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ENABLING DISCOVERY | POWERING EDUCATION | SHAPING WORKFORCES

Learning Objectives

- At the end of this webinar, participants will be able to:
- Explain the role of radiation therapy (RT) to the prostate with regards to clinical outcomes in mHSPC
- Describe the relevance of volume of metastatic disease in relation to improved outcomes of RT in mHSPC

ASCO 2023: The role of prostate radiation with best systemic therapy

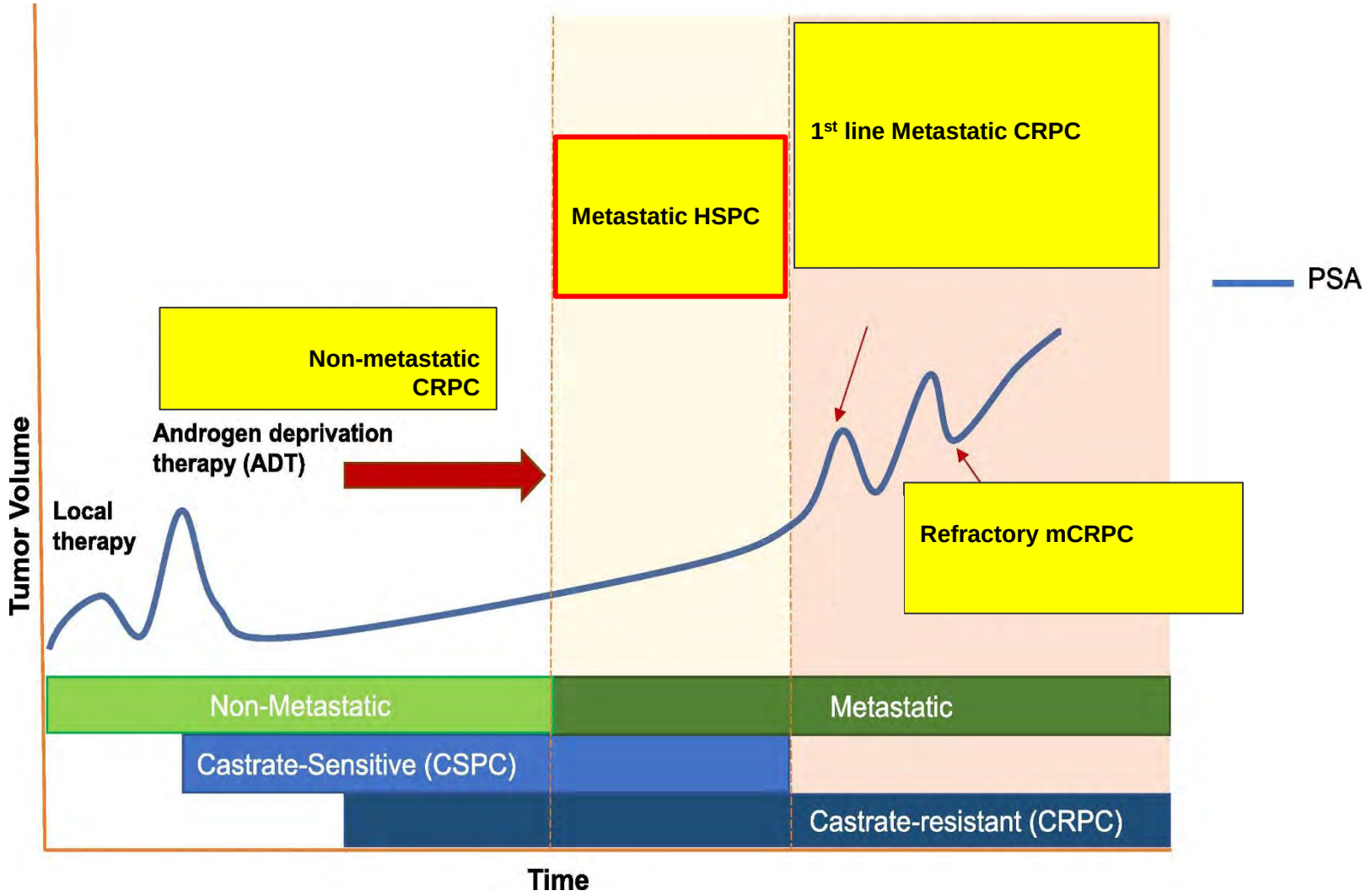
Disclosures

- **Honoraria:** Bayer, OncLive, MEDACorp, Oncology Learning Network, Aptitude Health, Targeted Oncology, Blackstone, Journal of Clinical Pathways, Cancer Network, Clinical Care Options, Great Debates and Updates, Pfizer, Springer Healthcare, Lantheus, Color Health, Wiley

- **Advisory Board:** Clovis, Dendreon, Bayer, Eli Lilly, AstraZeneca, Astellas, Blue Earth, Janssen, Tolmar, Sanofi Aventis

- **Research Funding:** Bayer (Institution), Pfizer (Institution)

Clinical states of advanced prostate cancer



Alkhudair NA. *Saudi Pharm J.* 2019 Mar;27(3):368-372.

Strategies demonstrating OS benefit with ADT in mHSPC in randomized Phase 3 trials

Chemotherapy
- Docetaxel – CHAARTED, STAMPEDE

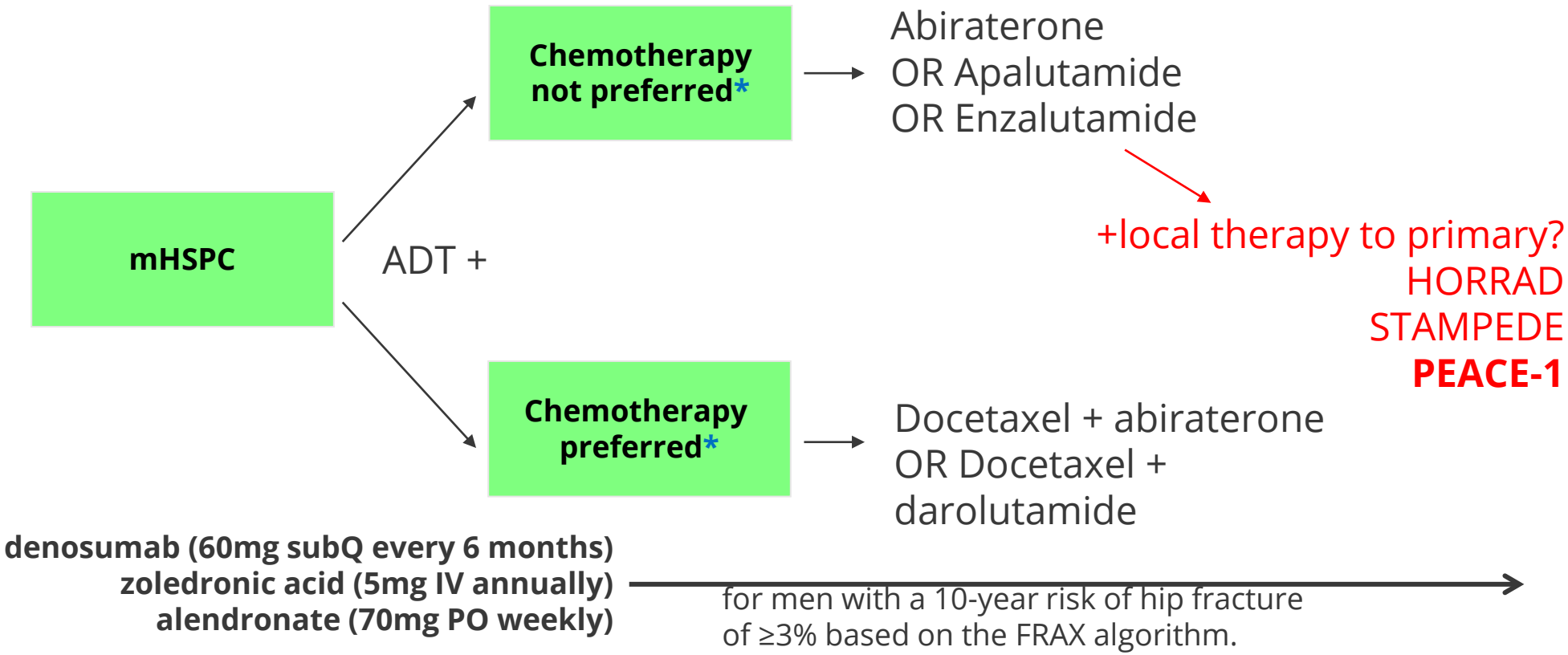
Androgen Receptor Pathway Inhibitors (ARPIs)
- Abiraterone – LATITUDE, STAMPEDE
- Enzalutamide – ENZAMET, ARCHES
- Apalutamide – TITAN

“Triplet” (addition to ADT + docetaxel backbone)
- Abiraterone – PEACE-1
- Darolutamde – ARASENS

Radiation to prostate
- STAMPEDE (OS benefit in patients with low volume disease)

➢ Eligibility for these trials require M1 disease by conventional imaging (bone scan + CT/MRI)

Systemic Therapy for Metastatic Hormone Sensitive Prostate Cancer 2022



*Considerations for chemotherapy preference

- low vs. high volume disease, prior local therapy vs. no (Gravis G, et al. European urology. 2018;73(6):847-855)
- chemotherapy fitness, symptom burden, cost / insurance coverage, patient preference
- Histologic / molecular features
  - Poorly differentiated, low PSA-producing
  - Genetic features (Velez MG, et al. Prostate Cancer Prostatic Dis. 2021 Jul 22.)
  - Gene expression profiling (Hamid AA, et al. ESMO 2021)

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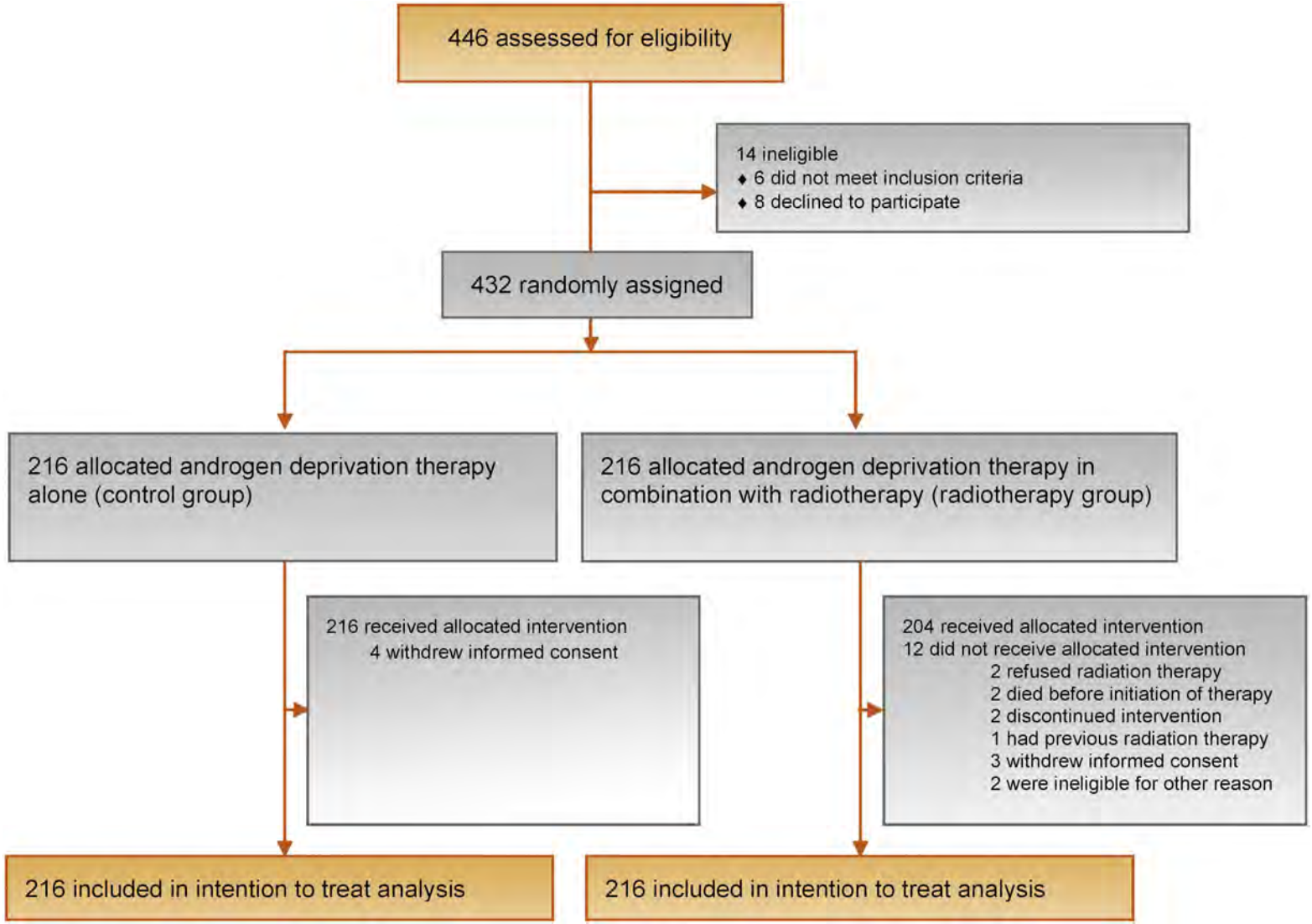
HORRAD



	ADT + radiotherapy (*n* = 216)	ADT alone (*n* = 216)
Age (range), yr.	67 (62–71)	67 (61–71)
PSA concentration at start of ADT, ng/ml		
Median (range).	125 (8–14 000)	149 (4–6991)
Osseous metastases		
<5 lesions	89 (41)	71 (33)
5–15	53 (25)	65 (30)
>15	74 (34)	80 (37)

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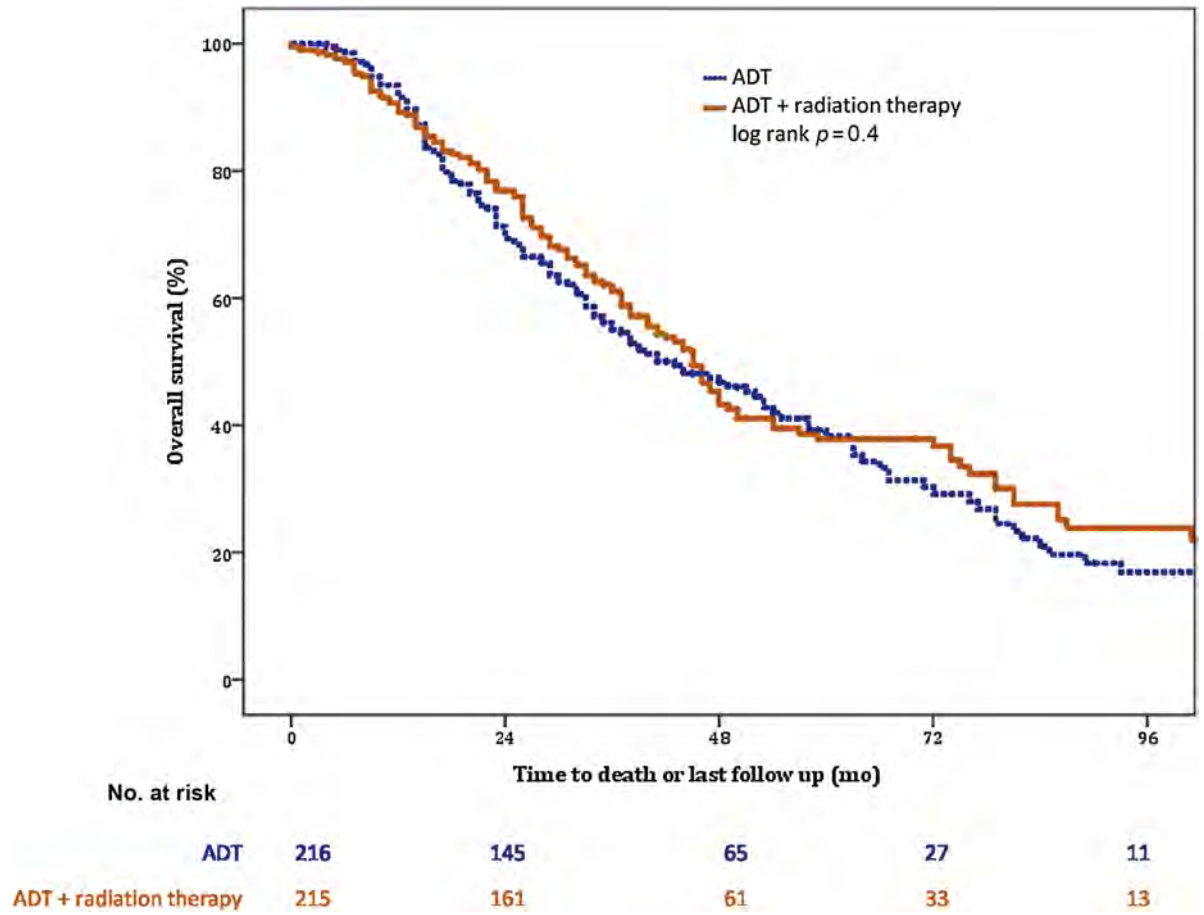
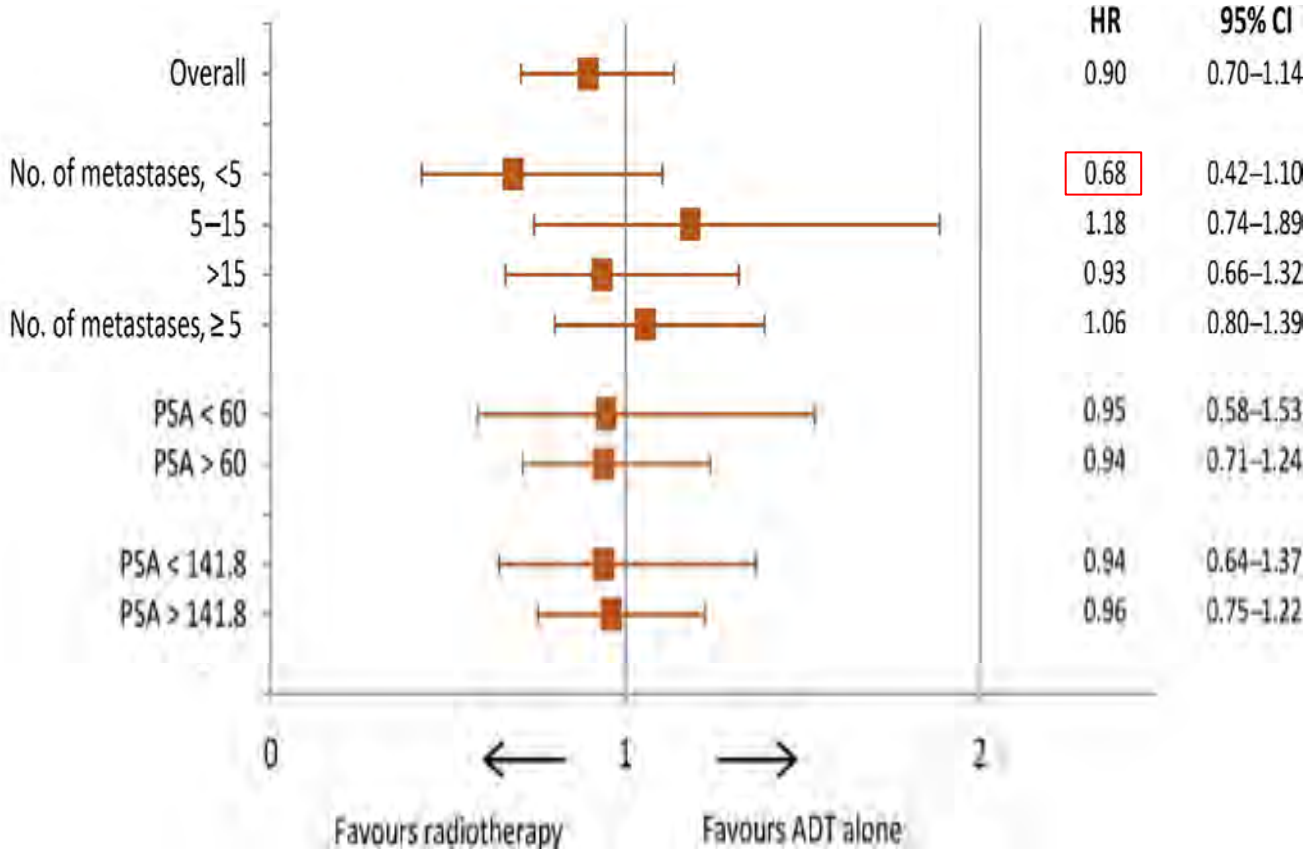
Boevé LMS, et al. *Eur Urol.* 2019 Mar;75(3):410-418.

HORRAD





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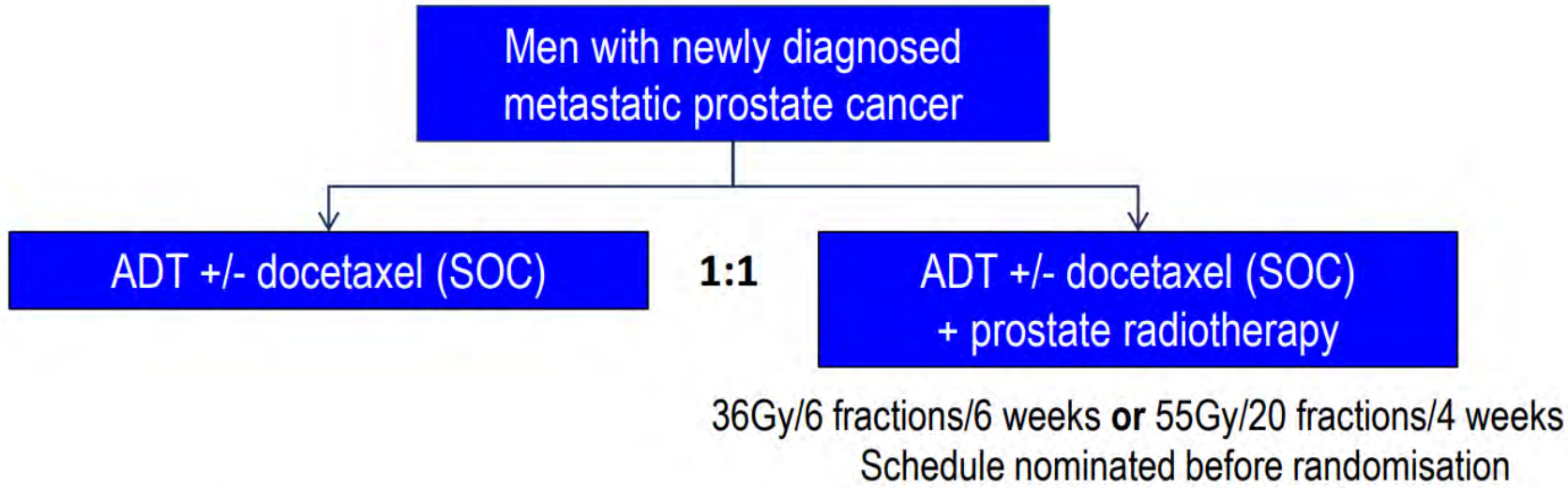
Boevé LMS, et al. *Eur Urol.* 2019 Mar;75(3):410-418.

STAMPEDE – RT comparison
Study Design



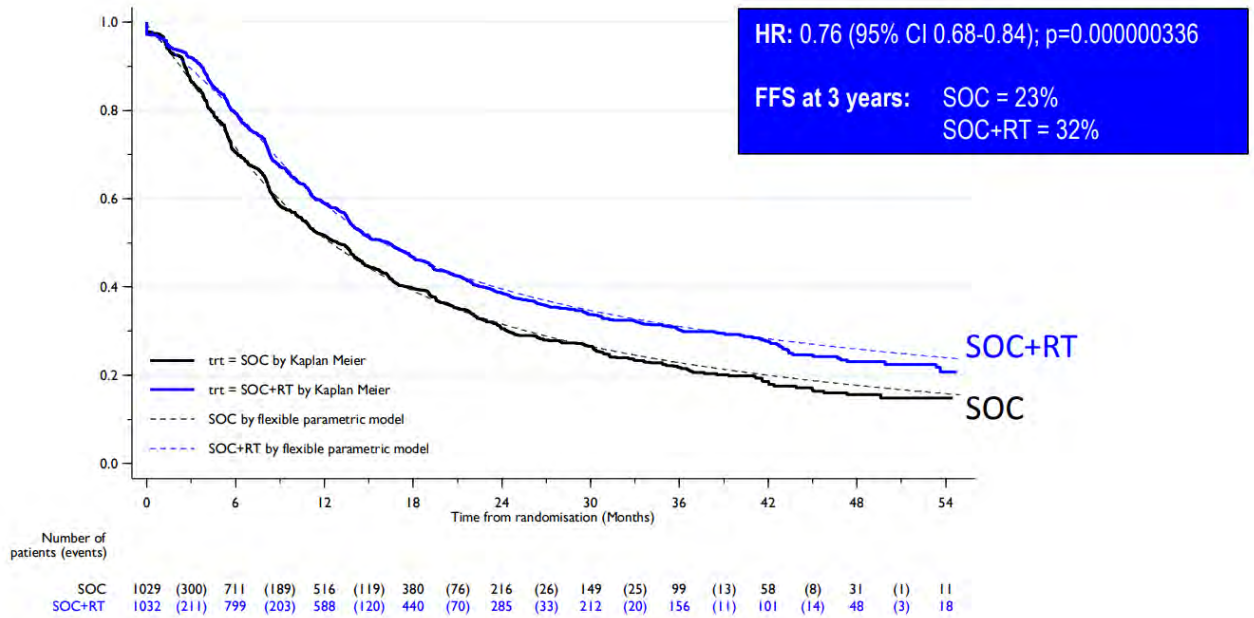
Stratification variables

Age (<70 vs ≥70 years), nodal involvement (N0 vs N1 vs Nx), randomising site,
WHO performance status (0 vs 1 or 2), type of ADT, aspirin or NSAID use, docetaxel use

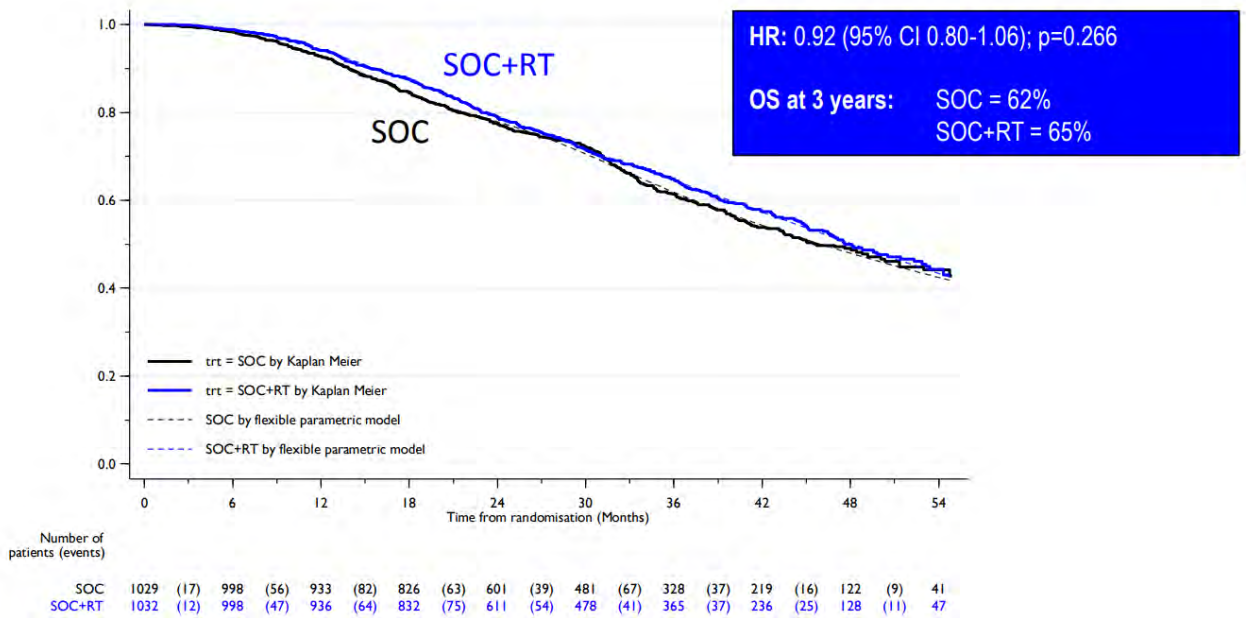
Parker CC, et al. Lancet. 2018 Dec 1;392(10162):2353-2366. [10]

STAMPEDE – RT comparison
Failure-Free Survival and Overall Survival in all patients

FFS



OS



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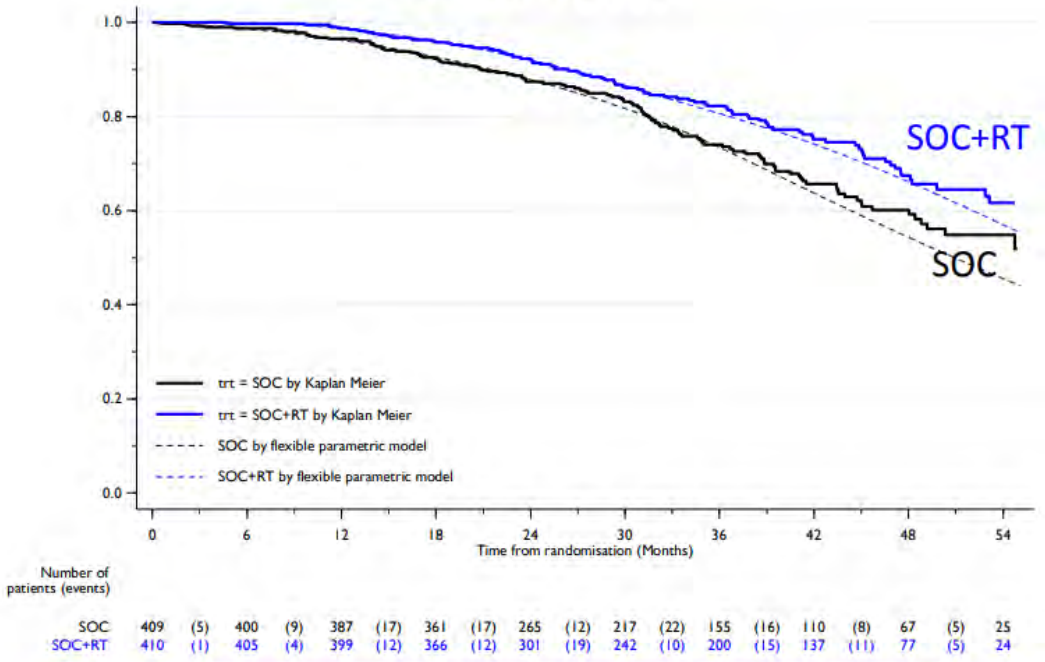
Parker CC, et al. Lancet. 2018 Dec 1;392(10162):2353-2366. [11]

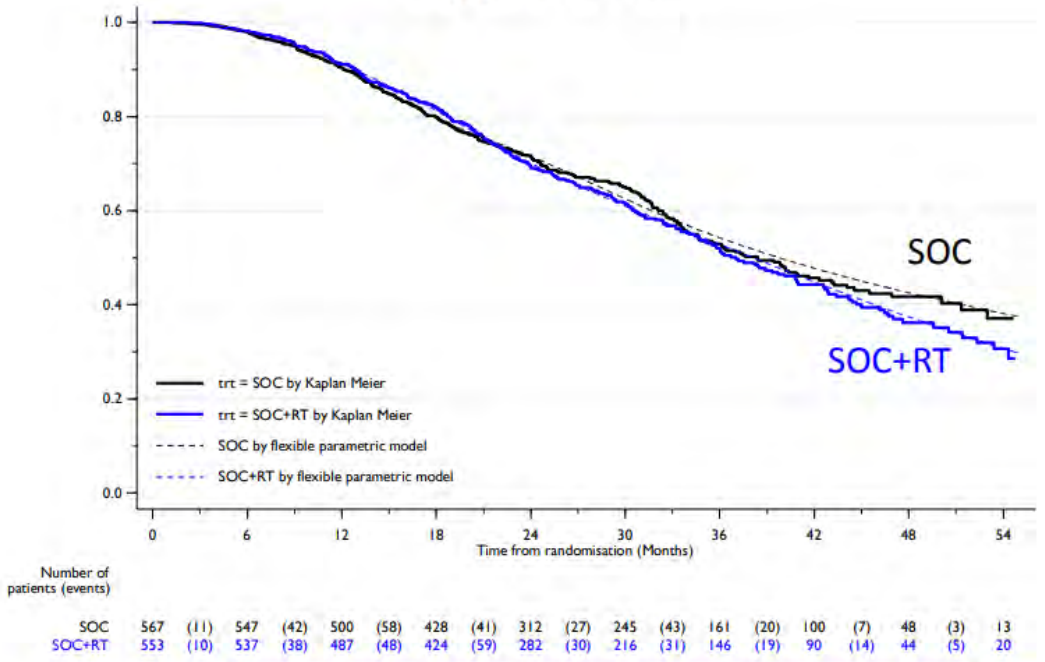
STAMPEDE – RT comparison
Overall Survival by Disease Burden

Low burden



HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%): SOC = 73%
SOC+RT = 81%

High burden



HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%

Parker CC, et al. Lancet. 2018 Dec 1;392(10162):2353-2366. [12]

Prostate RT in Metastatic Prostate Cancer

- Prostate RT with ADT improves OS in patient with low metastatic burden compared to ADT alone
  - ➢ Unknown OS benefit with docetaxel and/or abiraterone (**PEACE-1 RT comparison**, S1802 pending)
  - ➢ Unknown if OS benefit applies to surgery (TRoMbone, g-RAMPP pending)

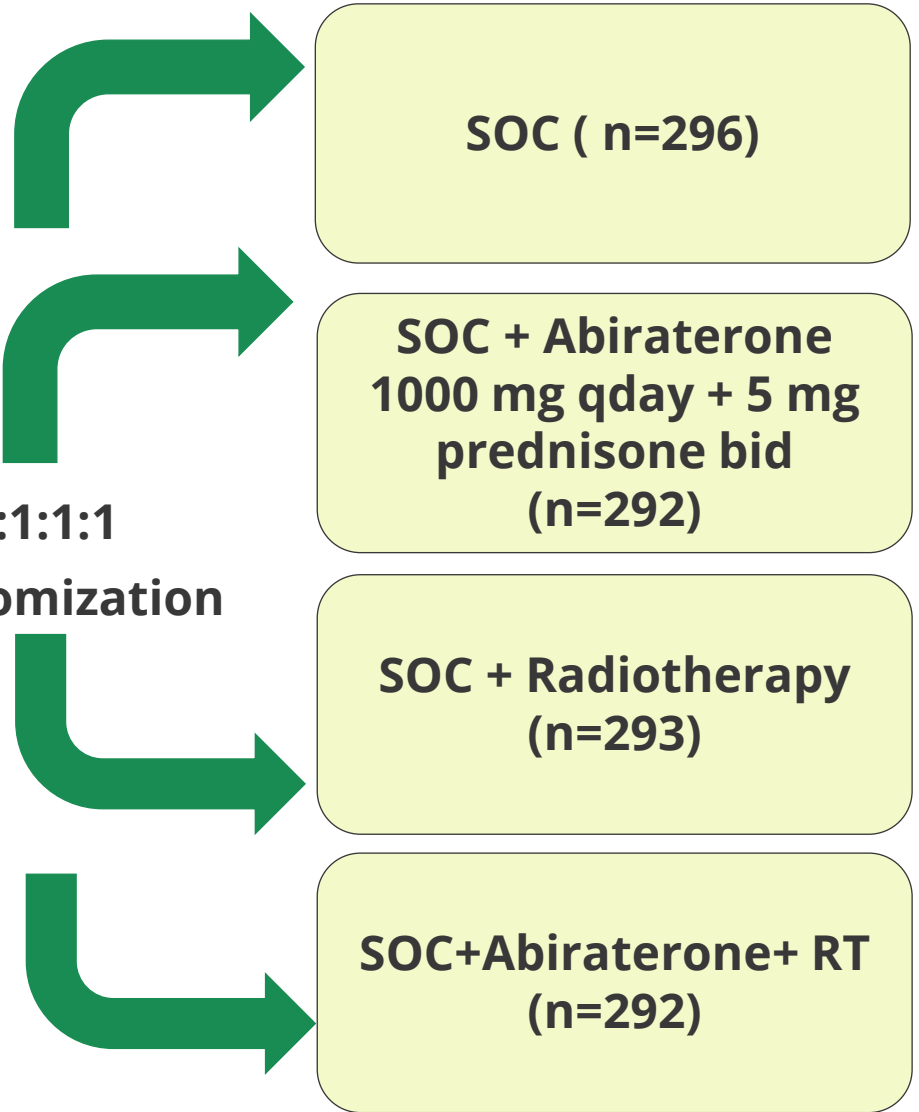
PEACE-1: Trial Design

- Open-label, randomized phase III trial with 2x2 factorial design

Included N=1173
- De novo mHSPC
- ECOG 0-2
- ≥ 1 lesion bone scan and/or CT imaging
- Continuous ADT

Stratified by:
- ECOG PS
- Metastatic site
- Type of castration
- Docetaxel exposure

1:1:1:1 Randomization



Endpoints

Primary
- Radiographic PFS
- Overall Survival

Secondary
- CRPC-free survival
- PSA response rate
- PSA at 6-8m
- Time to pain progression
- Time to chemo
- QOL

Fizazi, K. *et al. The Lancet 2022; 399*(10336), 1695–1707

PEACE-1: Treatments

PEACE-1 amended to allow for evolving SOC

- Nov 2013-2015: ADT alone (n=273)
- 2015-2017: Docetaxel permitted as part of SOC (n=592)
- 2017-Dec 2018: Docetaxel mandatory as part of SOC (n=308)

➢Statistics: Docetaxel as a Stratification factor

Fizazi, K. *et al. The Lancet 2022; 399*(10336), 1695–1707

Endpoints

Co-primary

- Radiographic progression-free survival (rPFS):
  - PCWG2 criteria
  - Imaging at least q6m after PSA rise
- Overall survival (OS)

Secondary

- Castration resistance-free survival
- Serious genitourinary event-free survival
- Prostate cancer specific survival
- Time to next skeletal-related event
- PSA response rate
- PSA at 8 months after initation of SOC
- Time to pain progression
- Time to chemotherapy for CRPC
- Quality of life
- Toxicity
- Changes in bone mineral density (BMD)
- Biomarkers
- Outcomes for pts with NE differentiation

Bossi A, *et al. Journal of Clinical Oncology* 41, no. 17_suppl (June 10, 2023) LBA5000-LBA5000.

Patients' Characteristics (Overall Population)

		SOC (+/- Abi) (n = 588)	SOC (+/- Abi) + Radiotherapy (n = 584)
Median age, year (Min-Max)		67 (43–88)	66 (37–94)
ECOG PS score, n (%)	0 1-2	411 (70) 177 (30)	413 (71) 171 (29)
Gleason score at diagnosis, n (%)	≤ 7 ≥ 8 Missing	142 (23) 429 (74) 17 (3)	136 (24) 441 (75) 7 (1)
Median time from diagnosis, month (IQR)		2.2 (1.5-3.1)	2.3 (1.5-3.2)
Metastatic sites, n (%)	Lymph nodes only Bone only Visceral	51 (9) 474 (81) 63 (11)	48 (8) 473 (81) 63 (11)
Disease volume, n (%)	Low High	253 (43) 335 (57)	252 (43) 332 (57)
Median baseline PSA, ng/mL (IQR)		13.1 (3.5-57.1)	12.6 (3-62.4)
Docetaxel, n (%)	Yes No	355 (60) 233 (40)	355 (61) 229 (39)

Bossi A, *et al. Journal of Clinical Oncology* 41, no. 17_suppl (June 10, 2023) LBA5000-LBA5000.

Patients' Characteristics (Low Volume Population)

		SOC (+/- Abi) (n = 253)	SOC (+/- Abi) + Radiotherapy (n = 252)
Median age, year (Min-Max)		67 (43–86)	66 (46–84)
ECOG PS score, n (%)	0 1-2	180 (71) 73 (29)	194 (77) 58 (23)
Gleason score at diagnosis, n (%)	≤ 7 ≥ 8 Missing	71 (27) 173 (70) 9 (3)	66 (26) 184 (73) 2 (1)
Median time from diagnosis, month (IQR)		2.5 (1.8-3.4)	2.6 (1.7-3.5)
Metastatic sites, n (%)	Lymph nodes only Bone only	47 (19) 206 (81)	41 (16) 211 (84)
Median baseline PSA, ng/mL (IQR)		10.3 (3.3-31)	9 (2.3-39.1)
Docetaxel, n (%)	Yes No	127 (50) 126 (50)	127 (50) 125 (50)

median follow-up : 73 months

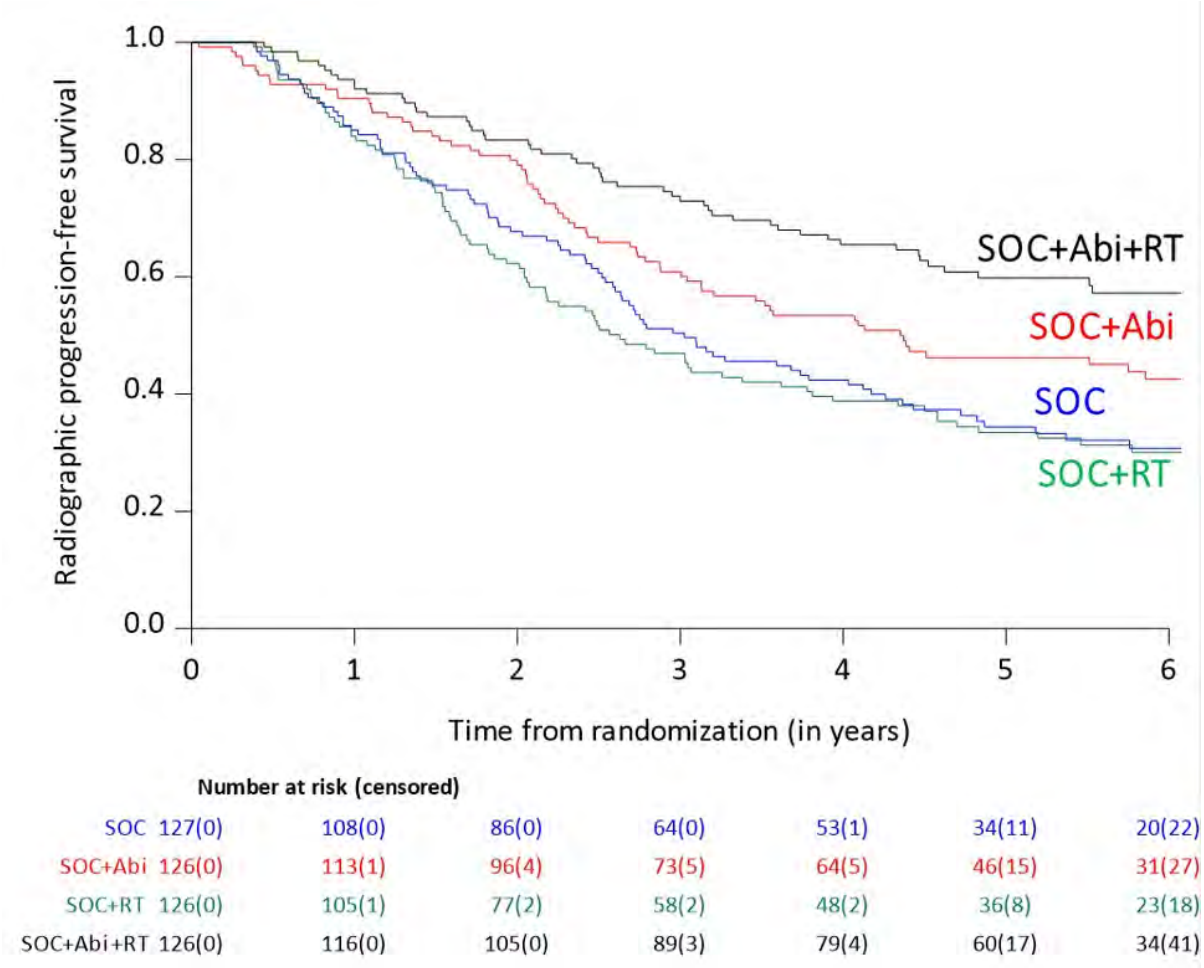
Bossi A, *et al. Journal of Clinical Oncology* 41, no. 17_suppl (June 10, 2023) LBA5000-LBA5000.

Statistical Analysis

- For rPFS, a qualitative interaction between RT and Abi was observed (p=0.026) and each experimental arm was assessed individually.

- For OS, the predefined threshold for a statistical interaction was not reached (p=0.12) and the 2 RT arms were pooled for the analysis.

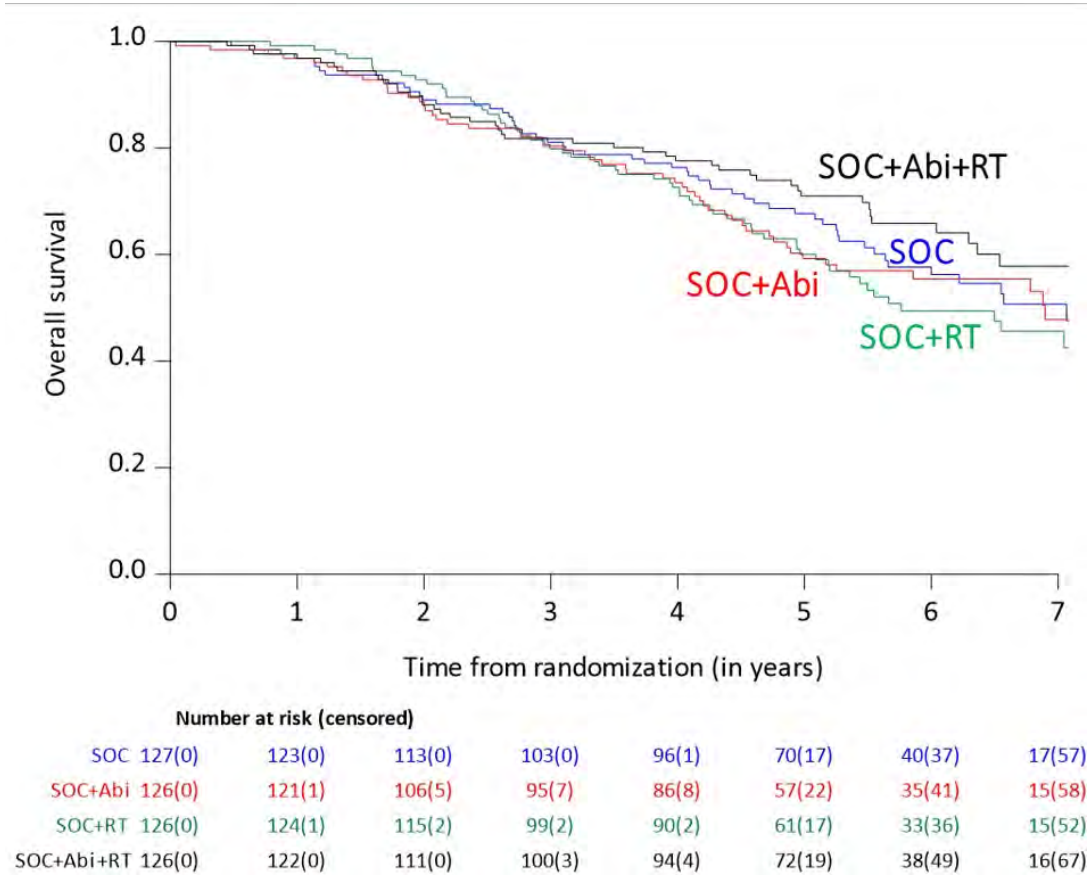
rPFS (low volume population)



	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (99.9% CI)	3.0 (2.3-4.8)	2.6 (1.7-4.6)	4.4 (2.5-7.3)	7.5 (4,0-NE)
Events, n.	87	89	74	55
HR (99.9%CI)*	Ref	1.11 (0.67-1.84)	0.76 (0.45-1,28)	0.50 (0.28-0.88)
Global p-value	<0.0001			
HR (99.9% CI)*	Ref	1.08 (0.65-1.80)	Ref	0.65 (0.36-1.19)
P-values arms w/wo Abi	0.61		0.02	

Bossi A, *et al. Journal of Clinical Oncology* 41, no. 17_suppl (June 10, 2023) LBA5000-LBA5000.

OS (low volume population)



	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (95.1% CI)	7.1 (5.6-NE)	5.8 (5.1-NE)	6.9 (5.0-NE)	NE (6.4-NE)
Events, n.	57	60	54	44
HR (95.1% CI)*	Ref	1.19 (0.82-1.72)	1.05 (0.72-1.54)	0.81 (0.55-1.21
Global p-value	0.29			
HR (95.1% CI)*	Ref	1.18 (0.81-1.71)	Ref	0.77 (0.51-1.16)
P-values arms w/wo Abi	0.39		0.21	

Bossi A, *et al. Journal of Clinical Oncology* 41, no. 17_suppl (June 10, 2023) LBA5000-LBA5000.

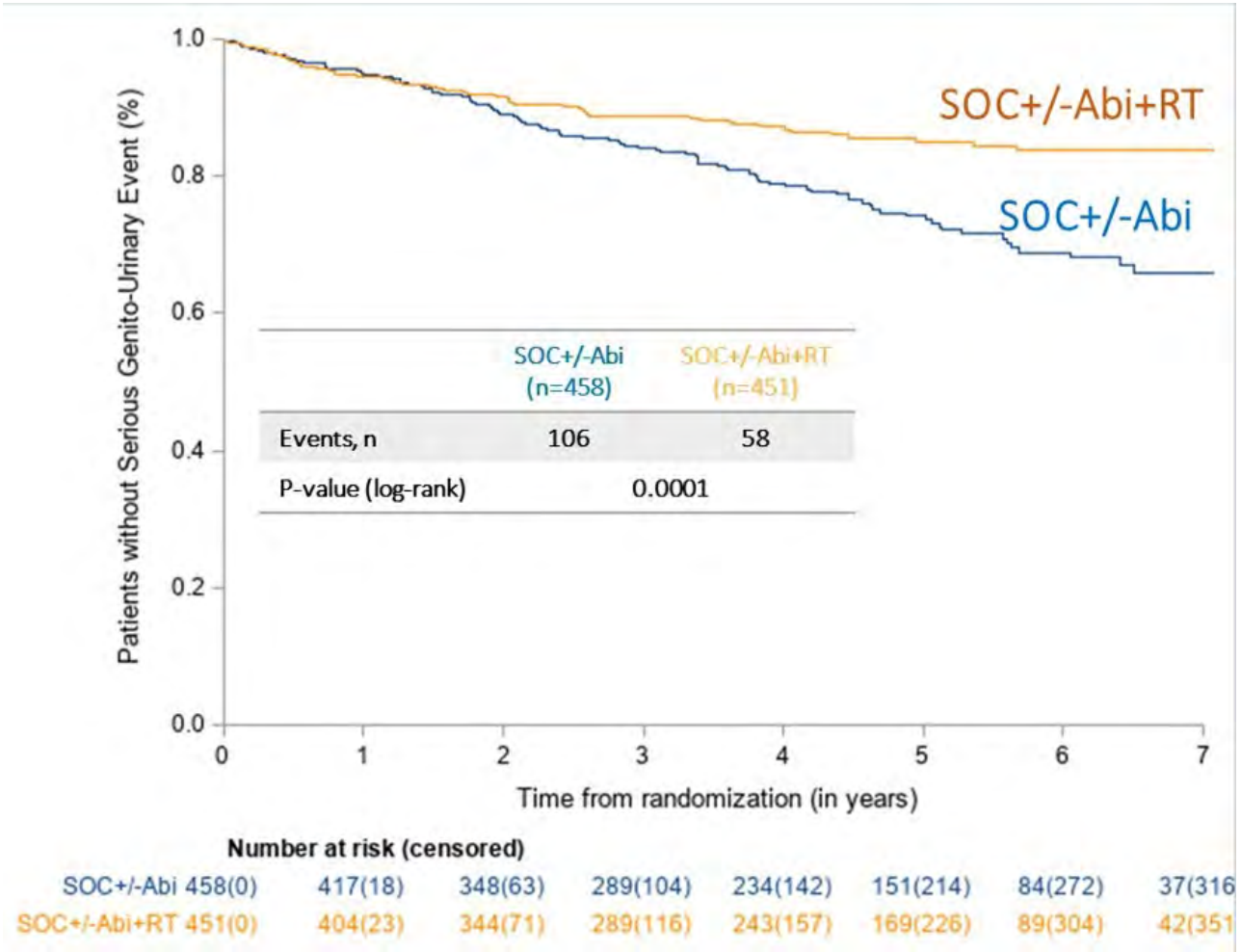
Serious Genito-Urinary Events* (low volume population)

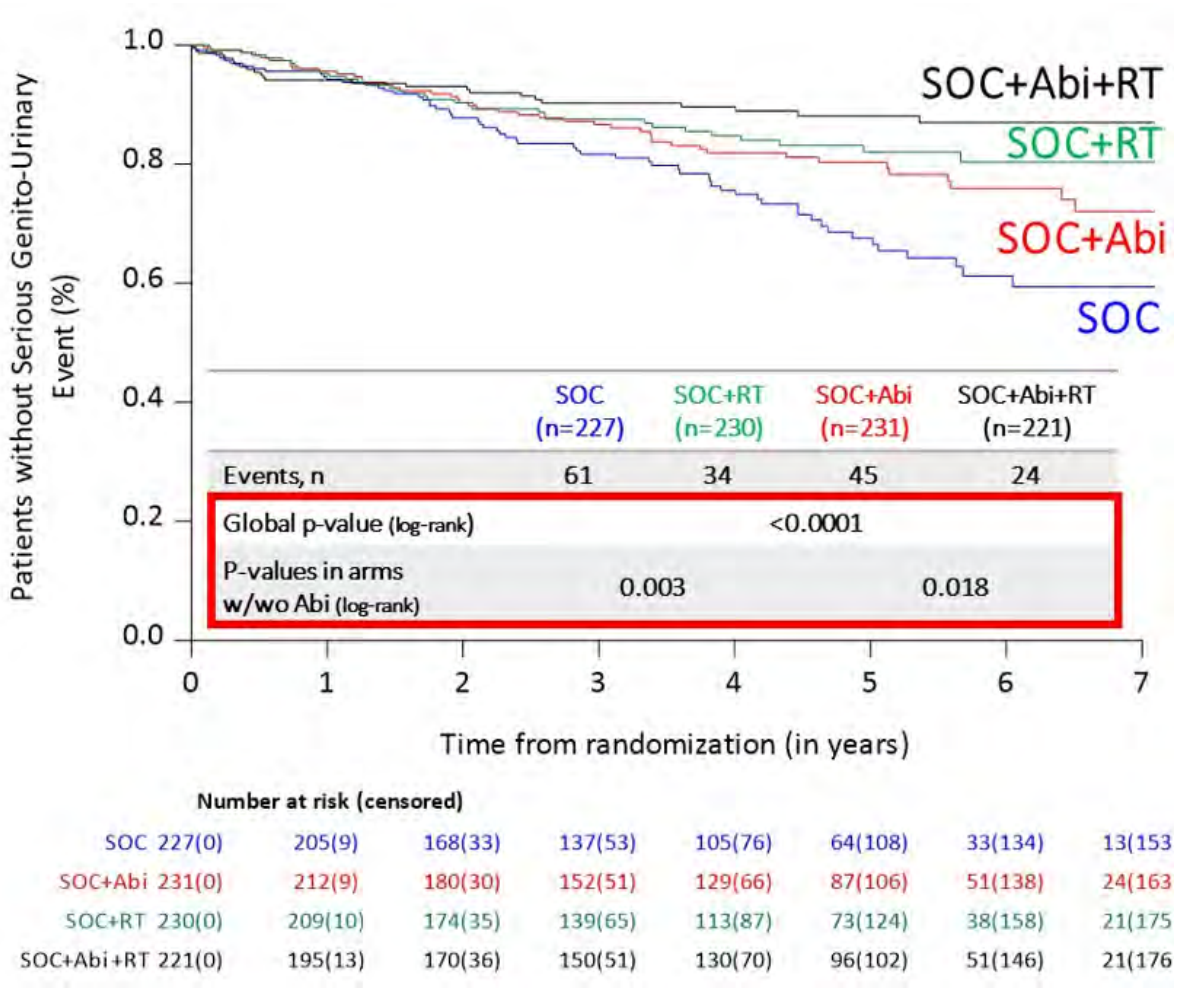
	No RT (n=200)	RT (n=198)
Urinary Catheter	9	6
Double J Stent	13	12
Nephrostomy	2	1
Prostate RT or TURP	27	4 TURP (all RT)
Radical Prostatectomy	1	1

*with available data regarding serious genito-urinary events

Bossi A, *et al. Journal of Clinical Oncology* 41, no. 17_suppl (June 10, 2023) LBA5000-LBA5000.

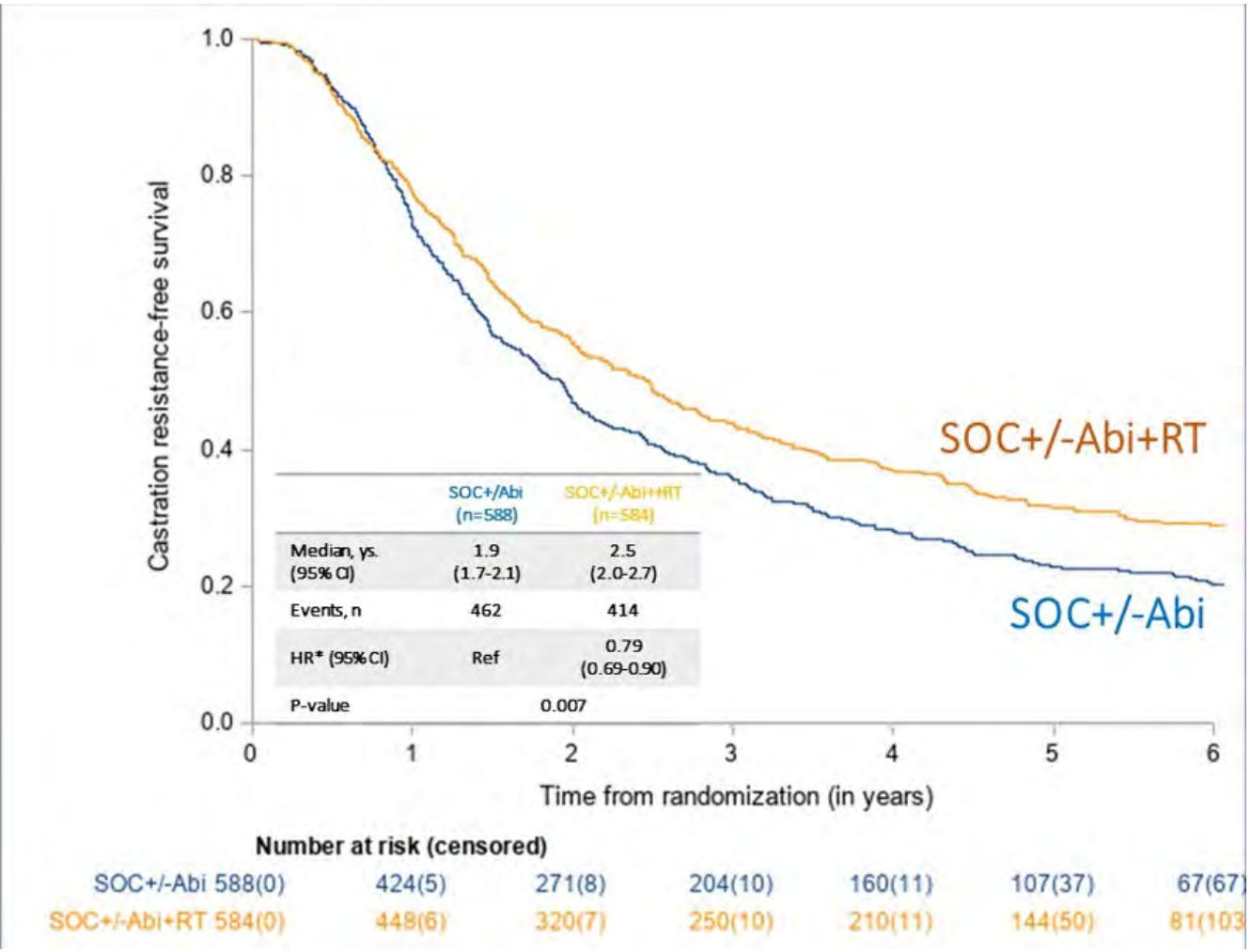
Time to Serious Genito-Urinary Events (overall population)

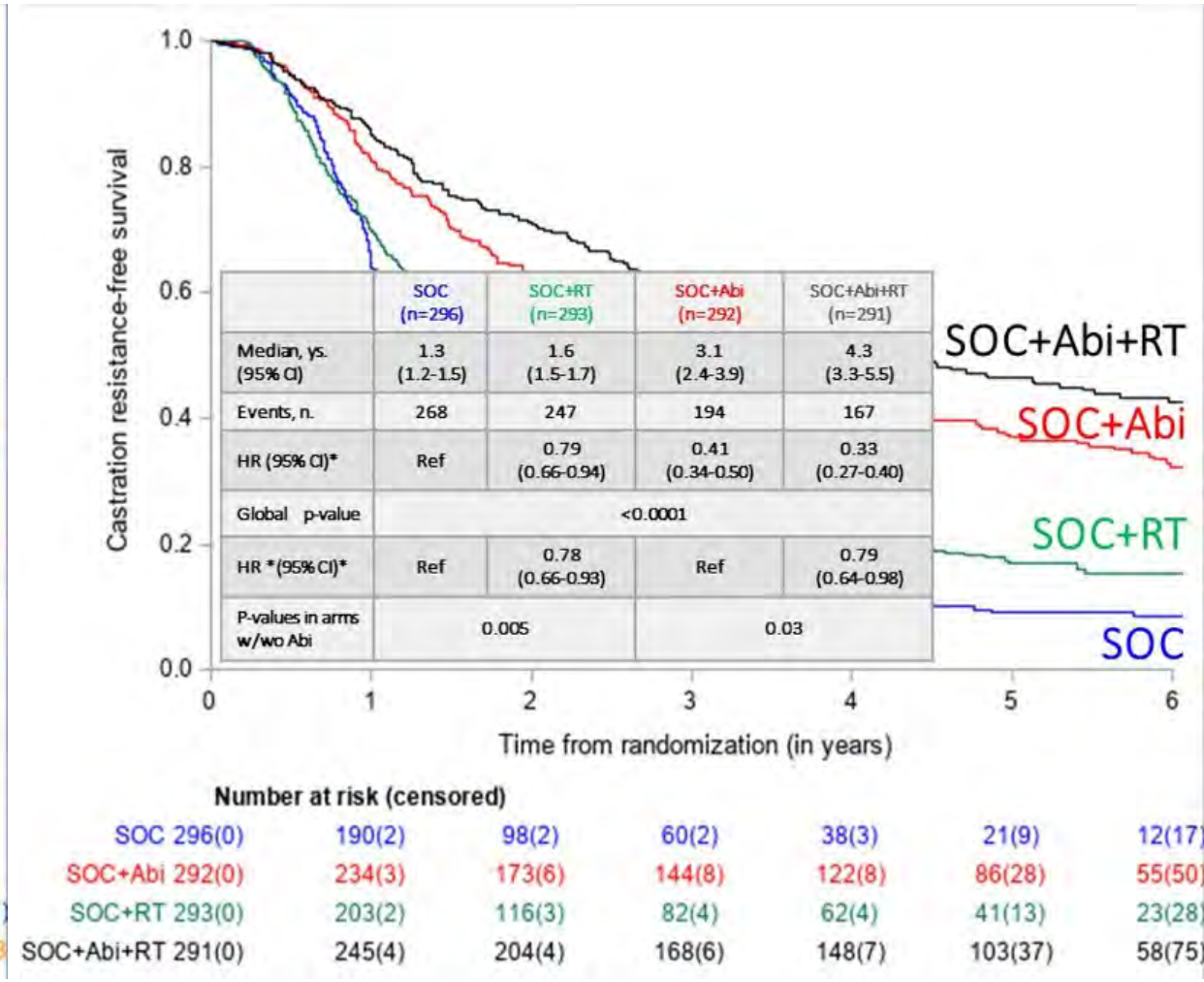




Bossi A, et al. Journal of Clinical Oncology 41, no. 17_suppl (June 10, 2023) LBA5000-LBA5000.

Castration Resistance-Free Survival (overall population)





Bossi A, *et al. Journal of Clinical Oncology* 41, no. 17_suppl (June 10, 2023) LBA5000-LBA5000.

Toxicity, Grade 3-5 (overall safety population)

	SOC+/-Abi (n=604)	SOC+/-Abi+RT* (n=560)
	n (%)	n (%)
Hypertension	110 (18)	127 (23)
Neutropenia	40 (7)	29 (5)
Febrile neutropenia	20 (3)	19 (3)
Hepatotoxicity	22 (4)	18 (3)
Fatigue	17 (3)	12 (2)
Gastro-Intestinal disorders	29 (5)	17 (3)
Rectal Haemorrhage	0 (0)	5 (1)

*Safety population: patients who received any part of study treatmenst, according to study treatments actually received

Conclusions

- Combining prostate RT with intensified systemic treatment (Abiraterone w/wt docetaxel) improves rPFS and CRPC free-survival in men with low burden, de-novo mHSPC.

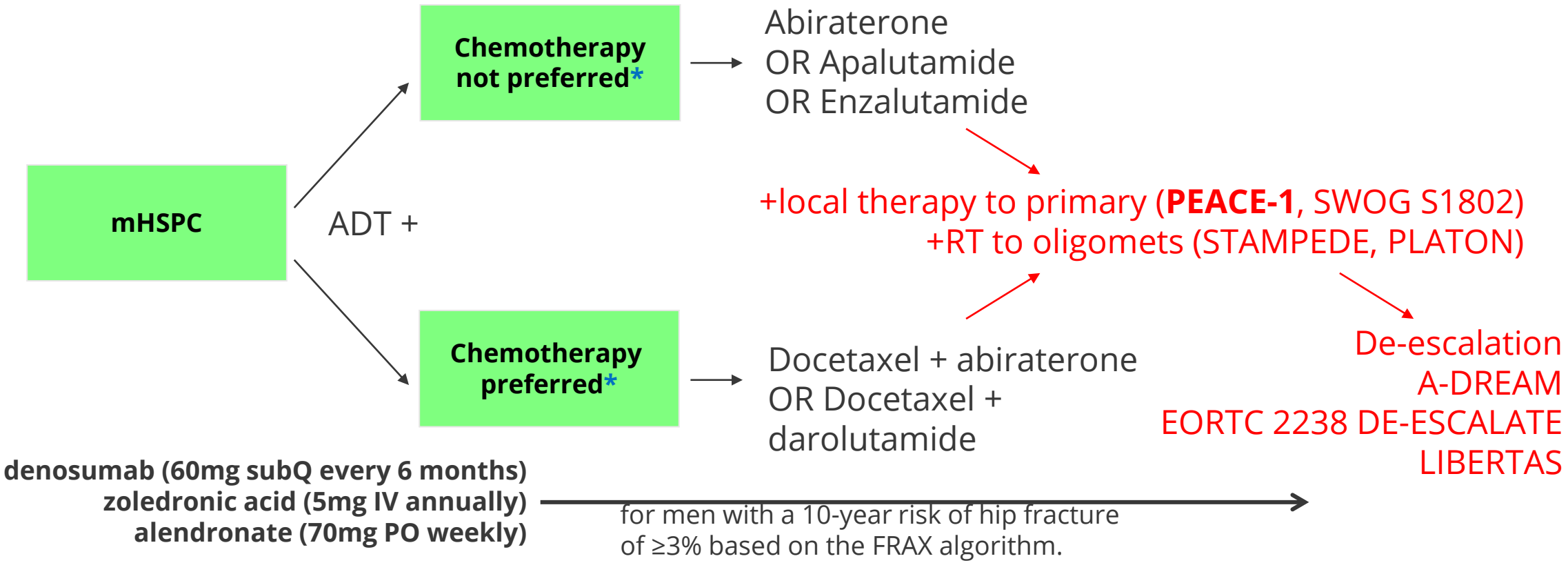
- No detectable impact of prostate RT on OS in PEACE-1, minimal added toxicity.

- PEACE-1 also establishes a role of RT in the prevention of serious GU events, irrespective of the metastatic burden.

- HORRAD, STAMPEDE, and PEACE-1 support the role of prostate RT in low burden mCSPC

- RT may also be considered in selected patients with de-novo high burden mHSPC
  – FFS benefit seen in overall population in STAMPEDE
  – Prolongation of time to serious GU event, CRPC-free survival in overall population of PEACE-1

Systemic Therapy for Metastatic Hormone Sensitive Prostate Cancer 2023



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  - Genetic features (Velez MG, et al. Prostate Cancer Prostatic Dis. 2021 Jul 22.)
  - Gene expression profiling (Hamid AA, et al. ESMO 2021)

Select Ongoing Randomized Phase III Trials in mHSPC

Trial	Regimens	Population
PSMAddition (NCT04720157)	ADT ± **^{177}Lu-PSMA-617**	mHSPC, **PSMA-positive** (planned N = 1,126)
TALAPRO-3 (NCT04821622)	Enzalutamide ± **talazoparib**	mHSPC, **DDR mutation** (planned N = 550)
AMPLITUDE (NCT04497844)	Abiraterone + prednisone ± **niraparib**	mHSPC, **HRR gene alteration** (planned N = 788)
KEYNOTE-991 (NCT04191096)	ADT + enzalutamide ± **pembrolizumab**	mHSPC, no prior AR inhibitor (planned N = 1232)
CAPItello-281 (NCT04493853)	ADT + abiraterone acetate ± **capivasertib**	De novo mHSPC, **PTEN deficiency** (planned N = 1000)
CYCLONE-3 (NCT05288166)	ADT + abiraterone acetate ± **abemaciclib**	High-risk mHSPC (planned N = 900)

Questions?

Castrate-Sensitive Prostate Cancer: Overview of Selected Prognostic/Predictive Biomarkers

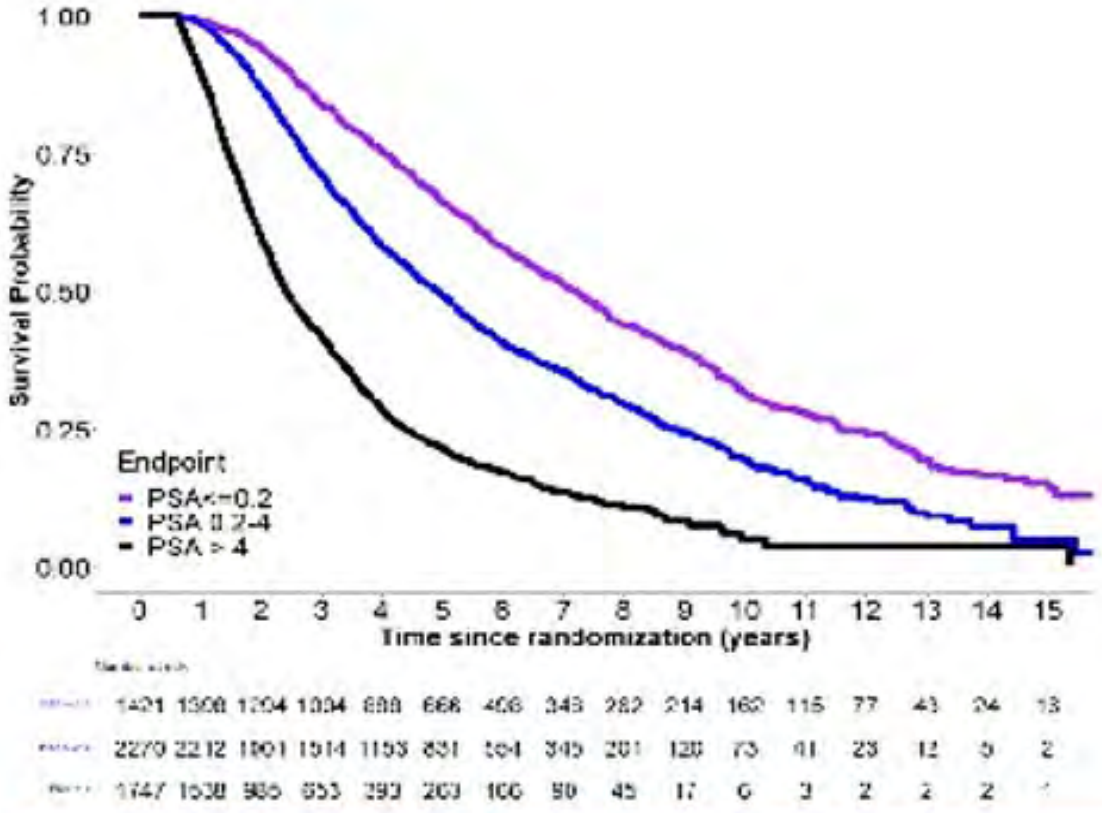
Oliver Sartor, MD
Director of Radiopharmaceutical Trials
Mayo Clinic
Rochester, MN

Huge Evolution in Management of Prostate Cancer

- **Old School**
  - Surgery
  - Highly fractionated external beam radiation
  - Brachytherapy
  - ADT
  - Chemotherapies
  - CTs/MRIs/bone scans
- **New School**
  - Molecular imaging
  - SBRT
  - Genetics
  - AI and machine learning
  - Targeted Therapies
    - Radiopharmaceuticals
    - Antibody drug conjugates
    - CAR T cells
  - Combinations too…..

What Biomarkers Apply to "Hormone-Sensitive" Prostate Cancer?

- Prognostic Biomarkers
  - Multiple Older Biomarkers
    - Patient
      - Hemoglobin, performance status, alkaline phosphatase
    - Tumor
      - Gleason, PSA, LDH, disease volume, visceral disease
  - Genetic based
  - Image based
  - AI/Machine learning
- Predictive Biomarkers
  - Genetic based
  - Image based
  - AI/Machine learning



PSA Levels ng/dL	Median OS (years; 95% CI)
≤0.2	6.6(6.1,7.1)
0.2-4	4.3 (4.1,4.6)
>4	1.8(1.7,2.0)

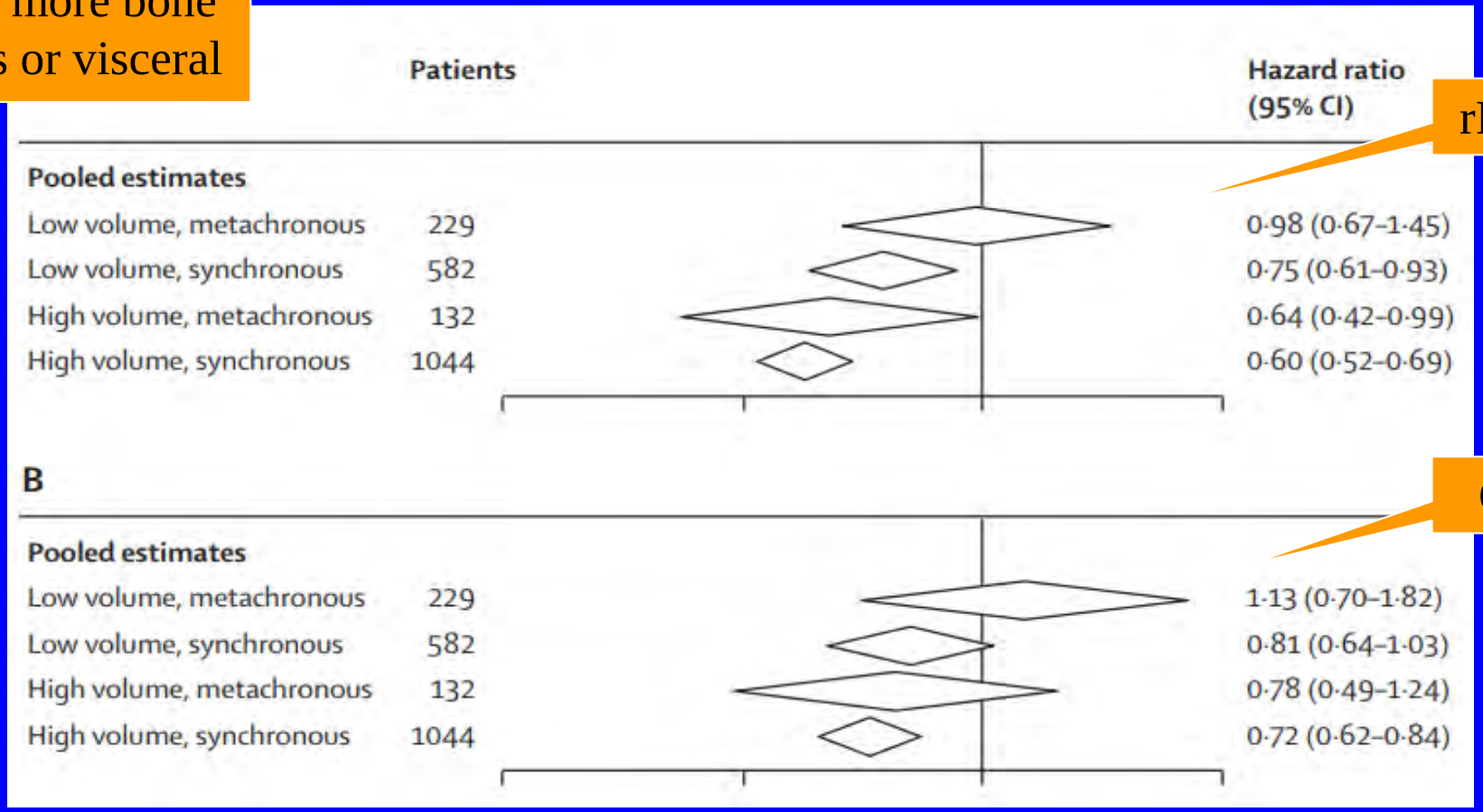
Prognostic Importance of PSA at 7 month "Landmark" in mCSPC

Halabi et al. ASCO #5070, 2023

Prediction of Docetaxel Impact on PFS and OS in Metastatic Castrate-Sensitive Prostate Cancer

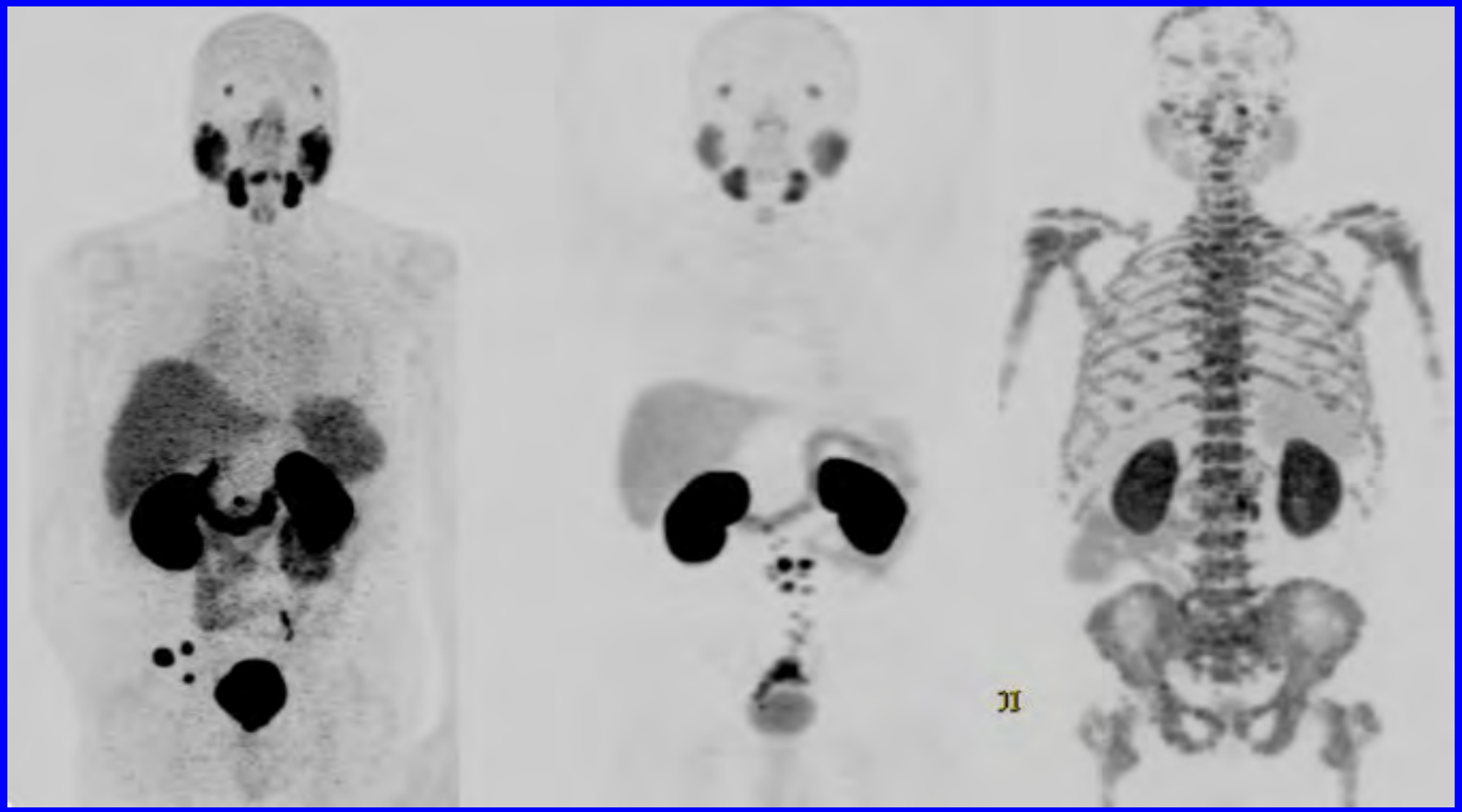
Vale et al. Lancet Oncol 24:783, 2023

High volume
4 or more bone mets or visceral



Molecular Imaging

Molecular Imaging (i.e. PSMA PET)

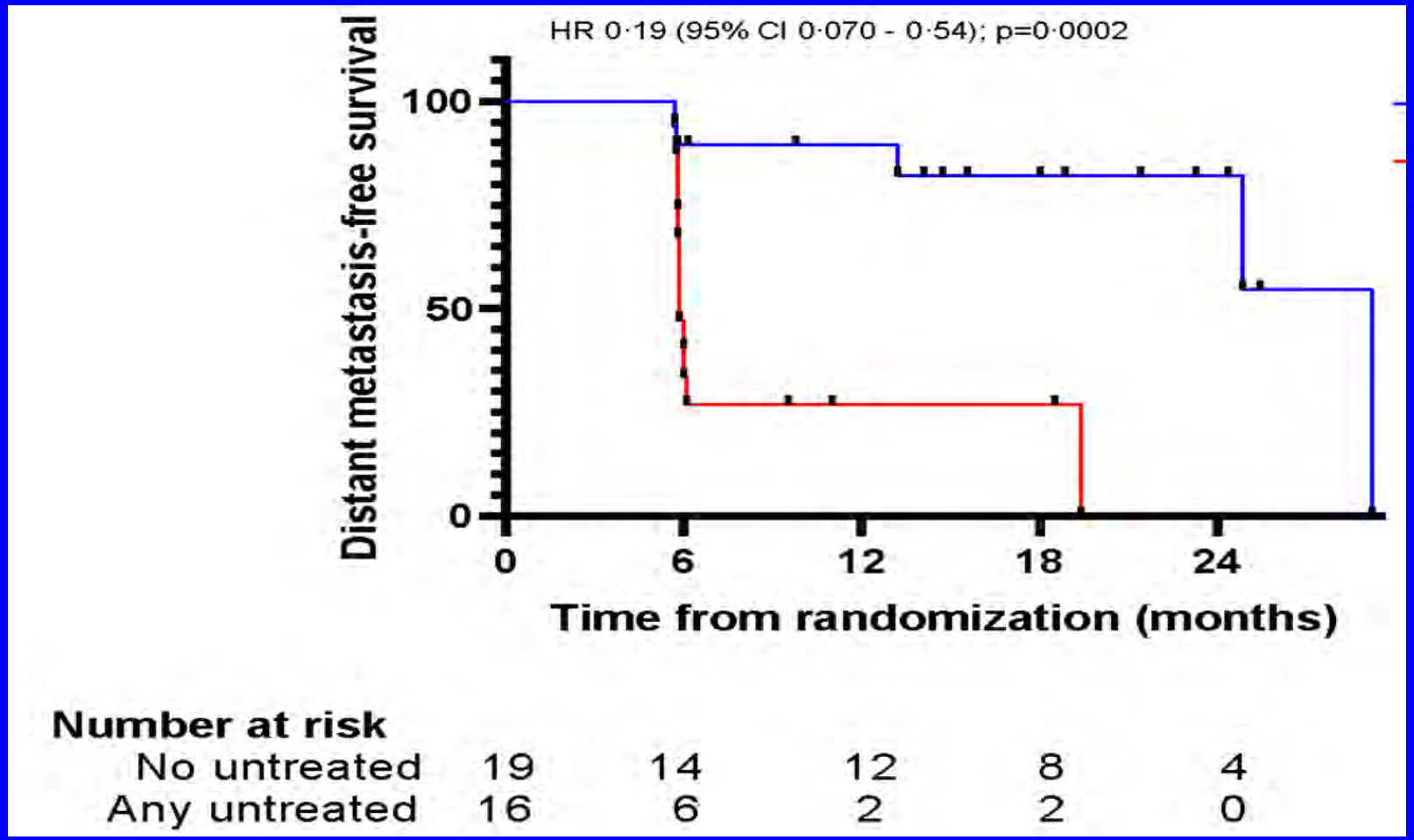


PSMA PET gives important prognostic and predictive implications (predictive for SBRT response and PSMA-Lu-177 response)

Prognosis:
PSMA PET Improves Prognosis for Men with Both Localized and Metastatic Disease

- **Localized Disease**
  - Better prognosis as you eliminate the patients with PSMA-PET positive metastatic disease
- **Metastatic Disease**
  - Expands the definition of metastatic disease
  - PSMA PET positive only disease are lower disease burden than those with positive conventional imaging

PSMA PET as a Predictive Biomarker for Stereotactic Ablative Radiotherapy (SABR or SBRT)

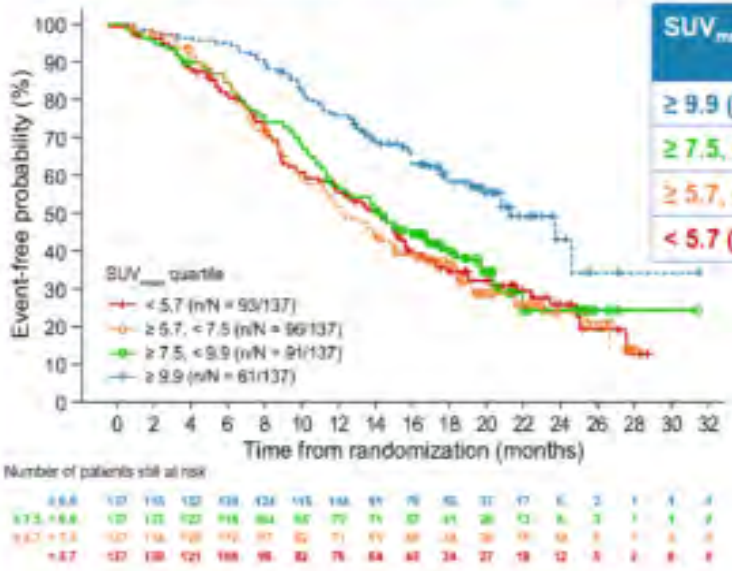


Phillips et al. JAMA Oncol 2020

PSMA uptake in mCRPC associates with better survival after PSMA-617 Lu-177 treatment and in MV analyses

OS by whole-body SUV_{mean} quartiles (FAS)

- Higher whole-body SUV_{mean} was associated with improved OS



SUV_{mean} quartile	Median OS (months)
≥ 9.9 (highest)	21.4
≥ 7.5, < 9.9	14.6
≥ 5.7, < 7.5	12.6
< 5.7 (lowest)	14.5

PSMA PET as a Predictive Biomarker

SUV_{mean}	OS HR [95% CI], *p* value
Univariate analysis	**0.92** [0.89, 0.95], < 0.001
Multivariate analysis	**0.88** [0.84, 0.91], < 0.001

Kuo et al. Clin Oncol 40, 2022 (suppl 16; abstr 5002)

Phase III Trials Using PSMA PET in HSPC

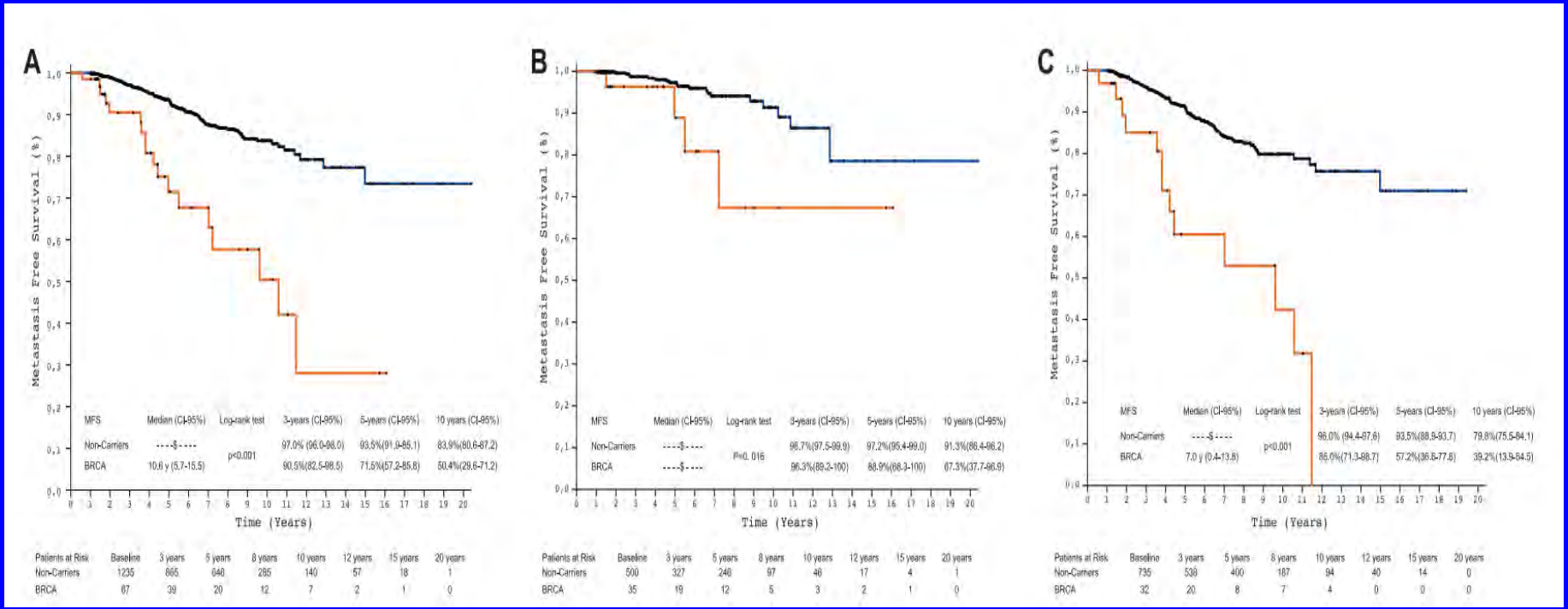
- PSMA DC: An Open-label Study Comparing Lutetium (177Lu) Vipivotide Tetraxetan Versus Observation in PSMA Positive Oligo-Metastatic Prostate Cancer
  - PSMA PET positive ONLY: All patients get PSMA PET directed SBRT and half will be randomized to PSMA-617 Lu-177

- PSMAddition: Phase III Study Comparing 177Lu-PSMA-617 in Combination With SoC, Versus SoC Alone, in mHSPC
  - Conventional imaging positive and PSMA PET positive pts randomized to ADT + ARPI of choice +/- PSMA Lu-177

Genetics

We have long known that prognosis is worse in BRCA mutated patients after either surgery or radiation

Castro et al. Eur Urol 68:186-193, 2015



Combined Surgery Radiation

Predictive Genetic Biomarkers FDA Approved for PARP inhibitors in mCRPC

- Panoply of homologous recombination repair genes
  - *BRCA2*, *BRCA1*, *PALB2*, *RAD54L*, etc.
    - Olaparib monotherapy
    - Talozaparib + enzalutamide
    - Olaparib + abiraterone (BRCA1/2 only)
    - Rucaparib monotherapy (BRCA1/2 only)

Do they apply to HSPC?

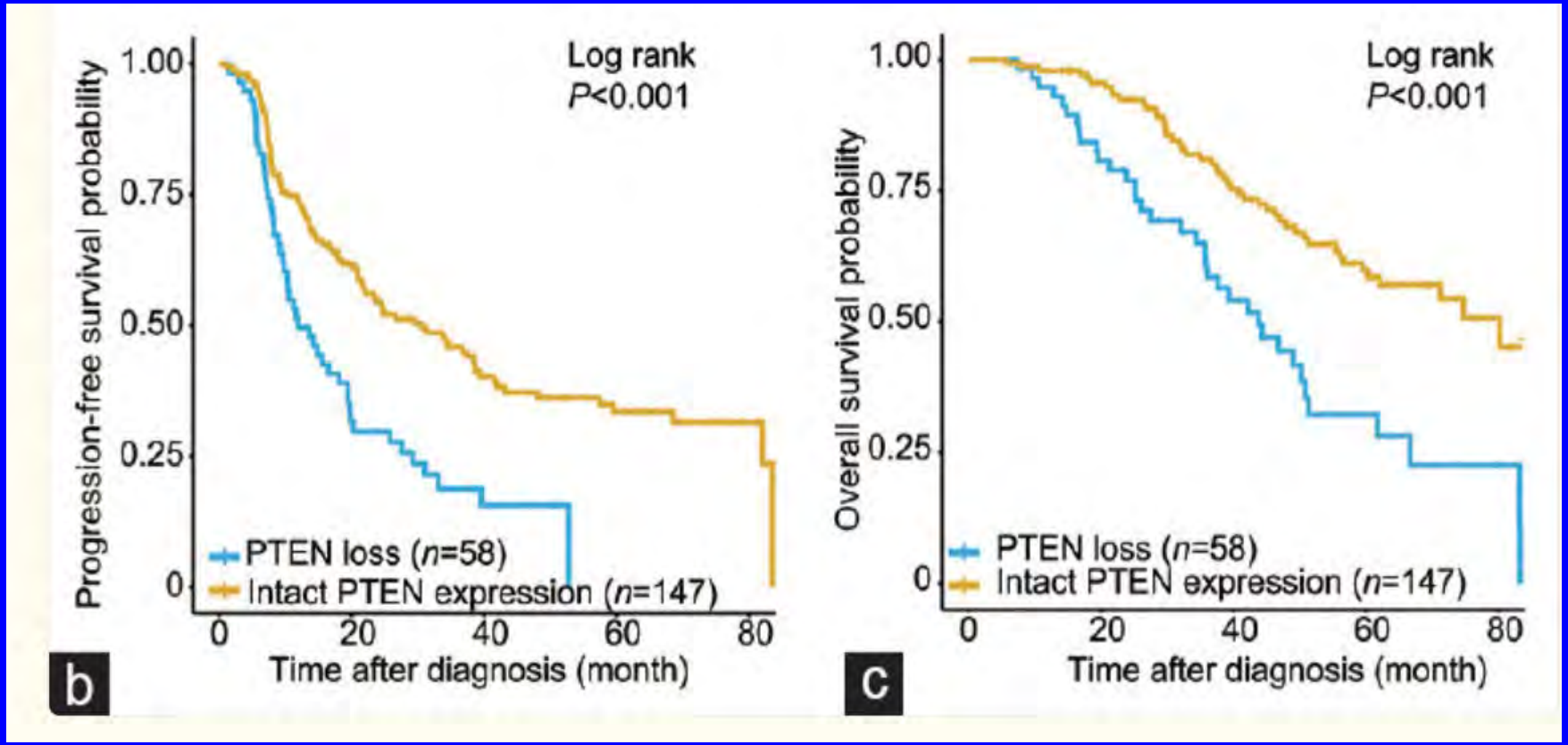
Select Phase III Trials Using Mutation Selection in HSPC

- TALAPRO-3: A phase 3 randomized doiuble blind study of talozaparib with enzalutamide versus enzalutamide placebo with enzalutamide in men with DDR gene mutated metastatic castration sensitive prostate cancer.

- AMPLITUDE: Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects With Metastatic Prostate
  - Includes both DDR-mutated and non-DRR mutated tumors

PTEN loss is common and has important prognostic implications in hormone-sensitive metastatic prostate cancer

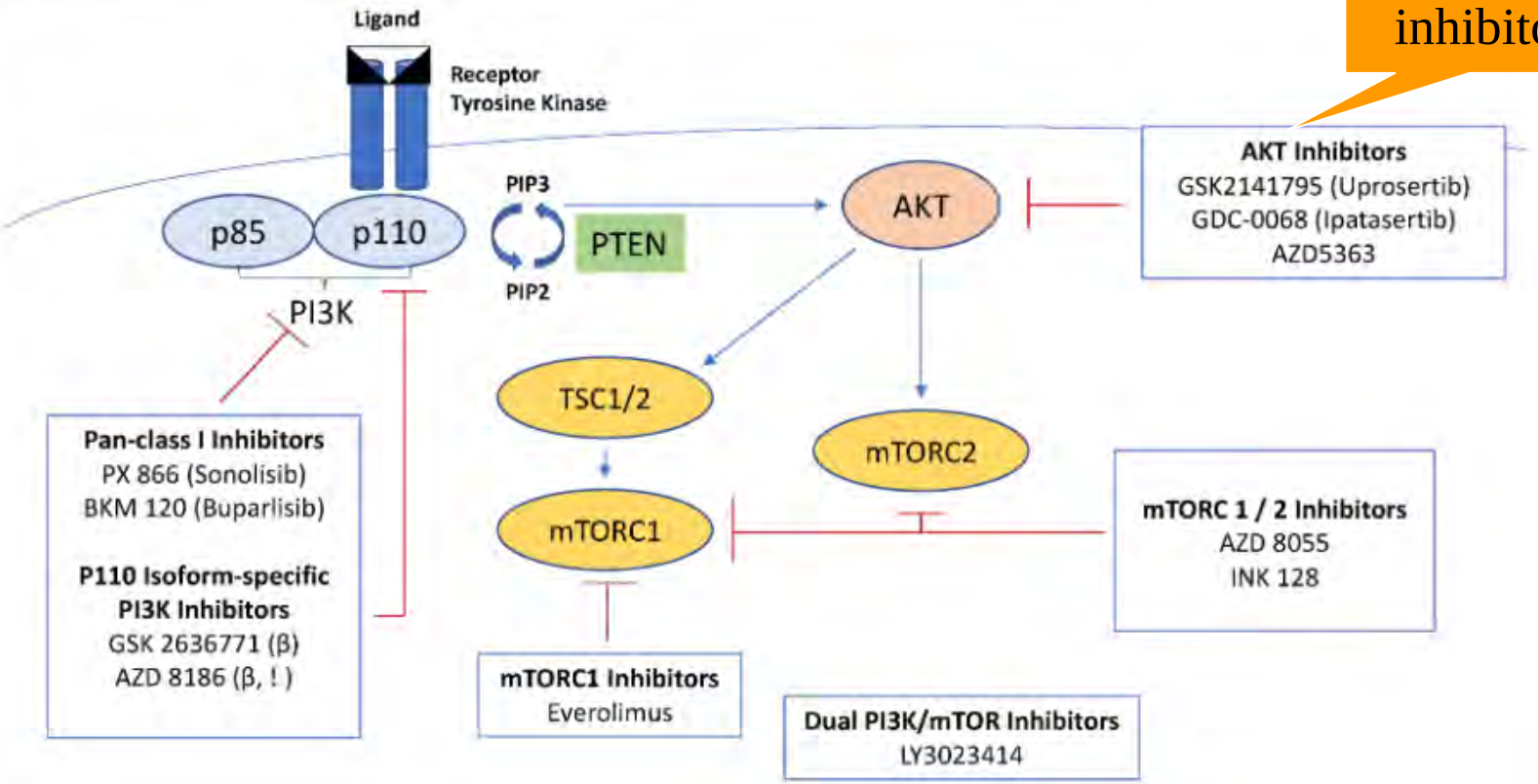
Zhang et al. Asian J Androl. 24: 50–55, 2022



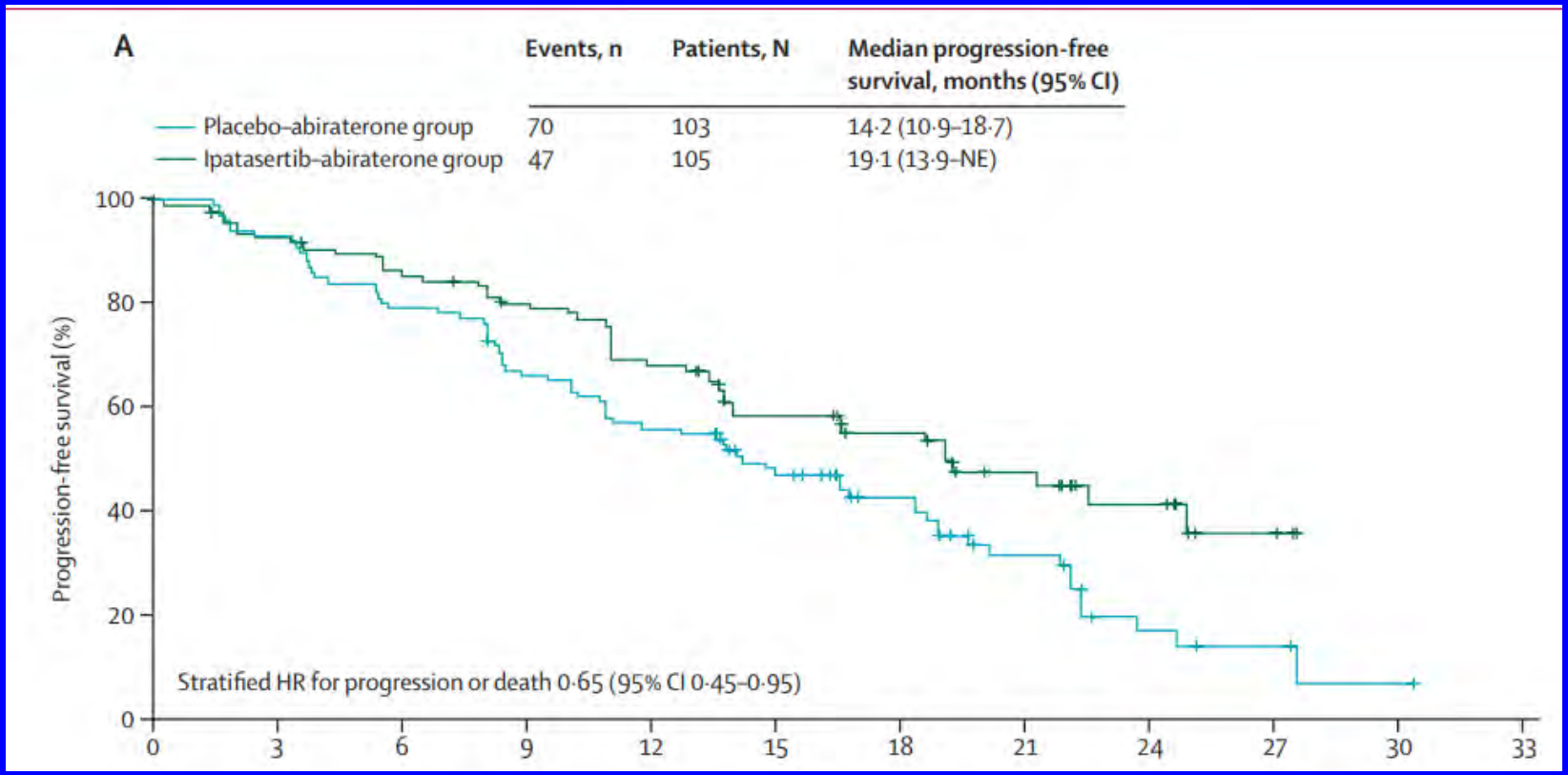
PTEN Loss Activates AKT and Other Downstream Signals

Crumbaker et al. Cancers 9:34 (2017)

Figure 1. PI3K pathway targeting agents in development for the treatment of prostate cancer.



Ipatasertib (AKT inhibitor) rPFS in the NGS-defined PTEN-loss group (mCRPC)



Sweeney et al. Lancet 398:121

Phase III Trial Using PTEN loss Selection in CSPC

- CAPItello-281: Capivasertib + Abiraterone as Treatment for Patients With mHSPC and PTEN Deficiency

Many Studies of Genomic Classifiers Demonstrate the Importance of Transcriptomic Signatures in Prognosis

Table 2. Multivariable Analysis of GC for Distant Metastasis, Death From Prostate Cancer, and Overall Survival[a]

	DM		PCSM		OS	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
GC score	1.17 (1.05-1.32)	.006[b]	1.39 (1.20-1.63)	<.001[b]	1.17 (1.06-1.29)	.002[b]
Treatment vs placebo	0.62 (0.39-0.97)	.04[b]	0.53 (0.30-0.92)	.02[b]	0.82 (0.57-1.19)	.29
Age ≥65 vs <65, y	1.30 (0.83-2.06)	.25	1.52 (0.88-2.66)	.14	1.95 (1.33-2.91)	<.001[b]
African American vs non-African American	0.88 (0.28-2.13)	.80	0.86 (0.17-2.73)	.83	1.35 (0.57-2.77)	.47
Gleason 8-10 vs ≤7	2.11 (1.24-3.47)	.007[b]	2.53 (1.38-4.49)	.003[b]	1.87 (1.20-2.85)	.007[b]
T3 vs T2	1.42 (0.82-2.58)	.22	2.01 (0.97-4.62)	.06	1.24 (0.79-1.97)	.35
PSA level at trial entry	1.16 (0.88-1.49)	.26	1.37 (1.01-1.80)	.04[b]	1.08 (0.84-1.35)	.53
Positive surgical margins	0.71 (0.44-1.16)	.17	1.26 (0.68-2.44)	.46	0.98 (0.64-1.53)	.92
Non-nadir vs nadir (<0.5 ng/mL)	1.31 (0.62-2.51)	.46	2.10 (0.92-4.26)	.07	1.98 (1.13-3.30)	.02[b]

Abbreviations: DM, distant metastasis; GC, genomic classifier; OS, overall survival; PCSM, death from prostate cancer; PSA, prostate-specific antigen.

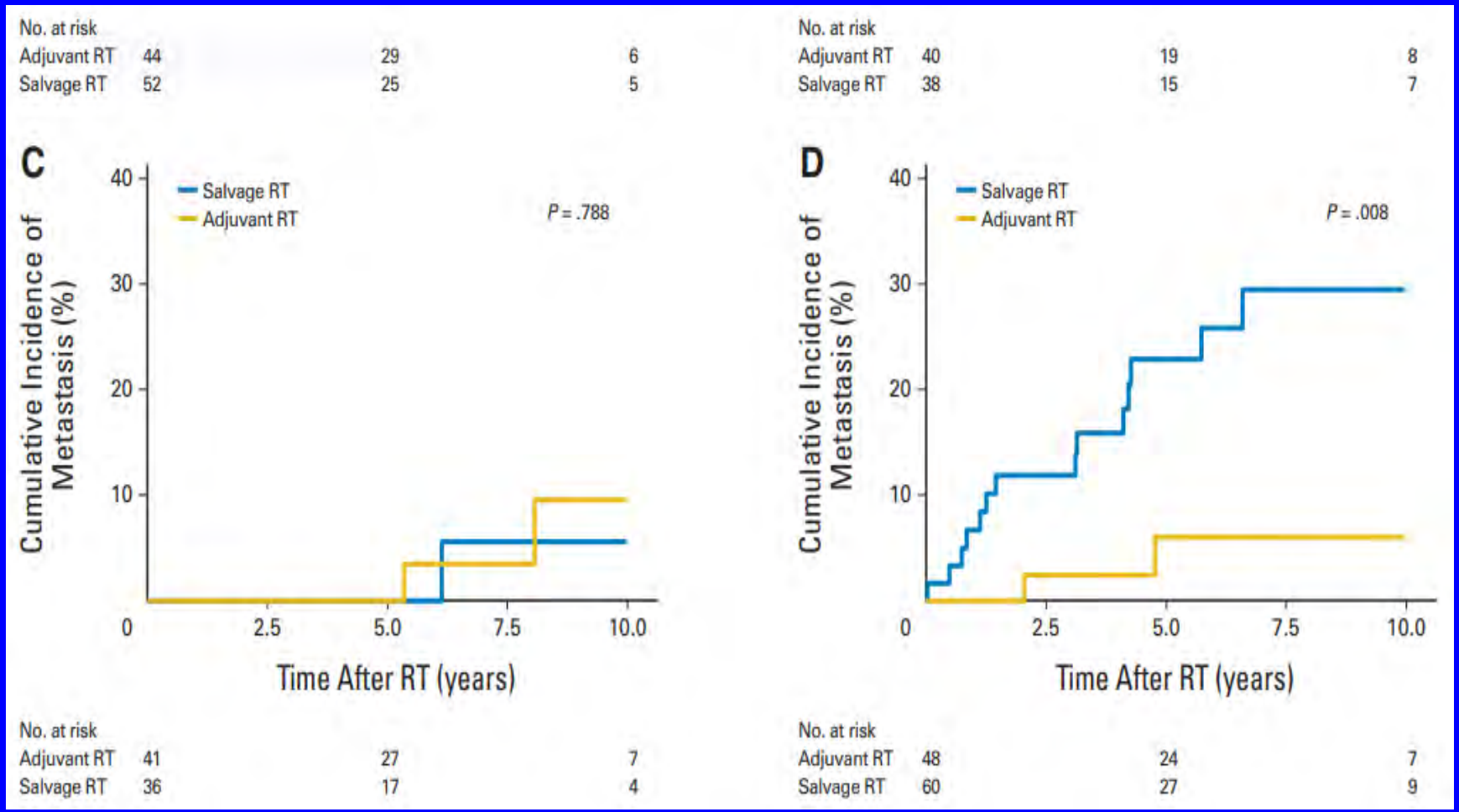
[a] One patient was dropped from the analyses owing to missing Gleason information. The median age of the analytic cohort was 65 years. Race/ethnicity, Gleason score, cancer stage, and nadir status were grouped according to the trial protocol. Hazard ratios of GC were per 0.1 unit increased.

[b] $P < .05$.

One Example: Feng et al. JAMA Oncol 7:544

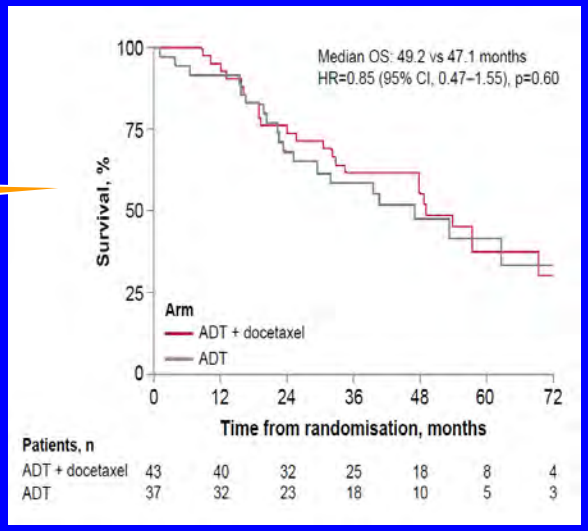
Genomic Classification as a Predictive Biomarker for "Adjuvant" Radiation

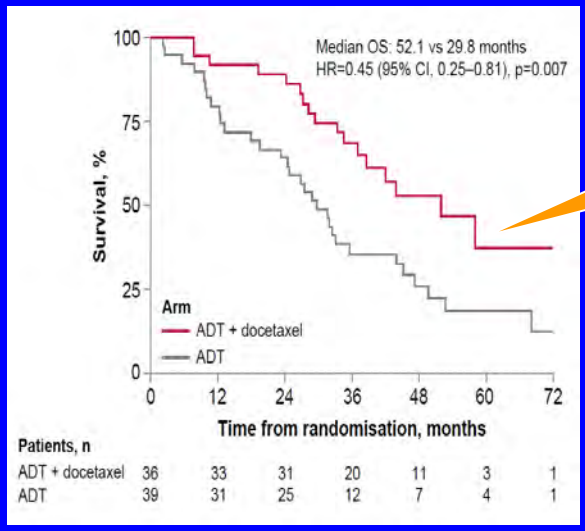
Den et al. JCO 33:941, 2015



Hypothesis generation: Transcriptomic profiling may serve as a predictive biomarker for docetaxel

Basal



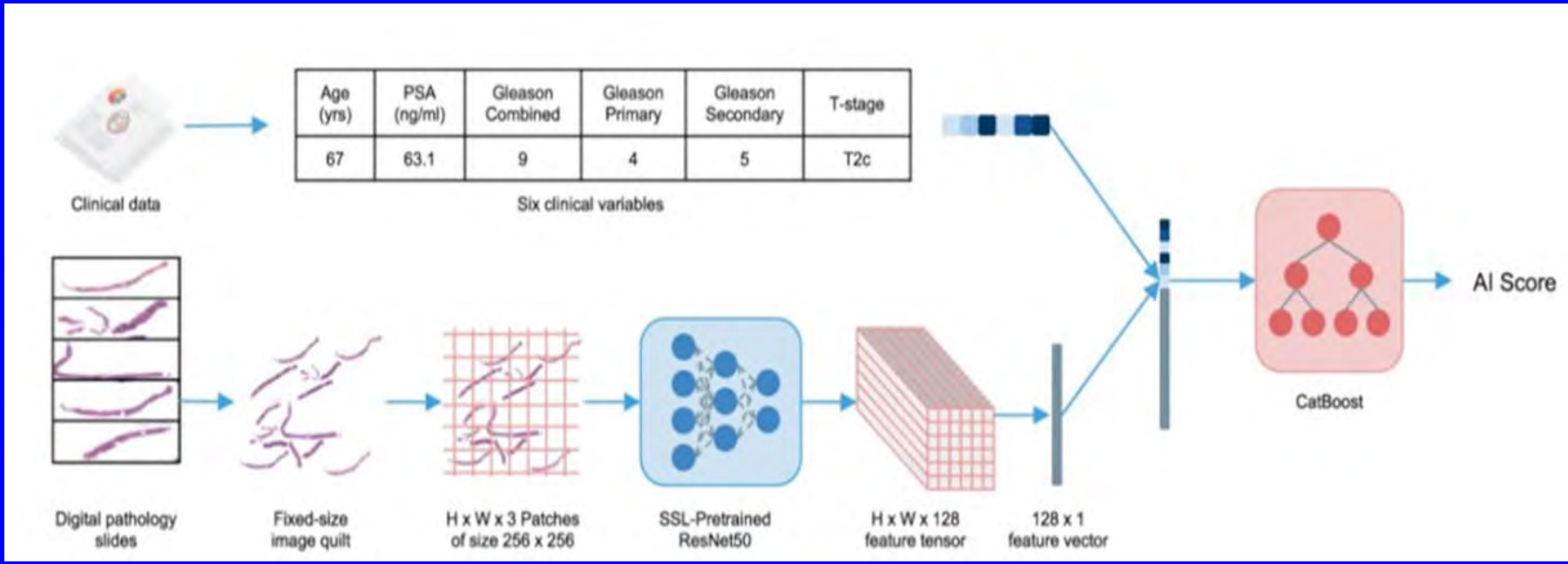


Luminal B

Docetaxel + ADT vs ADT appears to improve OS in luminal B subtype only

PAM50, Prediction Analysis of Microarray 50.
Hamid et al. ASCO GU 2020 #162

Artificial Intelligence
ArteraAI

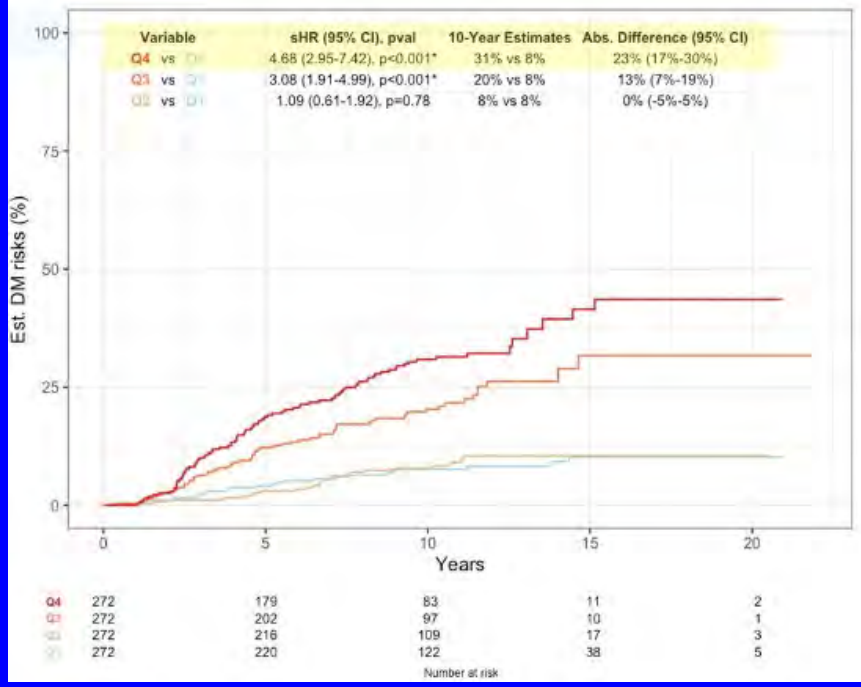


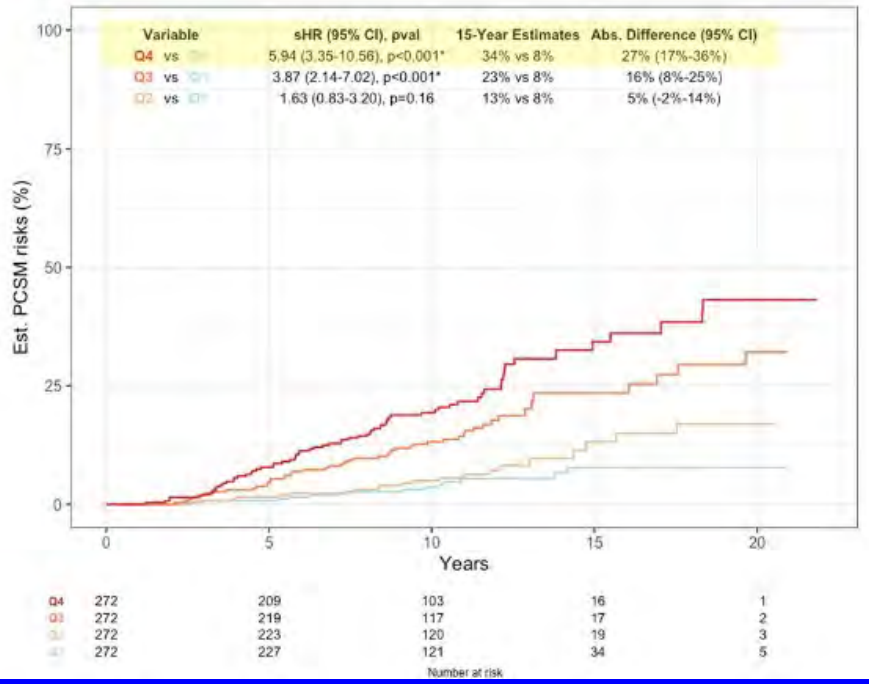
AI Model Prognostic in High Risk Localized Prostate Cancer

Spratt et al. ASCO

Results

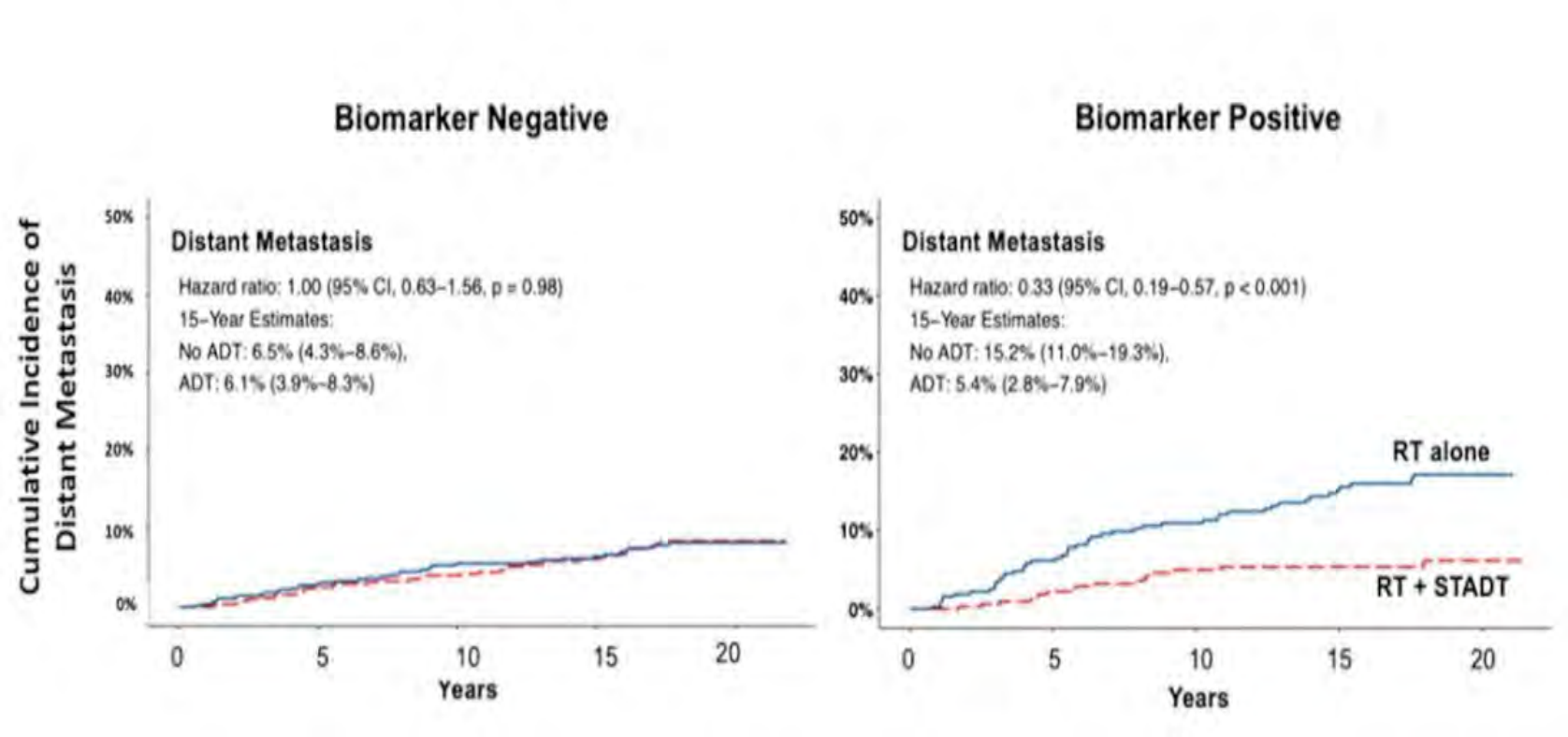
MMAI model identifies substantial differences in absolute risk of DM and PCSM in high-risk patients





Artificial Intelligence in Prostate Cancer: Prediction of Responsiveness to ADT (Artera AI)

Mohamad et al. ASTRO 2022



Summary
Prognostic/Predictive Biomarkers in CSPC

- Multiple prognostic biomarkers are available today but the real challenge is determining what therapies are best

- Genetics, transcriptomics, molecular imaging, and AI are rapidly evolving and multiple new phase III trials may be practice changing