Treatment Intensification for high-risk localised and N+ prostate cancer

Silke Gillessen, MD
Medical Oncology
Oncology Institute of Southern Switzerland (IOSI), Bellinzona
Università della Svizzera Italiana, Lugano, Switzerland
silke.gillessen@eoc.ch

Disclosures

- **Personal honoraria** for participation in advisory boards from Amgen, MSD; other honoraria from Radio-televisione Svizzera Italiana (RSI), German-speaking European School of Oncology (DESO); invited speaker for ESMO, Swiss group for Clinical Cancer Research (SAKK), Swiss Academy of Multidisciplinary oncology (SAMO), Orikata academy research group, China Anti-Cancer Association Genitourinary Oncology Committee (CACA-GU); travel grants from ProteoMEdiX, Bayer and AstraZeneca.
- **Institutional honoraria** for participation in advisory boards or in Independent Data Monitoring Committees and Steering Committees from AAA International, Amgen, AstraZeneca, Astellas Pharma, Bayer, Bristol-Myers Squibb, Janssen, Modra Pharmaceuticals, MSD, Myriad Genetic, Novartis, Orion, Pfizer, Roche, Telixpharma, Tolermo Pharmaceutcials; other honoraria from PeerVoice, Silvio Grasso Consulting, WebMD-Medscape.
- Co-inventor on patent application (WO 2009138392 A1) for a method for biomarker discover (granted in China, Europe, Japan and the US)
- Member of the scientific committee of ESMO guidelines; member of the EAU guideline panel for prostate cancer; past chair of the EORTC GU group; Member of the STAMPEDE trial management group.

Definition EAU High-risk

Table 4.3: EAU risk groups for biochemical recurrence of localised and locally-advanced prostate cancer

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a*	PSA 10–20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b*	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c*	any PSA any GS (any ISUP grade) cT3-4* or cN+**
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

**** Based on digital rectal examination.***

***** Based on CT/bone scan.***

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Definition NCCN High-risk and Very high-risk

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
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

REGIONAL RISK GROUP (ANY T, N1, M0)

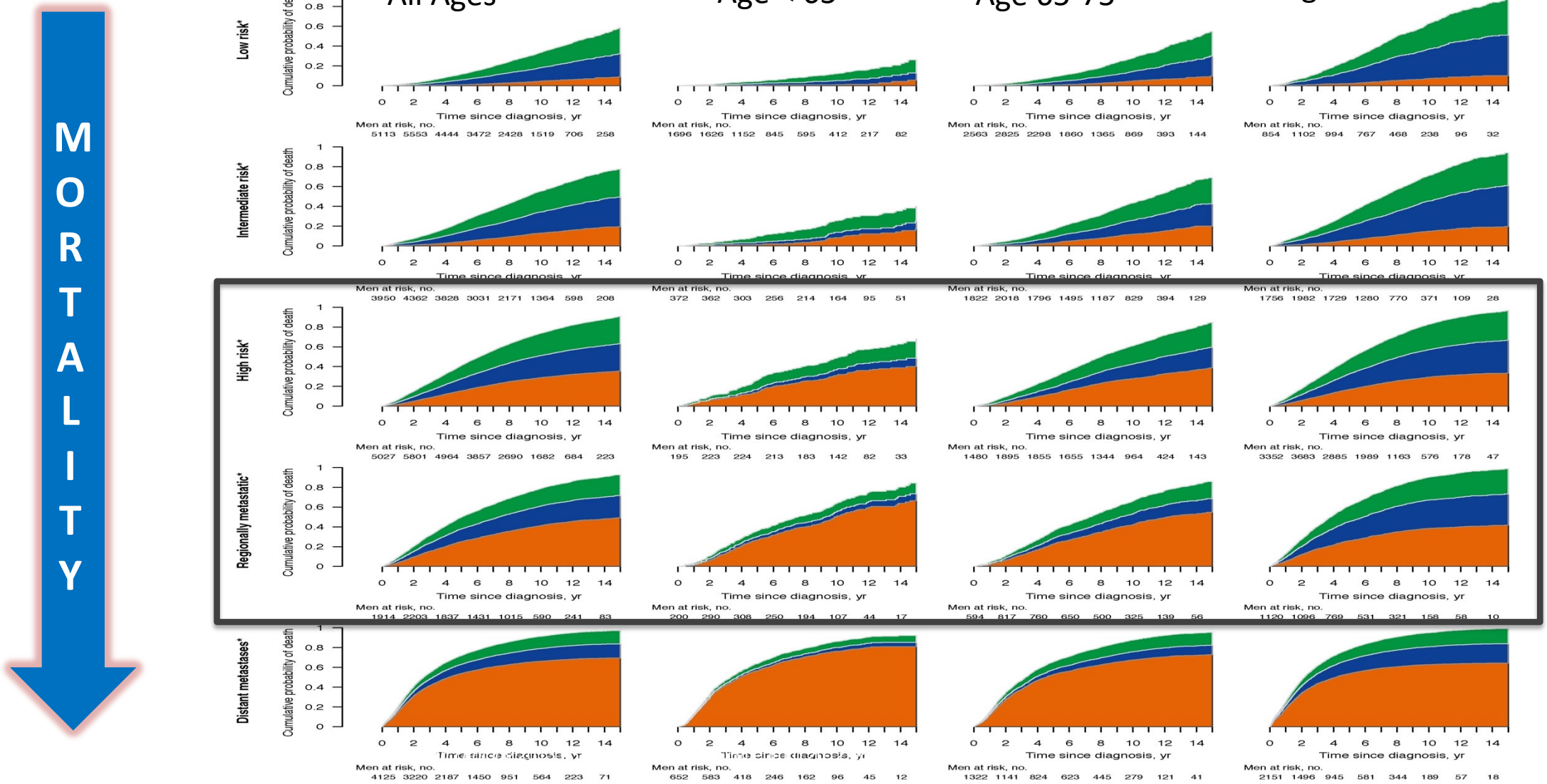
“High-risk” trials with RT plus ltADT: Heterogenous group of patients

Data from the ICECaP consortium (individual patient data from randomised trials)
N= 3606

5-yr MFS (%, 95% CI)	Gleason 7		Gleason 8-10	
	Tx1-2	*T3-4*	*Tx1-2*	*T3-4*
PSA <10	-	87 (82-91)	82 (76-87)	75 (69-80)
PSA 10-20	-	81 (75-85)	84 (77-89)	79 (73-83)
PSA >20	84 (79-87)	80 (76-83)	74 (67-79)	77 (73-80)
cN1	76 (67-82)		64 (58-69)	

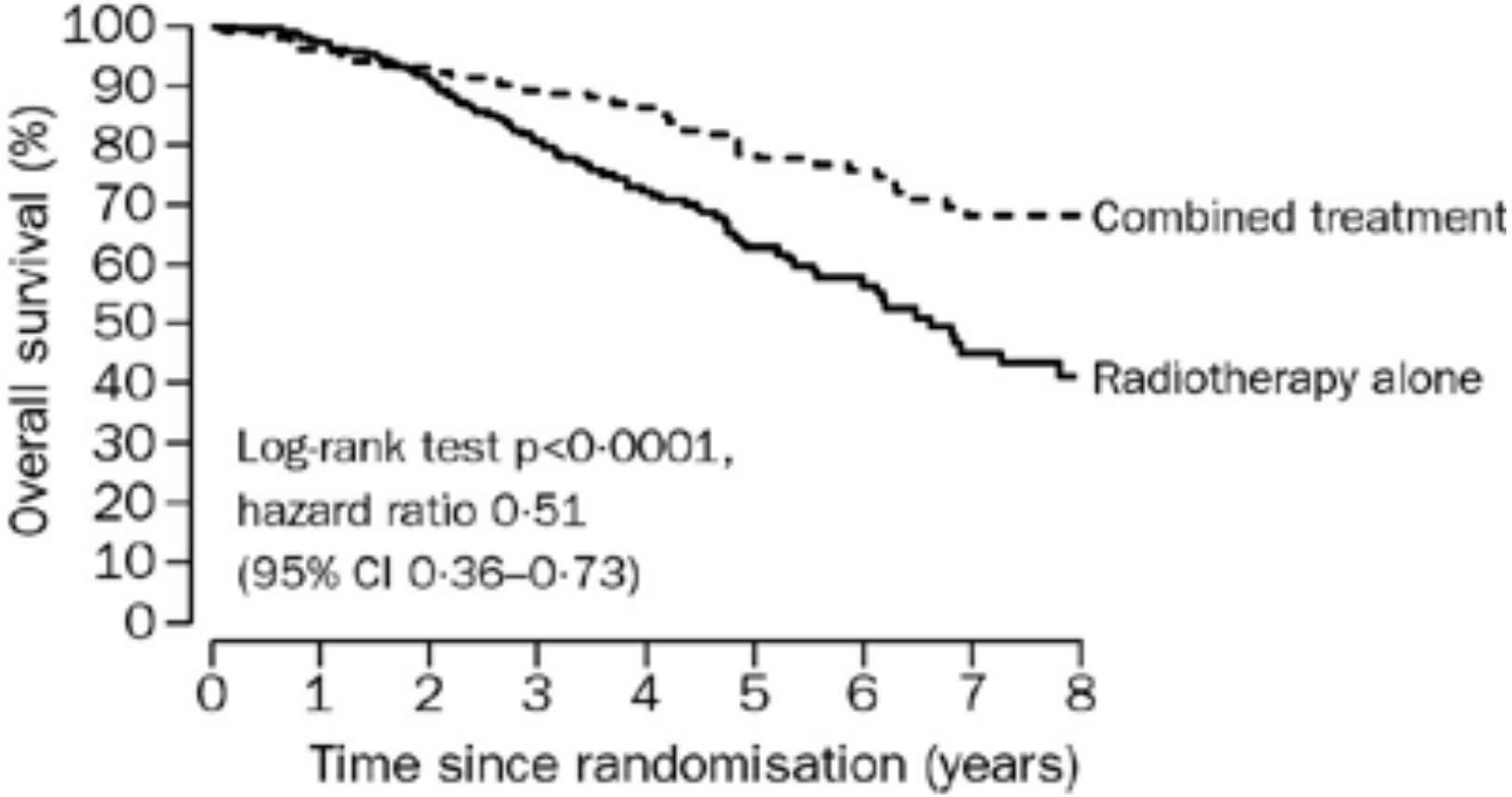
Ravi P et al. ESMO 2023

High-Risk Localised and locally advanced Prostate Cancer: Mortality closer to metastatic than to "organ confined"



Rider et al Eur Urol 2013

RT for high-risk localised Prostate Cancer:
Benefit from adding ADT to Radiotherapy



O	N	Number of patients at risk							
81	208	199	177	146	106	70	46	30	16
50	207	197	183	166	142	93	71	43	24

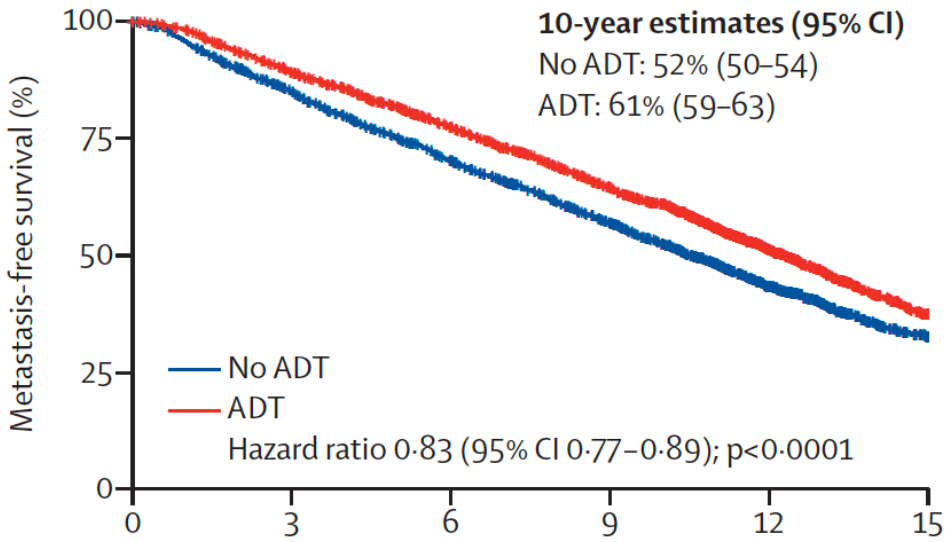
Bolla M et al. Lancet. 2002;360:103-108

Adding ADT…

- To radical Radiotherapy: Standard!

Recent meta-analysis of 12 randomized trials:

ADT adds to RT
(~80% of pts intermediate- or high-risk)



Number at risk (number censored)						
No ADT (1600 events)	2576 (2)	2128 (63)	1695 (133)	1289 (224)	722 (514)	335 (761)
ADT (1399 events)	2555 (4)	2226 (56)	1828 (166)	1415 (282)	754 (689)	332 (951)

Kishan A, *Lancet Oncol* 2022

Adding ADT…

- To radical Prostatectomy:

Neoadjuvant treatment no standard (no effect on relapse free survival/CSS)

Adjuvant ADT in general no standard (except pN+)

SWOG S9921 (n=961) Chemo-ADT vs ADT for adverse risk at prostatectomy no arm without ADT

GETUG-20 results awaited

Liu W et al. *Asian J Androl* 2021; Messing ME et al. *New Engl J Med* 1999 and *Lancet Oncol 2006*; Hussain M et al., *J Clin Oncol* 2018

Further Intensification

1. Adding Docetaxel

GETUG-12: ADT +/- Docetaxel for high risk localised prostate cancer: 12 year Update

ADT=Androgen Deprivation Therapy

Inclusion:

- **Gleason≥ 8**

or

- **PSA>20**

or

- **T3/T4**

or

- **pN+**

2002-2006
26 French Centres

RANDOMISE

n=413

ADT (3 years)

Docetaxel Estramustine x 4 cycles

Local Treatment* at 3 months

ADT (3 years)

Local Treatment* at 3 months

***87% Radiotherapy**

1° Endpoint: Relapse Free Survival (RFS)

Fizazi K et al. ESMO 2018

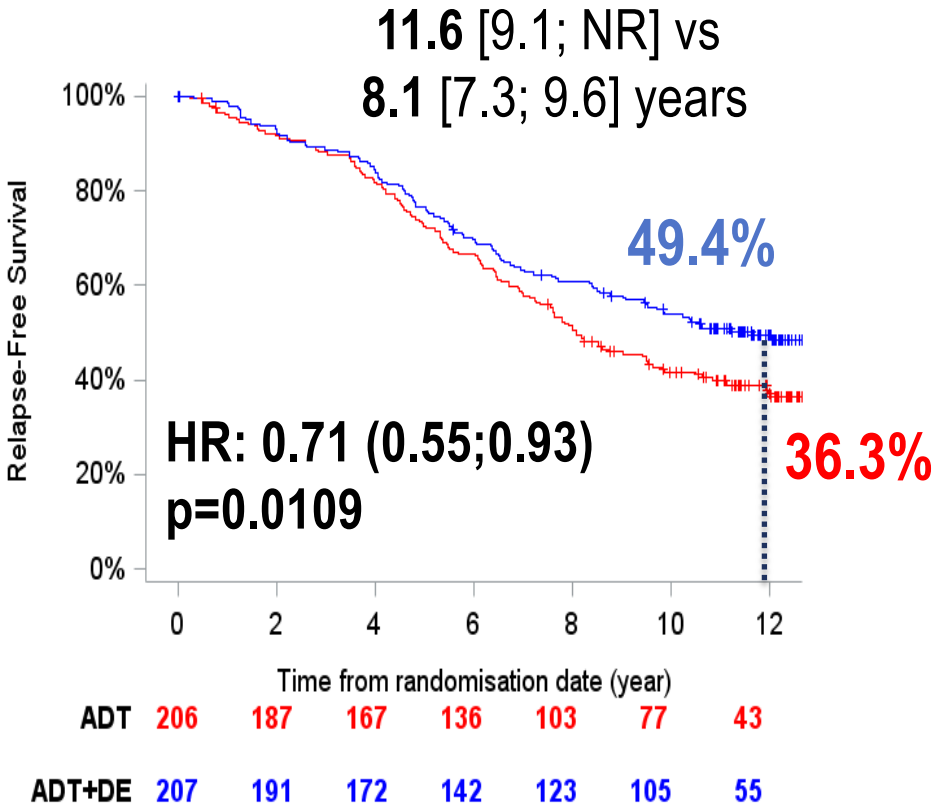
GETUG-12: Results

Significantly improved
- **RFS,** Clinical RFS
- PSA response

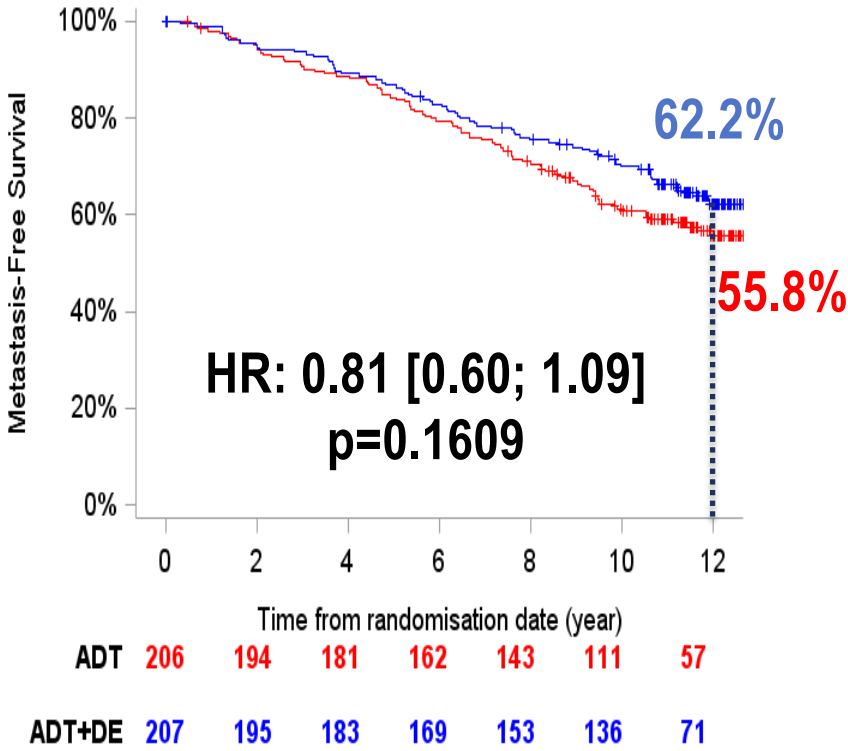
Safety
2% neutropenic fever
No toxic deaths
No increase in second cancers

QoL: No negative impact at 1 year

Primary endpoint:
Relapse Free Survival (RFS)



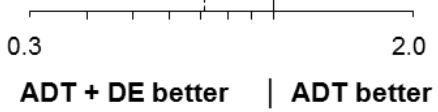
Metastases Free Survival



Fizazi K et al. ESMO 2018

GETUG-12: Subgroup Analysis RFS

Stratification Factors	No. Events / No. Entered ADT + DE	ADT	Hazard Ratio	HR [95% CI]
Gleason Score ≤ 7	52/120	76/118		0.57 [0.40;0.81]
Gleason Score > 7	54/87	51/88		0.95 [0.64;1.40]
T (TNM): T1-T2	32/67	39/67		0.83 [0.52;1.32]
T (TNM): T3-T4	74/140	88/139		0.67 [0.49;0.91]
PSA ≤ 20ng/m	42/84	48/85		0.75 [0.49;1.13]
PSA > 20ng/m	64/123	79/121		0.69 [0.50;0.97]
pN=0	61/148	73/146		0.78 [0.55;1.10]
pN=1 or 2	45/59	54/60		0.64 [0.43;0.95]
Overall	**106/207**	**127/206**		**0.71 [0.55;0.93]**

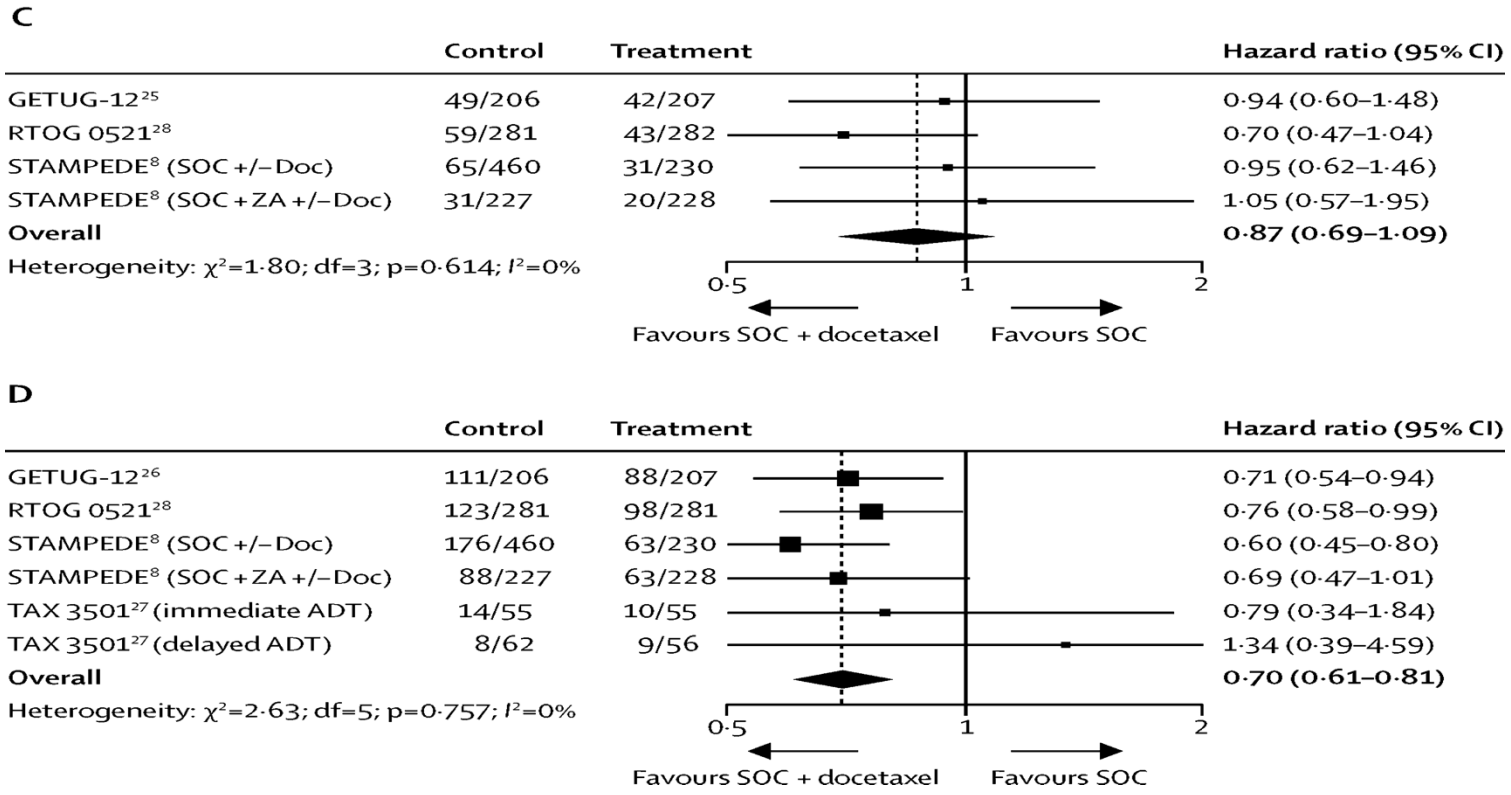


Fizazi K et al. ESMO 2018

Meta-Analysis: Docetaxel in Localized High Risk Prostate Cancer

Overall Survival
HR 0.87
2% Improvement

Failure Free Survival
HR 0.7 (0.61, 0.81), p<0.0001



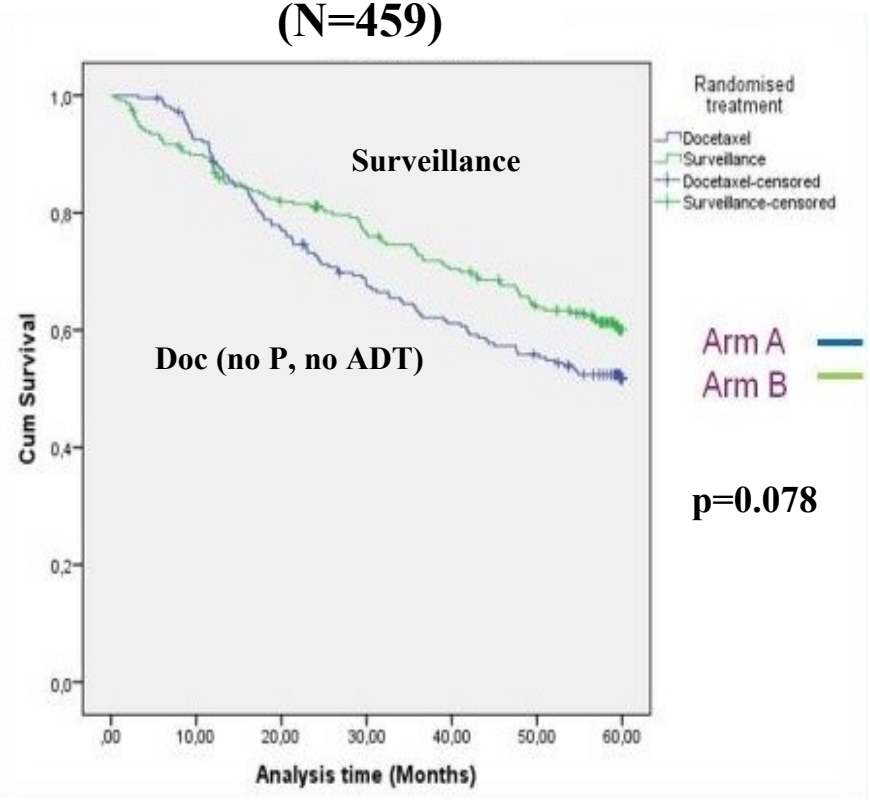
Results based on 2348 men / 842 events

8% absolute reduction in failure (from 70% to 62%) at 4 years

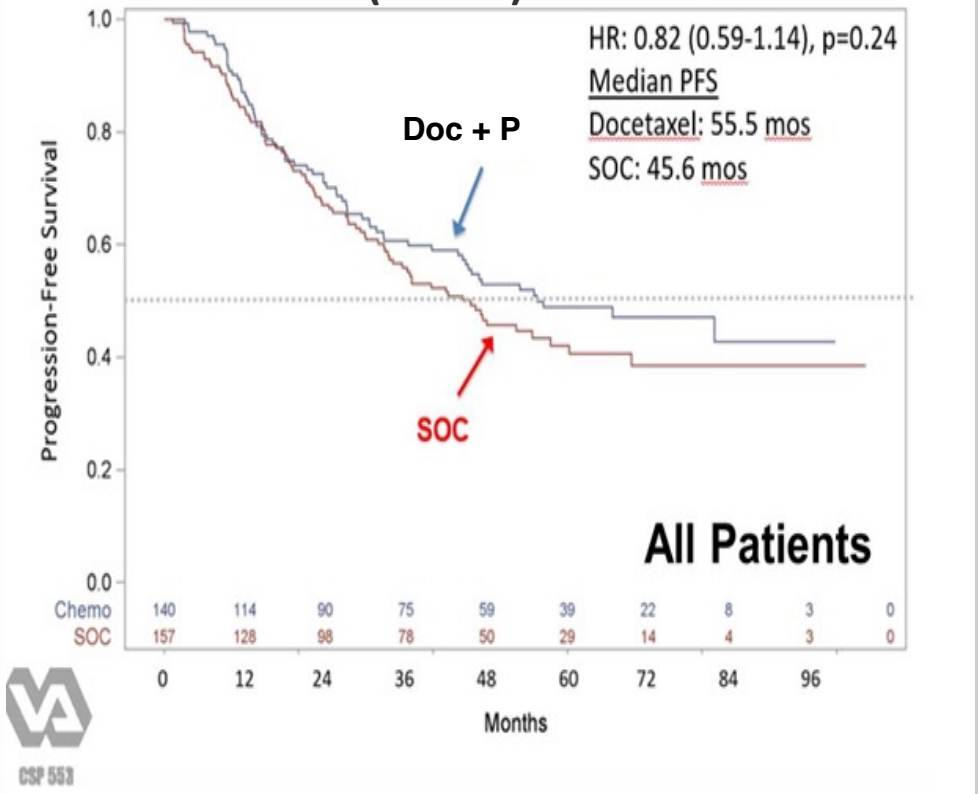
Vale et al 2016 Lancet Oncology

Docetaxel adjuvant after radical prostatectomy (no ADT): Negative

SPCG12/Ad Pro
PFS
(N=459)



VA CSP #553
(N=297)



Doc=docetaxel; P=prednisone.

Ahlgren GM et al. Eur Urol 2018; Lin DW et al Eur Urol 2020

Further Intensification

1. Adding Abiraterone/Prednison

Abiraterone acetate plus prednisolone with or without enzalutamide added to androgen deprivation therapy compared to ADT alone for men with high-risk nonmetastatic prostate cancer: primary combined analysis from two comparisons in the STAMPEDE platform protocol

Gerhardt Attard, Louise Brown, Noel Clarke, Laura Murphy, William Cross, Rob Jones, Silke Gillessen, J.Martin Russell, Adrian Cook, Jo Bowen, Anna Lydon, Ian Pedley, Omi Parikh, Simon Chowdhury, Zafar Malik, David Matheson, Chris Parker, Matthew Sydes, Mahesh Parmar, Nicholas James **on behalf of the STAMPEDE investigators***

Conducted by Medical Research Council Trials Unit at University College London, U.K.

ClinicalTrials.gov number, NCT00268476 & Current Controlled Trials number, ISRCTN78818544

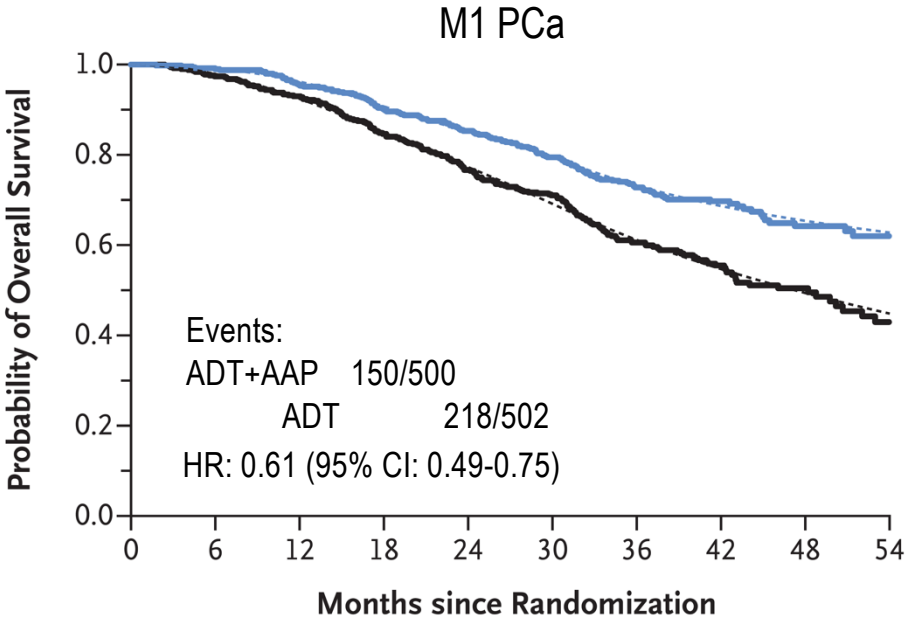
*113 U.K. and Swiss sites: list of investigators and collaborators at www.stampedetrial.org

www.stampedetrial.org

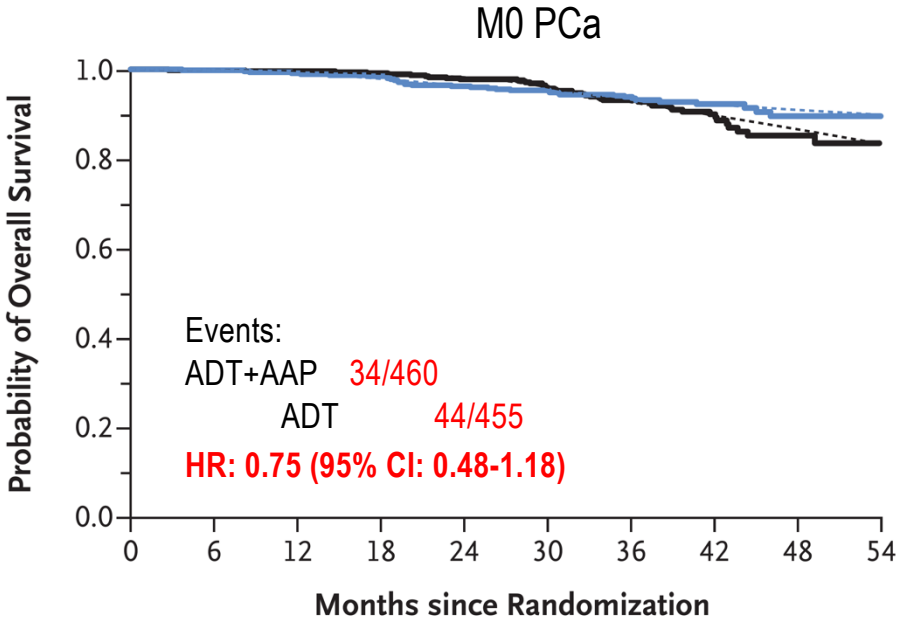
2021 ESMO congress

Background

- ADT + AAP/ENZ/apalutamide improve outcomes of M1 PCa[1-5]
- Uncertain benefit in M0 PCa[1] – STAMPEDE trial



No. of Patients (no. of deaths)									
Combination therapy	500	(22)	469	(50)	415	(57)	256	(18)	81
ADT alone	502	(35)	460	(80)	371	(73)	215	(23)	60



No. of Patients (no. of deaths)									
Combination therapy	460	(4)	448	(13)	425	(10)	285	(7)	80
ADT alone	455	(2)	449	(8)	435	(19)	276	(13)	63

AAP, abiraterone acetate and prednisolone/prednisone
ENZ, enzalutamide; M1, metastatic

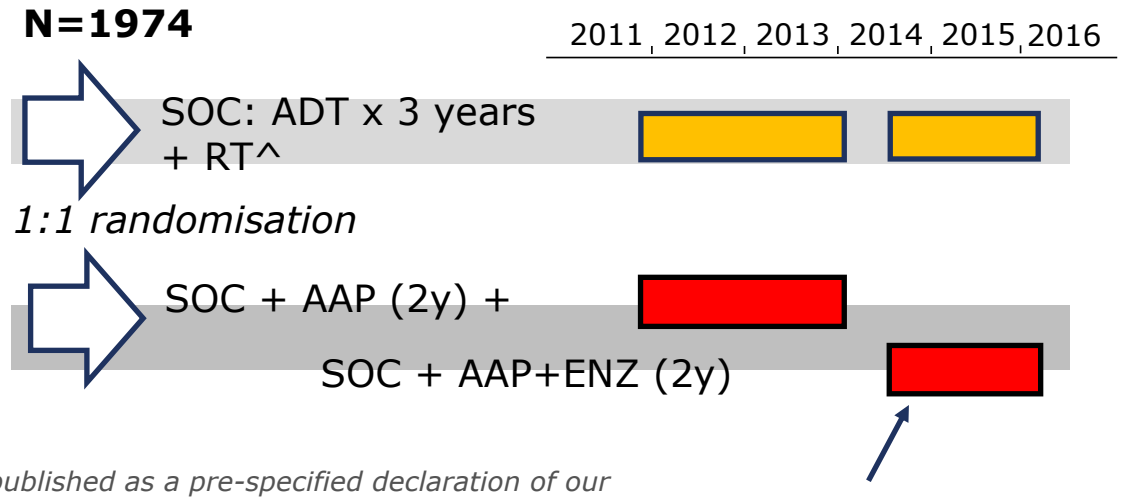
Is there a benefit for AAP in high-risk M0 PCa?

Attard G. et al. ESMO 2021; Lancet Oncol 2023

1. James ND, et al. N Engl J Med 2017;377:338-51.
2. Armstrong AJ, et al. J Clin Oncol 2019;37:2974-86.
3. Chi KN, et al. N Engl J Med 2019;381:13-24.
4. Davis ID, et al. N Engl J Med 2019;381:121-31.
5. Fizazi K, et al. N Engl J Med 2017;377:352-60.

Study Design

2019 - amended the reporting plan* to split M1 & M0, power the 1ary end-point on MFS, meta-analyse with new data from AAP+ENZ comparison



- No overlapping controls
- Same protocol & eligibility criteria
- 2 years AAP+/-ENZ
- No evidence of OS benefit with AAP+/-ENZ in mCRPC [1]

**published as a pre-specified declaration of our intentions: Attard G, et al. Eur Urol. Epub 2021 Jul 14*

Solid bars: period of accrual

SOC, standard of care
^when indicated
[1]Morris MJ, et al. J Clin Oncol 2019;37:5008

Attard G. et al. ESMO 2021; Lancet Oncol 2023

STAMPEDE: M0 Patient population (n=1974)

M0
No evidence of metastases on bone scan and CT scan of pelvis, abdo, chest (pre-defined stratification criterion)

Newly-diagnosed
Any of:
- Node-Positive
- ≥2 of: Stage T3 or T4
  PSA≥40ng/ml
  Gleason 8, 9 or 10

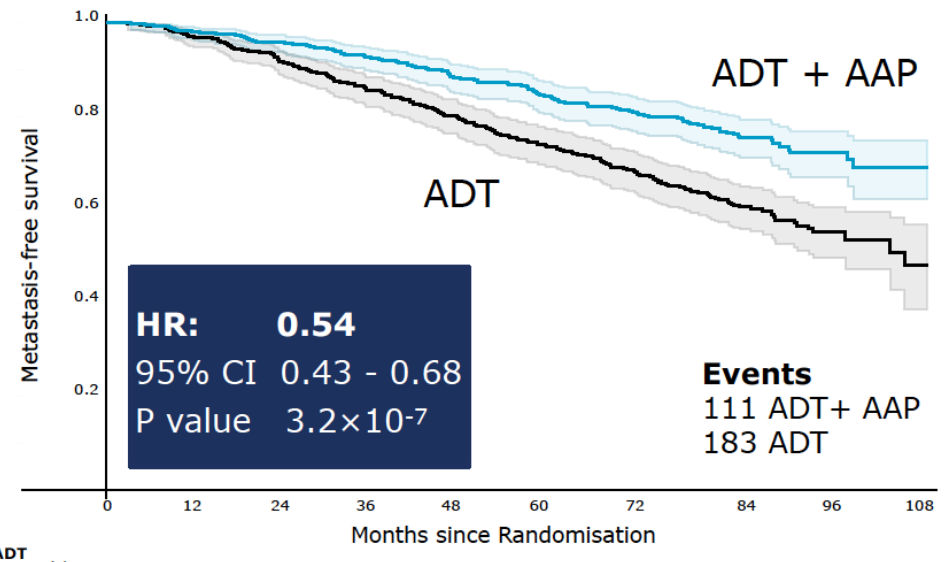
3%

Relapsing after previous RP or RT
Any of:
- Node-positive
- PSA≥4ng/ml, rising & doubling time <6m
- PSA≥20ng/ml

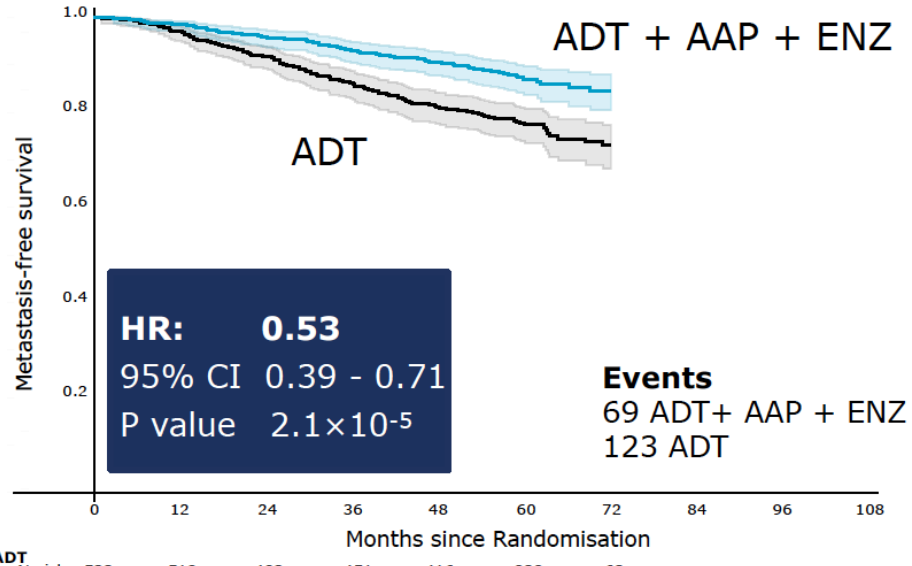
All patients
Written informed consent
Fit for all protocol treatment
Fit for follow-up

Full criteria: www.stampedetrial.org

Abiraterone in STAMPEDE M0: Metastasis-free survival



ADT										
At-risk	455	438	411	385	351	318	266	172	53	9
Censored	0	3	4	5	8	15	40	112	222	263
Event	0	14	40	65	96	122	149	171	180	183
ADT+AAP										
At-risk	459	441	426	411	391	362	312	198	71	14
Censored	0	9	13	13	14	22	58	157	279	334
Event	0	9	20	35	54	75	89	104	109	111



ADT							
At-risk	533	512	483	451	416	232	63
Censored	0	5	7	9	18	186	347
Event	0	16	43	73	99	115	123
ADT+AAP+ENZ							
At-risk	527	507	491	473	448	260	57
Censored	0	12	15	18	31	203	402
Event	0	8	21	36	48	64	68

Kaplan-Meier estimates with 95% CI in lighter shade

Interaction HR: 1.02, 95% CI: 0.70 – 1.50, P=0.908

2021 ESMO congress

Attard G. et al. ESMO 2021; Lancet Oncol 2023

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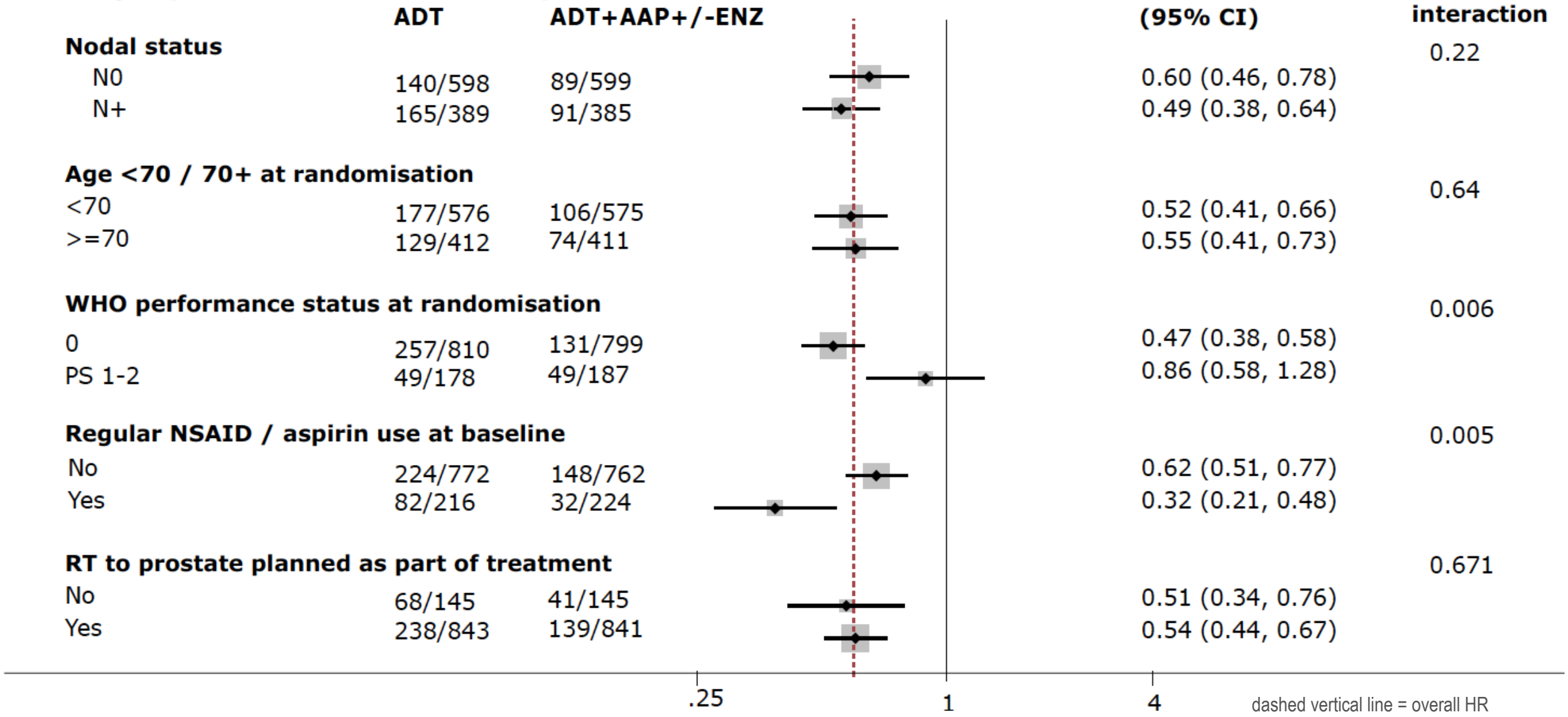
Metastasis-free survival: Subgroup analysis

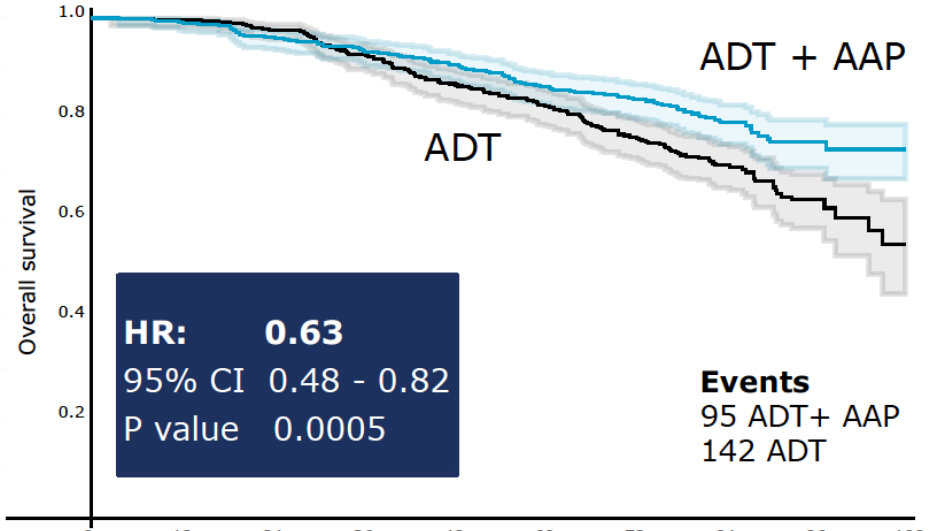
Subgroup	*N events/N patients* ADT	ADT+AAP+/-ENZ	Hazard Ratio (95% CI)	P value for interaction
Nodal status				0.22
N0	140/598	89/599	0.60 (0.46, 0.78)	
N+	165/389	91/385	0.49 (0.38, 0.64)	
Age <70 / 70+ at randomisation				0.64
<70	177/576	106/575	0.52 (0.41, 0.66)	
>=70	129/412	74/411	0.55 (0.41, 0.73)	
WHO performance status at randomisation				0.006
0	257/810	131/799	0.47 (0.38, 0.58)	
PS 1-2	49/178	49/187	0.86 (0.58, 1.28)	
Regular NSAID / aspirin use at baseline				0.005
No	224/772	148/762	0.62 (0.51, 0.77)	
Yes	82/216	32/224	0.32 (0.21, 0.48)	
RT to prostate planned as part of treatment				0.671
No	68/145	41/145	0.51 (0.34, 0.76)	
Yes	238/843	139/841	0.54 (0.44, 0.67)	



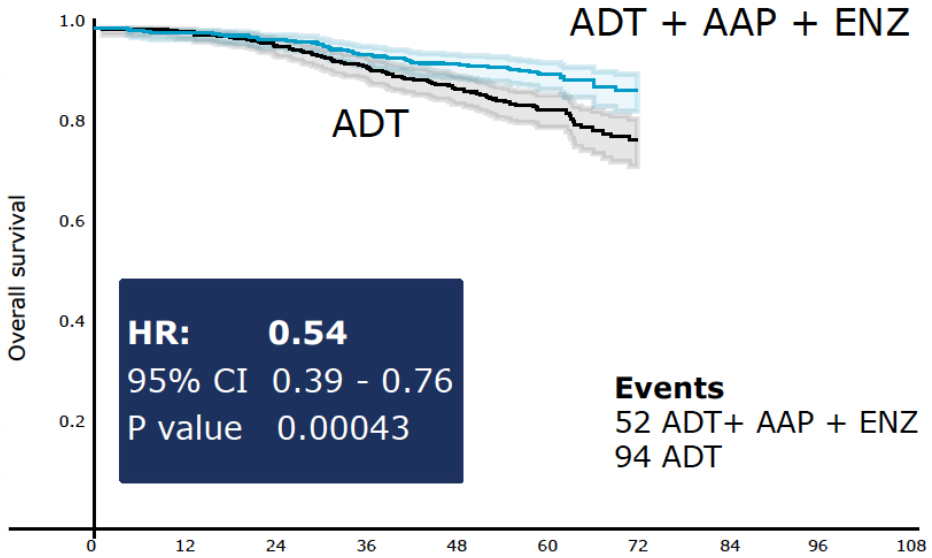
dashed vertical line = overall HR
weighting is by sample size

Attard G. et al. ESMO 2021; Lancet Oncol 2023

Abiraterone in STAMPEDE M0: Overall Survival



ADT										
At-risk	455	450	440	417	388	361	302	200	63	10
Censored	0	3	4	5	8	16	48	129	254	303
Event	0	2	11	33	59	78	105	126	138	142
ADT + AAP										
At-risk	459	446	429	418	403	376	328	205	74	16
Censored	0	9	13	13	14	22	59	166	291	348
Event	0	4	17	28	42	61	72	88	94	95



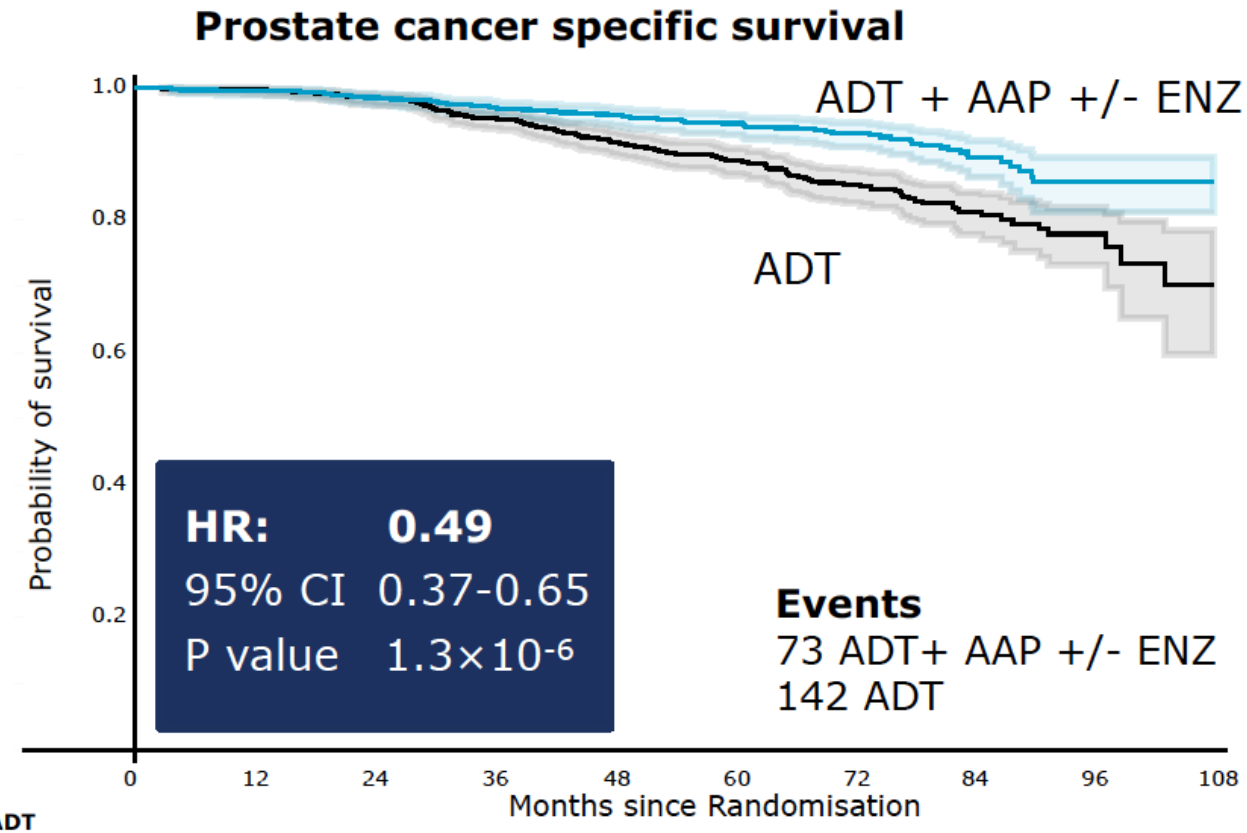
ADT							
At-risk	533	524	507	484	449	249	66
Censored	0	5	7	9	20	200	373
Event	0	4	19	40	64	84	94
ADT+AAP+ENZ							
At-risk	527	510	499	481	458	269	58
Censored	0	12	16	19	32	212	418
Event	0	5	12	27	37	46	51

Kaplan-Meier estimates with 95% CI in lighter shade

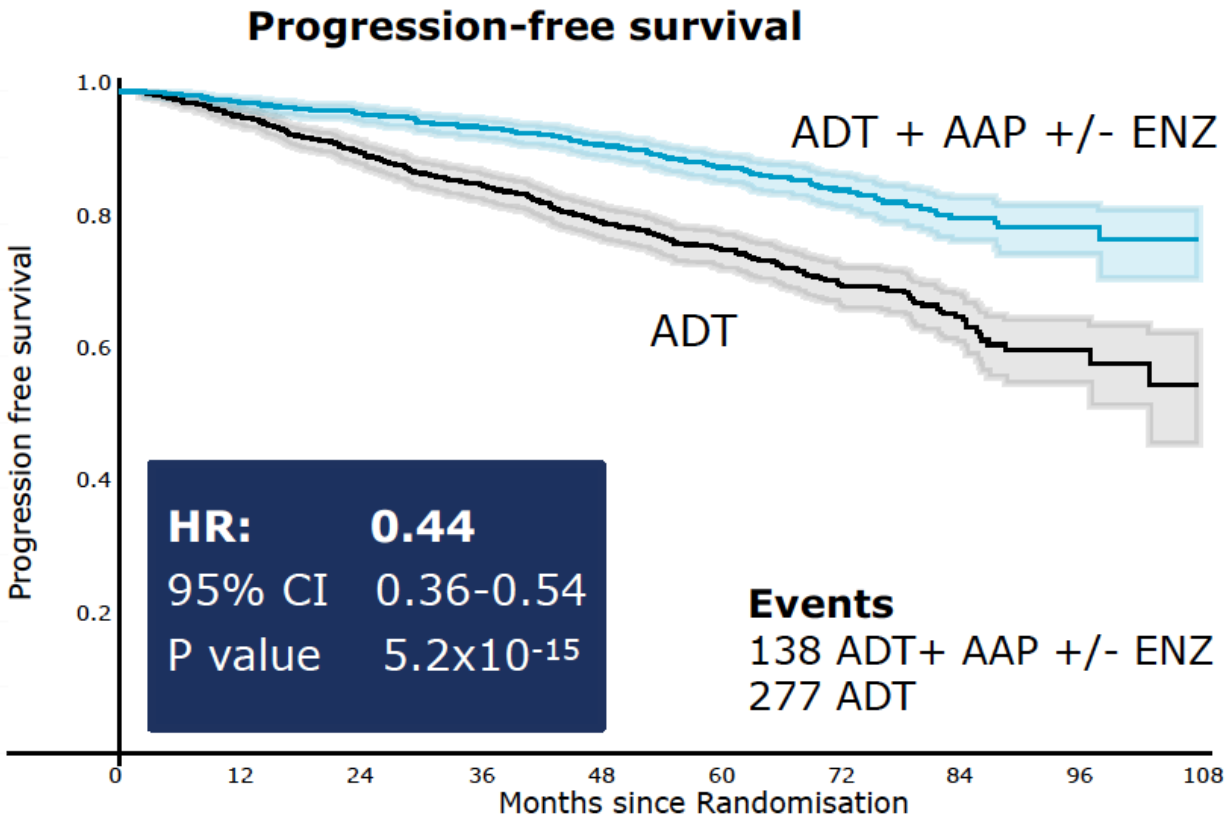
Interaction between comparisons, P=0.5

Attard G. et al. ESMO 2021; Lancet Oncol 2023

Other secondary outcome measures



ADT										
At-risk	988	973	946	894	831	600	362	197	63	10
Censored	0	13	26	50	80	287	505	657	786	836
Event	0	2	16	44	77	101	121	134	139	142
ADT+AAP+/-ENZ										
At-risk	986	954	927	895	857	639	384	204	74	16
Censored	0	28	45	64	90	298	545	714	839	897
Event	0	4	14	27	39	49	57	68	73	73



At-risk	988	940	879	811	734	517	301	157	47	8
Censored	0	12	20	42	67	248	435	564	666	703
Event	0	36	89	135	187	223	252	267	275	277
At-risk	986	942	911	873	825	598	351	186	69	14
Censored	0	28	44	62	86	284	513	665	780	834
Event	0	16	31	51	75	104	122	135	137	138

6-year prostate cancer specific survival improved from 85% to 93%

Kaplan-Meier estimates with 95% CI in lighter shade

Attard G. et al. ESMO 2021; Lancet Oncol 2023

Adverse events

Worst toxicity grade in 1st 2 years	ADT only (AAP comparison)		ADT only (AAP + ENZ comparison)		AAP		AAP + ENZ	
	N (454)	%	N (530)	%	N (456)	%	N (522)	%
3	118	26	160	30	151	33	**277**	**53**
4	12	3	12	2	17	4	**23¶**	**4**
5	0	0	0	0	3*	1	4^	1

¶Toxicities with the largest difference between AAP vs AAP+ENZ = (Gr 3) erectile dysfunction, hypertension, fatigue, (Gr 3/4) transaminitis

*1 event each of rectal adenocarcinoma, pulmonary haemorrhage and a respiratory disorder

^2 events each of septic shock and sudden death

Attard G. et al. ESMO 2021; Lancet Oncol 2023

ADT + AAP @ 84 months	STAMPEDE high-risk M0	M1 low volume*	M1 high volume
Alive	79% (75-83)	63% (56-69)	34% (28-40)
No relapse	72% (68-77)	52% (45-59)	29% (23-35)
Deaths attributed to prostate cancer	60%	70%	82%

Courtesy G. Attard

Systemic treatment for „high-risk“ prostate cancer: Conclusions and current standards

- Definition of “high-risk” important, heterogenous group
- 36% of patients in GETUG-12 have no PSA relapse at 12 years with standard treatment alone
- Genomic tests or AI-based test to guide adjuvant treatment decisions?

Systemic treatment for „high-risk“ prostate cancer: Conclusions and current standards

- Long term ADT (18-36m) is standard together with RT
- Docetaxel added to ADT (and RT) reduces relapse-free survival, but no significant effect on overall survival
- **2 years** of Abiraterone added to ADT (and RT) improves OS and is a new standard of care in “very” high risk prostate cancer (STAMPEDE Definition)

6.2.3.4 Guidelines for radical and palliative treatment of high-risk localised disease*

Recommendations	Strength rating
Watchful Waiting (WW)	
Offer WW to asymptomatic patients with life expectancy < 10 years.	Strong
Radical prostatectomy (RP)	
Radical prostatectomy can be safely delayed for at least 3 months.	Weak
Offer RP to selected patients as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk PCa.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure (see Section 6.2.4.1).	Strong
Radiotherapeutic treatment	
Offer patients intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) with 76–78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).	Strong
Offer patients with good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery or radiotherapy	
Do not offer either whole gland or focal therapy.	Strong
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

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HIGH- OR VERY-HIGH-RISK GROUP

EXPECTED PATIENT SURVIVAL[l]	INITIAL THERAPY	ADJUVANT THERAPY
>5 y or symptomatic[dd]	EBRT[p] + ADT[u] (1.5–3 y; category 1) or EBRT[p] + brachytherapy[p] + ADT[u] (1–3 y; category 1 for ADT) or EBRT[p] + ADT[u] (2 y) + abiraterone[ee] (for very-high-risk only[ff])	
	RP[q] + PLND[gg]	Adverse feature(s) and no lymph node metastases:[s,t] EBRT[p] ± ADT[u] or Monitoring, with consideration of early RT for detectable and rising PSA or PSA >0.1 ng/mL (See PROS-9)
		No adverse features or lymph node metastases
		Lymph node metastasis:[bb] ADT[u,cc] (category 1) ± EBRT[p] (category 2B) or Monitoring, with consideration of early treatment for detectable and rising PSA or PSA >0.1 ng/mL (See PROS-9)
≤5 y and asymptomatic	Observation[r] or ADT[u,hh] or EBRT[p,hh]	Best supportive care

69-year-old fit man with EAU high-risk localised disease, not fulfilling STAMPEDE criteria

Radical Prostatectomy or Radiation Therapy + ADT?

Multidisciplinary Decisions and Discussions with the patient

For RP:

- If a “lower” high-risk*, e.g. Gleason 7, PSA 21, T2a, frequently no further treatment necessary
- If a “higher” high-risk e.g. Gleason 10, PSA 35 and T2c: likelihood for multimodality treatment including RT and ADT high: What evidence do we have for the added value of RP?

**Chys B et al. Frontiers in Oncology 2020*

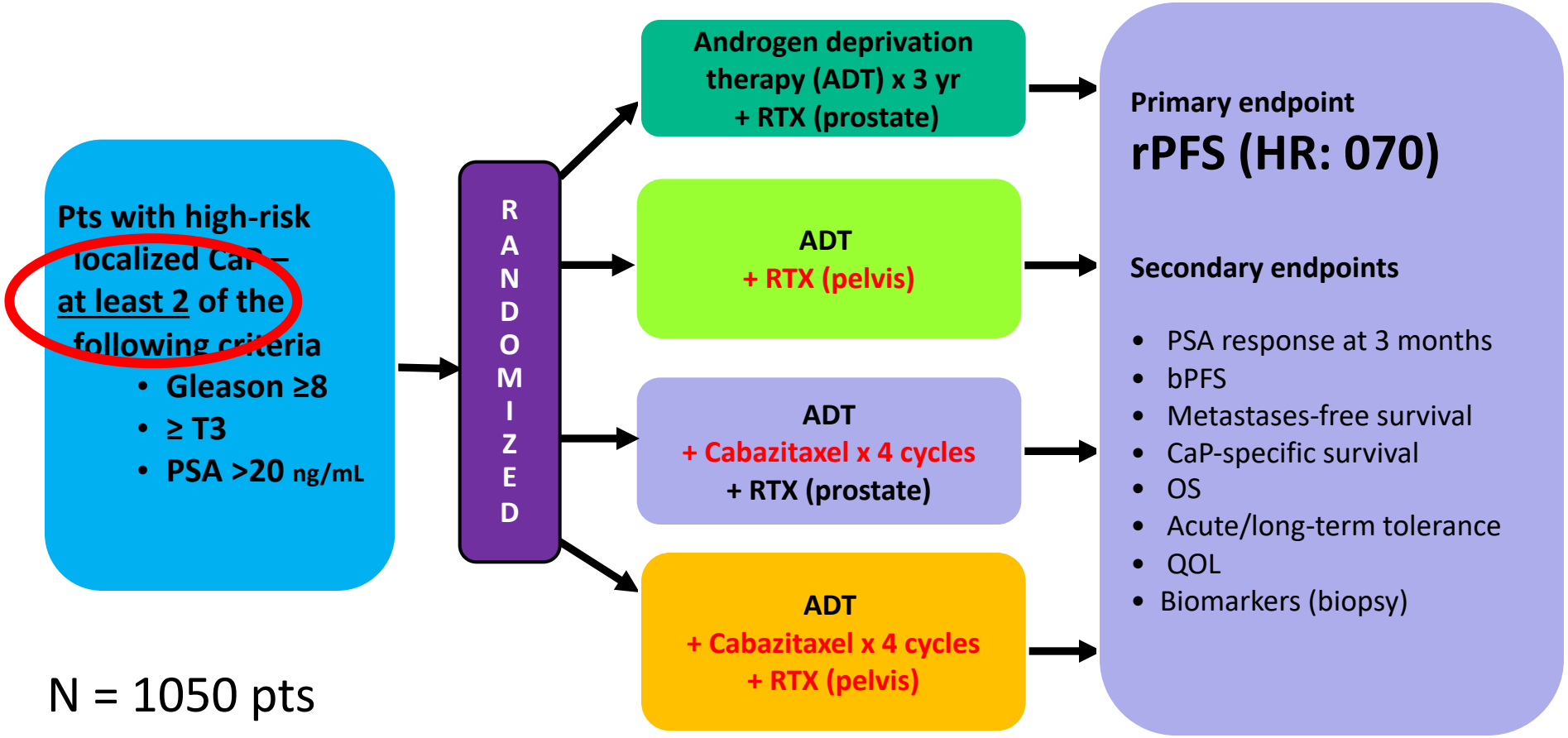
69-year-old fit man with EAU very high-risk localised disease including cN+, fulfilling STAMPEDE criteria

Multidisciplinary Decisions and discussions with the patient

Radiation Therapy + 3 years of ADT+ Abi/Pred for 2 years

Future and ongoing studies together with Radiotherapy for treatment intensification

PEACE-2: European Phase III Trial of Cabazitaxel and Pelvic Irradiation in Patients with High-Risk Localized Prostate Cancer



N = 1050 pts

Study sponsor: Unicancer

ClinicalTrials.gov. Identifier: NCT01952223.

Courtesy K. Fizazi

ANZUP Cancer Trials Group Limited

ENZARAD

Eligibility

Localised prostate cancer
High risk of recurrence
Suitable for EBRT

Stratification

Gleason score 8-10
T3-4 disease
N1 disease
PSA ≥20 ng/mL
Brachytherapy boost
Pelvic nodal RT
Study Site

R 1:1

Enzalutamide 160mg daily for 24 months
+ LHRHA for 24 months
+ RT starting after 16 weeks ± brachy ± nodal

Conventional NSAA for 6 months
+ LHRHA for 24 months
+ RT starting after 16 weeks ± brachy ± nodal

Endpoints

Metastasis-free survival (primary)
Overall survival
Cause specific survival
PSA progression free survival
Clinical progression free survival
Castration-resistance
Health related quality of life
Adverse events
Incremental cost-effectiveness

800 participants
2 years accrual + 5.5 years minimum additional follow-up
80% power to detect 33% reduction in the hazard of metastasis or death, assuming a metastasis-free survival rate at 5 years of 76% in the control group

*Conventional Non-Steroidal Anti-Androgens: bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg tid

Courtesy C. Sweeney

Ongoing trials: Darolutamide augments systemic therapy for localized high-risk prostate cancer: DASL-HiCaP

Very High Risk Locally Advanced Prostate Cancer

Conventional Imaging Negative for Distant Metastases (allow pelvic LN)

Patients estimated to have 85% MFS on XRT + 2 yrs ADT

Stratify by
1) LN involvement
2) Docetaxel use
3) Definitive XRT vs post-RP

Arm A
XRT or post RP XRT + ADT 2yrs + NSAA 2 yrs

Arm B
XRT or post RP XRT + ADT 2 yrs + darolutamide

Hypothesis:
The addition of darolutamide will improve 5yr MFS* rate from 85% to 91%

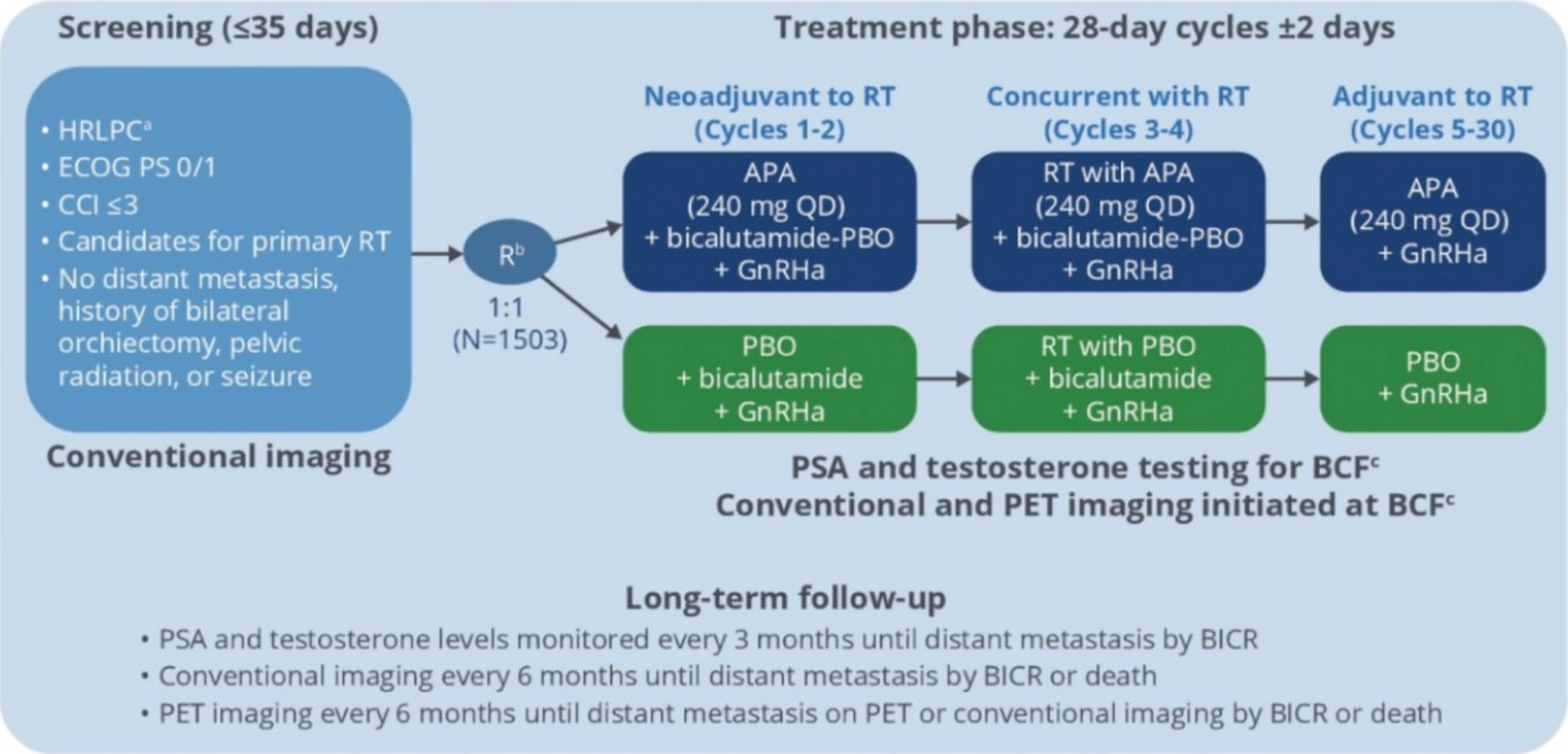
Sub-study: Learn prognostic value of PSMA-PET Positive outside of XRT field with conventional scan negative
- *Can we de-escalate systemic therapy in PSMA negative pts?*

Run in collaboration with ANZUP / Canada (CCTG) / Ireland-UK (CTI) / USA

First data about baseline characteristics at ASCO GU 2024

Courtesy C. Sweeney

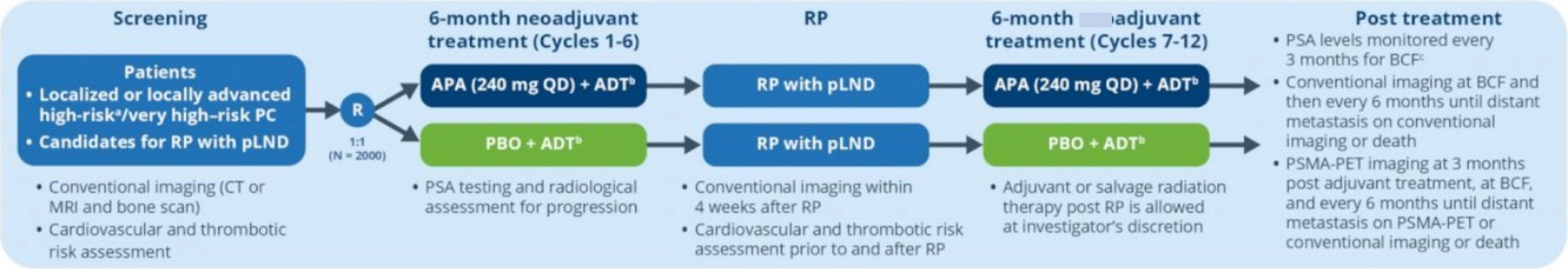
ATLAS Trial



H Sandler ASCO 2022 Trials in Progress

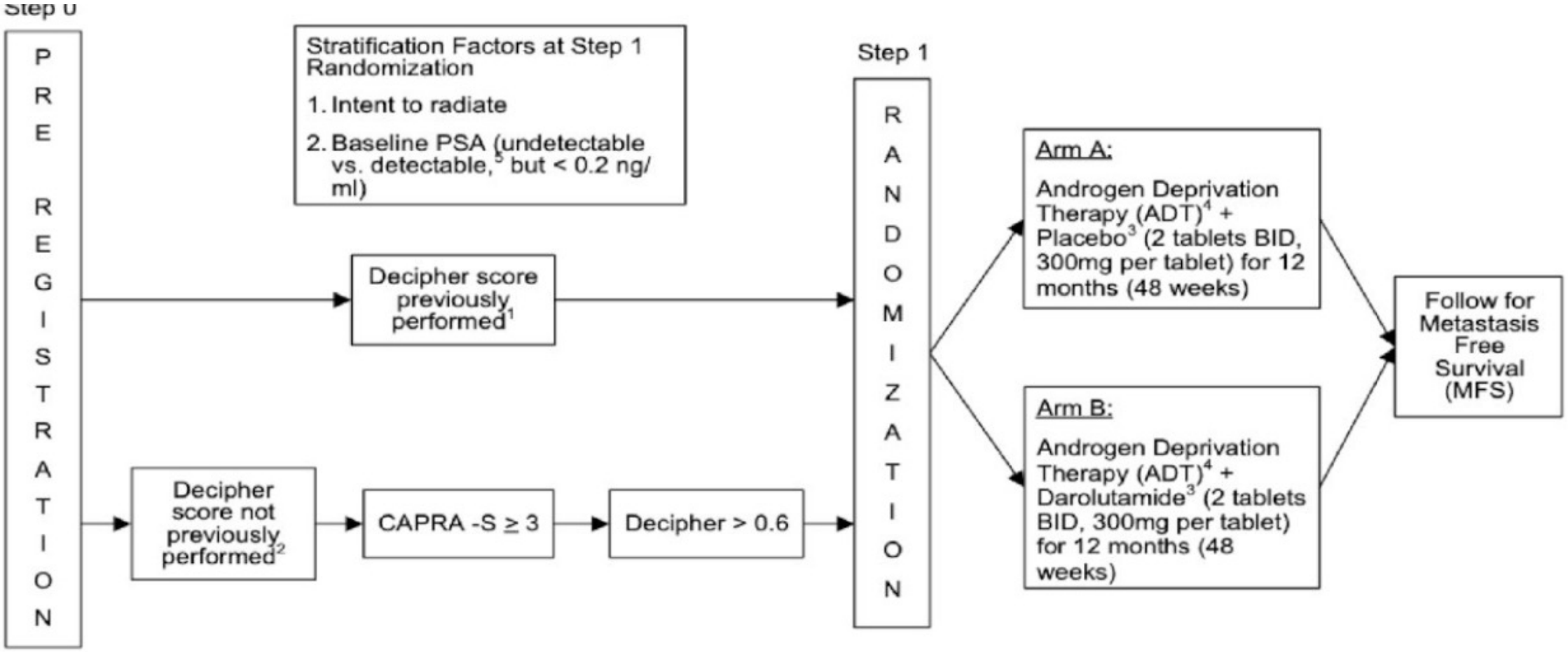
Future and ongoing studies together with Radical Prostatectomy for treatment intensification

PROTEUS Trial



AS Kibel, ASCO GU 2022 Trials in Progress

ERADICATE Trial



A Morgans ASCO 2022 Trials in Progress

Thank you for your attention!

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