Systemic treatment intensification for high-risk localised prostate cancer

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Disclosure slide

- On the Institute of Cancer Research rewards to inventors list for abiraterone
- Patent under consideration for plasma methylation signatures as biomarkers for prostate cancer (GB1915469.9)
- Principal investigator for trials sponsored by Janssen and Pfizer/Astellas
- Received:
  - Consulting fees and travel support from Astellas, Janssen, Medivation/Pfizer, Astra Zeneca, Novartis, Bayer, Essa, Ferring, Roche/Ventana and Sanofi-Aventis
  - Speaker's fees from Astellas, Ferring, Ipsen, Janssen, Astra Zeneca and Sanofi-Aventis
  - Grant support from Janssen and Astra Zeneca

Does patient have metastases on CT or bone scan?

Is he at high-risk of having metastases?

Is clinical-pathological risk assessment equivalent to detection of mets on PSMA-PET CT?

Does patient have metastases on CT or bone scan? No

Is he at high-risk of having metastases? Yes

Is clinical-pathological risk assessment equivalent to detection of mets on PSMA-PET CT?
?

STAMPEDE M0 Patients

Newly-diagnosed

Any of:

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

Relapsing after previous RP or RT

Any of:

- Node-positive
- PSA≥4ng/ml, rising & doubling time <6m
- PSA≥20ng/ml

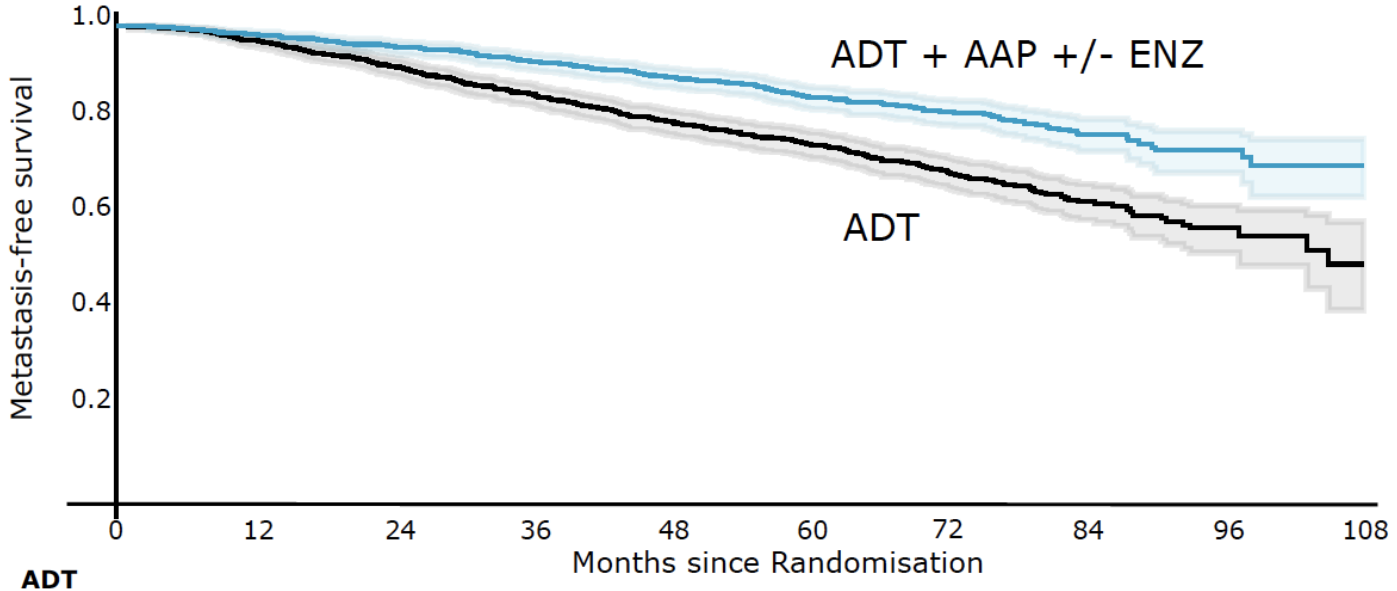
Radiotherapy to prostate +/- nodes

- 99% newly-diagnosed, N0
- 71% newly-diagnosed, N1
- 7% previously-treated patients

Median age = 68 years
Median PSA = 34 ng/ml
N1 = 39%
3% relapsing after prior treatment

Attard et al, Lancet. 2022 Jan 29;399(10323):447-460.

Metastasis-free survival



ADT										
At-risk	988	950	894	836	767	550	329	172	53	9
Censored	0	8	11	14	26	201	387	522	632	673
Event	0	30	83	138	195	237	272	294	303	306
ADT+AAP+/-ENZ										
At-risk	986	948	917	884	839	622	369	198	71	14
Censored	0	21	28	31	45	225	460	615	737	792
Event	0	17	41	71	102	139	157	173	178	180

Events
180 ADT+ AAP +/- ENZ
306 ADT

HR:	**0.53**
95% CI:	0.44-0.64
P value	2.9×10^{-11}

6-year MFS improved from 69% to 82%

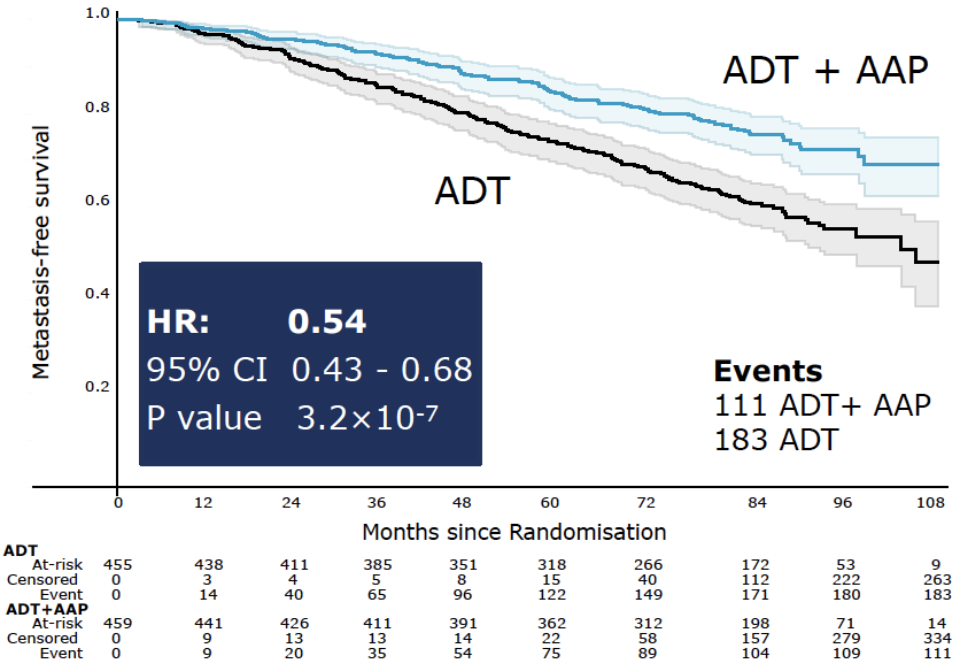
Clear and consistent benefit from adding abiraterone to ADT

Non-proportional hazards P=0.46

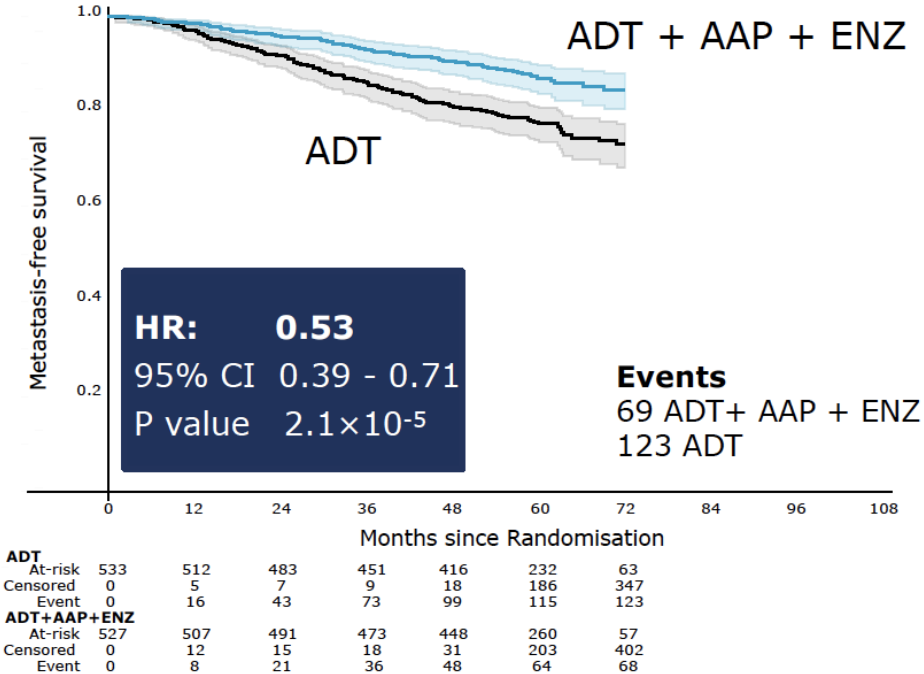
Median follow-up = 72 months

AAP, abiraterone acetate + prednisolone; ENZ, enzalutamide, Kaplan-Meier estimates with 95% CI in lighter shade

Metastasis-free survival by randomisation period



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

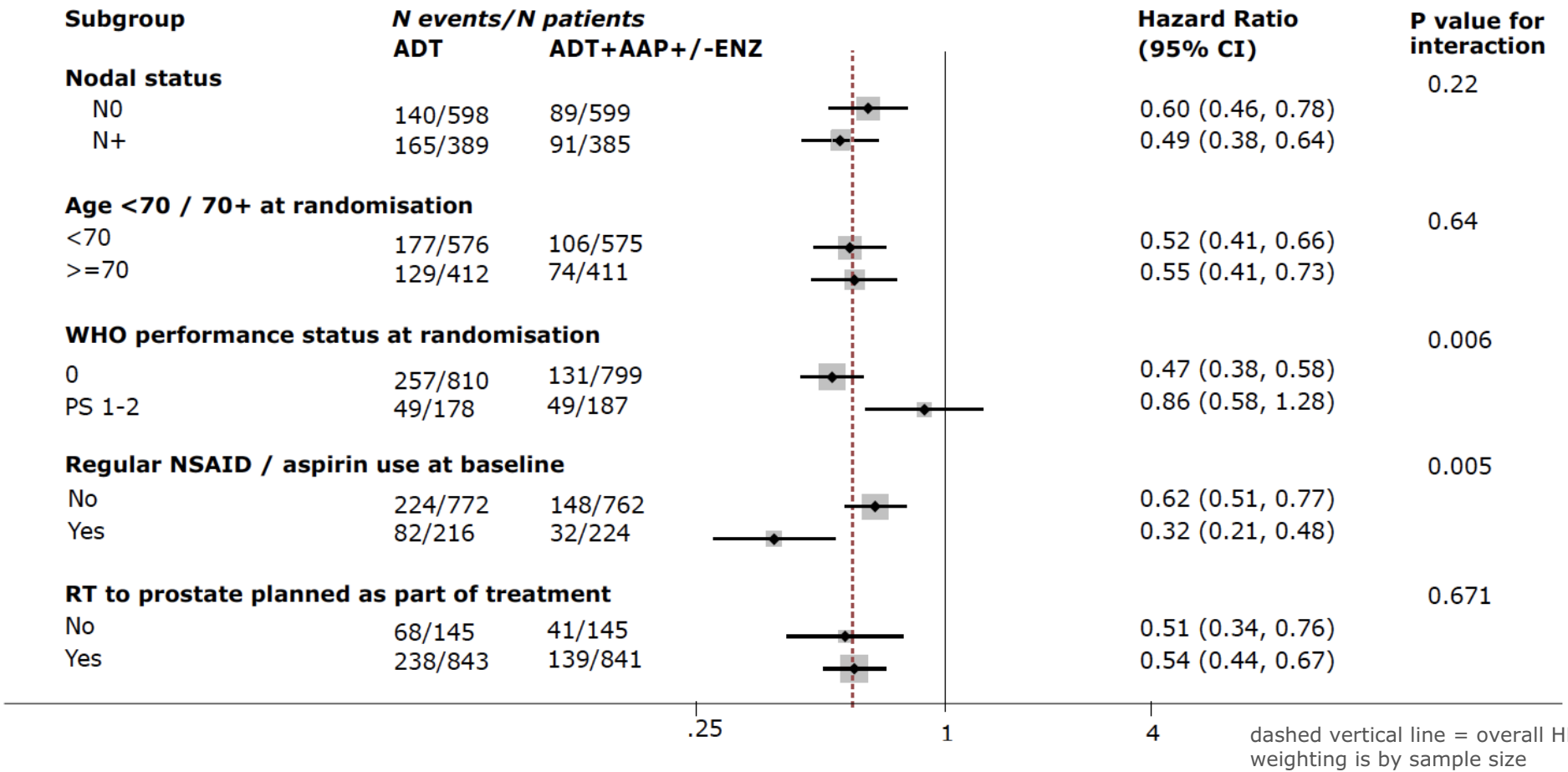


ADT							
At-risk	533	512	483	451	416	232	63
Censored	0	5	7	9	18	186	347
Event	0	16	43	73	99	115	123
ADT+AAP+ENZ							
At-risk	527	507	491	473	448	260	57
Censored	0	12	15	18	31	203	402
Event	0	8	21	36	48	64	68

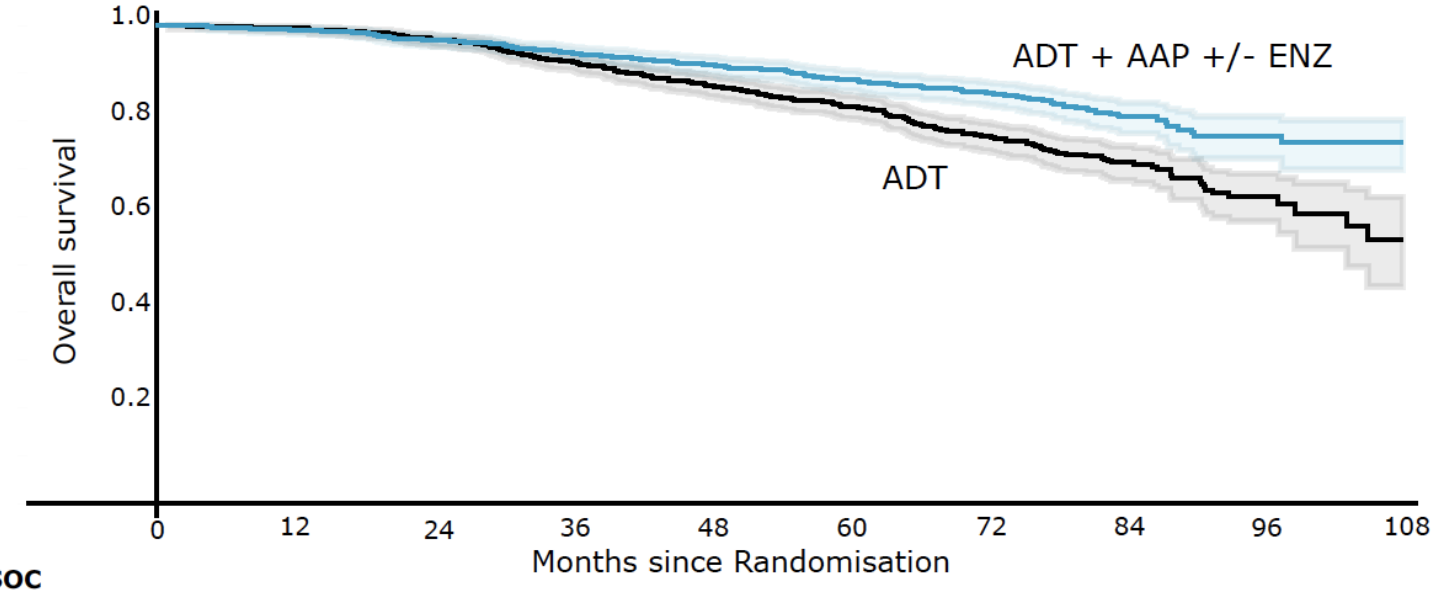
Kaplan-Meier estimates with 95% CI in lighter shade

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

Metastasis-free survival: Subgroup analysis



Overall survival



Events
147 ADT+AAP +/- ENZ
236 ADT

HR: 0.60
95% CI 0.48 to 0.73
P value 9.3×10^{-7}

SOC										
At-risk	988	974	947	901	837	610	368	200	63	10
Censored	0	8	11	14	28	216	421	568	693	742
Event	0	6	30	73	123	162	199	220	232	236
SOC+AAP+/-ENZ										
At-risk	986	956	928	899	861	645	386	205	74	16
Censored	0	21	29	32	46	234	477	641	766	823
Event	0	9	29	55	79	107	123	140	146	147

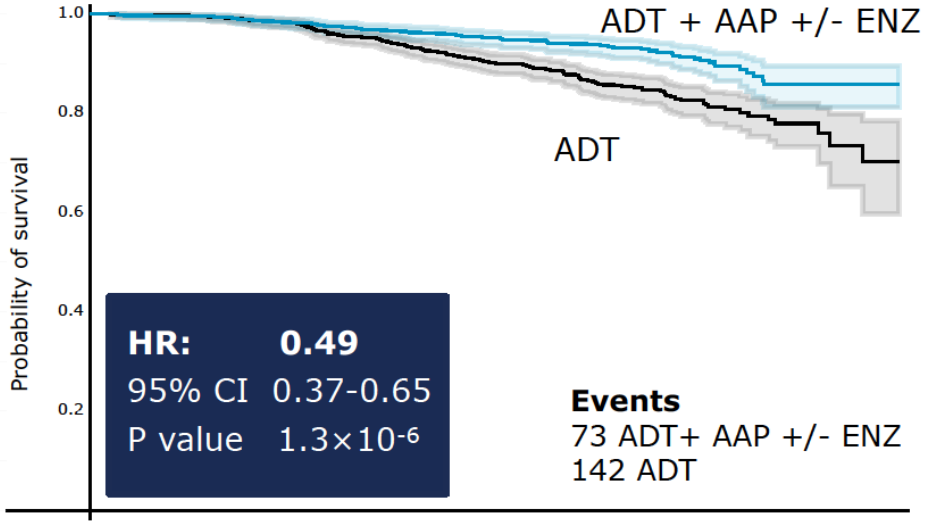
6-year survival improved from 77% to 86%

Prostate cancer deaths: **60%** of deaths with ADT
50% of death with AAP

Non-proportional hazards P=0.1

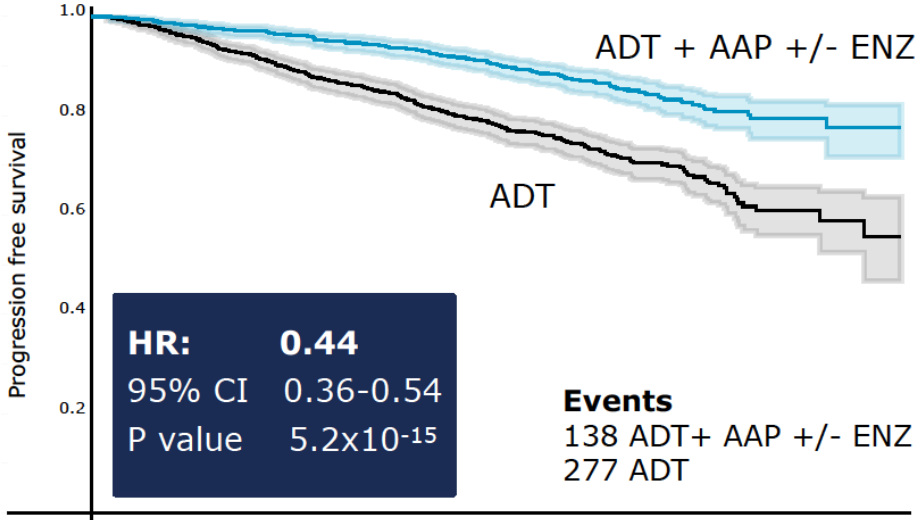
Other secondary outcome measures

Prostate cancer specific survival



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

Progression-free survival



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%

Conclusions

- **2 years** of AAP-based therapy significantly improves MFS & overall survival of very high-risk ”M0” PCa starting ADT and should be considered **standard of care**

- Adding ENZ to AAP increases toxicity but has no discernible effect on efficacy

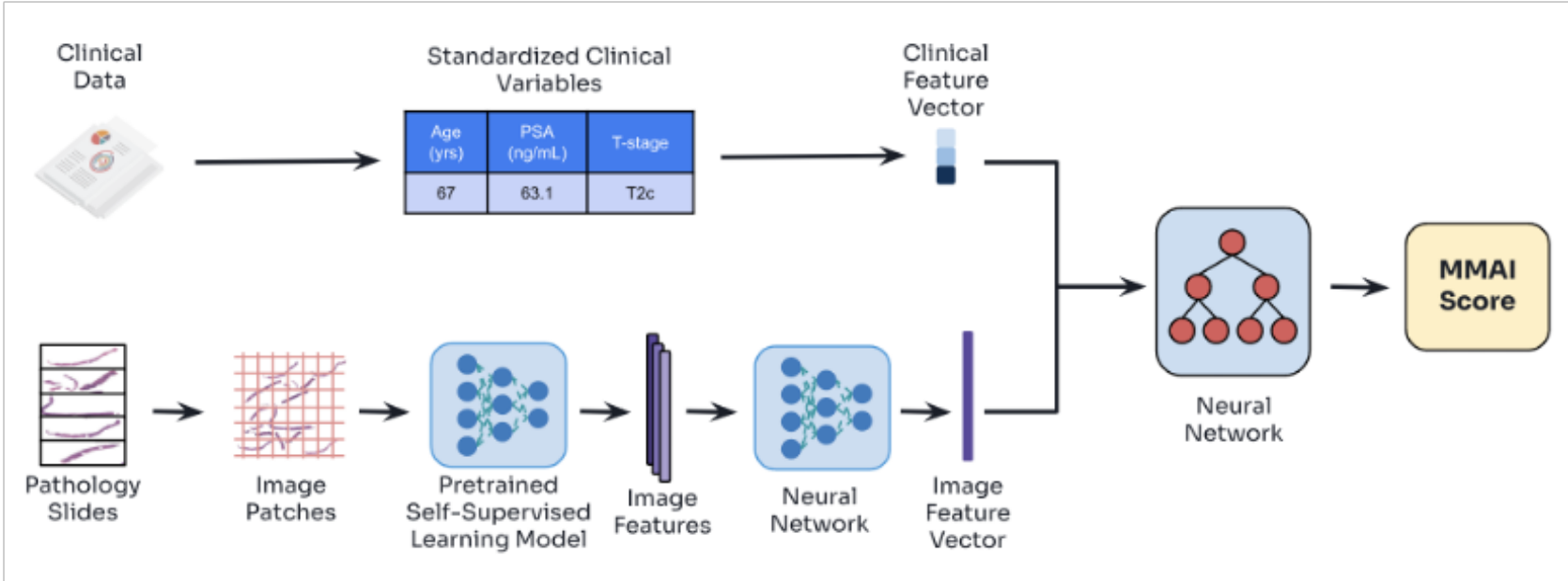
Limitations

- Limited reporting of long-term complications beyond 2 years
- Have no data on treatment durations other than 2 years
- Relapsed patients were under-represented (*now addressed by Embark*)
- No evidence for single-agent AR antagonist efficacy (*will be soon addressed by ENZARad, DASL-HiCaP, ATLAS*)
- No evidence for intensification with surgery (*will be addressed by PROTEUS*)

How inclusive of all NCCN high-risk M0 can one be and still show an OS benefit?

Study Design: STAMPEDE M0 and ArteraAI

Substudy within STAMPEDE to test digital pathology AI-guided treatment selection



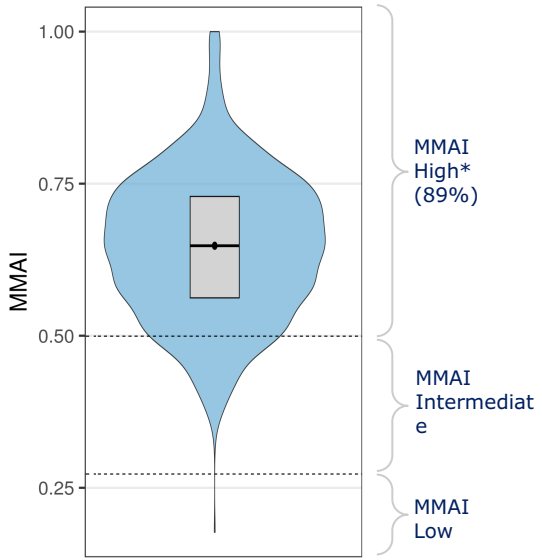
Association between MMAI and outcome were analyzed using Cox (MFS) or Fine-Gray regression with death before event as competing risks (PCSM/DM)
Treatment-by-MMAI interaction tests were conducted

Parker et al, Lancet Digital Health, 2025 Jun 3:100885.
Parker et al, ASCO 2025

MMAI score is prognostic within very high-risk disease

Subgroup	Endpoint	(s)/HR (95% CI)	P value
M0	MFS	1.42 (1.29-1.56)	<0.001
	PCSM	1.65 (1.43-1.90)	<0.001
	DM	1.54 (1.36-1.74)	<0.001
N0M0	MFS	1.51 (1.31-1.74)	<0.001
	PCSM	1.95 (1.47-2.60)	<0.001
	DM	1.61 (1.32-1.96)	<0.001
N1M0	MFS	1.26 (1.10-1.43)	<0.001
	PCSM	1.38 (1.18-1.62)	<0.001
	DM	1.38 (1.18-1.63)	<0.001

Continuous MMAI score (per 1 SD increase)



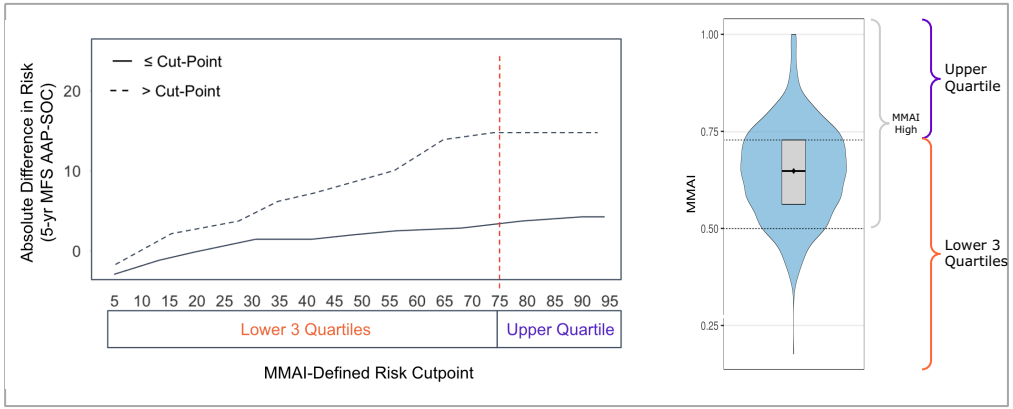
Using clinically-established prognostic cut-offs, 89% (N=1,189) of M0 patients were MMAI *High**

**As per ArteraAI Prostate Test cut-offs*

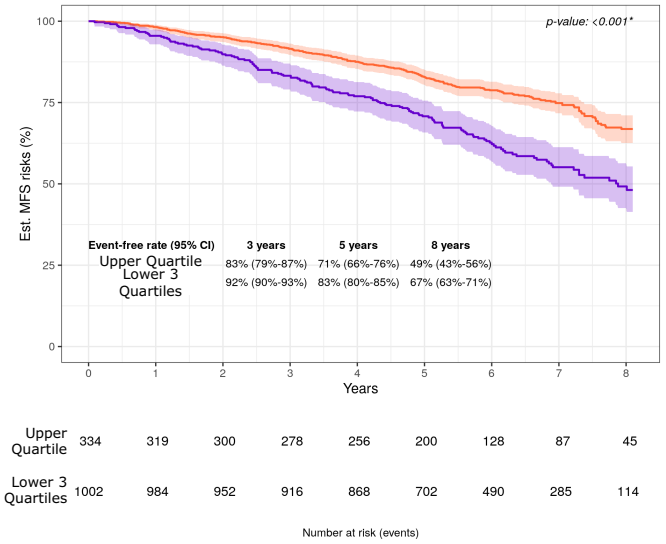
Parker et al, Lancet Digital Health, 2025 Jun 3:100885.
Parker et al, ASCO 2025

MMAI cut-point for selecting patients for intensification

- Exploratory grid search performed to identify MMAI score cut-point that maximizes treatment benefit from abiraterone

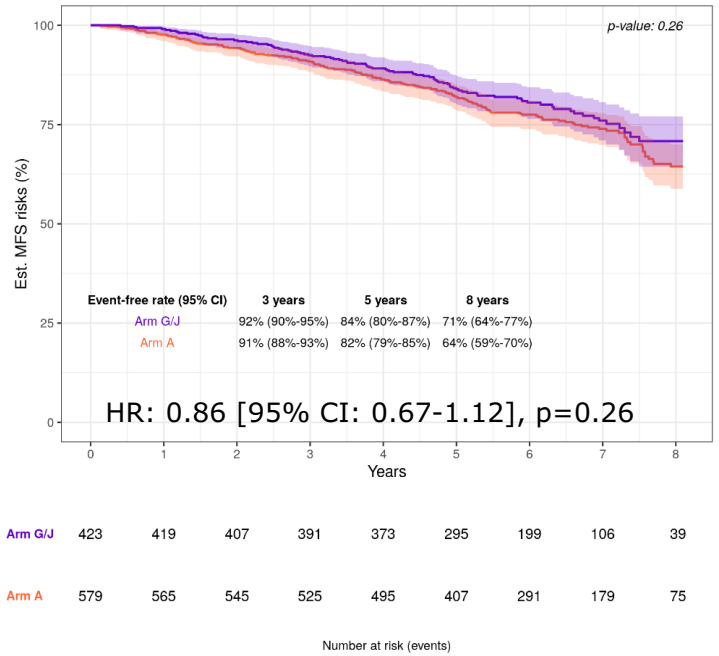


Exploratory grid search to identify MMAI cut-point (5-percentile intervals)
Illustrative example only - not based on real data

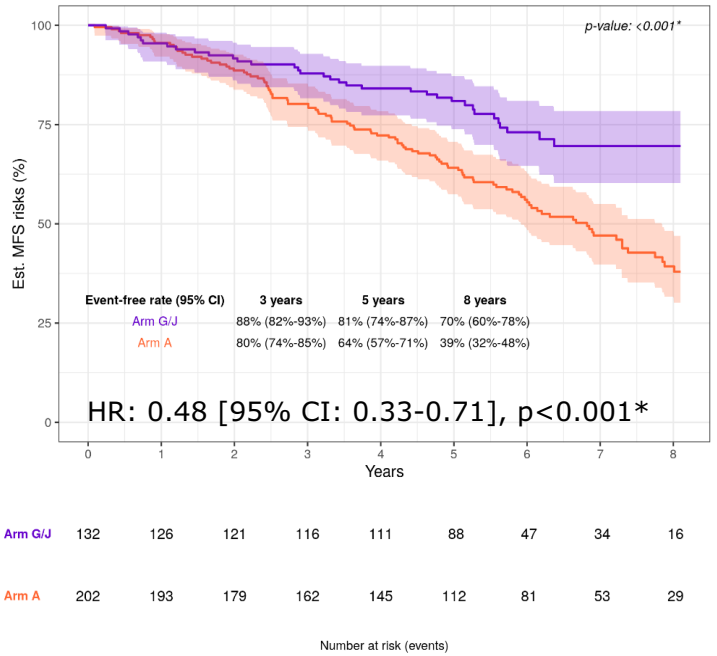


MMAI risk scores stratify patients with differential benefit from abiraterone

Lower 3 Quartiles of MMAI-Defined Risk



Upper Quartile of MMAI-Defined Risk



M0 patients with MMAI scores in the upper quartile of risk more likely to benefit from abiraterone

MMAI-treatment interaction effect p value = 0.01*

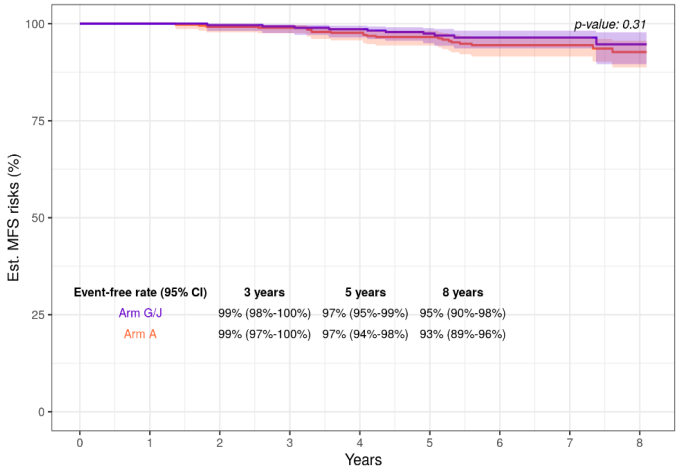
Patients in the upper quartile of MMAI-defined risk derive the greatest benefit from abiraterone

Endpoint*	Group	SOC	SOC+AAP	Absolute Difference in Risk	Interaction p-value
MFS	**Upper Quartile**	**64% (57%-71%)**	**81% (74%-87%)**	**17%**	0.01*
	Lower 3 Quartiles	82% (79%-85%)	84% (81%-87%)	2%	
PCSM	**Upper Quartile**	**17% (12%-23%)**	**9% (5%-15%)**	**8%**	0.04*
	Lower 3 Quartiles	7% (5%-9%)	4% (3%-7%)	3%	
DM	**Upper Quartile**	**22% (16%-28%)**	**10% (6%-16%)**	**12%**	0.40
	Lower 3 Quartiles	13% (10%-15%)	8% (5%-11%)	5%	

*Estimated 5-year risk

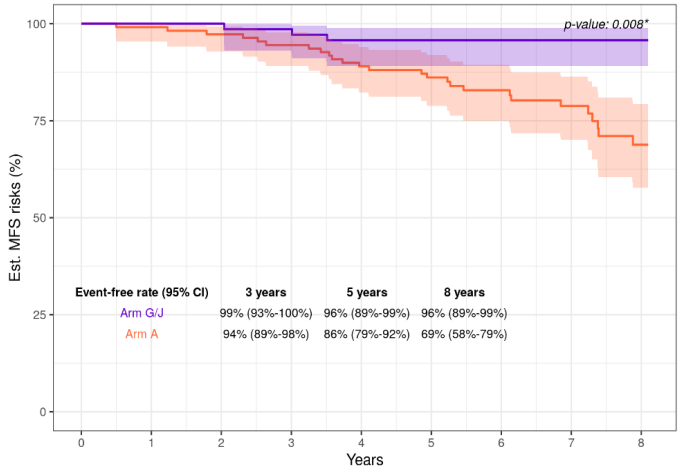
Differential treatment benefit from abiraterone in N0M0

Lower 3 Quartiles of MMAI-Defined Risk



Number at risk (events)									
Arm G/J	277	274	271	263	255	202	133	73	26
Arm A	381	380	374	369	357	305	215	141	65

Upper Quartile of MMAI-Defined Risk



Number at risk (events)									
Arm G/J	70	69	69	67	63	49	26	19	6
Arm A	109	106	104	99	87	74	60	39	20

N0M0 patients with MMAI scores in the upper quartile of risk more likely to benefit from abiraterone
MMAI-treatment interaction effect p value = 0.02*

Limitations & Future Directions

- Cut-point derived retrospectively to optimize treatment effect differentiation
- Additional validation challenging due to absence of comparable randomized trials in this setting
- Future studies will explore predictive utility:
  - With other ARPI therapies (e.g. apalutamide, enzalutamide)
  - In other AAP-treated populations, including metastatic prostate cancer