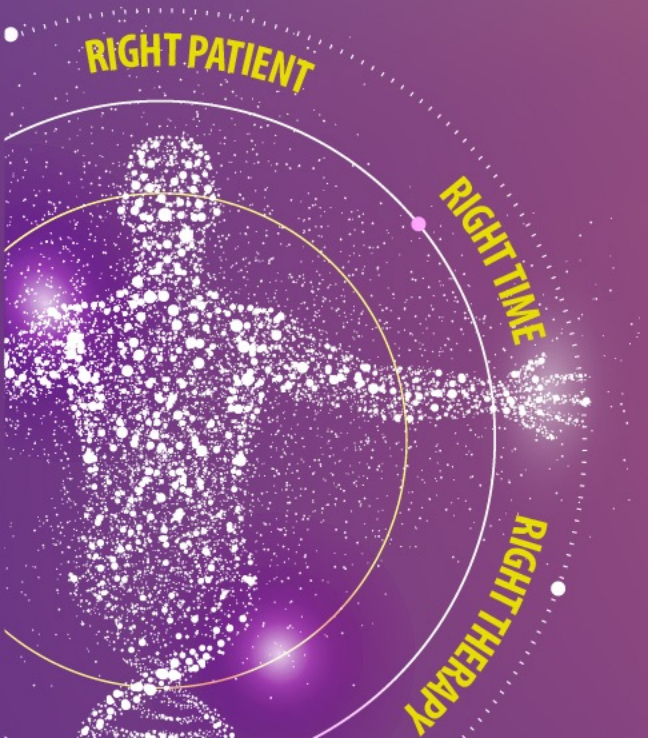
TERZA EDIZIONE

PersonMed

PATIENT CENTRIC APPROACH ON ADVANCED PROSTATE CANCER

› IL VALORE DEL TEMPO ‹



16-17 GIUGNO 2022

NAPOLI

Renaissance Naples Hotel Mediterraneo
Via Ponte di Tappia, 25

mHSPC

L. Galli , G. Francolini

BP (DOB 27/06/1947)

Past clinical history:

Hypertension, Hypercholesterolemia, Prostate hypertrophy

Recent clinical history:

PSA 20

mpMRI: prostate of 48x42x45 mm, PIRADS 3

Prostate biopsy (March 2021): prostate adenocarcinoma Gleason 5+5

Diagnostic workup??

Bone scan+CT scan?

Choline PET/CT?

PSMA PET/CT?

European Association of Urology

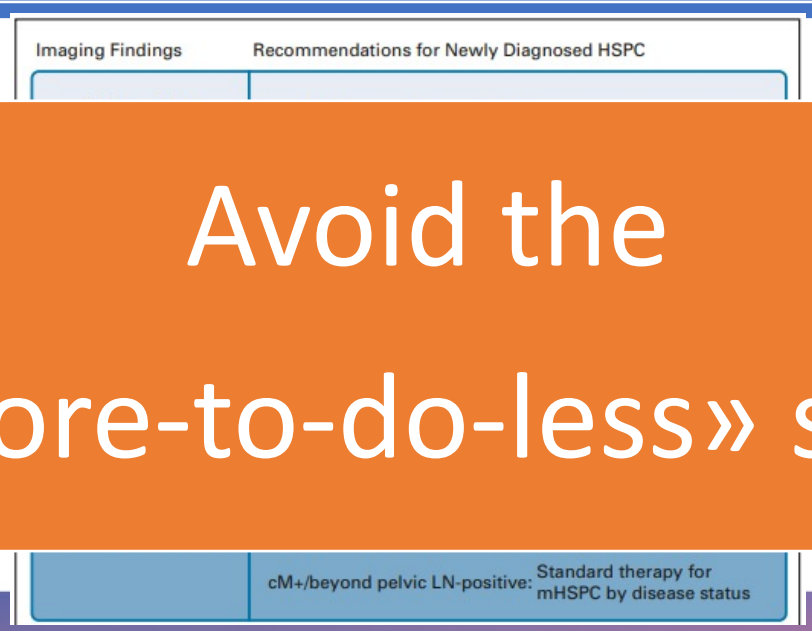
High-risk localised disease/locally advanced disease	
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong
When using PSMA PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes.	Strong

Evolving Role of Prostate-Specific Membrane Antigen-Positron Emission Tomography in Metastatic Hormone-Sensitive Prostate Cancer: More Questions than Answers?

For those with a newly diagnosed PCa who do not have systemic metastatic disease on CIM, therapy should be based on curative-intent standards of care whether disease on PSMA-PET remains localized to regional lymph nodes or extends to disease outside of the pelvis

Many patients with this clinical picture were included in trials where systemic + local therapy improved OS (pooled

Until data provide better guidance, if a PSMA-PET/CT is obtained, we advise clinicians to base treatment decisions on the extent of disease seen on CIM



Avoid the

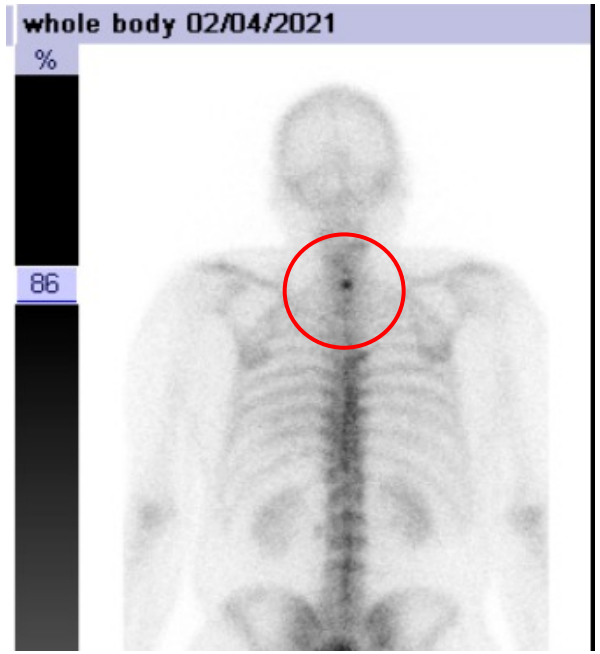
«see more-to-do-less» strategy!

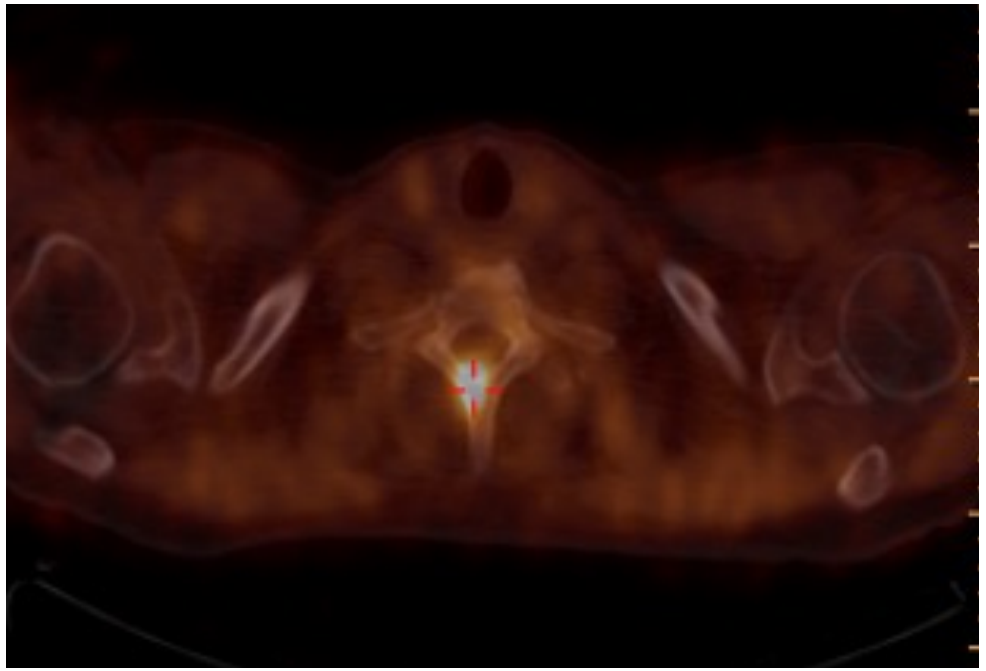
CT scan (26/03): Negative

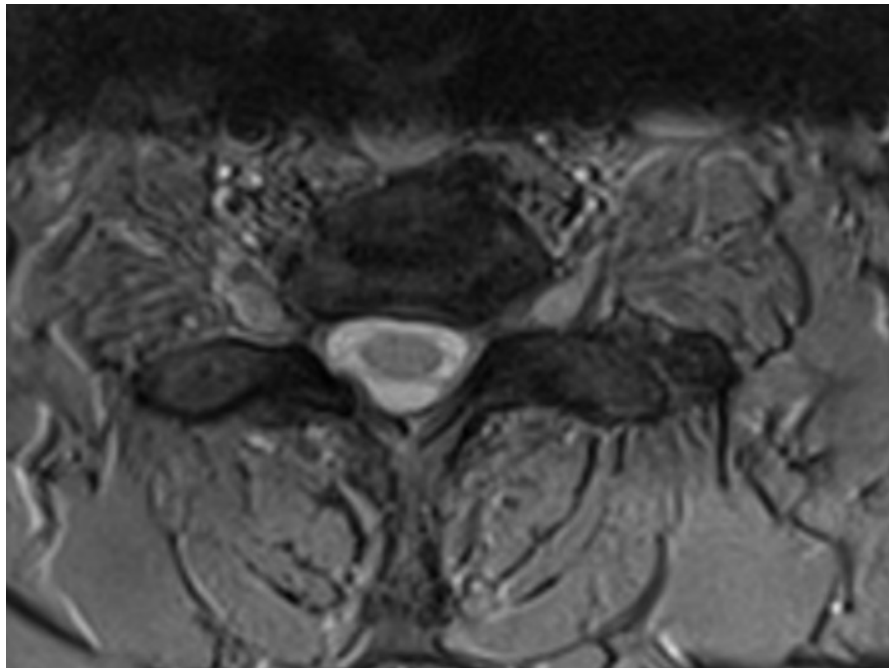
Bone scan 02/04: Suspect on T1

Cervical MRI: Suspect on T1

PET 15/04: Positive on T1





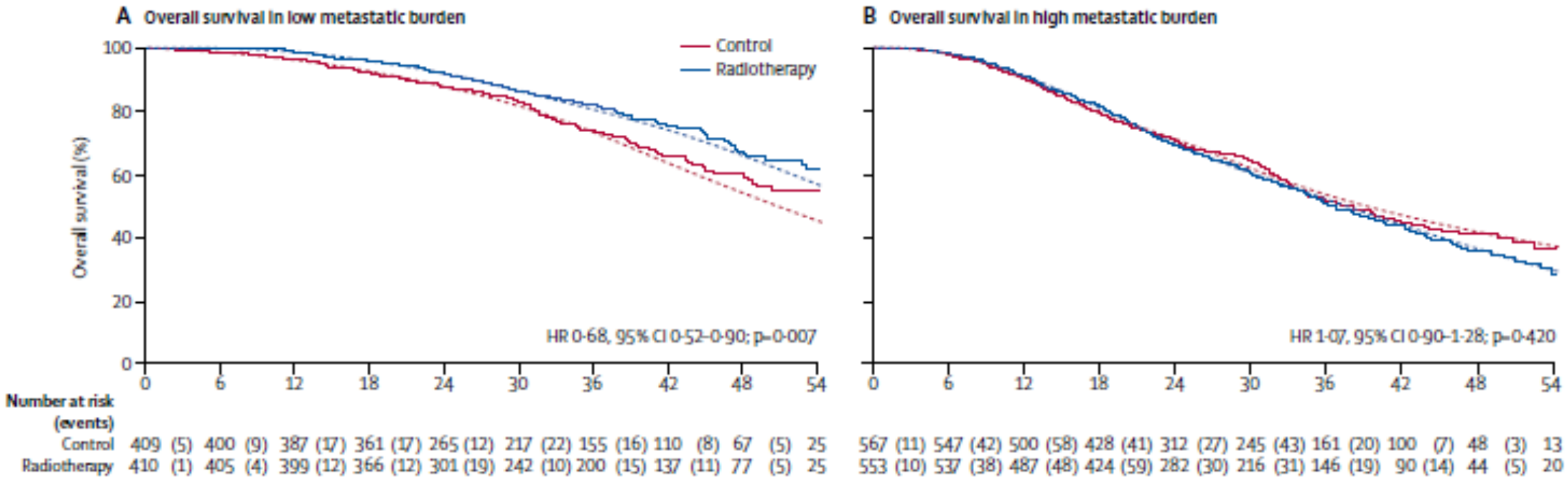


Which treatment strategy for a low burden, de novo mHSPC?

Up to 2021..

- ADT alone
- ADT+RT on Primary
- ADT+RT on Primary and M+
- ADT+RT on M+

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

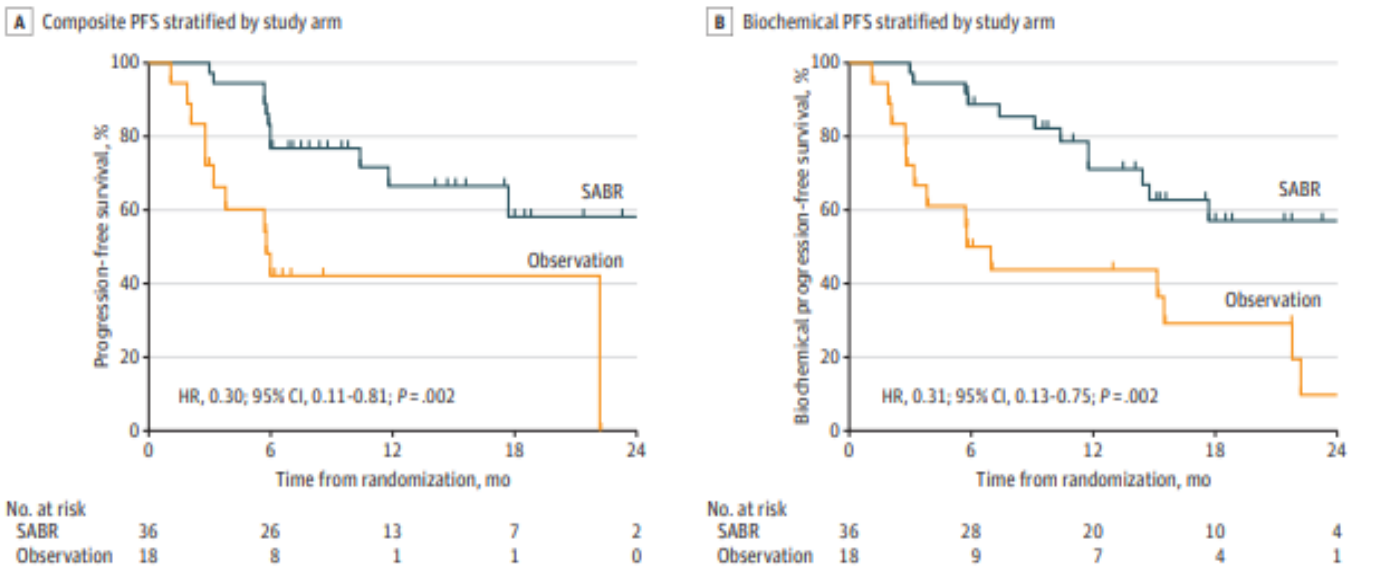


Parker, Lancet 2018

JAMA Oncology | Original Investigation

Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer

The ORIOLE Phase 2 Randomized Clinical Trial



54 men with recurrent hormone-sensitive prostate cancer and 1-3 metastases (no ADT)

Randomized in a 2:1 ratio to receive SABR or observation

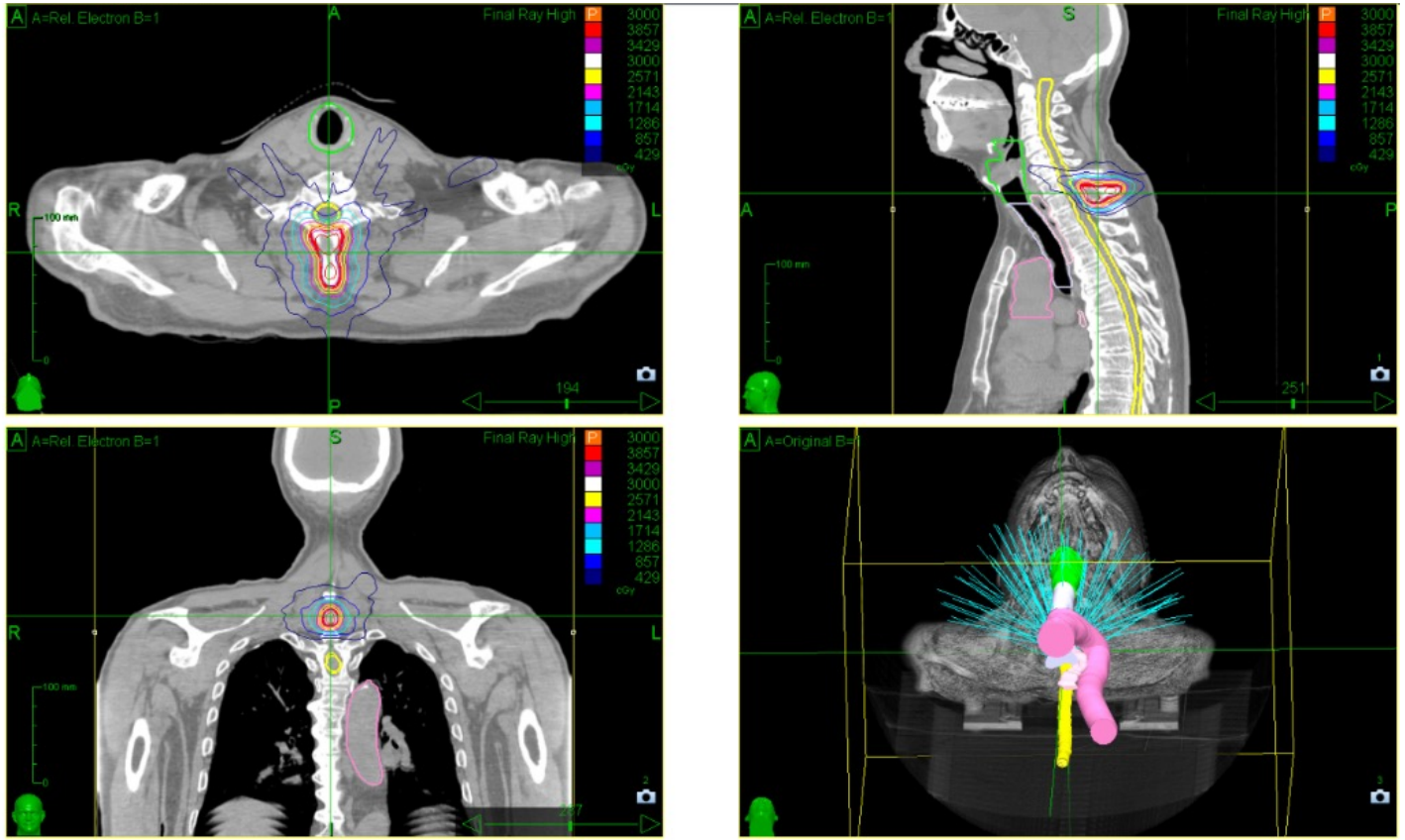
Treatment with SABR improved median progression-free survival (P = .002).

Total consolidation of PSMA radiotracer-avid disease decreased the risk of new lesions at 6 months (P = .006)

Phillips, JAMA, 2020

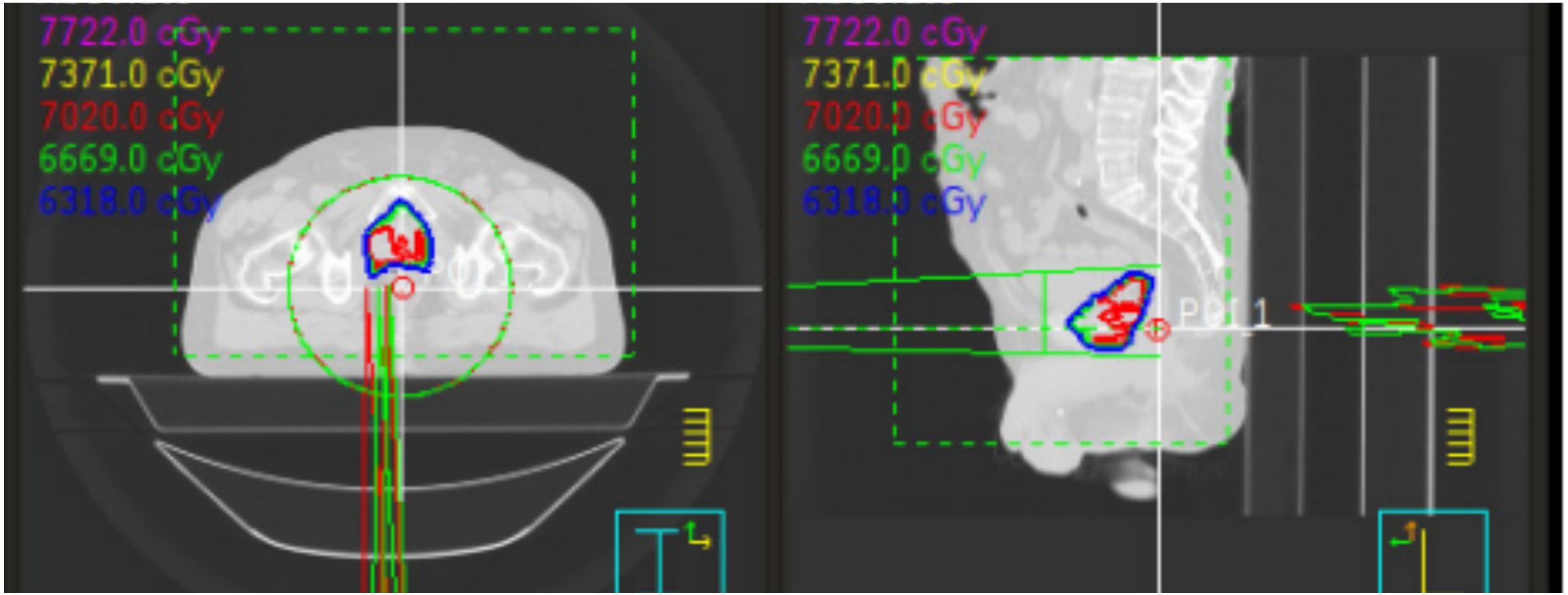
Patient started ADT but had a concomitant treatment due to complicated anal fistula… so we were forced to start from PFS benefit…

30 Gy in 3 fraction to 70% IDL administered with Cyberknife robotic stereotactic technique (26/05-28/05)



After fistula recovery, patient started prostate radiotherapy on 01/12/2021

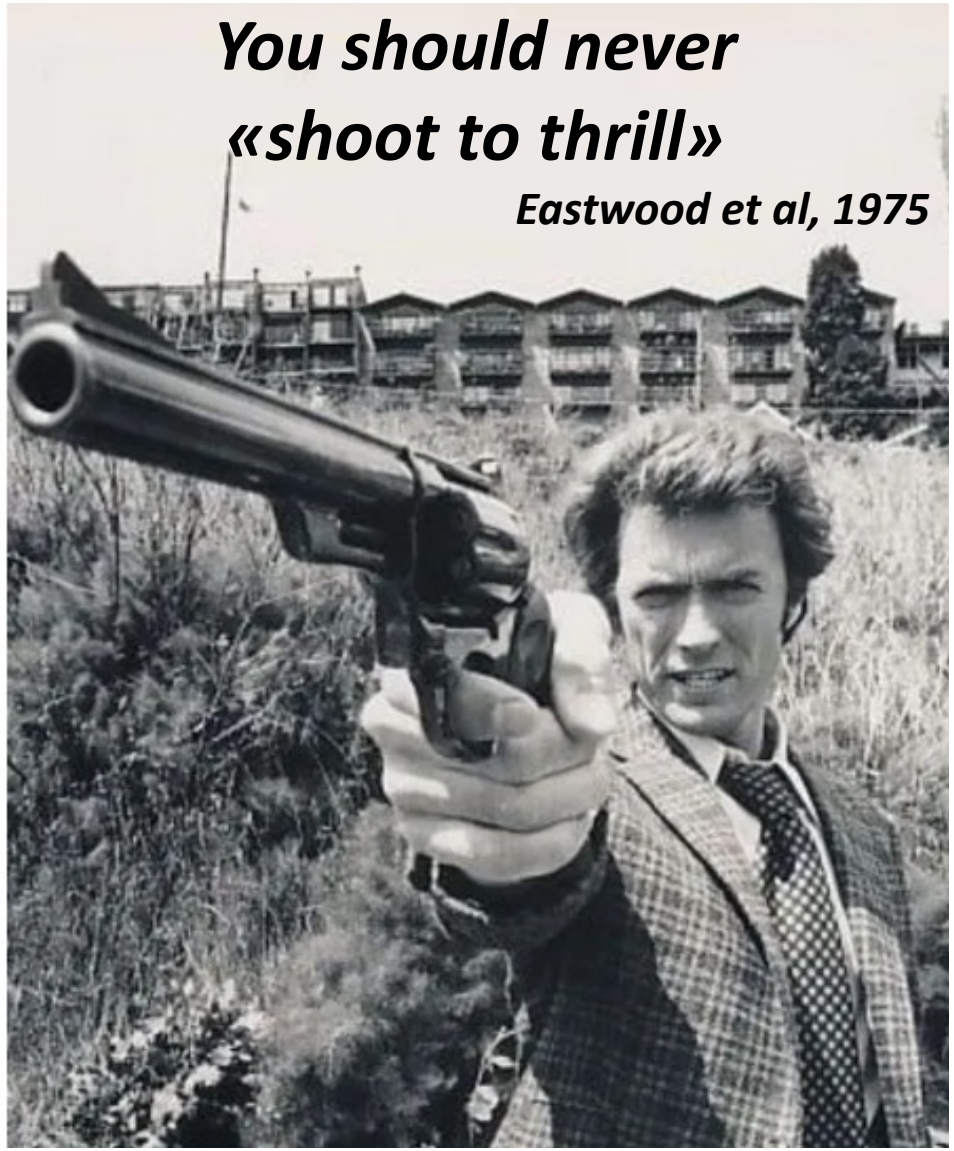
(70.2 Gy in 26 fractions, IMRT VMAT)



Regimen	Preferred Dose/Fractionation	Low Volume M1[a]
EBRT		
Moderate Hypofractionation (Preferred)	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	
	2.75 Gy x 20 fx	✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	
Ultra-Hypofractionation	7.25–8 Gy x 5 fx 6.1 Gy x 7 fx	
	6 Gy x 6 fx	✓

(alpha/beta 1.5)

- 36 Gy in 6 fractions: 77.1 Gy EQD2
- 55 Gy in 20 fractions: 66.8 Gy EQD2
- 70.2 Gy in 26 fractions: 84.2 Gy EQD2



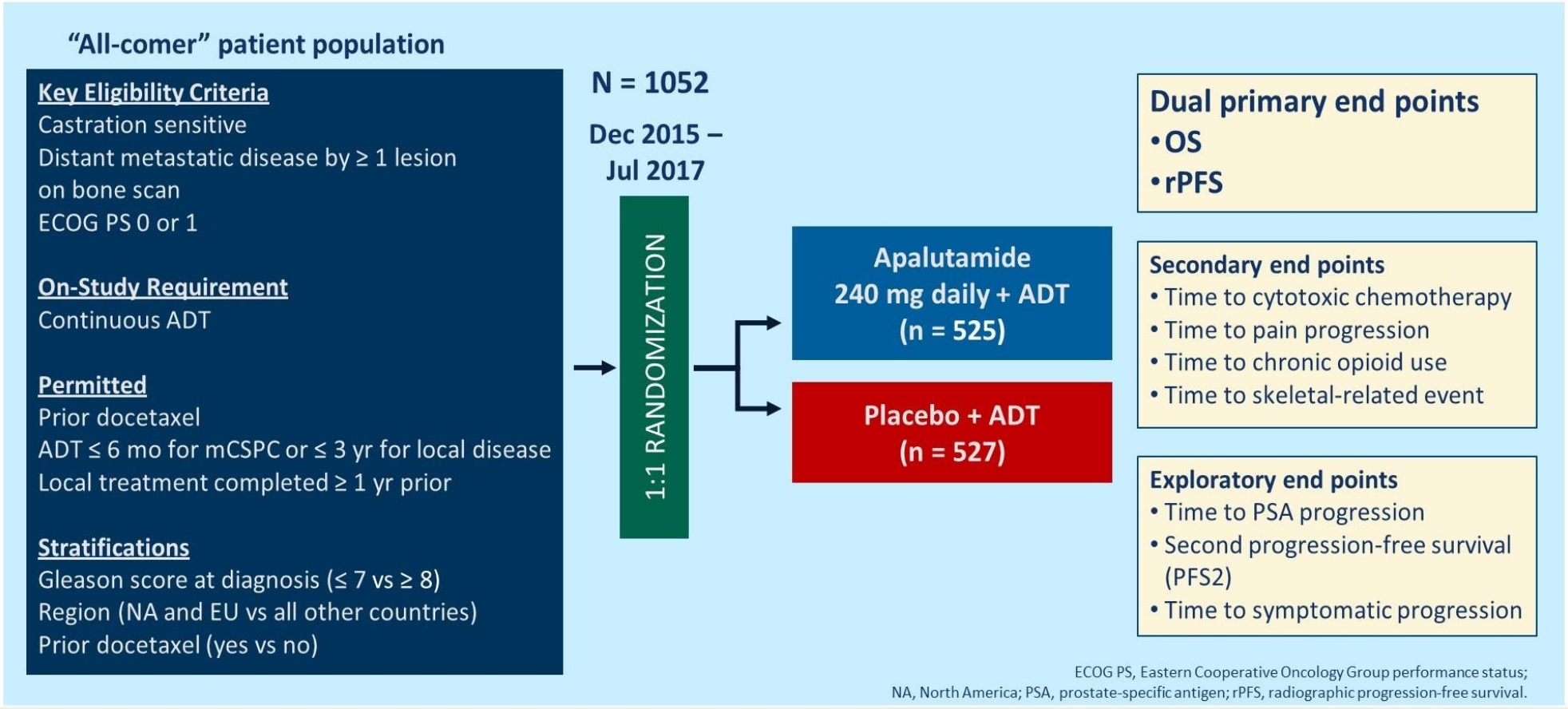
Up to 2021..

- ADT alone
- ADT+RT on Primary
- ADT+RT on Primary and M+
- ADT+RT on M+

After 2021..

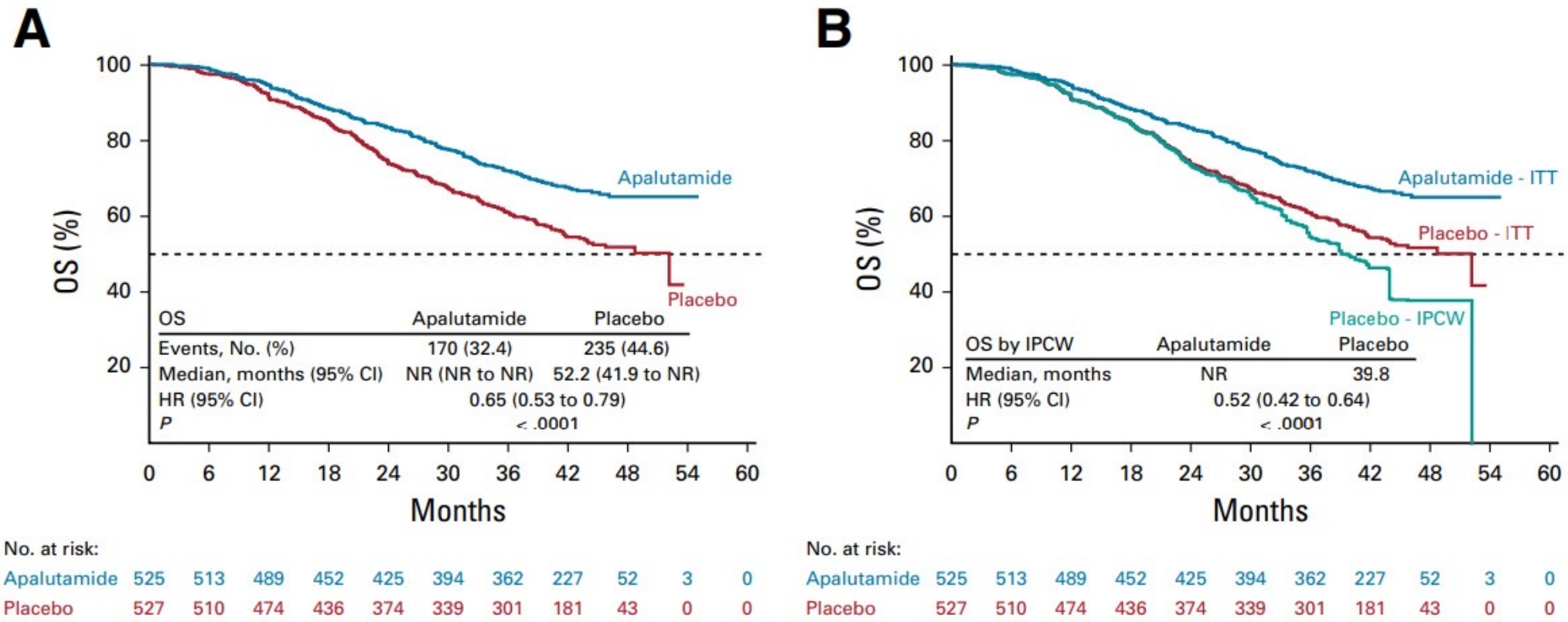
- ADT+ARsi alone
- ADT+ARsi+RT on Primary
- ADT+ARsi+RT on Primary and M+
- ADT+ARsi+RT on M+

APALUTAMIDE: TITAN Dual primary endpoint: OS PFS

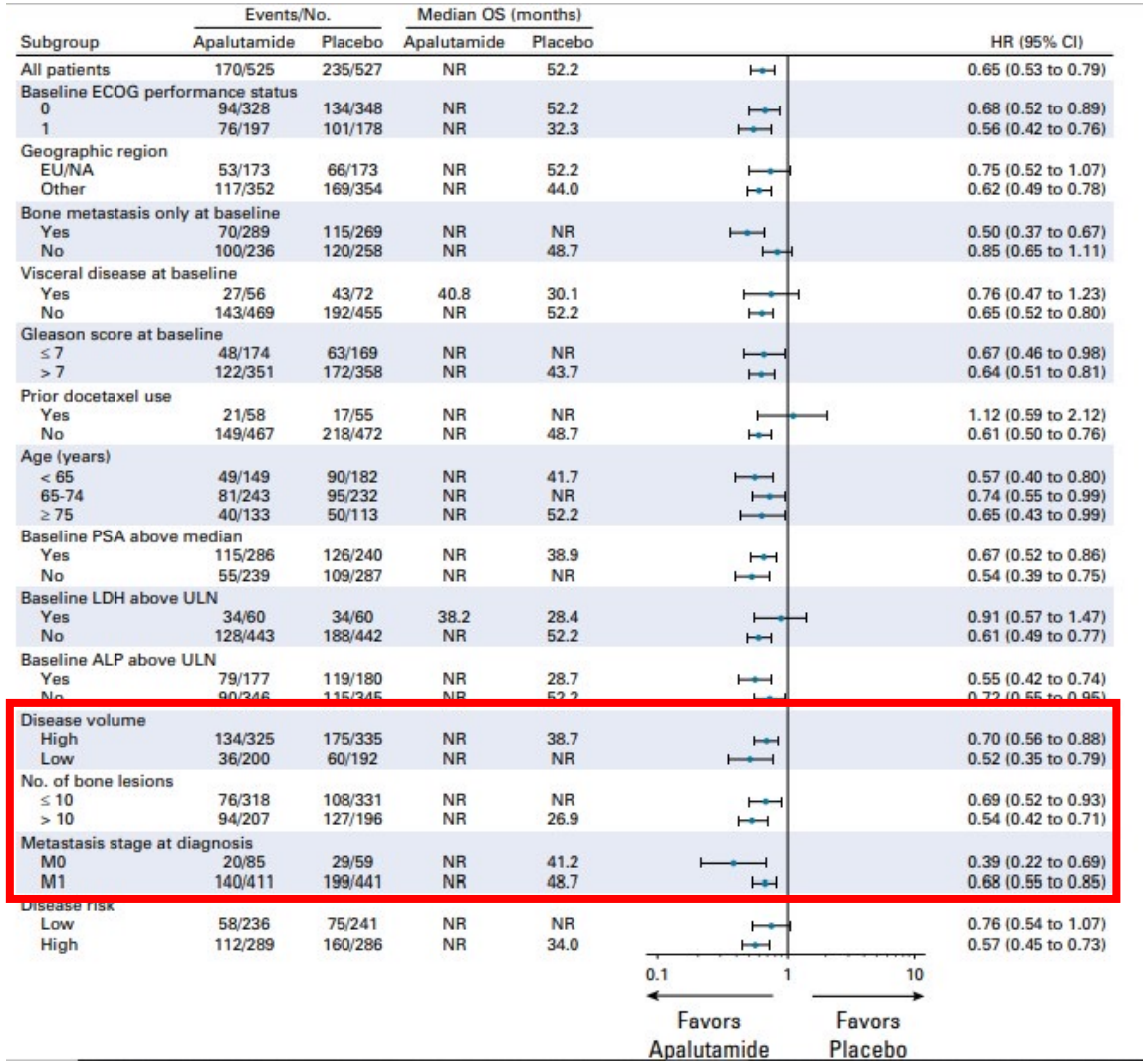


ECOG PS, Eastern Cooperative Oncology Group performance status; NA, North America; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

Kaplan-Meier estimates of (A) OS and (B) OS adjusted for patient crossover from placebo to apalutamide using the IPCW sensitivity analysis



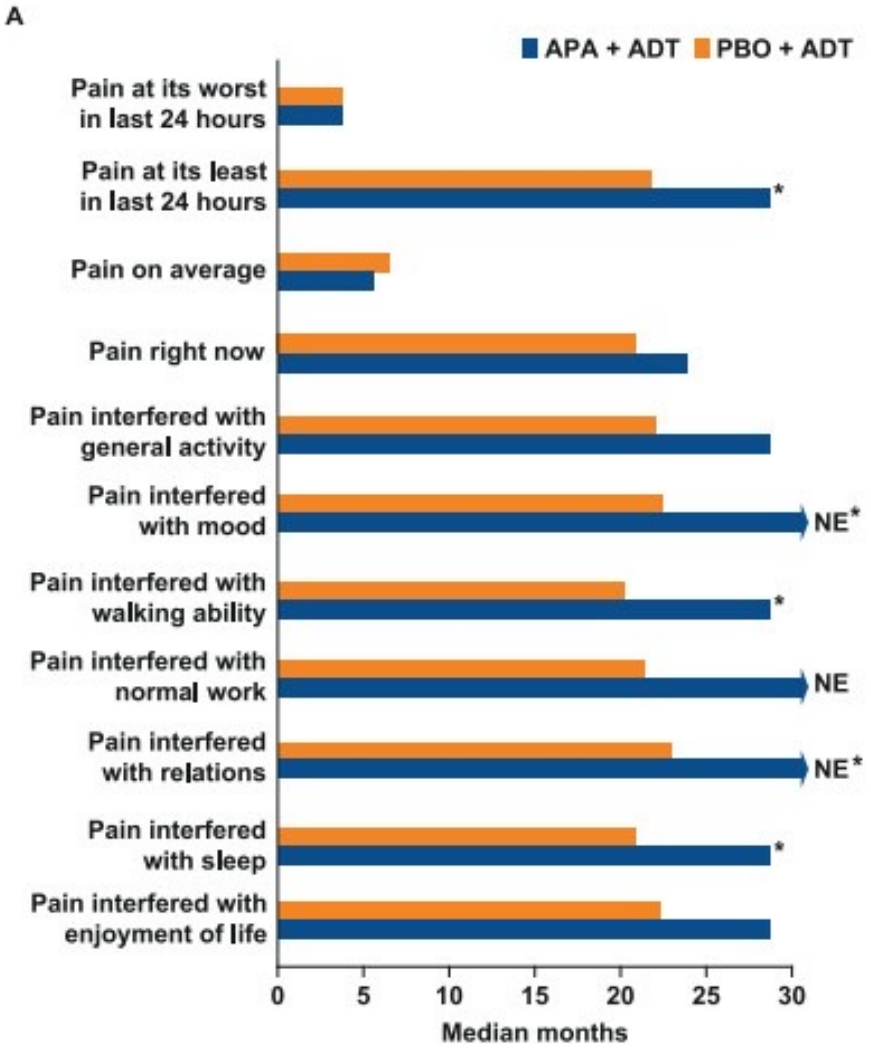
Chi, JCO 2021

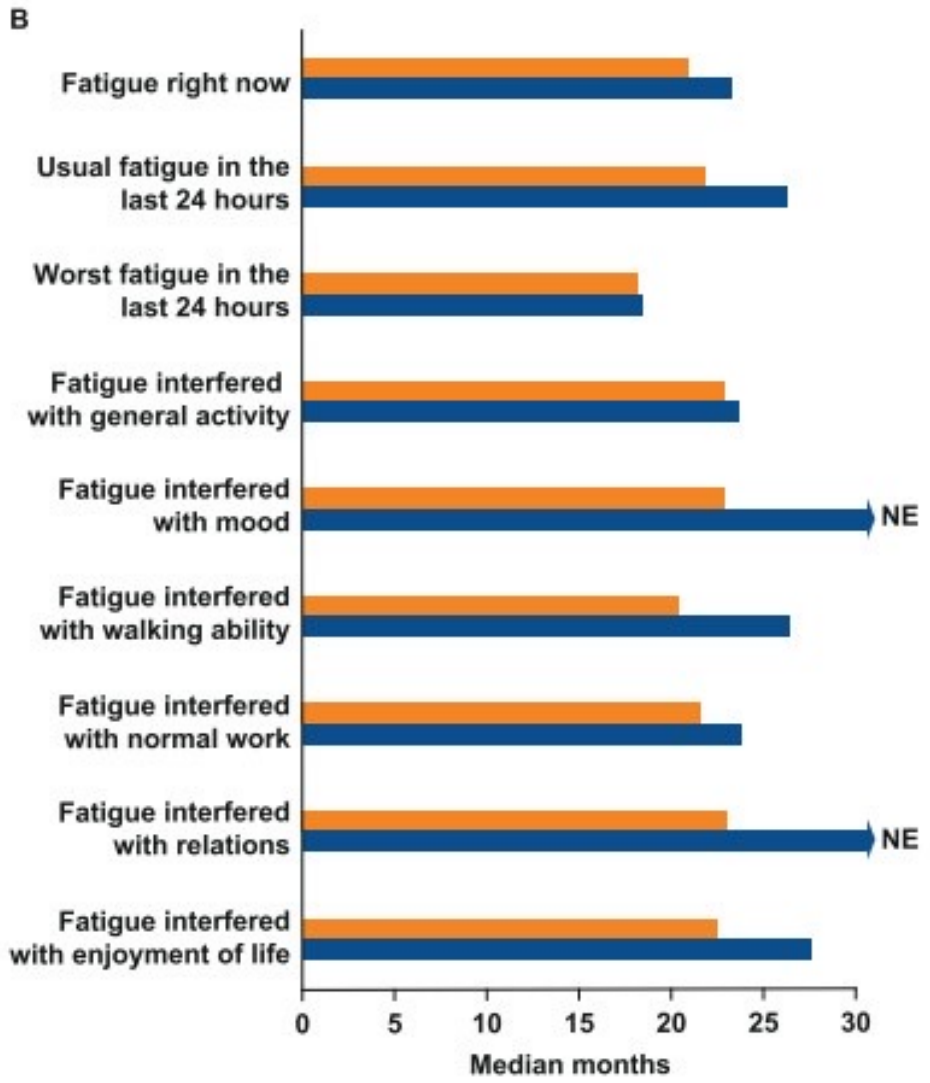


Subgroup	Events/No. Apalutamide	Events/No. Placebo	Median OS (months) Apalutamide	Median OS (months) Placebo	HR (95% CI)
All patients	170/525	235/527	NR	52.2	0.65 (0.53 to 0.79)
Baseline ECOG performance status					
0	94/328	134/348	NR	52.2	0.68 (0.52 to 0.89)
1	76/197	101/178	NR	32.3	0.56 (0.42 to 0.76)
Geographic region					
EU/NA	53/173	66/173	NR	52.2	0.75 (0.52 to 1.07)
Other	117/352	169/354	NR	44.0	0.62 (0.49 to 0.78)
Bone metastasis only at baseline					
Yes	70/289	115/269	NR	NR	0.50 (0.37 to 0.67)
No	100/236	120/258	NR	48.7	0.85 (0.65 to 1.11)
Visceral disease at baseline					
Yes	27/56	43/72	40.8	30.1	0.76 (0.47 to 1.23)
No	143/469	192/455	NR	52.2	0.65 (0.52 to 0.80)
Gleason score at baseline					
≤ 7	48/174	63/169	NR	NR	0.67 (0.46 to 0.98)
> 7	122/351	172/358	NR	43.7	0.64 (0.51 to 0.81)
Prior docetaxel use					
Yes	21/58	17/55	NR	NR	1.12 (0.59 to 2.12)
No	149/467	218/472	NR	48.7	0.61 (0.50 to 0.76)
Age (years)					
< 65	49/149	90/182	NR	41.7	0.57 (0.40 to 0.80)
65-74	81/243	95/232	NR	NR	0.74 (0.55 to 0.99)
≥ 75	40/133	50/113	NR	52.2	0.65 (0.43 to 0.99)
Baseline PSA above median					
Yes	115/286	126/240	NR	38.9	0.67 (0.52 to 0.86)
No	55/239	109/287	NR	NR	0.54 (0.39 to 0.75)
Baseline LDH above ULN					
Yes	34/60	34/60	38.2	28.4	0.91 (0.57 to 1.47)
No	128/443	188/442	NR	52.2	0.61 (0.49 to 0.77)
Baseline ALP above ULN					
Yes	79/177	119/180	NR	28.7	0.55 (0.42 to 0.74)
No	90/346	115/345	NR	52.2	0.72 (0.55 to 0.95)
Disease volume					
High	134/325	175/335	NR	38.7	0.70 (0.56 to 0.88)
Low	36/200	60/192	NR	NR	0.52 (0.35 to 0.79)
No. of bone lesions					
≤ 10	76/318	108/331	NR	NR	0.69 (0.52 to 0.93)
> 10	94/207	127/196	NR	26.9	0.54 (0.42 to 0.71)
Metastasis stage at diagnosis					
M0	20/85	29/59	NR	41.2	0.39 (0.22 to 0.69)
M1	140/411	199/441	NR	48.7	0.68 (0.55 to 0.85)
Disease risk					
Low	58/236	75/241	NR	NR	0.76 (0.54 to 1.07)
High	112/289	160/286	NR	34.0	0.57 (0.45 to 0.73)

Outcome not related to the disease volume

Chi, JCO 2021





Agarwal , The Journal of Urology 2021

ARCHES study design

Key eligibility criteria

- mHSPC (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG PS 0-1
- Current ADT duration ≤3 months in the metastatic setting, unless prior docetaxel, then ≤6 months

Stratification factors

- Volume of disease (low vs. high[a])
- Prior docetaxel therapy for mHSPC (none, 1–5, or 6 cycles)

N=1150

R 1:1

- Enzalutamide 160 mg/day + ADT
- Placebo + ADT

Key discontinuation criteria

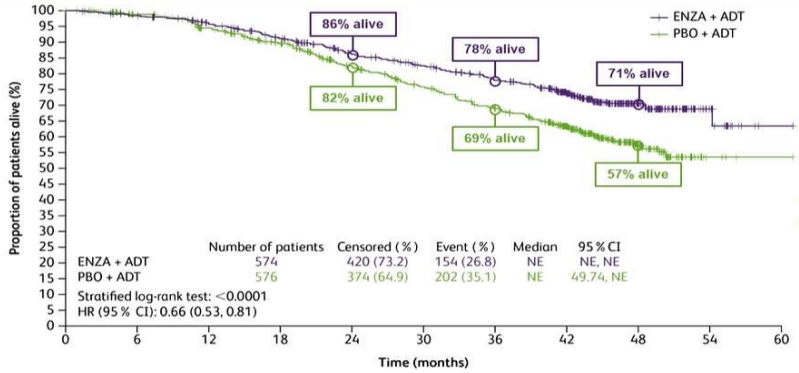
Radiographic progression, unacceptable toxicity, or initiation of an investigational agent or new therapy for prostate cancer

First patient randomized	**rPFS** final analysis **OS** interim analysis Other secondary endpoints	**OS** final analysis
March 21, 2016	October 14, 2018	May 28, 2021

[a]Defined as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must be in a bony structure beyond the vertebral column and pelvic bone.
ADT=androgen deprivation therapy; CT=computed tomography; ECOG PS=Eastern Cooperative Oncology Group performance status; mHSPC=metastatic hormone-sensitive prostate cancer; MRI=magnetic resonance imaging; OS=overall survival; rPFS=radiographic progression-free survival.

ESMO 2021

Overall survival (ITT)



Patients at risk

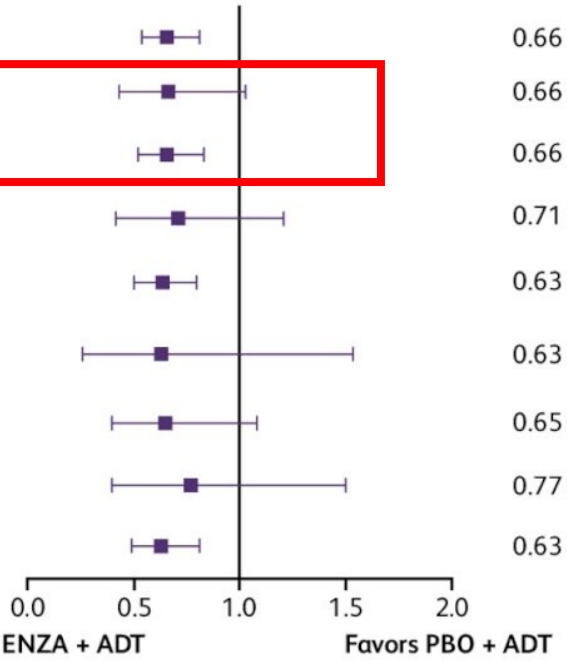
ENZA + ADT	574	559	535	498	457	427	396	316	120	17	1
PBO + ADT	576	548	511	468	404	363	322	232	80	4	1

- **As of May 28, 2021: 356 deaths (enzalutamide plus ADT, 154; placebo plus ADT, 202) were observed**
- **Median follow-up time: 44.6 mo**
- **Median treatment duration:**
  - **Enzalutamide plus ADT: 40.2 mo**
  - **Placebo plus ADT: 13.8 mo**
  - **Placebo plus ADT crossover: 23.9 mo**

ADT=androgen deprivation therapy; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; ITT=intent-to-treat; NE=not evaluable; PBO=placebo.

Figure 1. OS in Patients With Low- and High-Volume[a] Disease and M0 and M1 disease at Initial Diagnosis

Subgroup	ENZA + ADT N (E)	PBO + ADT N (E)	HR (95% CI)
Overall	574 (154)	576 (202)	0.66 (0.53, 0.81)
Low-volume disease	220 (35)	203 (46)	0.66 (0.43, 1.03)
High-volume disease	354 (119)	373 (156)	0.66 (0.52, 0.83)
M0 at diagnosis	117 (24)	129 (31)	0.71 (0.41, 1.21)
M1 at diagnosis	448 (127)	442 (170)	0.63 (0.50, 0.79)
Low-volume disease/ M0 at diagnosis	63 (8)	67 (12)	0.63 (0.26, 1.54)
Low-volume disease/ M1 at diagnosis	151 (26)	133 (34)	0.65 (0.39, 1.08)
High-volume disease/ M0 at diagnosis	54 (16)	62 (19)	0.77 (0.39, 1.50)
High-volume disease/ M1 at diagnosis	297 (101)	309 (136)	0.63 (0.48, 0.81)



[a]High-volume disease was defined as presence of metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must have been in a bony structure beyond the vertebral column and pelvic bone, per CHAARTED criteria.[8]

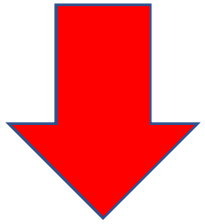
ADT=androgen deprivation therapy; CI=confidence interval; E=number of events; M0=no distant metastases; M1=distant metastases; N=number of patients; OS=overall survival.

Outcome not related to the disease volume

Andrew J. Armstrong, ASCO GU 2022

Patient reported only G1 acute GU toxicity (complete recovery) after 3 months

Patient continued ADT and is currently under follow up (last PSA 0.08 on 25 March 2022)



What will we do after 2-3 years from treatment start? ***Should we try to withold ADT?***

Take home messages:

- ADT alone should NOT considered anymore the standard for de novo low burden mHSPC
- Arsi showed to improve OS in all comers population
- RT to primary should not be denied, especially if next generation imaging has been performed
- Always consider a «go for Ablative strategy»

Open questions

- Benefit of local treatment if maximal hormonal treatment is administered? (Waiting for PEACE-1 Final results)
- What about long term ADT+Arsi if Local ablative treatment has been performed?