The role of RT in mHSPC: the primary, the oligometastases or both?

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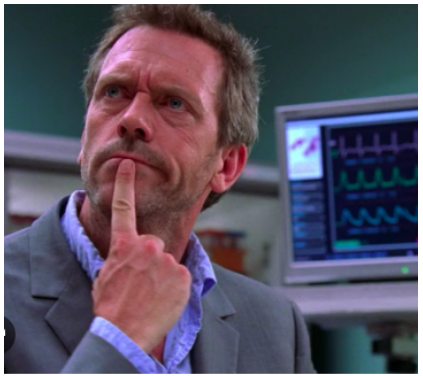
Disclosures

- Advisory Boards: Bayer, Johnson & Johnson, Astellas, Casen Recordati
- Congresses attendance: Bayer, Johnson & Johnson, Astellas, Casen Recordati, Ipsen, Lorca Marin
- Lectures: Bayer, Johnson & Johnson, Astellas, Casen Recordati

The role of RT in mHSPC: the primary, the oligometastases or both?

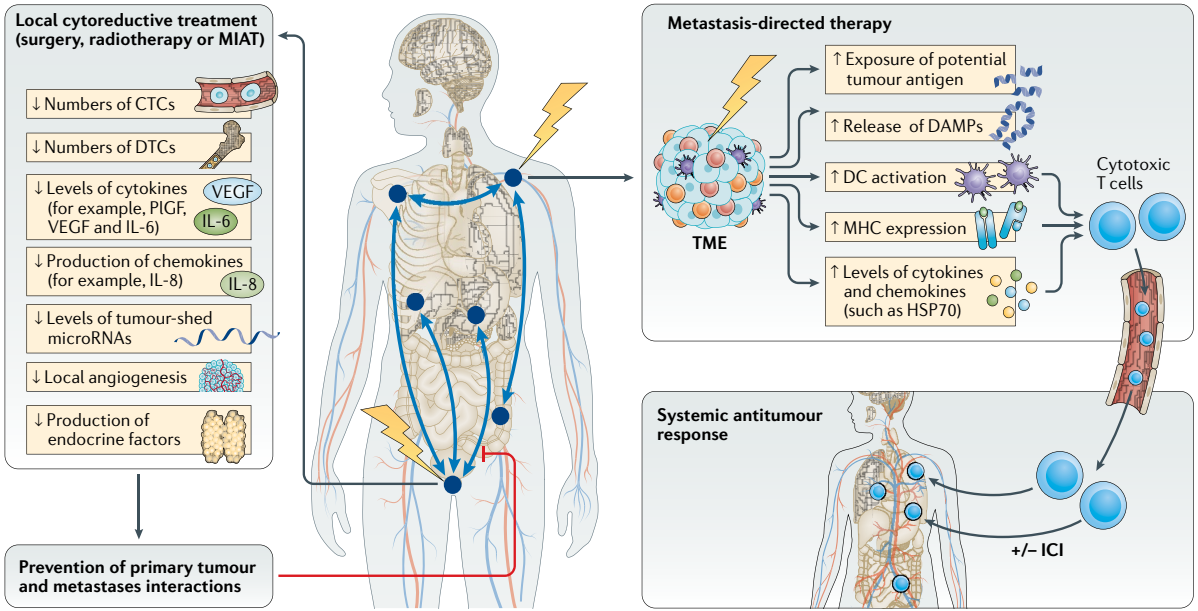
Definition and pivotal trials guiding clinical practise are based on conventional imaging

Upfront ADT+ARPI and local RT has shown better outcomes
↓
SOC



Rapid shift toward PSMA-PET for staging PC confers early detection of OmPC : “TRUE” OmPC?
↓
Local intensification Prostate+M1
&
De-escalated fixed duration systemic Tx

Benefit of radiotherapy in mHSPC



MJ Connor et al. Nature reviews Clinical Oncology, 2020

Biological Rationale

- To decrease the total tumor burden
- To induce an immunogenic response that releases substances that trigger systemic antitumor effects (abscopal effects)
- To abolish supportive interactions between the primary tumour and metastases

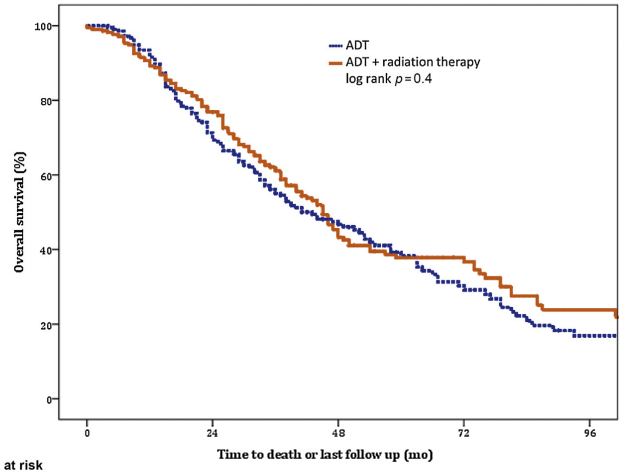
Clinical Rationale

- Citoreductive effect
- Destruction of resistant cells subclones → Delay systemic treatment
- Increased local control and reduction of urinary symptomatology

Benefit of prostate radiotherapy in low burden mHSPC

HORRAD TRIAL

R 1:1 ADT vs ADT + RT (70 Gy/35#; or 57,76/19# 3.04 , 3 d/w)



No. at risk

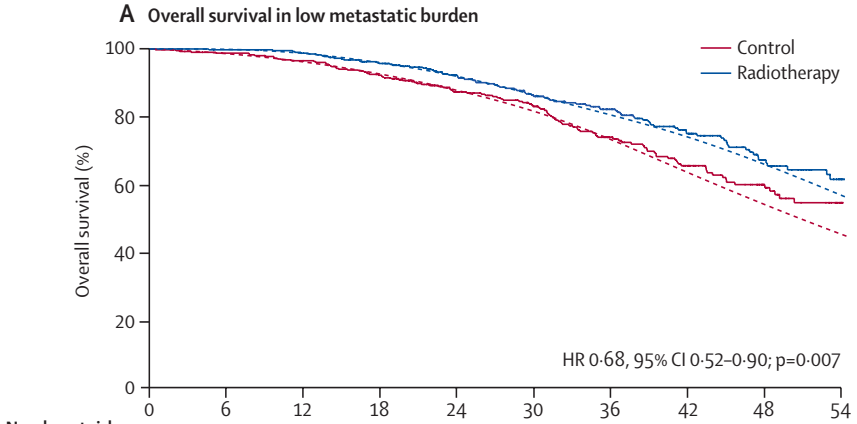
ADT	216	145	65	27	11
ADT + radiation therapy	215	161	61	33	13

Median OS 45m vs 43m
[HR]: 0.90; 95% CI: 0.70-1.14; p=0.4

Boeve et al, Eur Urol 2019

STAMPEDE TRIAL ("H")

R 1:1 ADT vs ADT + RT (55 Gy/20# 2.75 ; or 36/6# 6, 1 d/w)



Number at risk (events)

Control	409	(5)	400	(9)	387	(17)	361	(17)	265	(12)	217	(22)	155	(16)	110	(8)	67	(5)	25
Radiotherapy	410	(1)	405	(4)	399	(12)	366	(12)	301	(19)	242	(10)	200	(15)	137	(11)	77	(5)	25

Median OS 85.5m vs 63.6m
5y OS 65% vs 53%
HR = 0.68 (95% CI 0.52 to 0.79; p < 0.001 [p = 0.00004])

Parker et al, Lancet 2018

Benefit of prostate radiotherapy in low burden mHSPC

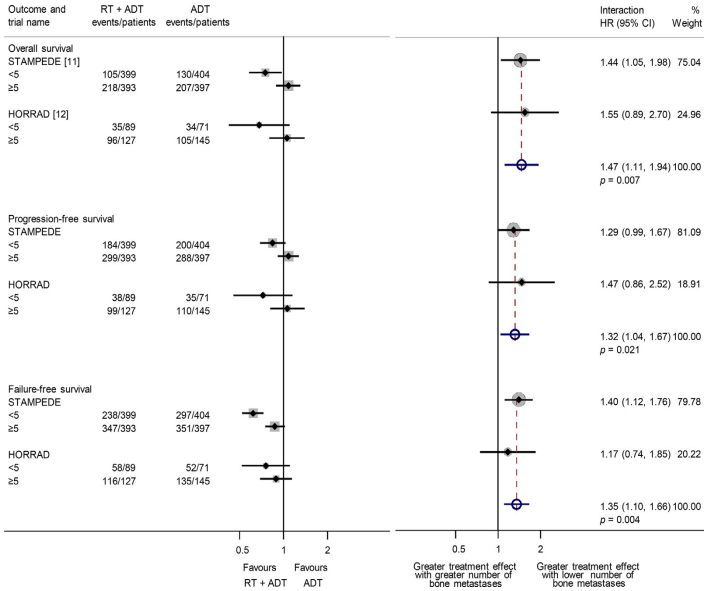
Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis

Table 1 – Characteristics of trials (or parts of trials) eligible for comparison A

Trial	Years of accrual	Number of men randomised	De novo or relapsed M1?	Treatment Radiotherapy	Control ADT	Median follow-up (survival)
Radiotherapy + ADT vs ADT						
STAMPEDE A1 [11] (arm H vs arm A)	2013–2016	1694	De novo	36 Gy, 6 fractions over 6 wk or 55 Gy, 20 fractions over 4 wk	ADT (LHRH agonist or antagonist or orchiectomy)	41.9 mo
HORRAD [12]	2004–2014	432	De novo	70 Gy, 35 fractions over 7 wk or 57.76 Gy, 19 fractions over 6 wk	ADT (LHRH agonist or orchiectomy)	47 mo
PEACE-1A1 (NCT01957436)	2013–2018*	234	De novo	74 Gy, 37 fractions within 7–8 wk	ADT (LHRH agonist or antagonist or orchiectomy)	Not yet available

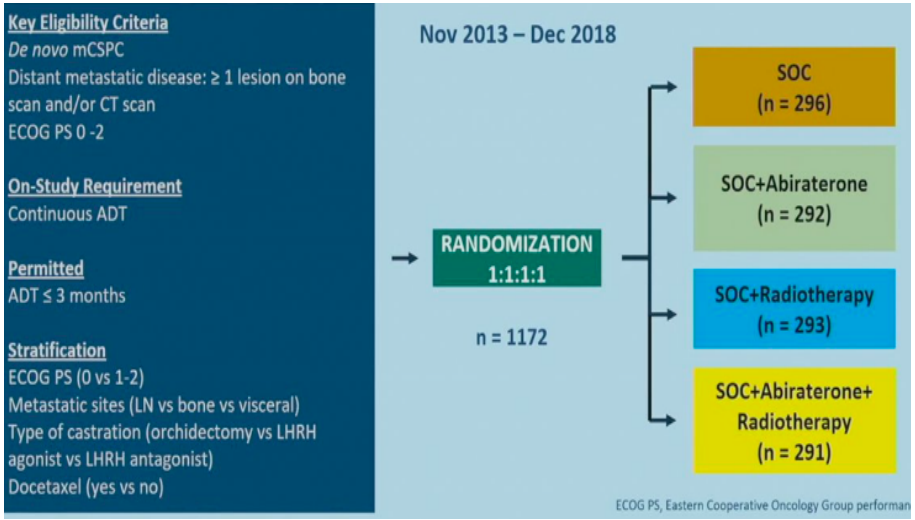
ADT = androgen deprivation therapy; LHRH = luteinising hormone-releasing hormone. *PEACE-1 closed to accrual between submission and acceptance of the manuscript

Sarah Burdett, European Urology 2019



There was 7% improvement in 3-yr survival in men with < 5 bone metastases.

Benefit of prostate radiotherapy in mHSPC: PEACE 1

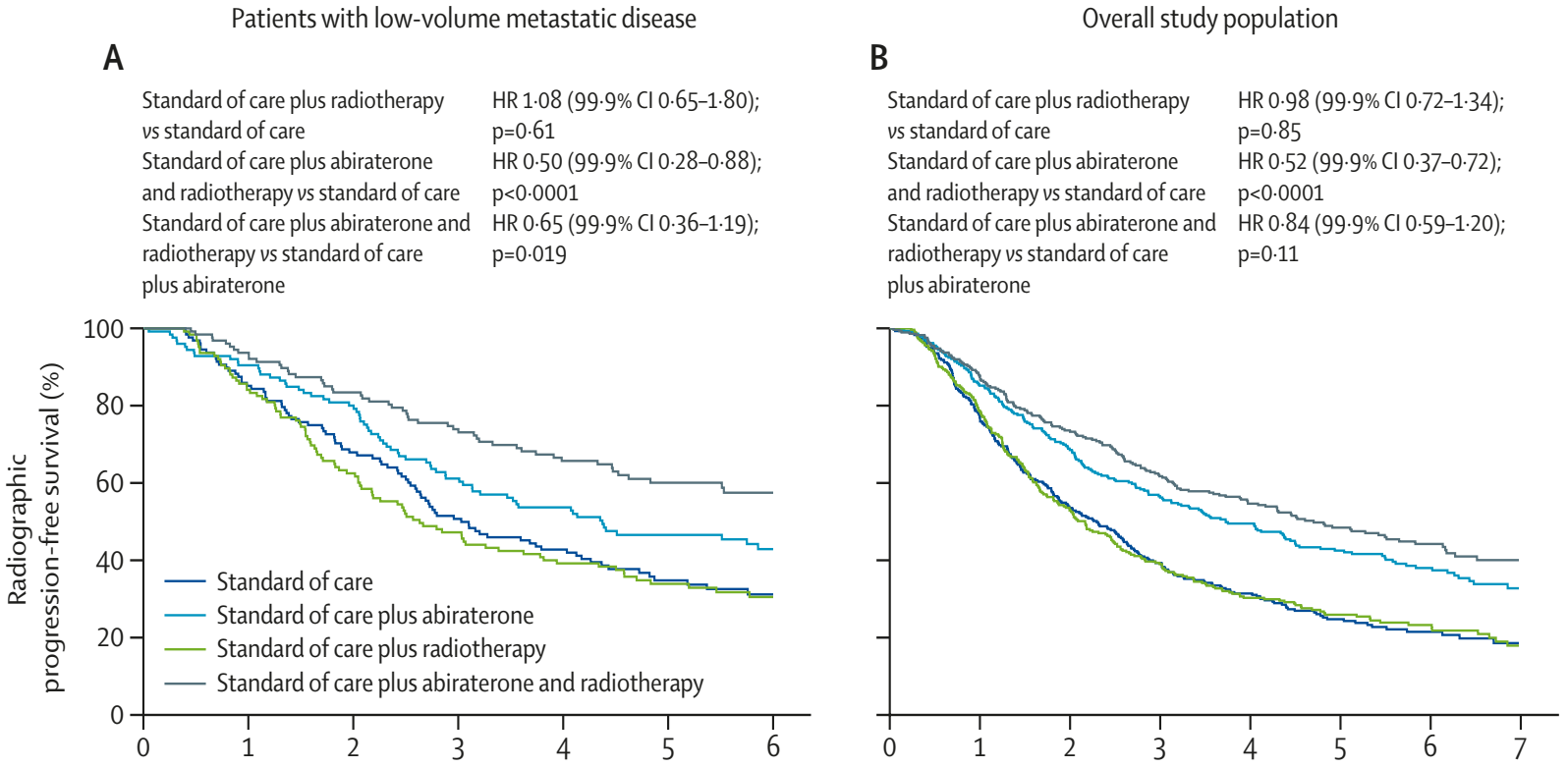


Patients' characteristics (overall population)

		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	411 (70)	413 (71)
	1-2	177 (30)	171 (29)
Gleason score at diagnosis, n (%)	≤ 7	142 (23)	136 (24)
	≥ 8	429 (74)	441 (75)
	Missing	17 (3)	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	51 (9)	48 (8)
	Bone only	474 (81)	473 (81)
	Visceral	63 (11)	63 (11)
Disease volume, n (%)	Low	253 (43)	252 (43)
	High	335 (57)	332 (57)
Median baseline PSA, ng/mL (IQR)		13.1 (3.5-57.1)	12.6 (3-62.4)
Docetaxel, n (%)	Yes	355 (60)	355 (61)
	No	233 (40)	229 (39)

https://www.urotoday.com/
A Bossi, Lancet 2024; 404: 2065–76

Benefit of prostate radiotherapy in mHSPC: PEACE 1

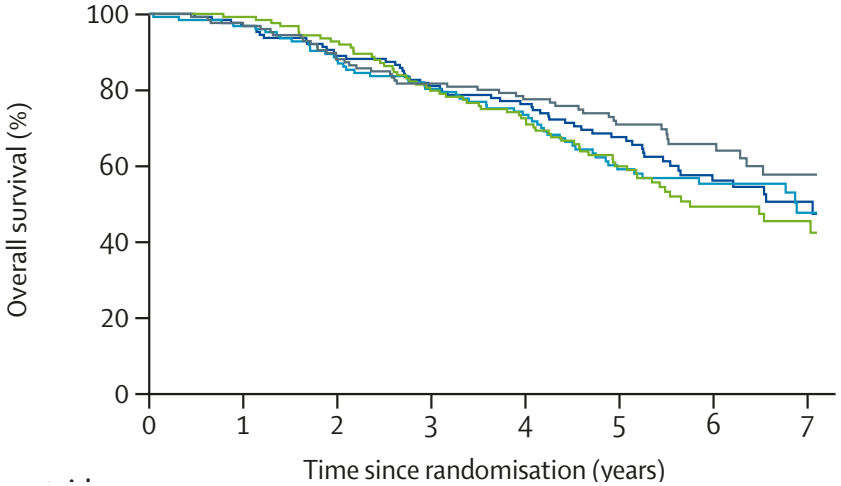


A Bossi, Lancet 2024; 404: 2065–76

Benefit of prostate radiotherapy in mHSPC: PEACE 1

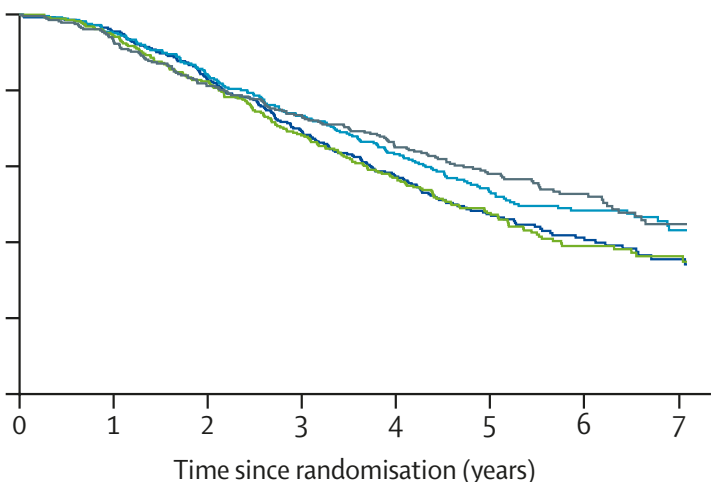
Patients with low-volume metastatic disease

Standard of care plus radiotherapy *vs* standard of care	HR 1·18 (95·1% CI 0·81–1·71); p=0·39
Standard of care plus abiraterone and radiotherapy *vs* standard of care	HR 0·81 (95·1% CI 0·55–1·21); p=0·30
Standard of care plus abiraterone and radiotherapy *vs* standard of care plus abiraterone	HR 0·77 (95·1% CI 0·51–1·16); p=0·21



Overall study population

Standard of care plus radiotherapy *vs* standard of care	HR 0·99 (95·1% CI 0·80–1·22); p=0·91
Standard of care plus abiraterone and radiotherapy *vs* standard of care	HR 0·75 (95·1% CI 0·60–0·94); p=0·010
Standard of care plus abiraterone and radiotherapy *vs* standard of care plus abiraterone	HR 0·95 (95·1% CI 0·75–1·20); p=0·68



A Bossi, Lancet 2024; 404: 2065–76

Benefit of prostate radiotherapy +/- ARPI in mHSPC:

Prostate Radiotherapy in Low-volume Metastatic Hormone-sensitive Prostate Cancer: A Network Meta-analysis

Soumyajit Roy et al, European Urology 2024; 86: 10–17

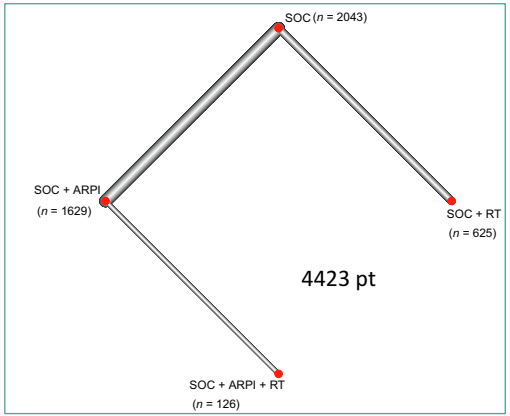


Table 1 – Summary of included randomized controlled trials

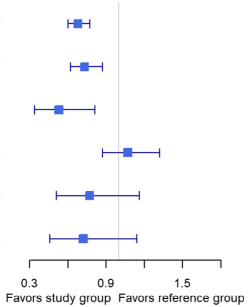
Study	Treatment	Number of patients with low metastatic burden	Proportion of patients with receipt of docetaxel [a]	Proportion of population with de novo presentation	Median follow-up duration (mo)
ARASENS (NCT02799602)	ADT + docetaxel	146	1.00	0.83	42.4
	ADT + docetaxel + ARPI (darolutamide)	154	1.00	0.82	43.7
ARCHES (NCT02677896)	ADT with/without docetaxel	203	0.18	0.63	44.6
	ADT with/without docetaxel + ARPI (enzalutamide)	220	0.18	0.70	44.6
ENZAMET (NCT02446405)	ADT with/without docetaxel	261	0.27	0.47	68.0
	ADT with/without docetaxel + ARPI (enzalutamide)	262	0.28	0.46	68.0
HORRAD (NCT00567580)	ADT	71	0.00	1.00	47.0
	ADT + RT	89	0.00	1.00	47.0
LATITUDE (NCT01715285)	ADT	110	0.00	1.00	51.8
	ADT + ARPI (abiraterone)	133	0.00	1.00	51.8
PEACE-1 (NCT01957436)	ADT with/without docetaxel	127	0.50	1.00	73.0
	ADT with/without docetaxel + ARPI (abiraterone)	126	0.50	1.00	73.0
	ADT with/without docetaxel + RT	126	0.50	1.00	73.0
	ADT with/without docetaxel + RT + ARPI (abiraterone)	126	0.50	1.00	73.0
STAMPEDE arm G (NCT00268476)	ADT	196	0.00	0.93	42.0
	ADT + ARPI (abiraterone)	206	0.00	0.93	42.0
STAMPEDE arm H (NCT00268476)	ADT with/without docetaxel	409	0.16	1.00	61.3
	ADT with/without docetaxel + RT	410	0.15	1.00	61.3
SWOG1216 (NCT01809691)	ADT	328	0.00	0.77	58.8
	ADT + ARPI (orteronel)	328	0.00	0.74	58.8
TITAN (NCT02489318)	ADT with/without docetaxel	192	0.10	0.84	44.0
	ADT with/without docetaxel + ARPI (apalutamide)	200	0.11	0.78	44.0

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; RT = radiotherapy.
[a] Reported as a proportion of the overall trial population.

Benefit of prostate radiotherapy +/- ARPI in mHSPC:

Hazard ratios (95% credible intervals) from pairwise comparisons of treatment groups from Bayesian fixed-effects network meta-analysis

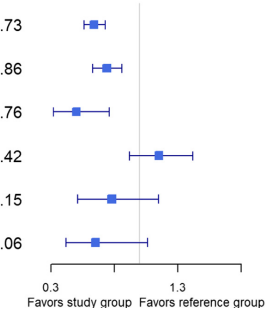
Pairwise Comparison	Hazard Ratio	95% Credible Interval
SOC plus ARPI versus SOC	0.68	0.60 to 0.77
SOC plus RT versus SOC	0.73	0.62 to 0.87
SOC plus ARPI plus RT versus SOC	0.53	0.34 to 0.81
SOC plus RT versus SOC plus ARPI	1.07	0.87 to 1.32
SOC plus ARPI plus RT versus SOC plus ARPI	0.77	0.51 to 1.16
SOC plus ARPI plus RT versus SOC plus RT	0.72	0.46 to 1.14



- De novo mHSPC :
  - Any combination > SOC
  - There was some evidence that the addition of prostate RT to ADT plus an ARPI

Hazard ratios (95% credible intervals) from Bayesian pairwise comparisons of treatment groups with adjustment for de novo population and docetaxel use

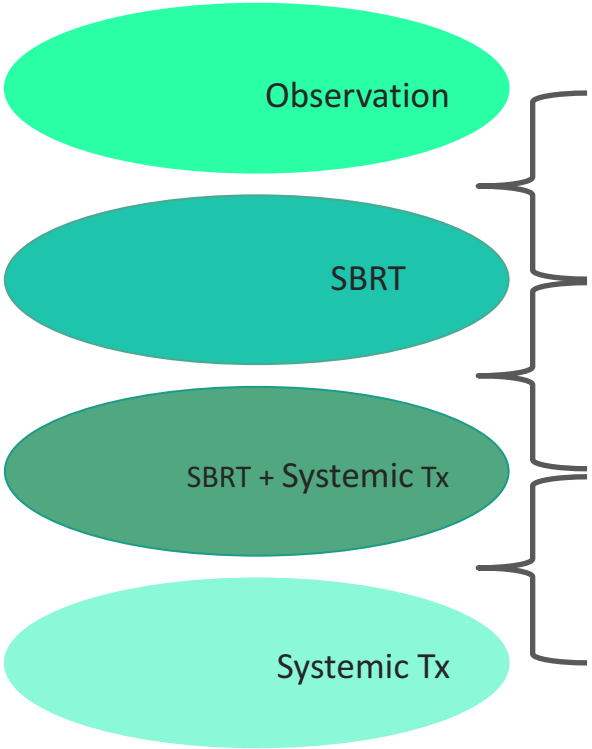
Pairwise Comparison	Hazard Ratio	95% Credible Interval
SOC plus ARPI versus SOC	0.64	0.56 to 0.73
SOC plus RT versus SOC	0.74	0.63 to 0.86
SOC plus ARPI plus RT versus SOC	0.50	0.32 to 0.76
SOC plus RT versus SOC plus ARPI	1.10	0.92 to 1.42
SOC plus ARPI plus RT versus SOC plus ARPI	0.77	0.51 to 1.15
SOC plus ARPI plus RT versus SOC plus RT	0.65	0.42 to 1.06



- De novo low-burden mHSPC :
  - Any combination > SOC
  - There was some evidence that the addition of prostate RT to ADT +ARPI reduces mortality

Soumyajit Roy et al, European Urology 2024;

Benefit of metastatic directed radiotherapy in mHSPC: trials



ORIOLE , STOMP

RADIOSA

EXTEND

Continuous ADT

Intermittent ADT

WOLVERINE X-MET

Adapted from Dr Ost presentation. ESTRO 2025

Benefit of metastatic directed radiotherapy in mHSPC

Trial	POPSTAR[1] Phase I	STOMP[2] Phase II	ORIOLE[3] Phase II	PSMA-MgRT[4] Phase II	GICOR[5] Phase II
Patients	N=33 < 4 M_1	N=62 < 4 M_1	N=52 < 4 M_1	N=37 < 6 M_1	N=81 (14pt CRPC) < 6 M_1
Randomized	No	1:1	1:2	No	No
Imaging	(NaF)-PET/CT scan	Choline-PET-CT	^{18}F-DCFPylPSMA PET*	[18F]DCFPyL PET-MR/CT	Choline-PET-CT
Arms	20 Gy/1#	Observation vs 30 Gy/3# or surgery	Observation vs 19.5-48 Gy in 3-5 #	SBRT 27-30 Gy(3#) Surgery	SBRT +ADT 24 months
Outcomes	@2y LC: 93% DPFS:39% ADT-FS: 48%	5y ADT free SV 8% vs 34 %	6 months progression 19% vs 61%	BCH resp:60% 22% BCH NED Med t to PSA prog 17.7 m	@3y Distant PFS 67%
Toxicity	G3:1 (3% vertebral fx)	No > G1 toxicity (fu:3y)	6 month G2 toxicity (5%)	> G 1 tox : 5% fu: 15.9 m	No > G2 toxicity fu:41m

S-Siva et al. Eur Urol[1], 2018 P. Ost et al. JCO 2017[2]. R. Phillips et al, JAMA Oncol 2020[3]. Rachel M. Glicksman et al. Eur Urol 2021[4]. AJ Conde-Moreno et al. Pract Radiat Oncol 2024[5]

Targeting all sites of disease

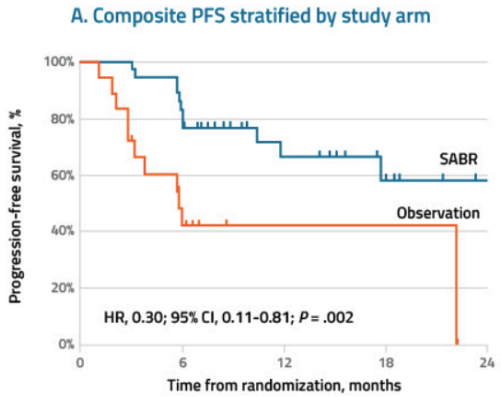
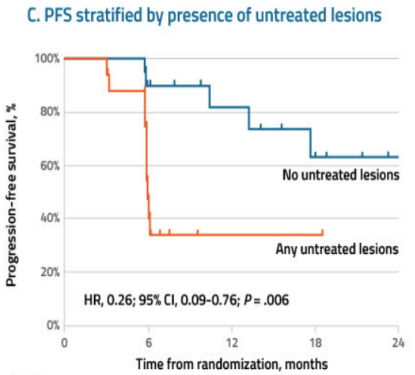


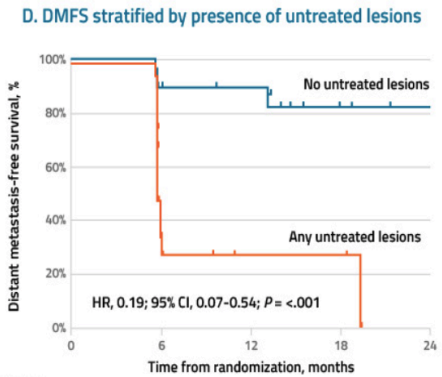
Figure 1

Outcome	MDT Median Timeto Event, months (95% CI)	Observation Median Time to Event, months (95% CI)	HR (95% CI)	P
PFS	11.9 (8 to 18.3)	5.9 (3.2 to 7.1)	0.44 (0.29 to 0.66)	<.001
rPFS	18.3 (12 to 36)	17 (13 to 22.8)	0.81 (0.50 to 1.29)	.37
CRPC	NR (62 to NR)	63 (53.9 to NR)	0.67 (0.34 to 1.31)	.24
OS	NR (84 to NR)	NR (73 to NR)	0.53 (0.13 to 2.11)	.36

0 0.5 1 1.5 2

Favors MDT Favors Observation





- 16 of 36 pt (44%) in SABR group PET + lesions not irradiated
- PD: no untreated lesions: 5% / untreated lesions: 38%
- New M1 at 180 days: no untreated lesions: 16% / untreated lesions: 63%

Phillips R, Shi WY, Deek M, et al. (2020). *JAMA Oncol,* 6(5):650–659. doi:10.1001/jamaoncol.2020.0147. Urotoday accessible en: https://www.urotoday.com/

GCs for outcome prediction of MDT for oligometastatic PC (ORIOLE AND STOMP)

116 pt
median follow-up was 52.5 months

NGS:(prostate tumor or blood).
A high risk mutational signature was defined as pathogenic somatic mutations within ATM, BRAC1/2, Rb1, and TP53.

The **median rPFS after MDT was 25.3 months** (95% CI, 17.0 to NR) without a high-risk mutation, compared with **8.0 months** (95% CI, 5.9 to NR) **with a high-risk mutation** (HR, 0.43; 95% CI, 0.20 to 0.95; P 5 .04

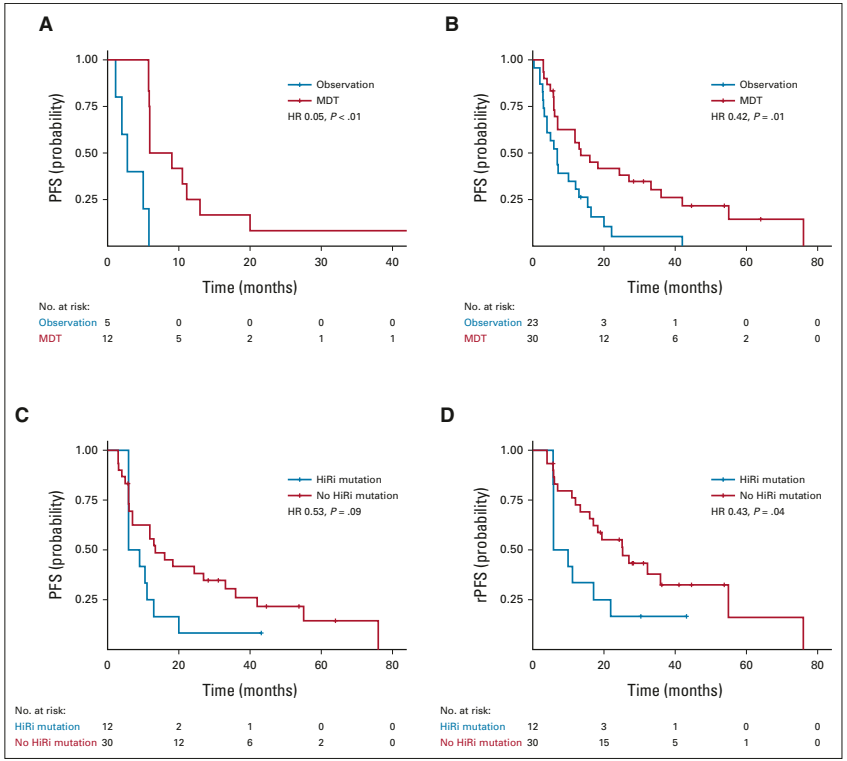


FIG 3. PFS stratified by treatment arm for those (A) with and (B) without a high-risk mutation stratified by treatment arm. MDT resulted in improvements in PFS in those both with and without a high-risk mutation, however, with a potential differential benefit resulting in relatively larger improvements in PFS in those with a high-risk mutation treated with MDT. (C) PFS and (D) rPFS in those treated with MDT stratified by high-risk mutation status. High-risk mutational status was prognostic for both PFS and rPFS in those treated with MDT, with longer times to events in those without a high-risk mutation. HiRi, high-risk; MDT, metastasis-directed therapy; OS, overall survival; PFS, progression-free survival; rPFS, radiographic progression-free survival.

Deek et al. J Clin Oncol 2022; 40:3377-3382.

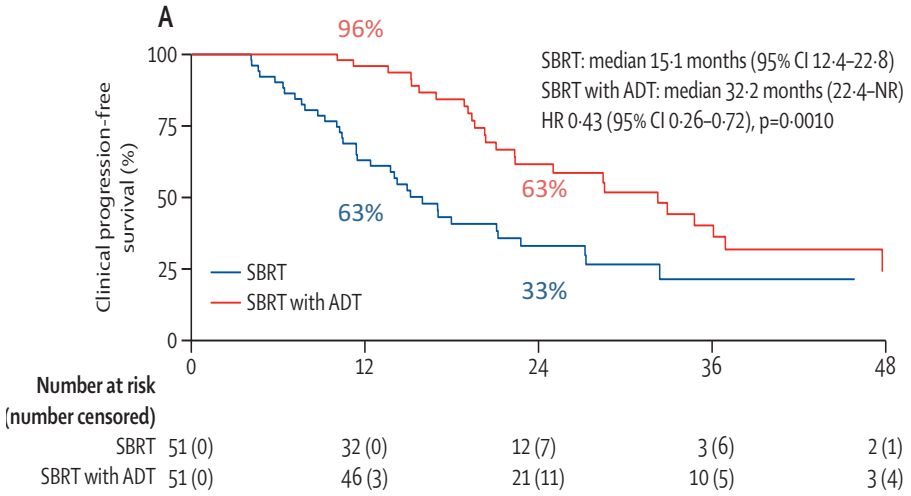
RADIOSA: SBRT vs SBRT+ADT

102 pt oligorecurrent HSPC: SBRT vs SBRT+ ADT (6m)

- Single center; (PET-CT* /BodyRM)
  30 Gy in 3# EOD or equivalent (BED >100 Gy)
- Primary endpoint: **Clinical progression free SV**

  Secondary: OS, PFS, ADT-free SV, LC, tCRPC, QoL

- N1, M1a and M1b
- PSA (enrolment): 1.65/1.84 (067-3.53)
- 1/3 PSADT < 3 m
- Mostly 1-2 lesions



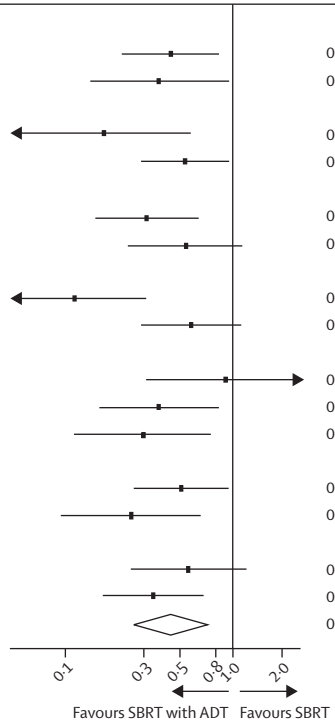
Median f-up: 31 m (IQR:16-36)

- Median BPFS: 12.6 /26.8 m; ADTFSV: NR/18 m; CRPC: 2% /14%; LC: 96%3/3 in-field
- Only 1 pt G3 toxicity (left ureter stenosis)
- Almost all patients with ADT recovered testosterone levels at 1 y.
- Higher risk of polymetastatic progression in the SBRT only group 29% vs 12% (p=0.018)

G Marvaso et al Lancet Oncol 2025; 26: 300–11

RADIOSA: SBRT vs SBRT+ADT

	SBRT		SBRT with ADT		HR (95% CI)
	Events/patients	Median (95% CI)	Events/patients	Median (95% CI)	
ISUP grade (primary tumour)					
ISUP 1–3	19/28	15·1 (11·4–NR)	18/36	32·2 (22·4–NR)	0·45 (0·23–0·86)
ISUP 4–5	16/23	16·0 (11·4–NR)	6/14	28·6 (20·0–NR)	0·38 (0·15–0·99)
Previous radiotherapy on pelvis					
Yes	11/13	12·4 (7·6–NR)	5/11	34·8 (19·4–NR)	0·18 (0·05–0·59)
No	24/38	18·0 (13·8–NR)	20/40	32·2 (22·4–NR)	0·54 (0·30–0·99)
Prostate-specific membrane antigen concentration at enrolment (ng/mL)					
>2	21/24	10·4 (9·21–15·1)	13/22	20·3 (18·9–NR)	0·32 (0·16–0·65)
0–2	14/27	27·2 (17·0–NR)	12/29	34·8 (28·5–NR)	0·55 (0·25–1·19)
Doubling time of prostate-specific membrane antigen (months)					
<3	15/16	10·9 (7·8–NR)	11/17	28·5 (20·3–NR)	0·12 (0·05–0·32)
>3	20/35	21·2 (17·0–NR)	14/34	32·9 (22·4–NR)	0·59 (0·30–1·17)
Disease stage at enrolment					
M1a	6/12	22·8 (12·4–NR)	8/13	25·0 (15·7–NR)	0·94 (0·32–2·76)
M1b	17/20	14·6 (10·2–21·2)	9/17	34·8 (19·6–NR)	0·38 (0·17–0·86)
N1	12/19	17·0 (11·4–NR)	8/21	36·1 (22·4–NR)	0·31 (0·12–0·77)
Number of oligometastases					
1	24/36	16·0 (13·8–27·3)	14/29	25·0 (20·3–NR)	0·50 (0·26–0·97)
2–3	11/15	11·4 (9·21–NR)	11/22	36·1 (32·2–NR)	0·26 (0·10–0·67)
Time from first curative treatment to radiotherapy (months)					
>43	13/23	22·8 (14·2–NR)	11/27	36·9 (21·1–NR)	0·55 (0·25–1·24)
≤43	22/28	13·8 (10·2–18)	14/24	28·5 (20·3–NR)	0·34 (0·17–0·68)
Overall	**35/51**	**15·1 (12·4–22·8)**	**25/51**	**32·2 (22·4–NR)**	0·43 (0·26–0·72)



→Benefit of SBRT alone?

- PSA 0-2
- T from first Treatment > 43 m
- PSADT > 3 m
- M1a

G Marvaso et al Lancet Oncol 2025; 26: 300–11

EXTEND: ADT vs ADT+SBRT

Intermittent ADT

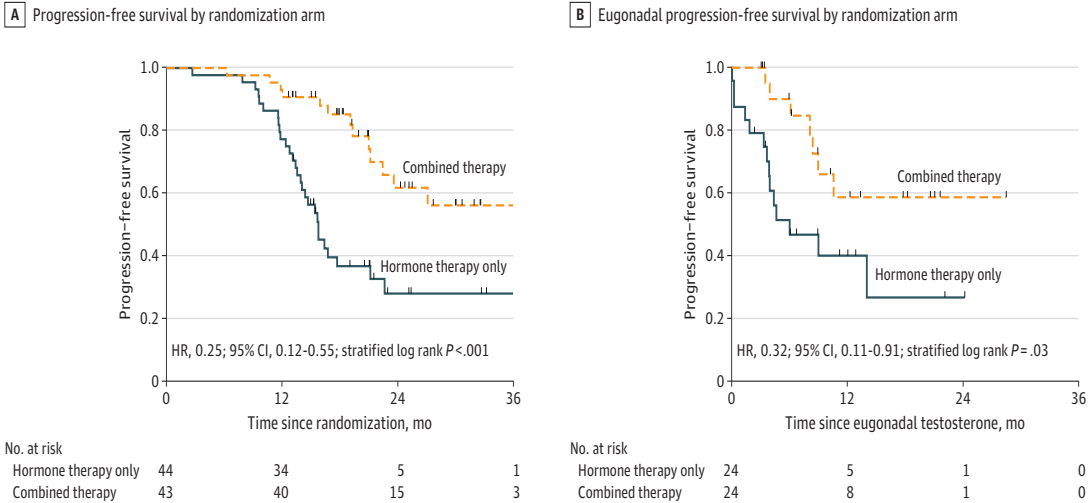
87 pt meth or synchr mHSPC; mCRPC (8%)

- N1, M1a, M1b, M1c
- *1-2 lesions
- *PSA < 2 ng/mL (57% ≤ 0.2 ng/mL)
- ≈ 25% Baseline imaging: Fluciclovine F18 PET/CT
- 42% ARPI
- RT all mets and prostate(if no previous RT)

- Median study follow-up: 22.0 m (11.6-39.2 m)

- No grade 4-5 toxicity

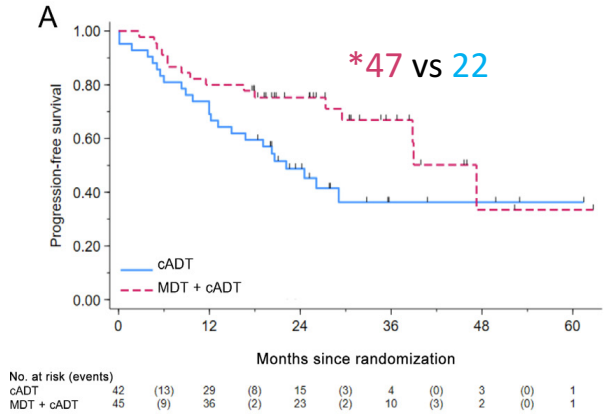
Figure 2. Primary and Key Secondary End Points

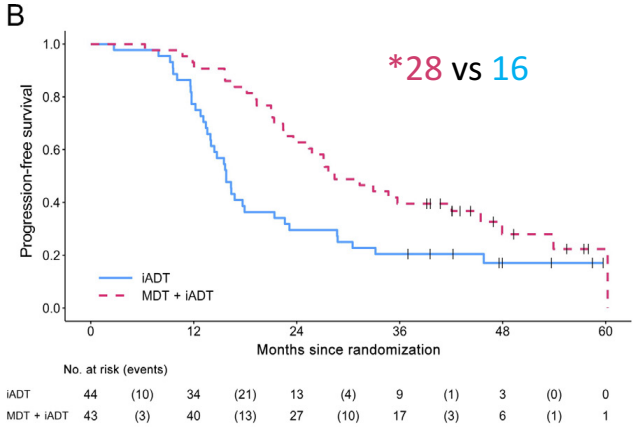


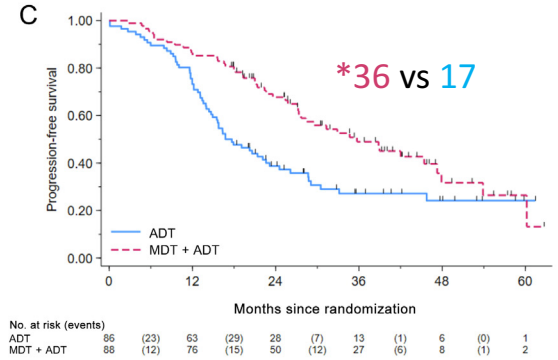
C Tang et al JAMA Oncol 2023

EXTEND: ADT vs ADT+SBRT

Continuous ADT







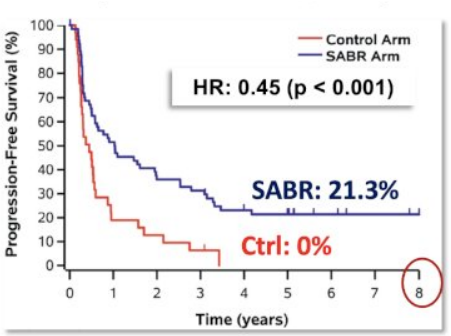
cADT: 87 pt meth or synchr mHSPC; mCRPC (39%)

- ≈ 39% Baseline imaging: PET/CT
- Median follow-up cADT: 31 m; iADT: 47 m; i+cADT: 42m
- *median PFS (m)

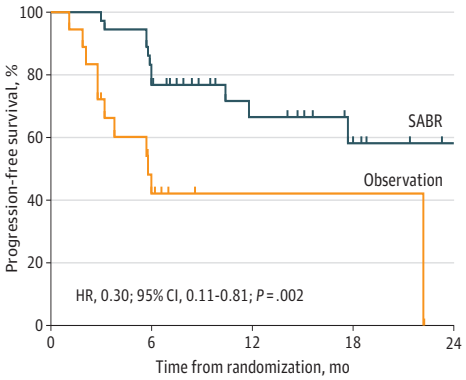
A D Sherry et al. European Urology (in press)

ASCO GU 2025: (**WOLVERINE**): An Analysis from the X-MET Collaboration

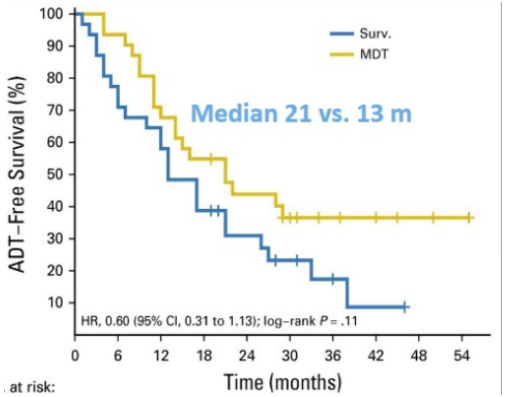
SABR-COMET (methacronous mHSPC,mCRPC)



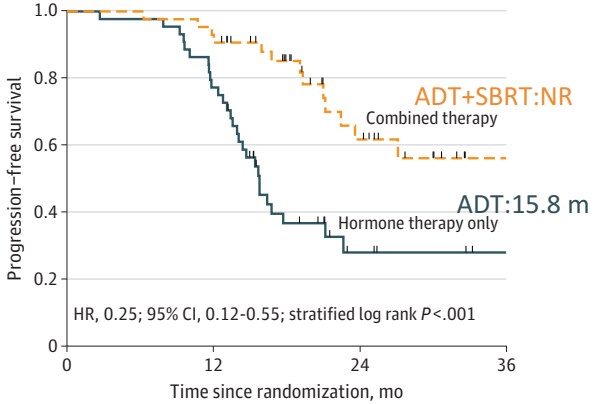
ORIOLE (methacronous mHSPC)



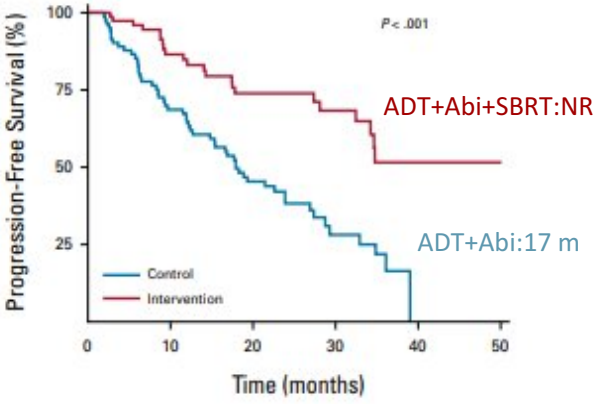
STOMP (methacronous mHSPC)



EXTEND (methacronous,synchronous mHSPC; mCRPC)



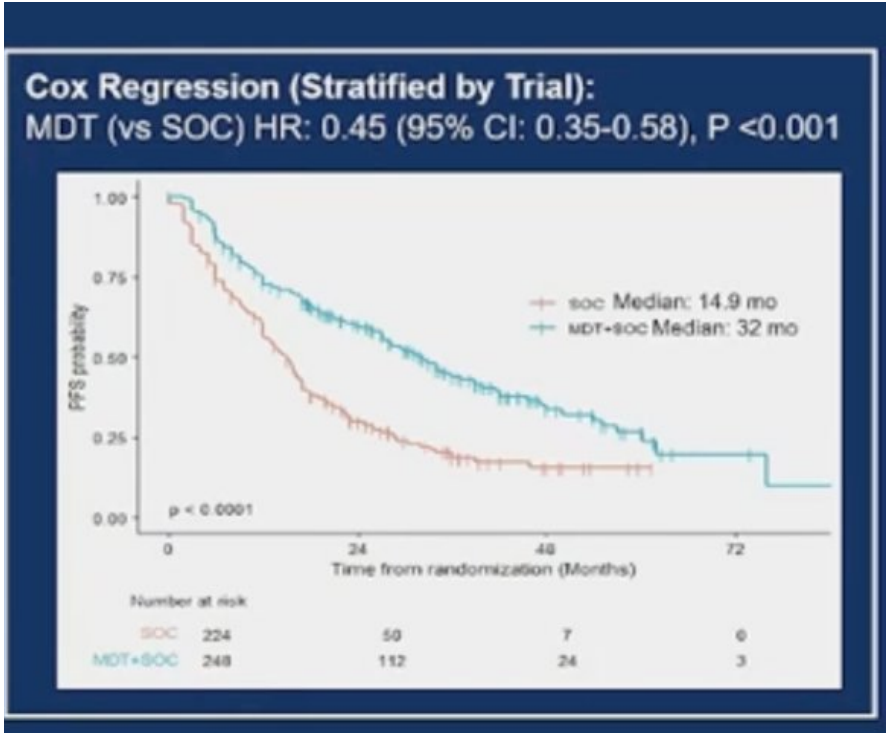
ARTO (mCRPC)



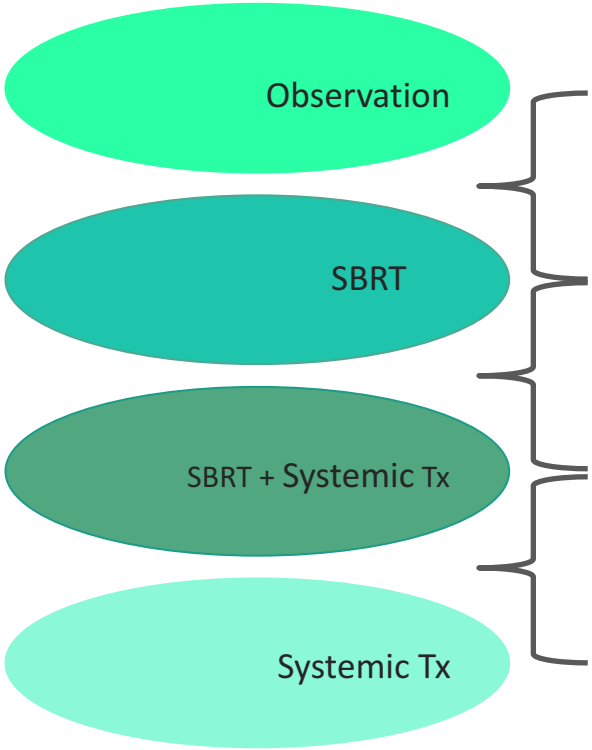
ASCO GU 2025: World-Wide Oligometastatic Prostate Cancer (omPC) Meta-Analysis Leveraging Individual Patient Data (IPD) from Randomized Trials (WOLVERINE): An Analysis from the X-MET Collaboration

Patient Characteristics

	SOC	MDT+SOC
2nd Generation ARPI	134 (60%)	125 (50%)
ADT Alone	40 (18%)	52 (21%)
Observation	50 (22%)	69 (28%)
PSA at enrollment (median)	1.9	1.9
Number of metastases (median)	2	2
CRPC = Yes	104 (46%)	95 (38%)
CRPC = No	120 (54%)	153 (62%)
Prior Primary Treated = No	37 (17%)	42 (17%)
Prior Primary Treated = Yes	185 (83%)	204 (82%)
Baseline Imaging = Conventional	79 (35%)	110 (44%)
Baseline Imaging = PET	145 (65%)	138 (56%)



Benefit of metastatic directed radiotherapy in mHSPC: trials



ORIOLE , STOMP

SBRT> OBSERVATION

RADIOSA

SBRT+ADT > SBRT

EXTEND

SBRT+SOC > SOC

Continuous ADT

Intermittent ADT

WOLVERINE X-MET

Adapted from Dr Ost presentation. ESTRO 2025

Benefit of Metastatic Directed Radiotherapy in mHSPC: Biomarkers

- High risk mutational signature :pathogenic somatic mutations within ATM, BRAC1/2, Rb1, and TP53
- PSMA extracellular vesicles (Mayo Clinic)
- Digital pathology + AI (e.g. ARTERA)
- mRNA markers (e.g. Decipher)
- TCR repertoire modulation

EXTEND: ADT vs ADT+SBRT

- Hypothesis: durable clinical outcomes after MDT + ADT were partially attributable to the induction of systemic antitumor immune responses.

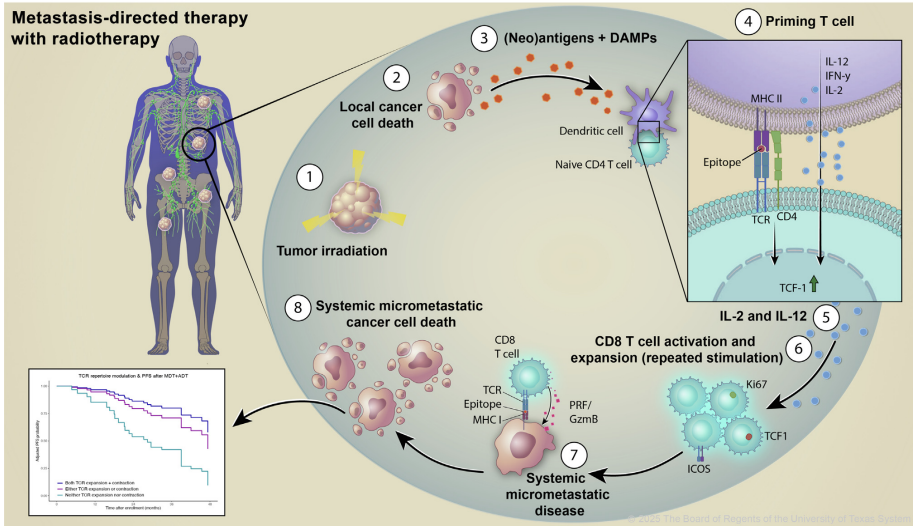
- MDT + ADT
  - durable response: PFS ≥ 3 yr
  - poor response: PFS < 1 yr

Durable responses to MDT+ADT:

- ↑IFN-γ and IL-12p70
- ↑markers of CD8$^+$ T-cell activation
- Antigen-specific T-cell activation and proliferation lead to TCR clonal expansion and TCR clonal contraction

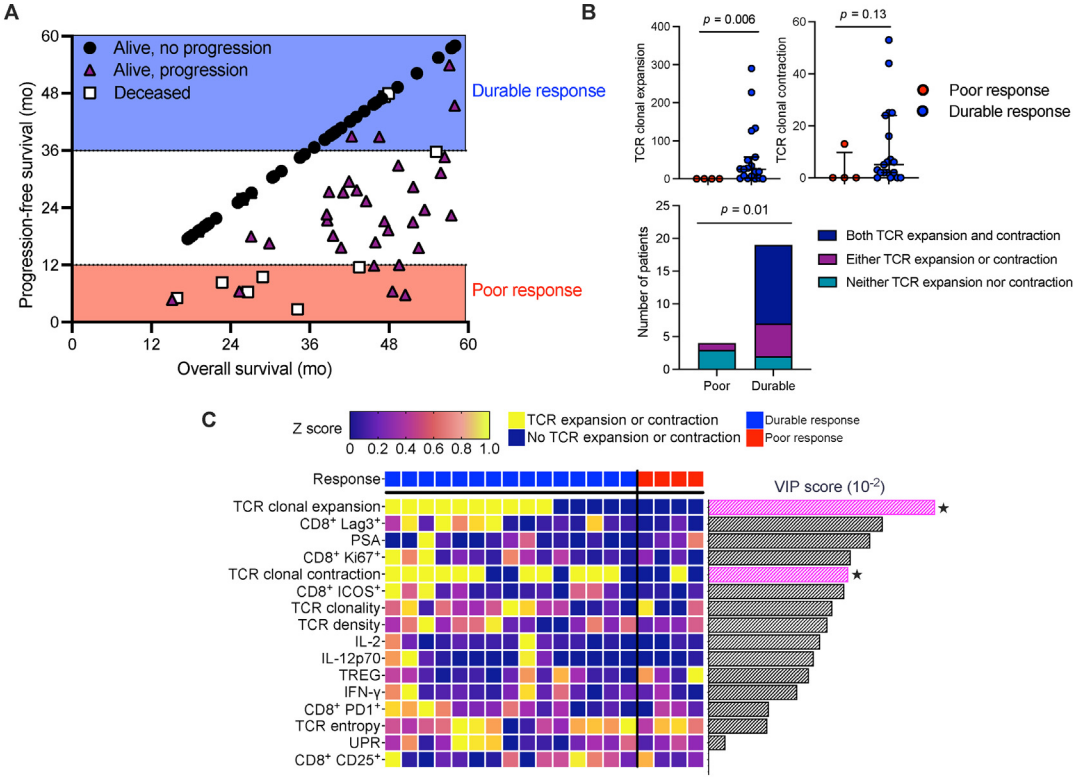
↓

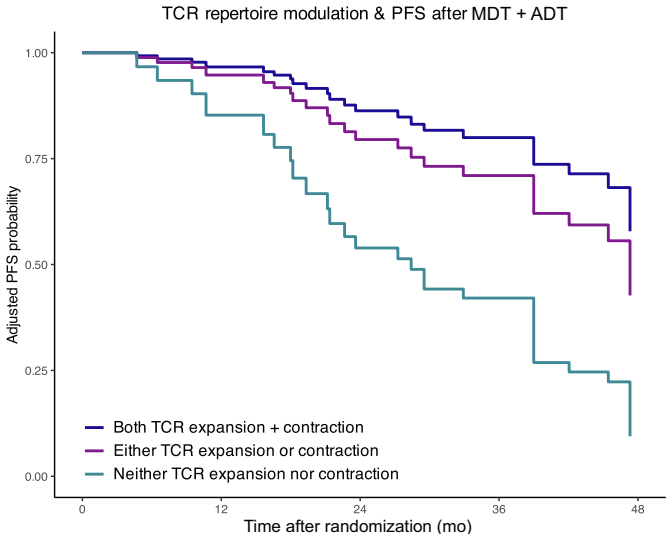
TCR repertoire modulation



A D Sherry et al. European Urology (in press)

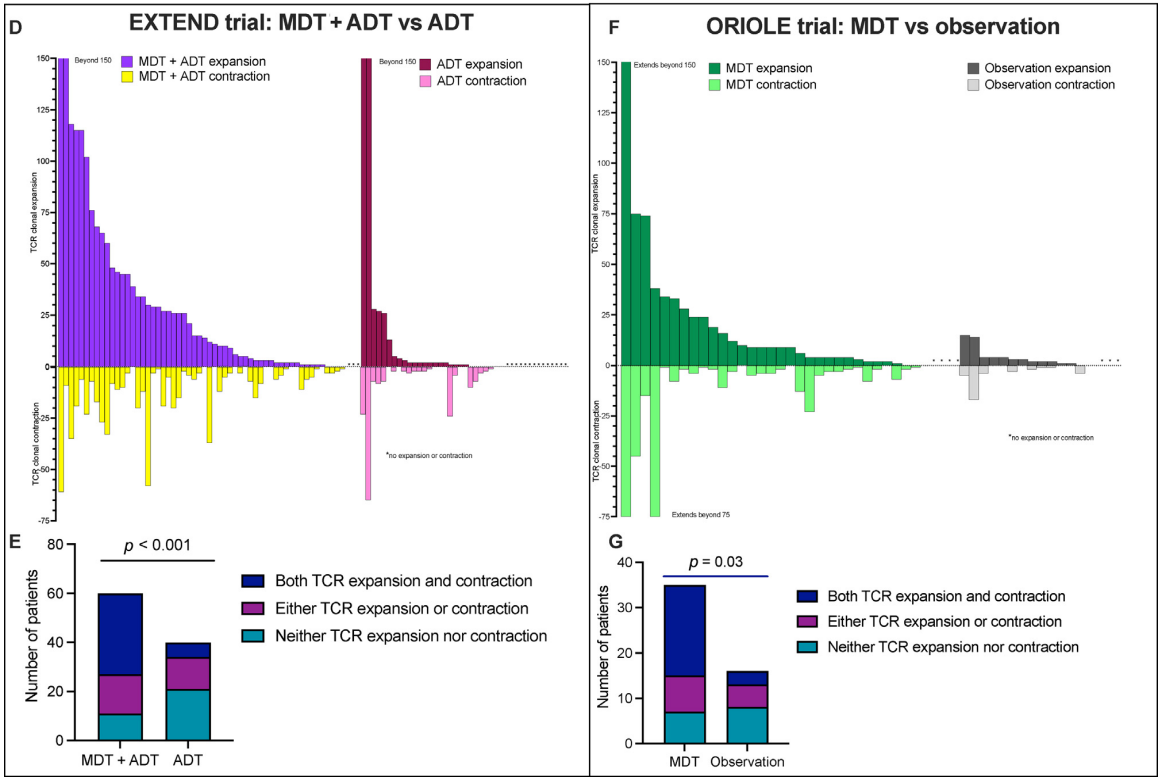
EXTEND: ADT vs ADT+SBRT





A D Sherry et al. European Urology (in press)

EXTEND: ADT vs ADT+SBRT



These results linked TCR modulation as a candidate blood-based biomarker for clinical outcomes associated with MDT + ADT.

A D Sherry et al. European Urology (in press)

CONCLUSIONS

- Published data suggest that in patients with de novo low-volume mHSPC, to add prostate RT to ADT +/- ARPI confers outcomes superior to one in which RT is omitted. Reflects the contemporary real-world data.
- For oligorecurrent HSPC , randomized trials show that SBRT-MDT safely delays systemic treatment initiation and increases progression-free survival.
- Current evidence supports MDT integration into clinical practice for selected oligometastatic patients.
- SBRT combined with short-term ADT yields superior PFS compared with either SBRT or ADT alone..
- We are making progress toward identifying biomarkers that will enable us to tailor the intensity and duration of systemic treatment associated to focal RT.