk of death with enzalutamide vs placebo



Darolutamide in Mo mCRPC – “Aramis”

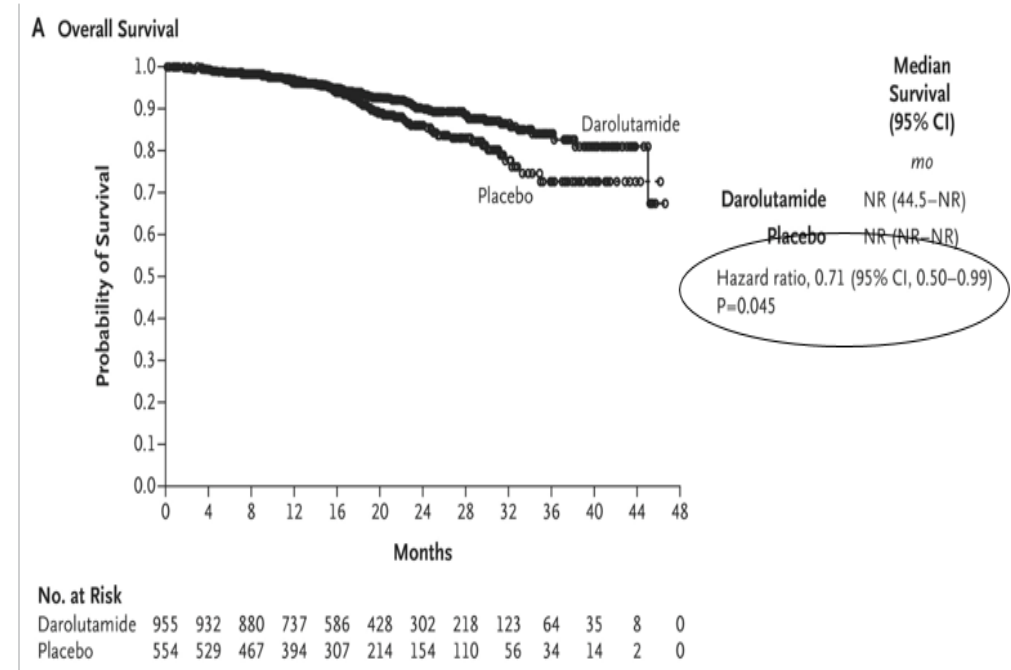
Metastasis-free survival

Fizazi, NEJM 2019



Overall Survival

Fizazi, NEJM 2019



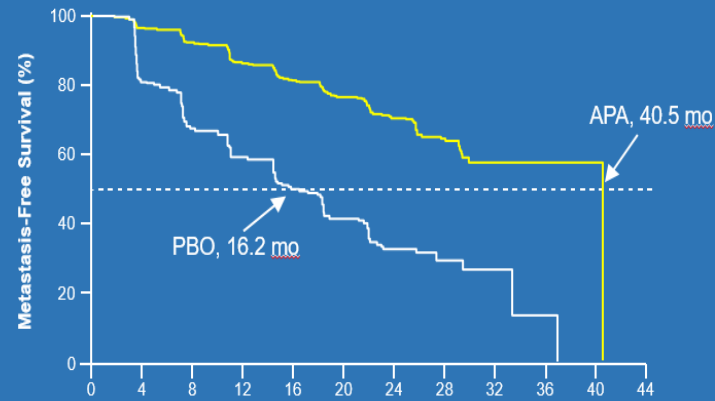


Apalutamide drug rxn

Apalutamide in M0 mCRPC – “Spartan”

Metastasis Free Survival

Small et al, NEJM 2018



No. at risk

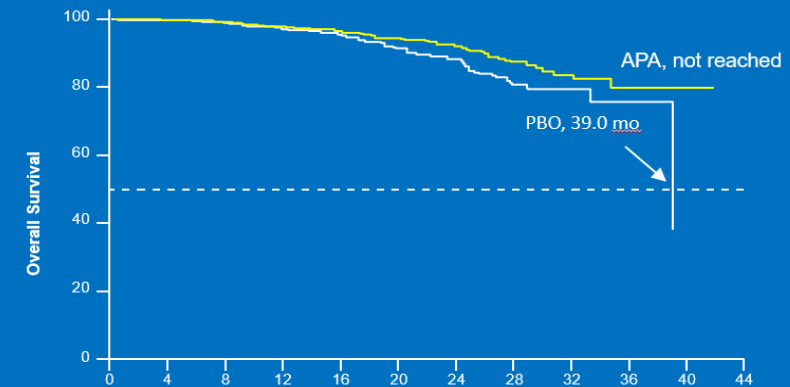
APA	806	713	652	514	398	282	180	96	36	16	3	0
PBO	401	291	220	153	91	58	34	13	5	1	0	0

HR, 0.28 (95% CI, 0.23-0.35)
 $P < 0.0001$

Overall Survival

Small, et al, NEJM 2018

SPARTAN-Overall Survival



No. at risk

APA	806	788	756	647	527	392	275	162	64	26	4	0
PBO	401	387	374	319	248	183	126	64	29	9	0	0

HR, 0.70 (95% CI, 0.47-1.04)
 $P = 0.07$

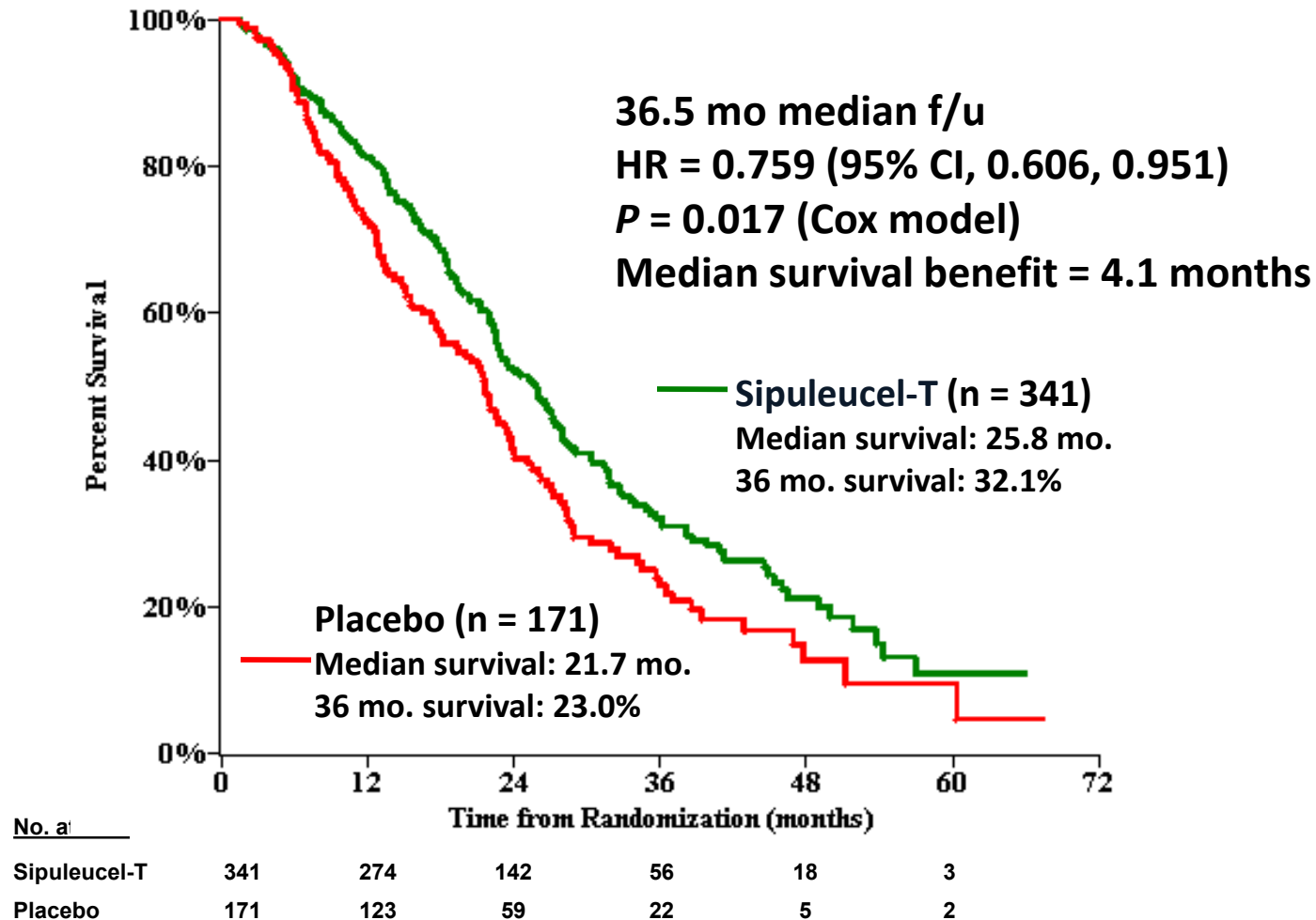
...Takeaways for M0 castration resistant prostate cancer

- Enzalutamide, apalutamide, darolutamide
- Treatment choices based on patient KPS, potential drug interactions, medical co-morbidities
- NO right choice
- Consider role of CNS penetration, risk of falls, fatigue, sz risk
- DOES M0 REALLY EXIST? WOULD M0 BE GONE IF PSMA IMAGING WAS PERFORMED?

Indication:

Asymptomatic of
minimally symptomatic
mCRPC

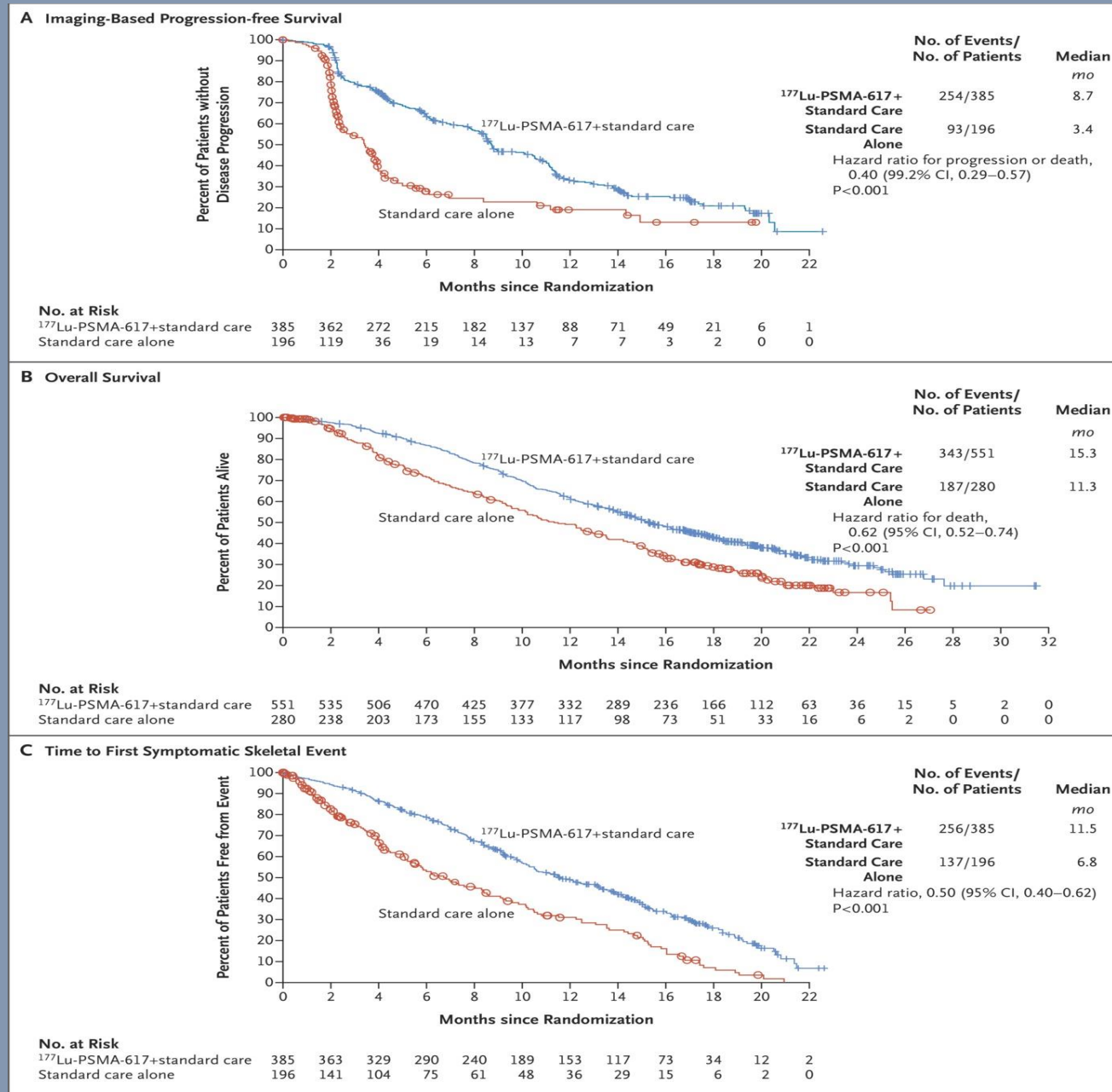
IMPACT OS (Sipuleucel-T) Final Analysis (349 events)



Bone-directed/Targeted therapies (PSMA/genomics)

- **Theranostics** - combination of using one radioactive drug to identify (diagnose) and a second radioactive drug to deliver therapy to treat the main tumor and any metastatic tumors.
- **Radioligand therapy** - delivers radiation to specifically targeted cancer cells, with a minimal effect on healthy cells
- **^{177}Lu -PSMA-617** binds to prostate cancer cells that express PSMA with high tumor-to-normal tissue uptake. Once bound, emissions from the radioisotope damage tumor cells, disrupting their ability to replicate and/or triggering cell death.
- phase III international **VISION trial** in combination with standard-of-care treatment, led to an increase in rPFS and OS. (Sartor, et al, N Engl J Med 2021;385:1091-103)
- Actinium, Thorium
- Radium-223

Imaging-based Progression-free Survival and Overall Survival (Primary Efficacy Outcomes) and Time to the First Symptomatic Skeletal Event (Key Secondary Outcome).



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
	<i>number of patients (percent)</i>			
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)

* Shown are data for all the patients who underwent randomization and received at least one dose of their assigned treatment (standard care, with or without ¹⁷⁷Lu-PSMA-617). Adverse events during the treatment period were those that occurred on or after the start of randomized treatment and up to 30 days after the last administration of the randomized treatment (standard care or ¹⁷⁷Lu-PSMA-617, whichever was later) or before subsequent anticancer treatment. Adverse events were coded with the use of Common Terminology Criteria for Adverse Events, version 5.0, and terms from the *Medical Dictionary for Regulatory Activities*, version 23.1. NA denotes not applicable.

† Patients who had been randomly assigned to receive ¹⁷⁷Lu-PSMA-617 plus standard care and who did not receive ¹⁷⁷Lu-PSMA-617 but did receive standard care were included in the control group (standard care alone) of the safety population; 3 patients had adverse events during cycle 1 of ¹⁷⁷Lu-PSMA-617 therapy that led to the interruption (in 2 of 205 patients [1.0%]) or discontinuation (in 1 [0.5%]) of that therapy.

‡ Five adverse events that led to death in the ¹⁷⁷Lu-PSMA-617 group were considered by the investigators to be related to the drug: pancytopenia (in 2 patients), bone marrow failure (in 1), subdural hematoma (in 1), and intracranial hemorrhage (in 1).

Takeaways for castration resistant M1 disease...

- Clinical trials
- Asymptomatic or minimally symptomatic – Sipuleucel-T (PROVENGE)
- SOC docetaxel as first line chemotherapy, second line is cabazitaxel
- If no prior ARSIs, can consider post chemo
- If chemo first, then can consider ARSIs
- Genomic profiling: BRCA+ rucaparib; other genomic abnormalities consider olaparib (broader indication although no strong data to support all genomic alterations cited in trial, esp ATM)
- Ra-223 for “symptomatic” metastatic disease
- Radioligand therapy: lutetium PSMA

Precision Medicine in Prostate Cancer

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

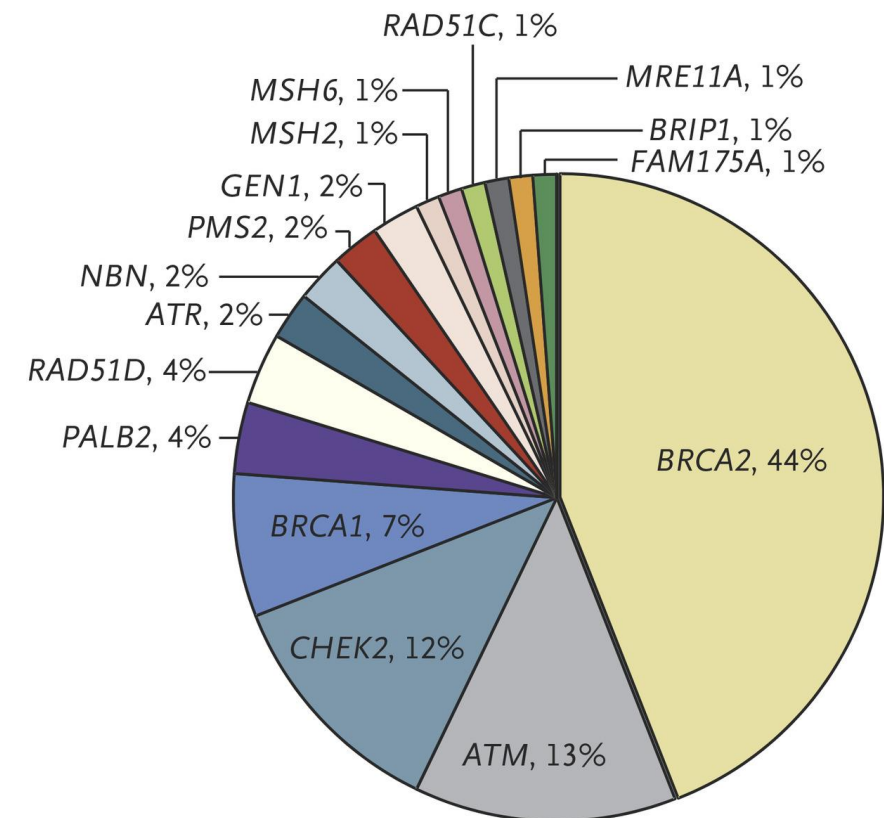
C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

August 4, 2016

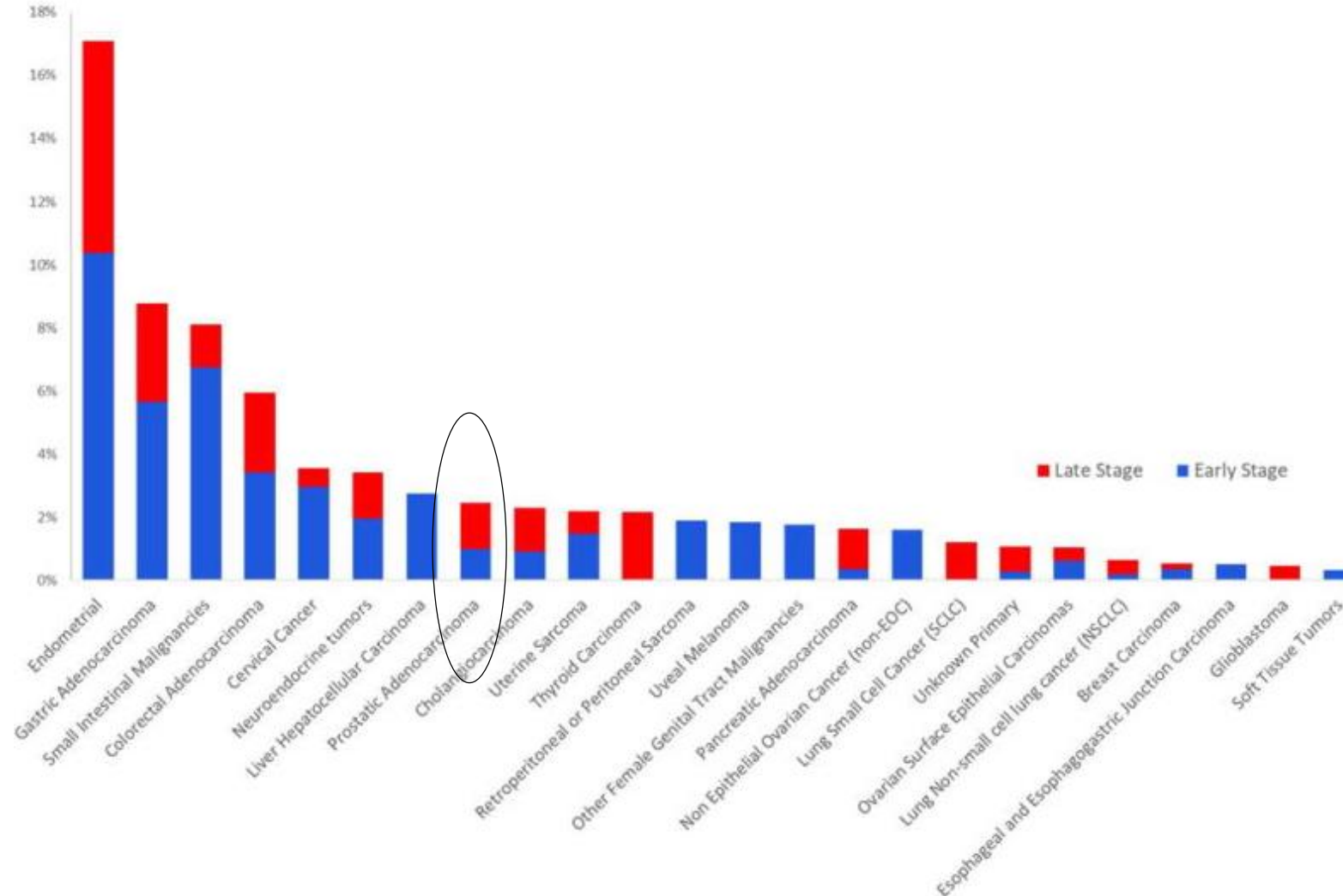
N Engl J Med 2016; 375:443-453

DOI: 10.1056/NEJMoa1603144

- Incidence of germline mutations in DNA damage repair genes in men with metastatic prostate cancer = 11.8%



Mismatch Repair Deficiency



Le et al. Science 2017

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

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

Prostate Cancer Stage or Risk Group (diagnosed at any age)

Metastatic, regional (node positive), very-high risk localized, high-risk localized prostate cancer

Family History^a and/or Ancestry

First-, second-, or third-degree relative with:

Prostate cancer at age ≤50 y

Colorectal or endometrial cancer at age ≤50 y

Male breast cancer at any age

Ovarian cancer at any age

Exocrine pancreatic cancer at any age

Metastatic, regional, very-high-risk, high-risk prostate cancer at any age

First-degree relative (father or brother) with:

Prostate cancer^b at age ≤60 y

First-, second-, or third-degree relatives with:

Prostate cancer at any age

Prostate cancer^b at any age

First- or second-degree relatives with:

Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper

tract urothelial, glioblastoma, biliary tract, and small intestinal cancer

Known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1*, *BRCA2*, *ATM*,

MLH2, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*

Ashkenazi Jewish ancestry

Personal history of breast cancer

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

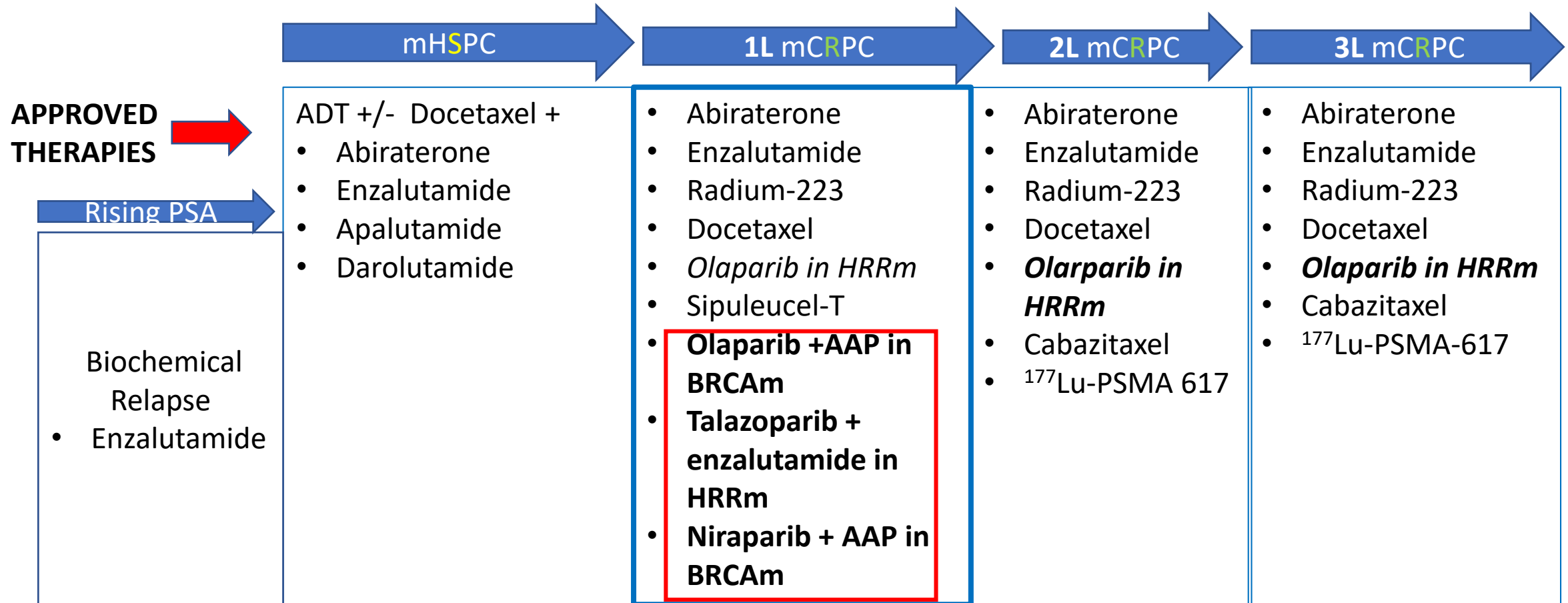
Prostate Cancer Tumor Characteristics (diagnosed at any age)

Intermediate-risk prostate cancer with intraductal/ciribriform histology^c

Prostate cancer^b AND a prior personal history of any of the following cancers:

Exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract, and small intestinal

PROSTATE CANCER LANDSCAPE IS SHIFTING RAPIDLY



Approved PARP Inhibitors in Prostate Cancer

Drug	Timing	Targets
Olaparib	mCRPC, either before or after chemotherapy	(Cohort A) BRCA1, BRCA2, ATM (Cohort B) BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, or RAD54L
Rucaparib	monotherapy	BRCA1, BRCA2

* Rucaparib in mCRPC s/p an ARSI **AND** prior taxane

Efficacy differences among the PARP_i Quartet: Olaparib/rucaparib/niraparib/talazoparib

- Ability to trap PARP on DNA
- All bind to PARP 1
- Pharmacokinetics, toxicity to kidney and liver vary
- Rucaparib is the least selective with indiscriminant binding to other PARP proteins and targets such as hexose-6-phosphate dehydrogenase.
- Talazoparib – 100-1000-fold better at trapping PARP on DNA c/w olaparib and rucaparib; latter are both better than an older generation PARP veliparib by a factor of 5-10.

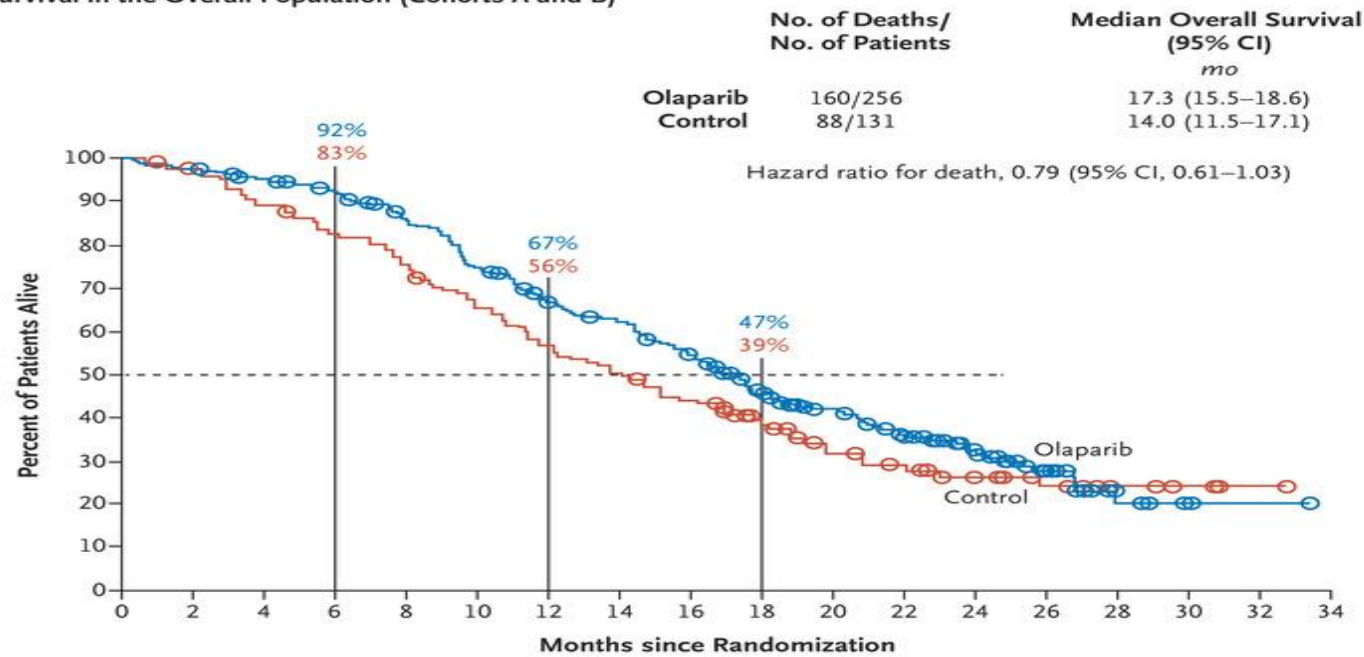
First in its class: olaparib

- Olaparib -treatment option for pts with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L) who have been treated previously with androgen receptor-directed therapy.
- Efficacy appears to be driven by the cohort of pts with at least one alteration in BRCA2, BRCA1, or ATM, and in pts with BRCA2 or BRCA1 mutations based on exploratory gene-by-gene analysis.

Phase III trials of ARSI + PARP inhibitor in 1st line treatment setting in mCRPC

- **PROpel:** Abiraterone/prednisone +/- Olaparib (Clarke, et al, NEJM 2022; Saad, et al, Lancet, 2023)
- **MAGNITUDE:** Abiraterone/prednisone +/- Niraparib (Chi, et al, J Clin Onc, 2023)
- **TALAPRO:** Enzalutamide +/- talazoparib (Agarwal, et al, Lancet, 2023)

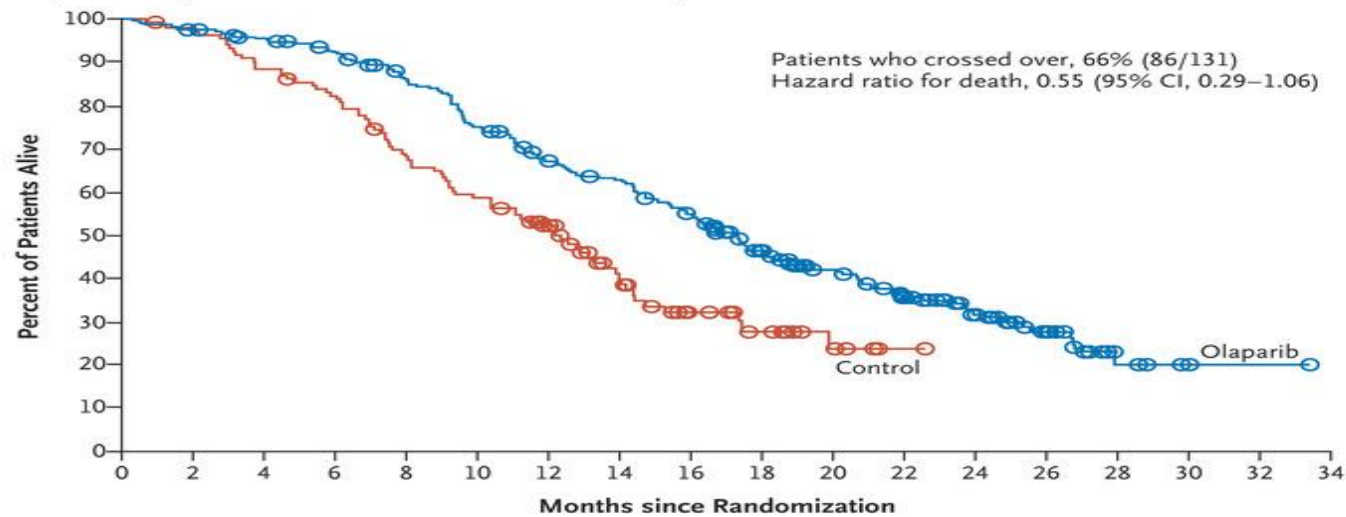
A Overall Survival in the Overall Population (Cohorts A and B)



No. at risk
Olaparib
Control

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

B Crossover-Adjusted Analysis of Overall Survival in the Overall Population



No. at risk
Olaparib
Control

256	249	240	228	209	182	157	146	126	96	73	56	39	22	7	2	1	0
131	125	114	105	86	74	54	33	19	12	6	1	0	0	0	0	0	0

PROfound Study

Olaparib with wide approval for diverse alterations including ATM; indication is for post abiraterone/enzalutamide

Rationale for PROpel...

- Preclinical work and results of a phase 2 trial of abiraterone (Abi) + Olaparib (Ola) suggested a combined antitumor effect when ola was combined with next-generation hormonal agent abiraterone to treat mCRPC
- double-blind, phase 3 trial of abi and ola vs abi and placebo in pts with mCRPC in the first-line setting
- randomly assigned (1:1) to receive Abi (1000 mg once daily) + prednisone or prednisolone with either Ola (300 mg twice daily) or placebo.
- Enrollment regardless of homologous recombination repair gene mutation (HRRm) status. HRRm status was determined following enrollment by tumor tissue and circulating tumor DNA tests.

PROpel: Phase III trial design

Patient population

- 1L mCRPC
- Asymptomatic, mildly symptomatic, symptomatic
- No prior abiraterone
- Other NHAs allowed if stopped ≥ 12 months prior to enrollment
- ECOG 0–1

Stratification factors

- Site of distant metastases: bone only vs visceral vs other
- Prior taxane at mHSPC: yes vs no

1:1

Abiraterone 1000 mg qd*
+
olaparib 300 mg bid
n=399

Full dose of abiraterone and
olaparib

Abiraterone 1000 mg qd*
+
placebo
n=397

Full dose of abiraterone

Primary endpoint

- rPFS by investigator assessment
(sensitivity analysis by blinded independent central review)

Key secondary endpoint

- OS

Additional preplanned analyses:

- TFST
- PFS2
- HRQoL
- HRRm status (by tissue and ctDNA after randomization and before primary analysis; see supplement)
- Safety and tolerability

DCO1: 30 July 2021
rPFS (primary)

DCO2: 14 March 2022
OS (interim)

DCO3: 12 October 2022
OS (final pre-specified)
current dataset

Analysis timeline:

*In combination with prednisone or prednisolone 5 mg bid.

bid, twice daily; ctDNA, circulating tumor DNA; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; HRRm, homologous recombination repair mutation; HRQoL, health-related quality of life; mHSPC, metastatic hormone-sensitive prostate cancer; PFS2, time to second progression or death; qd, once daily; TFST, time to first subsequent therapy or death.

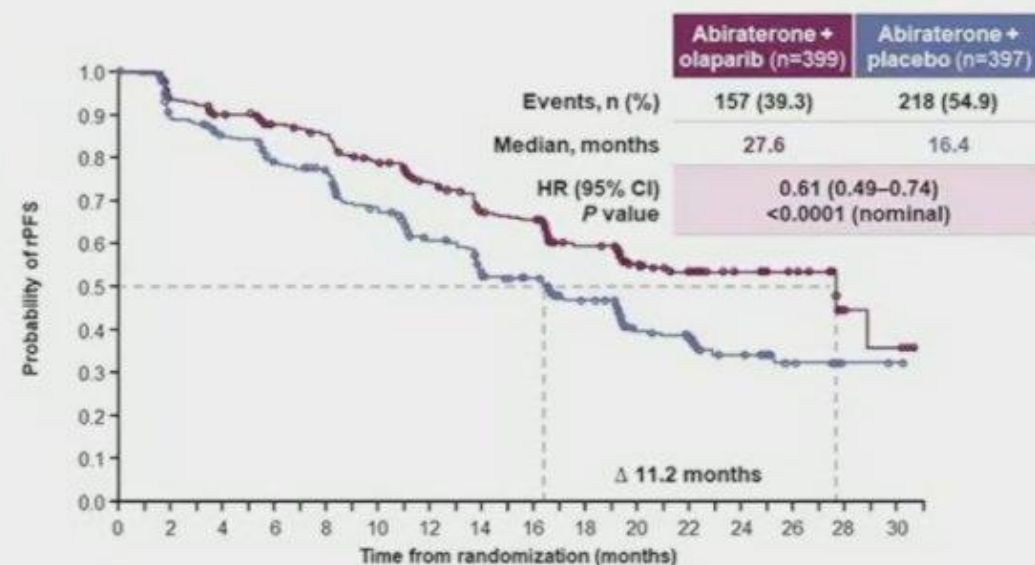
rPFS by investigator assessment (INV)



Number of patients at risk:

Abiraterone + olaparib 399	367	340	313	301	274	251	227	219	167	104	87	57	26	5	4
Abiraterone + placebo 397	359	338	306	297	264	232	198	186	141	87	73	43	17	2	1

rPFS by blinded independent central review (BICR)

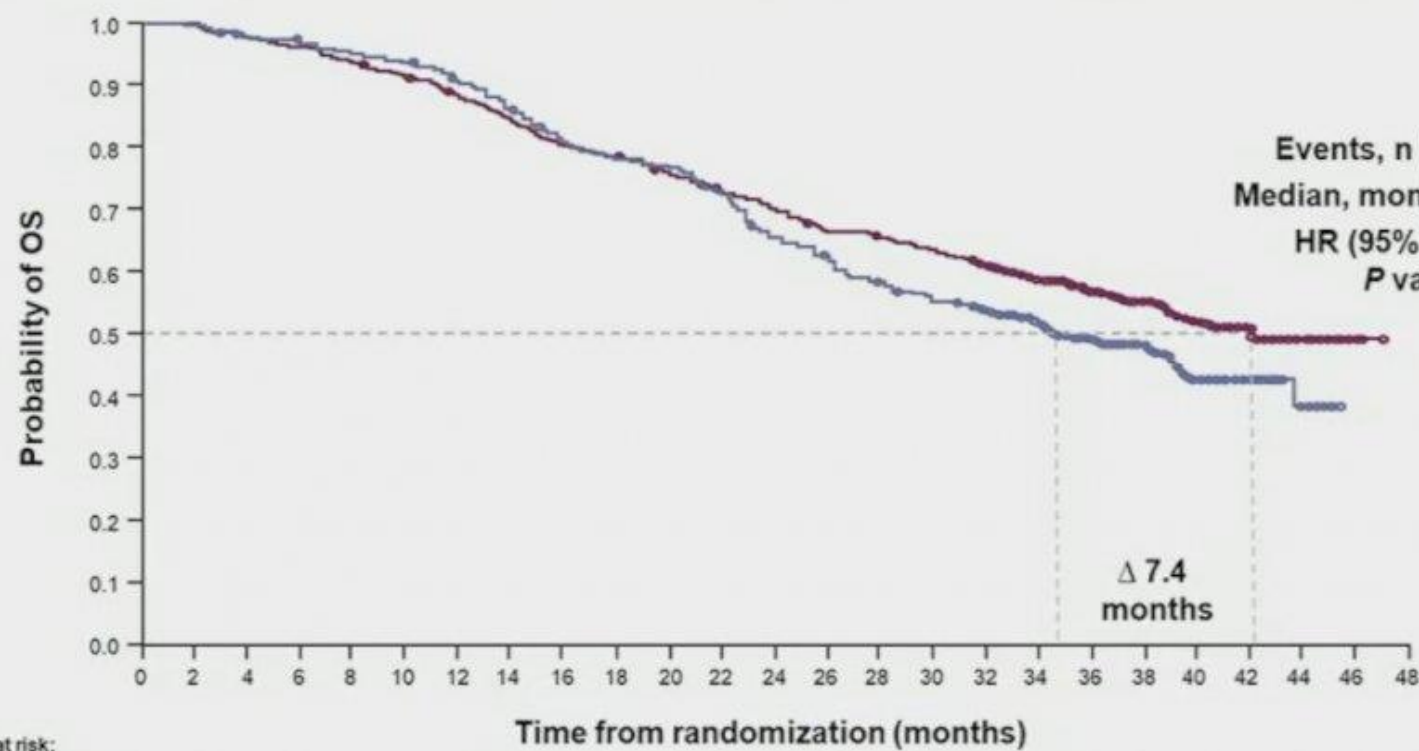


Number of patients at risk:

Abiraterone + olaparib 399	353	332	314	303	275	249	221	215	161	96	80	53	28	5	4
Abiraterone + placebo 397	345	322	294	282	245	209	177	168	126	73	62	38	16	2	1

Results...

- At median follow-up of 19.4 months, ola/abi significantly **improved median investigator-assessed rPFS from 16.6 to 24.8 months** (HR: 0.66, 95% CI: 0.54 – 0.81, $p < 0.001$).
- Consistent results observed when rPFS was assessed via blinded-independent central review (BICR).
- rPFS benefits observed irrespective of HRRm status; **magnitude of effect was higher in the HRRm** (HR: 0.50, 95% CI: 0.34 – 0.73) versus non-HRRm patients (HR: 0.76, 95% CO: 0.60 – 0.97).
- Subgroup analysis, rPFS benefits were observed irrespective of prior docetaxel exposure and metastatic site.
- pre-planned final OS analysis was presented at ASCO GU 2023 -**consistent trend towards an OS benefit with ola/abi in the overall ITT population** (data maturity: 47.9%; HR 0.81, 95% CI: 0.67 – 1.00, $p = 0.054$), with median OS of 42.1 and 34.7 months, respectively.



Number of patients at risk:

Abiraterone + olaparib

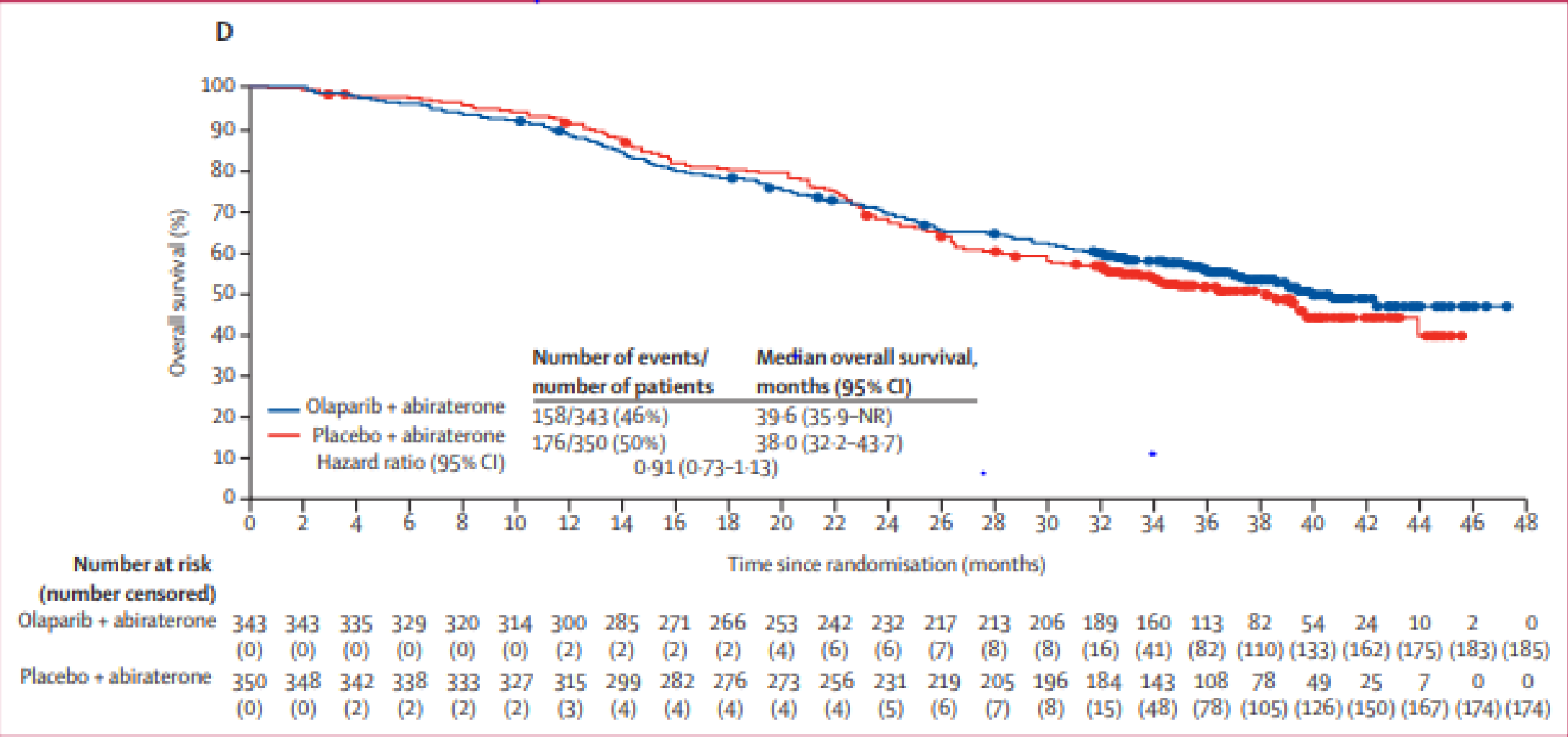
Abiraterone + placebo

399	399	391	385	374	364	349	334	318	312	298	283	273	258	253	246	226	192	135	96	63	29	10	2	0
397	395	388	383	376	370	355	337	316	305	301	282	254	241	225	213	201	157	119	84	53	25	7	0	0

	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	176 (44.1)	205 (51.6)
Median, months	42.1	34.7
HR (95% CI)	0.81 (0.67–1.00)	
P value	0.0544	
2-sided boundary for significance	0.0377	
47.9% maturity		

Update, Saad, et al, 2023- final prespecified overall survival analysis. Takeaway...

- PROpel - met its primary endpoint
- statistically significant improvement in **rPFS** with ola/abi in pts initially unselected by HRRm status
- benefit observed in all prespecified subgroups
- post-hoc exploratory assessment of OS done in aggregate HRRm, non-HRRm, BRCAmutated, and non-BRCA-mutated subgroups, with **BRCA-mutated pts deriving greatest rPFS and OS benefits with ola/abi.**
- Combo - FACT-P data showed no overall detriment on patients' health-related quality of life.
- **UPDATED analysis: OS - not statistically significantly different between treatment groups at the final prespecified analysis**
- 1^o endpoint of rPFS met; statistically significant and clinically meaningful difference in favor of combo



Kaplan-Meier estimates of OS: (A) Overall survival in the HRRm subgroup. (B) Overall survival in the non-HRRm subgroup. (C) Overall survival in the BRCA-mutated subgroup. (D) Overall survival in the non-BRCA-mutated subgroup. Data cutoff Oct 12, 2022. Any patient not known to have died at the time of analysis was censored on the basis of the last recorded date on which the patient was known to be alive. A circle indicates a censored observation. HRRm=homologous recombination repair gene mutation. NR=not reached. (Saad, et al, Lancet, Sept 12, 2023)

Limitations...

- BUT, should combo be used irrespective of germline or HRRm status?
- did not enroll pts who had progressed on a previous NHA pre-mCRPC.
- now noted is that many pts receive NHAs in the castration-sensitive setting.
- Notably, as enrollment in PROpel was not based on HRRm status or whether pts had asymptomatic, mildly symptomatic, or symptomatic disease pts were representative of those eligible for abiraterone in the real-world setting.

MAGNITUDE...

- phase III, randomized, double-blind, placebo-controlled, multicenter trial
- evaluated combination of Abi/prednisone +/- **niraparib** in mCRPC pts receiving first-line treatment.
- included biomarker pre-screened cohorts; all pts had HRR mutational status determined prior to study enrollment. HRR mutational status was determined using tissue and/or blood samples.
- Pts with gene alterations - (*ATM*, *BRCA1/2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *HDAC2*, or *PALB2*) detected by ≥ 1 assay were assigned to the HRR+ cohort; those with both assays negative were included in the HRR- cohort.
- Pts in the HRR+ and HRR- cohorts underwent 1:1 randomization to receive either reduced-dose niraparib 200 mg once daily (usual dose: 400 mg) and Abi 1,000 mg once daily plus prednisone 5 mg twice daily or placebo + Abi/prednisone.

MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study ³

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM-

Study start: February 2019

Patient eligibility

- L1 mCRPC
 - ≤4 months prior AAP allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score ≤3

Stratifications

- Prior taxane-based chemo for mCSPC
- Prior ARi for nmCRPC or mCSPC
- Prior AAP for L1 mCRPC
- HRR BM+ cohort only:
 - BRCA1/2 vs other HRR gene alterations

Prescreening for BM status^a

HRR BM+ panel:
ATM
BRCA1
BRCA2
BRIP1
CDK12
CHEK2
FANCA
HDAC2
PALB2

Allocation to cohort

HRR BM+
Planned N = 400

HRR BM-
Planned N = 600

1:1 randomization

Niraparib + AAP

Placebo + AAP

Niraparib + AAP

Placebo + AAP

Primary endpoint

- rPFS by central review

Secondary endpoints

- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

Other prespecified endpoints

- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM- status.

Note: Patients could request to be unblinded by the study steering committee and go on to subsequent therapy of the investigator's choice.

Plan...

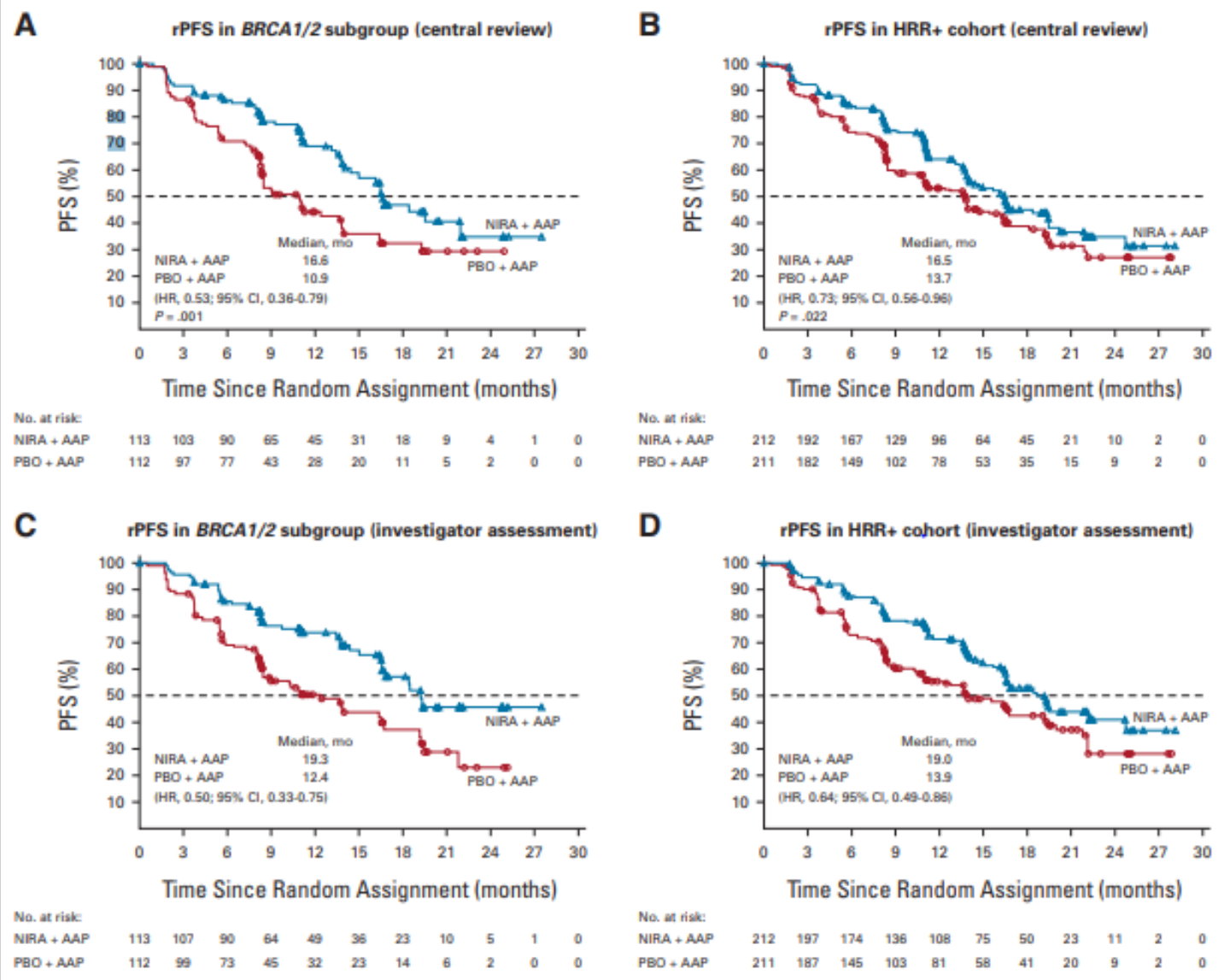
- Futility analysis preplanned given concerns that there was a lower likelihood of clinical benefit with combination treatment in the HRR-cohort,
- futility analysis planned for when approximately 200 pts had been enrolled and approximately 125 composite end point events (the first of either PSA progression, radiographic progression, or death) had occurred.
- For the HRR+ cohort, primary and secondary endpoints were tested using a pre-specified strategy.
- Primary rPFS endpoint was powered for and tested first in the *BRCA1/2* subgroup; if statistical significance attained, the remainder of the HRR+ patients would be analyzed. Approximately 50% of HRR+ patients were specified to be *BRCA1/2* positive.

RESULTS...

- futility analysis in the **HRR-** cohort (n=233) - **NO** benefit for niraparib/Abi vs placebo/Abi. The hazard ratio for the composite endpoint was 1.09, with futility defined as a hazard ratio greater than 1.0.
- Noted were grade ≥ 3 AEs occurred with addition of niraparib. Given the increased toxicity with no observed oncologic efficacy, the independent data monitoring committee recommended suspending enrollment in the HRR- cohort.

HOWEVER...

Chi, et al, J Clin Oncol, 2023



Conclusions... takeaway

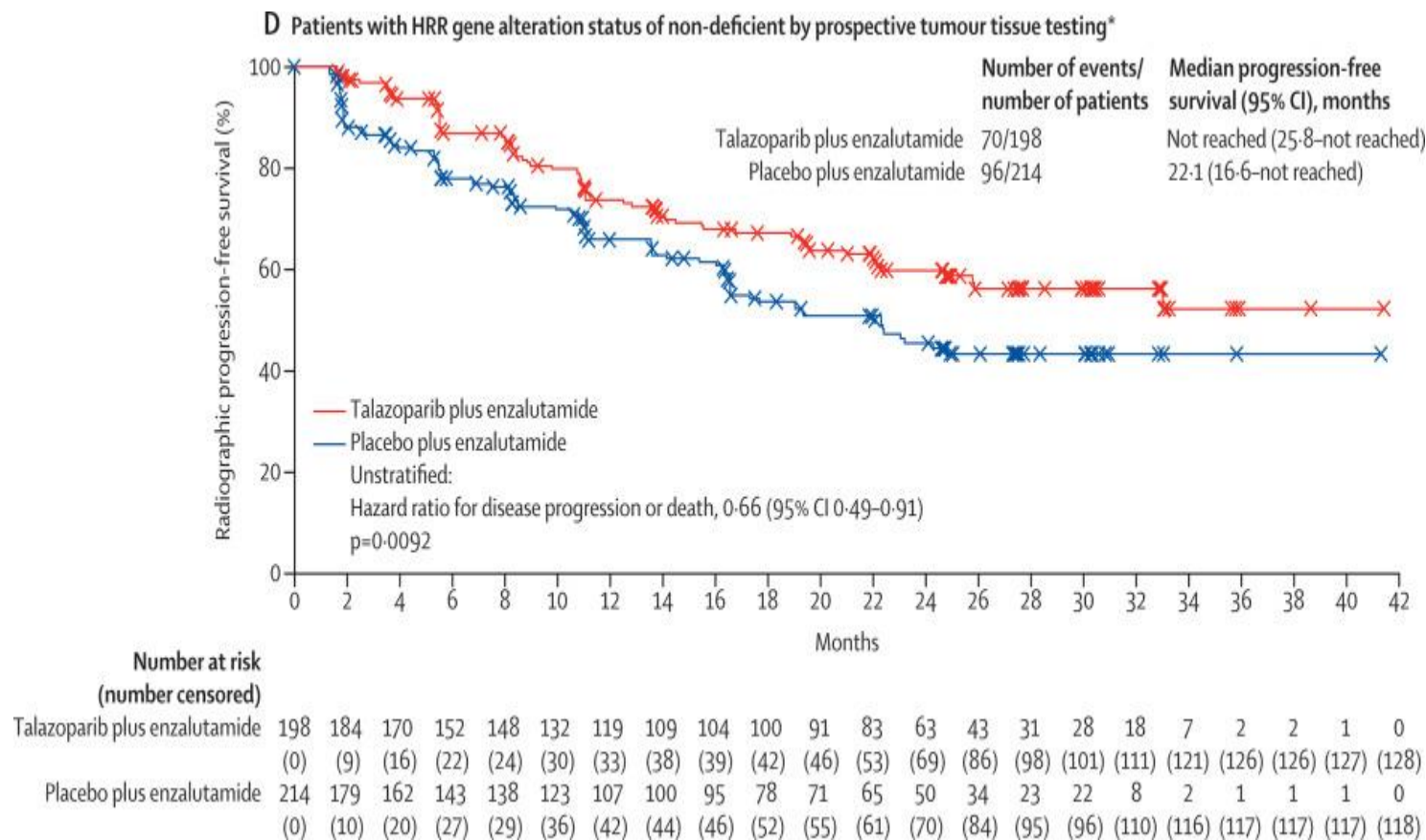
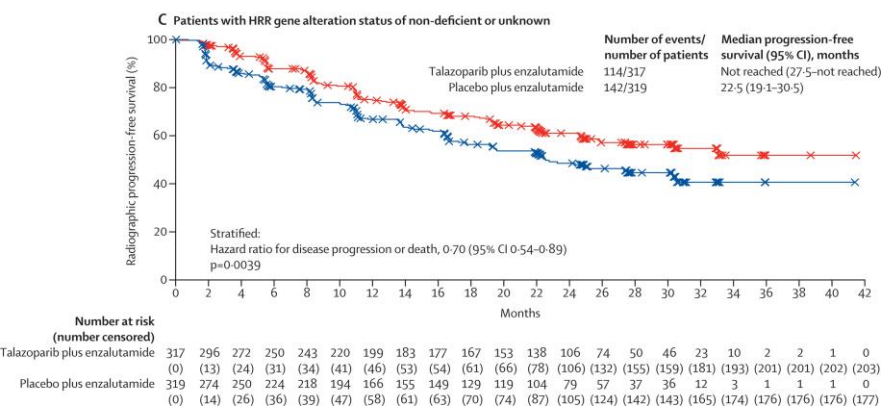
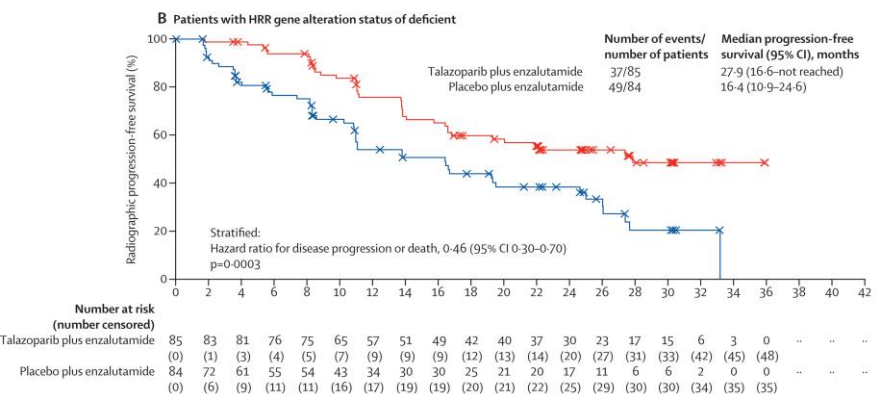
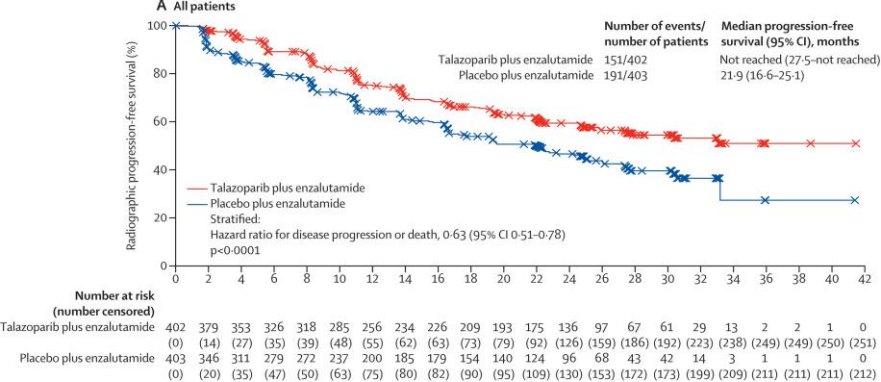
- Median rPFS in the BRCA1/2 subgroup - **significantly longer in the nira + AAP group** c/w placebo + AAP group (16.6 v 10.9 mo; HR, 0.53; 95% CI, 0.36 to 0.79; $P < .001$).
- overall HRRD cohort, **rPFS significantly longer in the niraparib + AAP group** c/w placebo + AAP group (16.5 v 13.7 months; HR, 0.73; 95% CI, 0.56 to 0.96; $P < .022$).
- improvement in 2° endpoints of time to symptomatic progression and time to initiation of cytotoxic chemotherapy.
- In the HRRD cohort, futility was declared per the prespecified criteria. Treatment with niraparib + AAP was tolerable, with anemia and hypertension as the most reported grade ≥ 3 adverse events.
- **CONCLUSION** *Combination treatment with niraparib + AAP significantly lengthened rPFS* **Approved**

Talapro...et al..

- Talapro 1, de bono, et al, talazoparib as monotherapy – durable antitumor activity in pts with DDR-HRR gene alterations ✓
- Talapro 2, Agarwal, et al, phase 3 talazoparib plus enza in pts with first line mCRPC with HRR gene-mutations *Approved* ✓
- Talapro 3, Agarwal, et al, phase 3 , double-blind, randomized study of enzalutamide plus talzoparib vs pacbro plus eza l pts with DDR gene mutated mCSPC - ongoing

Talapro 2

- Randomized double-blind, placebo controlled multi cohort trial
- N= 399 with HRR gene-mutated mCRPC
- 1:1 randomized to enza plus talazoparib 0.5mg po or placebo qd
- Randomized stratified by prior treatment with ARSI or docetaxel.
- HRR genes assessed prospectively
- Primary endpoint rPFS
- Statistically significant improvement in **rPFS** for combo c/w placebo with enzalutamide seen in HRR gene-mutated population: median NR vs 13.8 mo (HR 0.45: 95% CI: 0.33-0.61, p=0.0001)



Radiographic progression-free survival in all patients and according to HRR gene alteration status (assessed by blinded independent central review; all-comers intention-to-treat population)

HRR=homologous recombination repair. *Figure 2D shows an exploratory endpoint analysis by prospective tumour tissue testing to separate unknown from non-deficient HRR gene alteration status.

Radiographic progression-free survival in all patients and according to HRR gene alteration status (assessed by blinded independent central review; all-comers intention-to-treat population)

So.....final takeaway...

- **Yes**, we should do genomic profiling on all pts from diagnosis and during transition from hormone sensitive to castration resistant
- PARP inhibitors may not work for all BRCA mutations
- Consideration of BRCAness
- Multiple clonal metastases, each with their own genomic profiling
- Importance of both somatic and germline evaluation
- No one “right” method, ie, FoundationONE[®], Myriad[®], etc
- Cost may be limiting
- Not all PARPi are the same

Thank you