Das oligometastasierte Prostakarzinom – Zeit zur De-Eskalation

Oligometastatic prostate cancer – time for de-escalation?

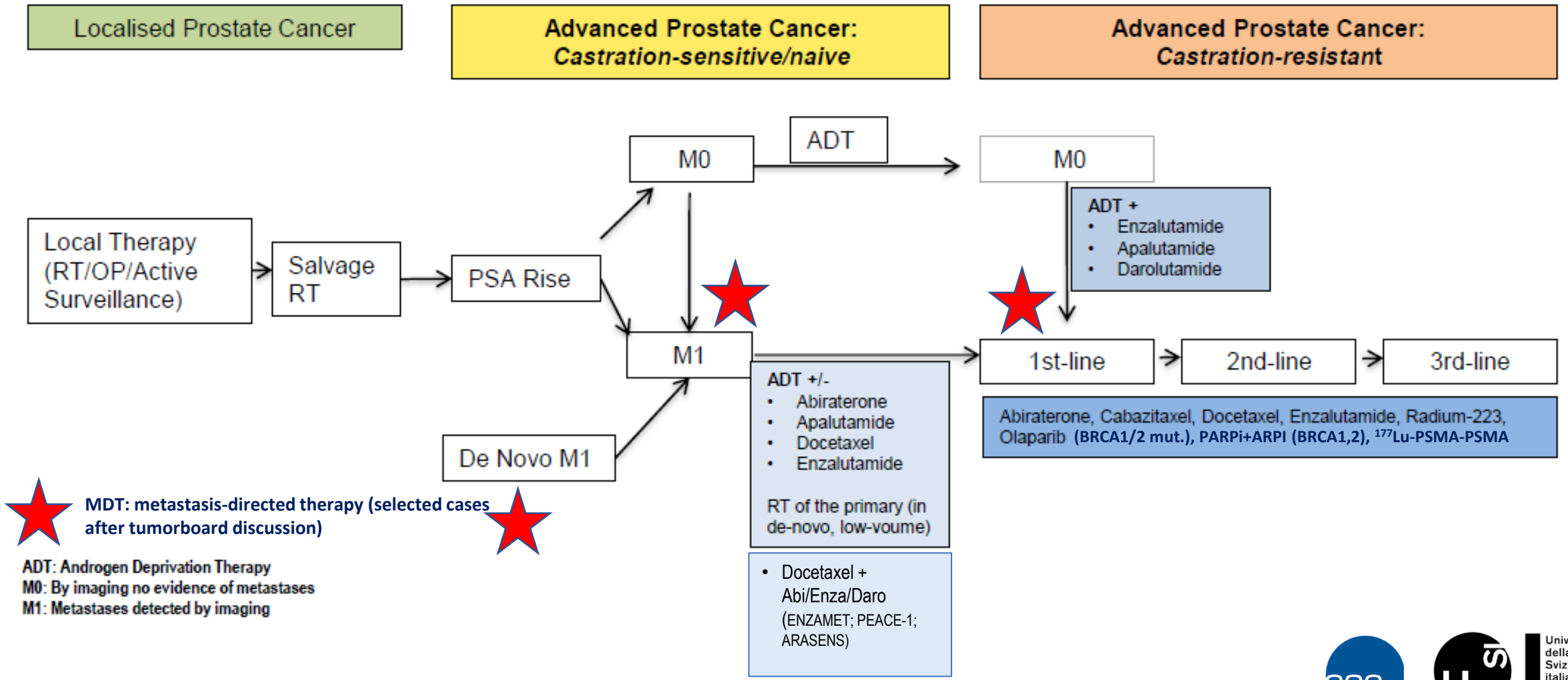
Basel, 11.10.2024

Priv. Doz. (PD) Dr. Ursula Vogl, MBA
Senior physician oncologist, lead of the urogenital cancers group IOSI
Clinical head of the Prostate Center of Southern Switzerland (CPSI)
President of the SAKK Project Group Urogenital Tumours
IOSI – Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland

Conflict of interest disclosure

Type of affiliation/financial interest	Sponsor
Speaker Honorary, Advisory Board **(institutional)**	Astellas, Janssen, Sanofi, Roche, MSD, Merck, Eisei, Bayer, Novartis AAA, Pfizer, BMS, Healthbooks, Ipsen, SAKK, SOHC
Speaker Honorary, other Honorary **(private)**	Grasso Consulting, Healthbooks, SAMO, Kantonsspital St. Gallen, Chur, Aarau, Inselspital Bern, OeGHO, ESO
Travel grants, Meeting Registrations **(private)**	Ipsen, Merck, Janssen, AstraZenaca
Grants	Fond'Action, Krebsliga

Prostate cancer treatment landscape 2024

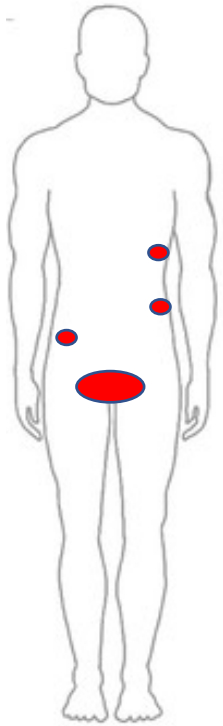


Adapted from Omlin A PROSCA 2019

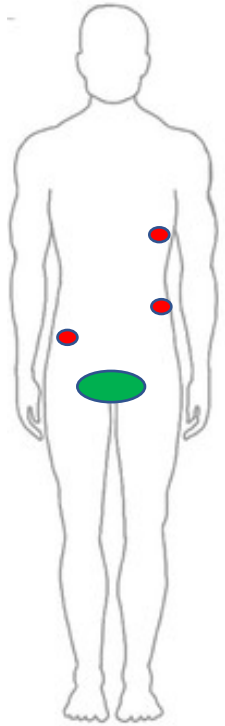
The oligometastatic PCa landscape

Uncontrolled lesion

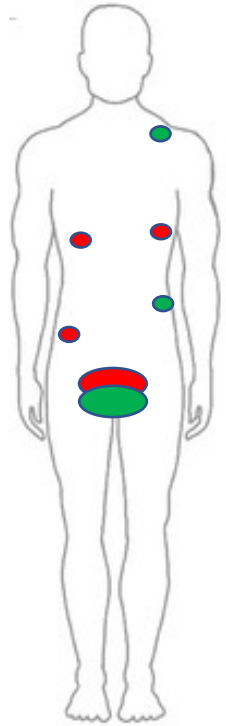
Controlled lesion



***De novo* oligometastases mHSPC (synchronous oligoM)**



Oligorecurrent mHSPC (metachronous oligoM)



Oligometastatic CRPC (≤ 5 mets)
Oligoprogressive (induced oligoM)

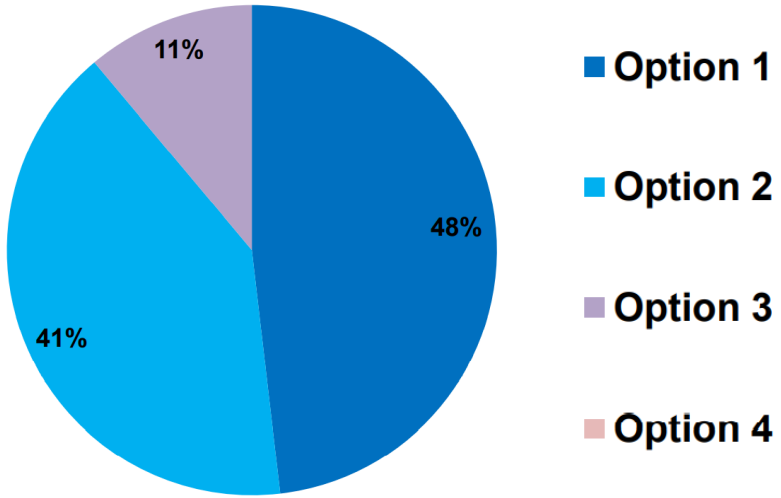
Oligometastatic prostate cancer – Definition

46% of panelists defined OMPCa as:

Patients with a limited number of synchronous or metachronous bone and/or lymph node metastases, excluding visceral metastases, that all can be treated with local therapy

No consensus on the cut-off of number of lesions:

1. ≤3 metastases
2. ≤5 metastases
3. No cut-off, any number that can be safely treated with ablative intent
4. Abstain

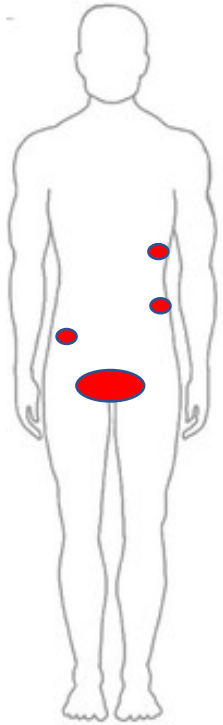


Gillessen, S *et al. Eur Urol*. 2020

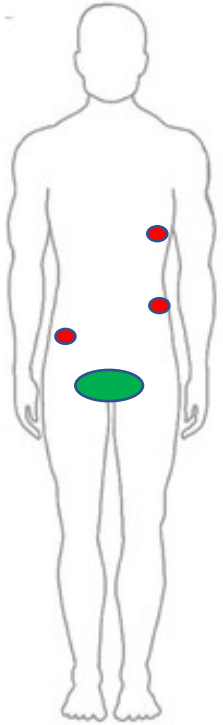
The oligometastatic PCa landscape

Uncontrolled lesion

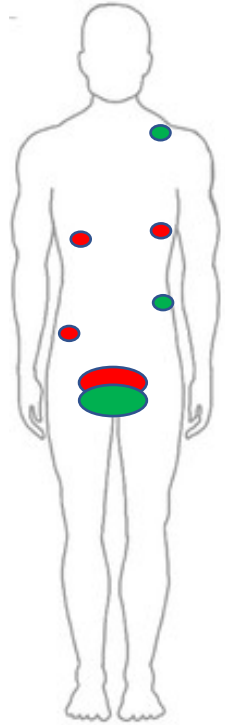
Controlled lesion



***De novo* oligometastases mHSPC (synchronous oligoM)**



Oligorecurrent mHSPC (metachronous oligoM)



Oligometastatic CRPC (≤ 5 mets)
Oligoprogressive (induced oligoM)

Systemic therapies: positive level 1 data

	N	Population	Control	Experimental	Outcome (HR OS)
CHAARTED (2015)	790	M1 (low/high)	ADT	ADT/Docetaxel	0.72 (0.59-0.89)
STAMPEDE (arm A+C) (2015)	1776	M0 and M1	ADT	ADT/Docetaxel	0.78 (0.66-0.93)
LATITUDE (2017)	1199	M1, high risk	ADT	ADT/Abi/pred	0.62 (0.51-0.76)
STAMPEDE (arm A+G) (2018)	1917	M0 and M1	ADT	ADT/Abi/pred	0.63 (0.52-0.76)
TITAN (2019)	1052	M1, all comers	ADT	ADT/Apa	0.67 (0.51-0.89)
ENZAMET (2022)	1125	M1, all comers	ADT	ADT/Enza ± Doce	0.70 (0.58-0.84)
PEACE-1 (2022)	1172	M1	ADT ± Doce ± RT	ADT ± Doce ± RT / Abi	0.82 (0.69-0.98)
ARASENS (2022)	1306	M1	ADT + Doce	ADT + Doce + Daro	0.68 (0.57-0.80)

Treatment for oligometastatic hormone-sensitive prostate cancer – Best evidence for treatment?

Oligometastatic low volume/burden		
Systemic treatment	**Clinical Trials**	**Overall Survival subgroup low volume/burden**
ADT + ARPI (Apalutamide, Enzalutamide)	**TITAN**	**ADT + placebo vs ADT plus Apalutamide** HR: 0.52 (95% CI 0.35-0.79)
	ENZAMET	**ADT plus NSAA vs ADT plus Enzalutamide** HR 0.54 (95% CI 0.39-0.74)
	ARCHES Synchronous low volume Metachronous low volume	**ADT+placebo vs ADT plus Enzalutamide** HR 0.65 (95%CI 0.39-10.08) HR 0.63 (95%CI 0.26-1.54)
ADT + Abiraterone	**STAMPEDE**	0.64 (95%CI 0.42-0.94)
ADT + radiotherapy to the prostate	**STAMPEDE ARM H**	**ADT vs ADT plus RT to the prostate** HR 0.64 (95% CI 0.52-0.79)
ADT + SOC + Abiraterone	**PEACE-1 (de-novo only)**	**ADT + SOC vs ADT + SOC + Abiraterone** HR 0.93 (95% CI 0.69-1.28)
ADT + Docetaxel + Darolutamide	**ARASENS**	**ADT + Docetaxel vs ADT + Docetaxel + Darolutamide** HR 0.68 (95% CI: 0.41-1.13)

Recently trial designs were more into **escalation** than de-escalation in mHSPC

- Triplet therapy (ADT+Docetaxel + ARPI) trials (with OS benefit) included low volume patients

  - PEACE-1 (de-novo) +/- RT to the primary

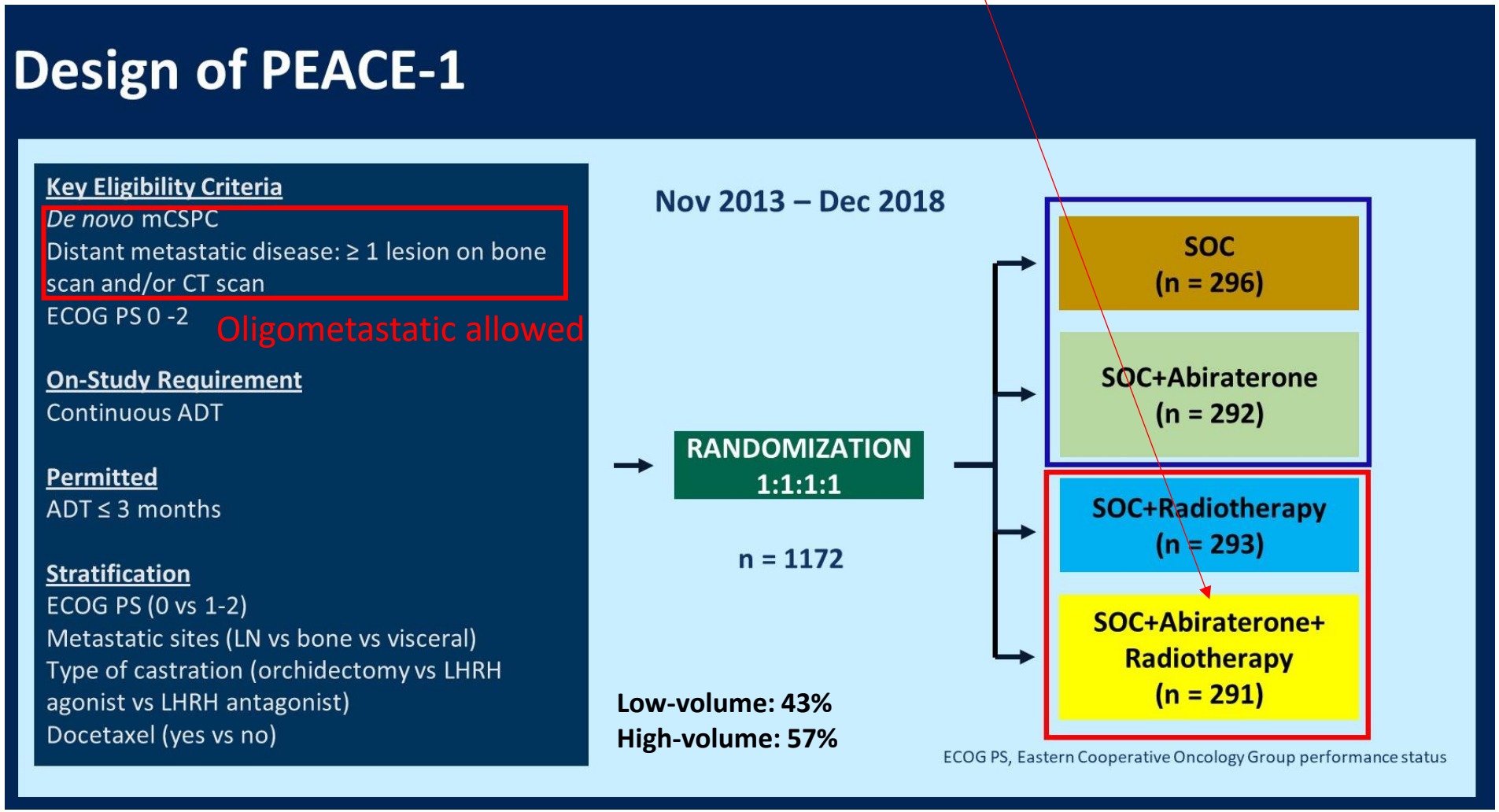
  - ARASENS

- Trials with «total therapy» including RT to the primary and SBRT to metastatic lesions
- Modern imaging PET PSMA introduces «stage migration» →

  - e.g. a non-metastic HSPC patient becomes oligometastatic

  low-volume mHSPC patients → escalation of treatment

Triplet therapy / Quadruplet therapy



Bossi A *et al.* ASCO GU 2023; Bossi A et al. Lancet Oncol 2024.

ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)[1]

Patients (N=1306)
- mHSPC
- ECOG PS 0 or 1
- Candidates for ADT and docetaxel

Stratification
- Extent of disease: M1a vs M1b vs M1c
- ALP < vs ≥ ULN

1:1 randomization (N=1305[a])

- Docetaxel × 6 → **Darolutamide 600 mg twice daily + ADT**
- **Placebo twice daily + ADT** → Docetaxel × 6

FPFV: Nov 2016
LPFV: June 2018

Study analysis

Data cut-off Oct 25, 2021

Endpoints

Primary: OS

Secondary
- Time to CRPC
- Time to pain progression
- SSE-free survival
- Time to first SSE
- Time to initiation of subsequent systemic antineoplastic therapy
- Time to worsening of disease-related physical symptoms
- Time to initiation of opioid use for ≥7 consecutive days
- Safety

- Of 1305 patients in the ARASENS full analysis set
  - **1005 (77%) had high-volume disease and 300 (23%) had low-volume disease**
  - **912 (70%) had high-risk disease and 393 (30%) had low-risk disease**

1. Smith MR, et al. *N Engl J Med.* 2022;386:1132-1142.
[a]One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations.
ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; SSE, symptomatic skeletal event; ULN, upper limit of normal.

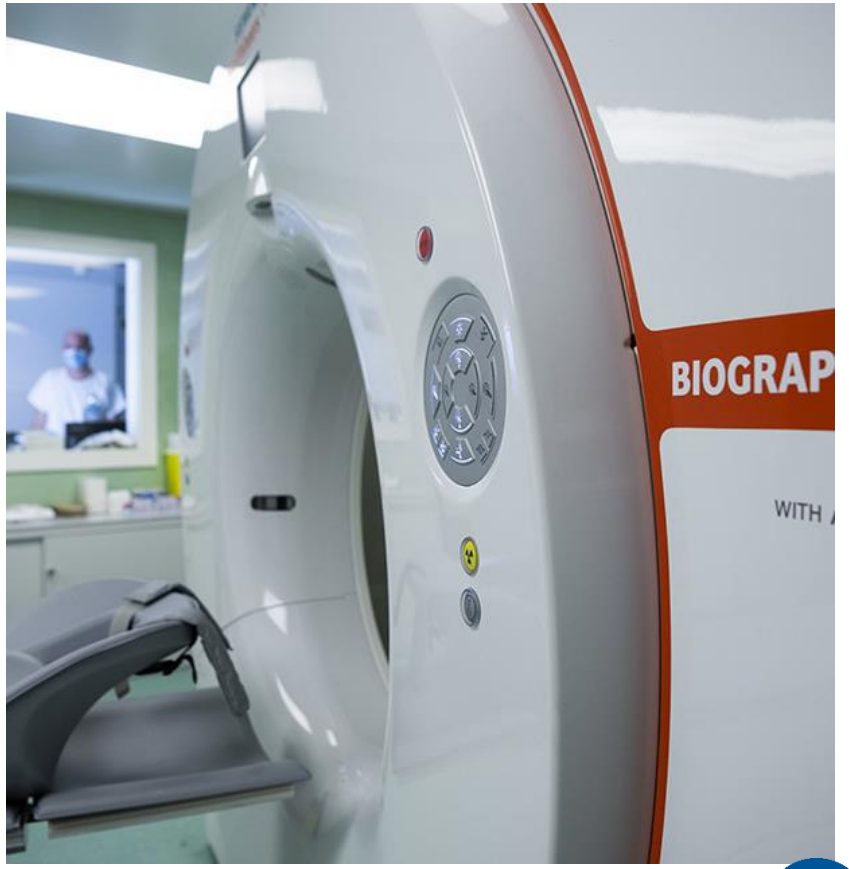
PRESENTED BY: Maha Hussain, MD, FACP, FASCO

The «problem» of modern imaging

How does imaging image oligometastatic disease?

All trials with level 1 evidence for systemic treatment have been done with conventional imaging (CT and bone scan)

- Oligometastatic by conventional imaging ?
- Oligometastatic by PSMA PET?



Clinical case

Mr. U., 62 years old

- Baker in activity
- Positive family history of prostate cancer (2 brothers with PCa)
- No smoker, BMI 22
- Obstructive urinary symptoms
- Comorbidities:

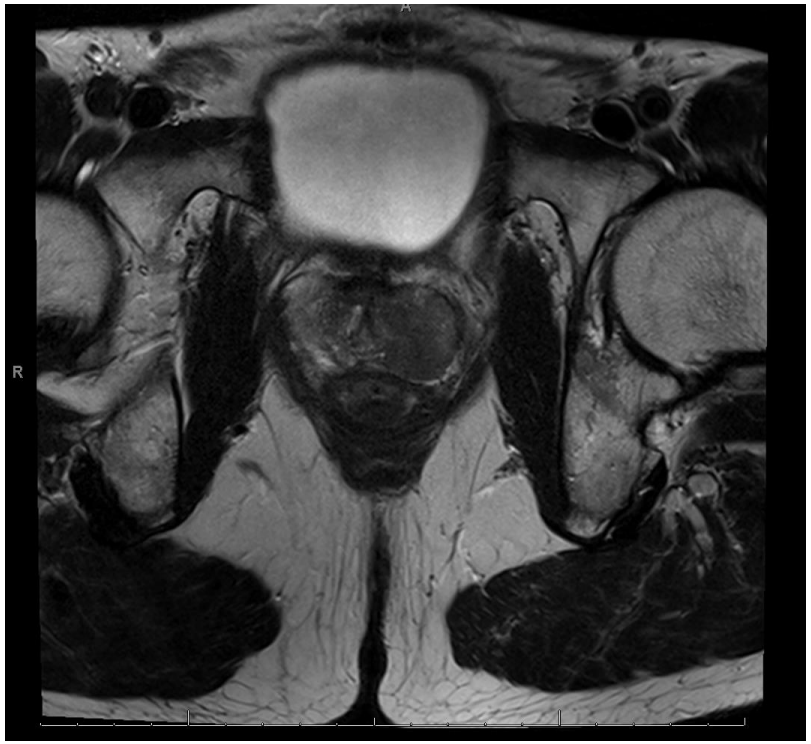
  - excision of cervical lipoma MDM2 negative

Come to clinics for urological evaluation after diagnosis of a PCa to the brother

Clinical case

Oncological history

- 07/2023 iPSA 24 ng/mL
- DRE: suspicious induration in the left lobe (cT3a)



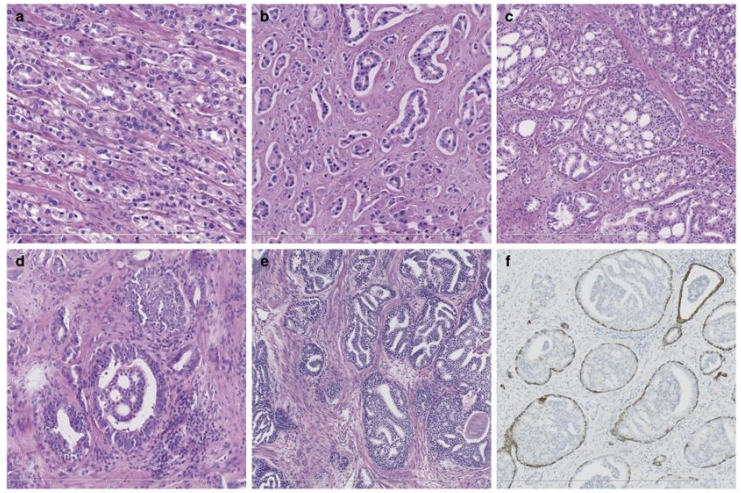
3T mpMRI: suspected lesion PIRADS 5 on the left lobe with extracapsular extension and invasion of the proximal seminal vesicle
No pelvic nodes. Unclear bone lesion in the pubic symphysis (metastasis)?

adapted from Zilli, T

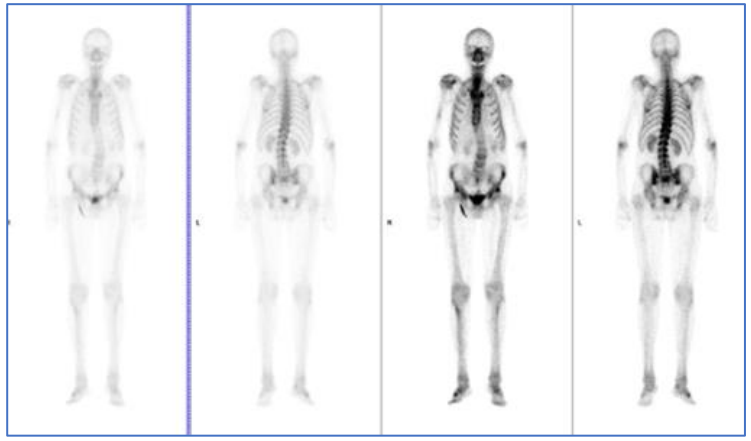
Clinical case

Oncological history

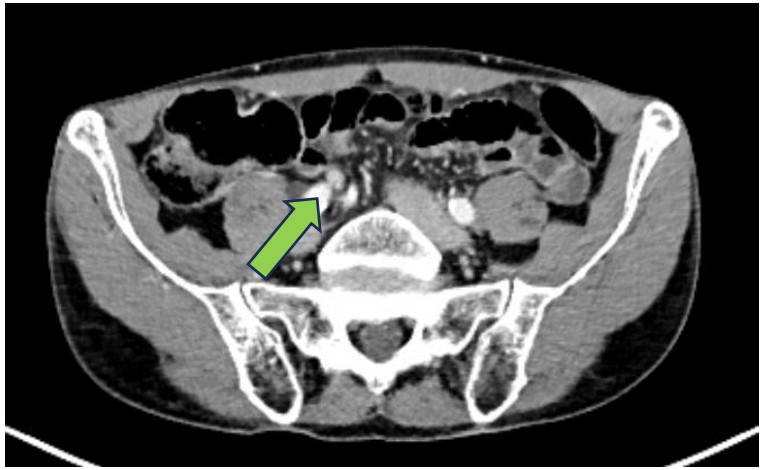
- Histology: prostate acinar adenocarcinoma, **Gleason score 7 (3+4), ISUP grade 2**, with **cribriform** and **intraductal** components and perineural invasion on the left lobe in the PIRADS 5 lesion; Gleason 3+3 in the systematic biopsies



Gleason grade 4 patterns and intraductal carcinoma. (a) Fused glands; (b) ill-defined glands; (c) cribriform glands; (d) glomeruloid gland; (e) intraductal carcinoma; and (f) 34BE12 immunohistochemistry, demonstrating the presence of basal cells supportive for intraductal carcinoma.
Kweldam et al. Mod Pathol 2015



Bone scan: negative

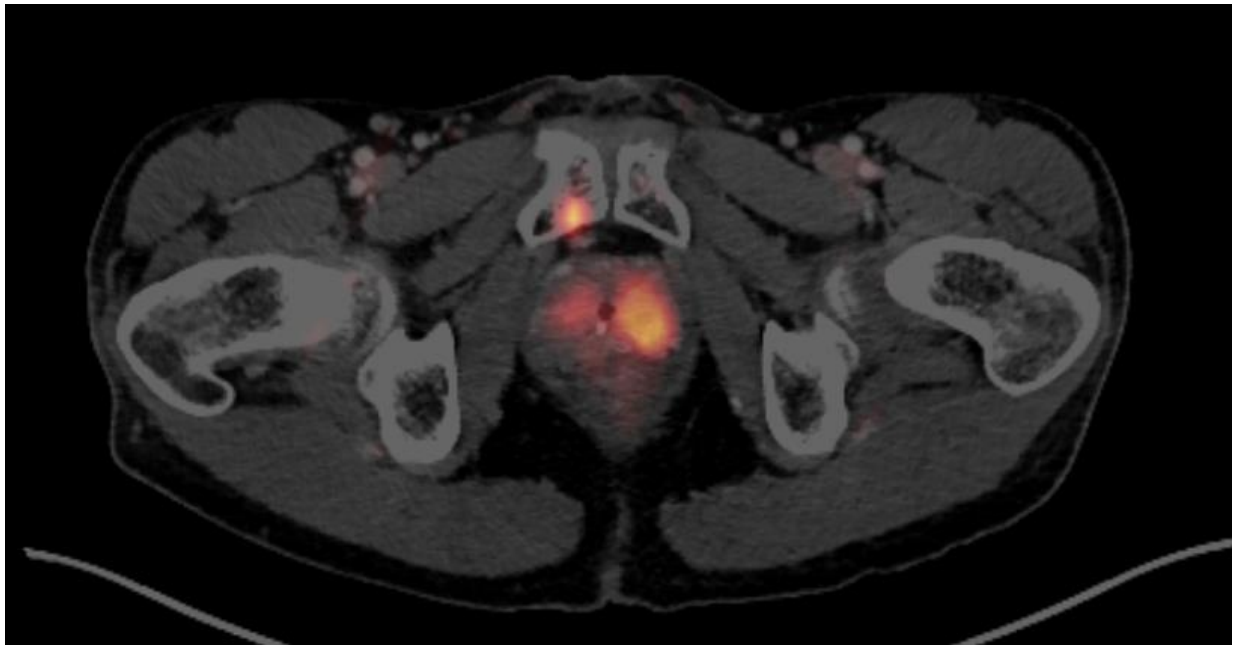


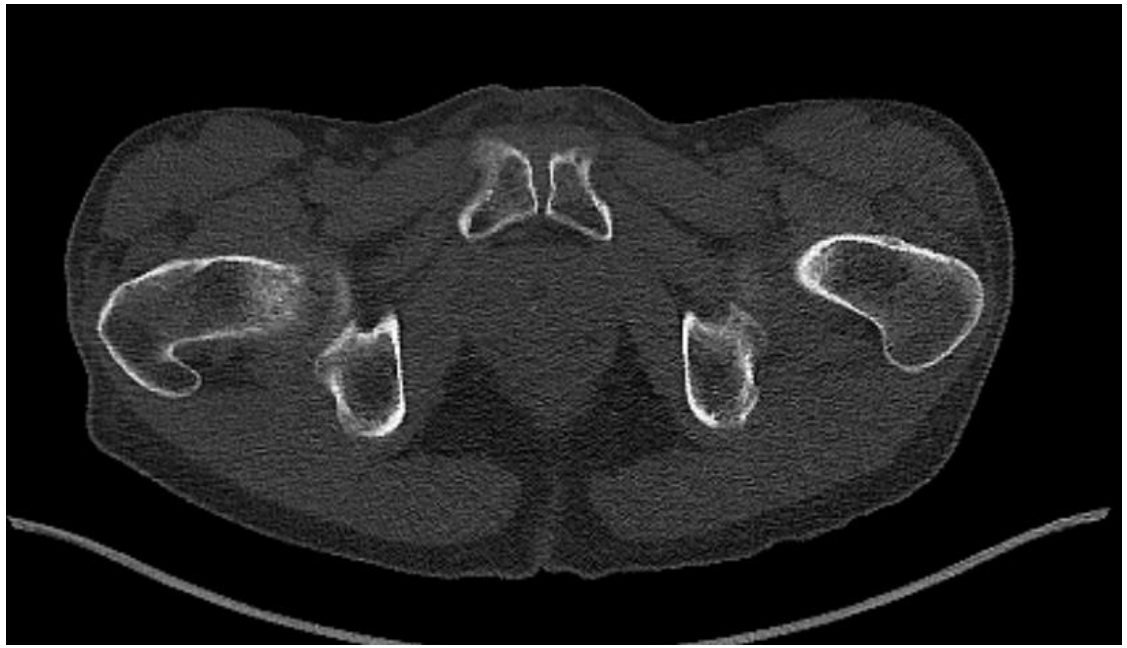
CT scan: node single common iliac R 10x8 mm

adapted from Zilli, T

Clinical case

- **18F-PSMA-1007-CT**: metabolic uptake on the left prostate lobe. Single bone uptake on the right pubic symphysis with no morphological correlation on CT images. Low uptake in the common iliac R nodal lesion (reactive *vs* metastatic)

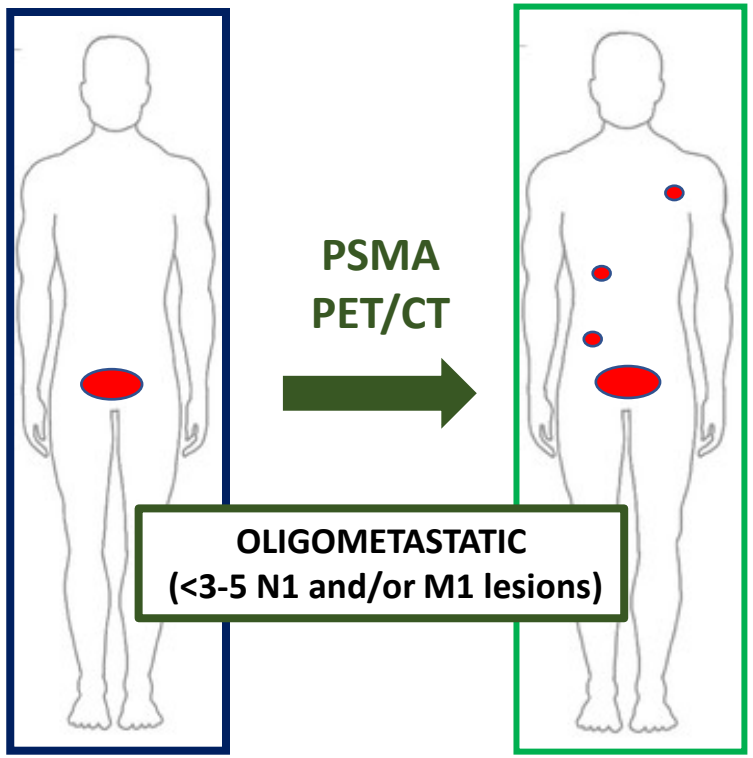




adapted from Zilli, T

The stage migration in the *de-novo* setting

STANDARD IMAGING (BONE SCAN + CT scan)



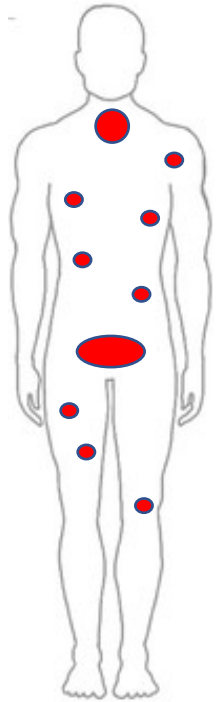
PRIMARY DISEASE

PSMA PET/CT

OLIGOMETASTATIC (<3-5 N1 and/or M1 lesions)

LOW-VOLUME CHARTEED
< 4 bone lesions

PSMA PET/CT



HIGH-VOLUME CHARTEED
≥ 4 bone lesions
(≥ 1 outside vetebral bodies/pelvis)
and/or visceral mets

Low risk localized — **NEXT-GENERATION IMAGING (PSMA PET-CT)** — **Full blown metastatic**

adapted from Zilli, T

Treatment Options for patient – APCCC expert's vote

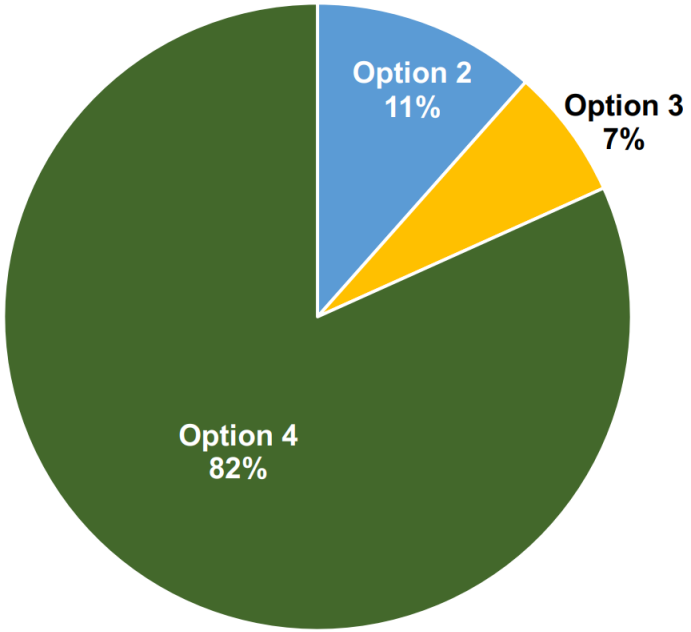
APCCC ADVANCED PROSTATE CANCER CONSENSUS CONFERENCE

3. mHSPC

Consensus questions APCCC 2024

74. In the majority of patients with synchronous low-burden mHSPC on conventional imaging, what is your treatment recommendation (regardless of the decision about metastases-directed therapy and regardless of the addition of docetaxel)?

1. ADT alone
2. ADT plus ARPI
3. ADT plus RT of the primary tumour
4. **ADT plus ARPI plus RT of the primary tumour**
5. Abstain/unqualified to answer

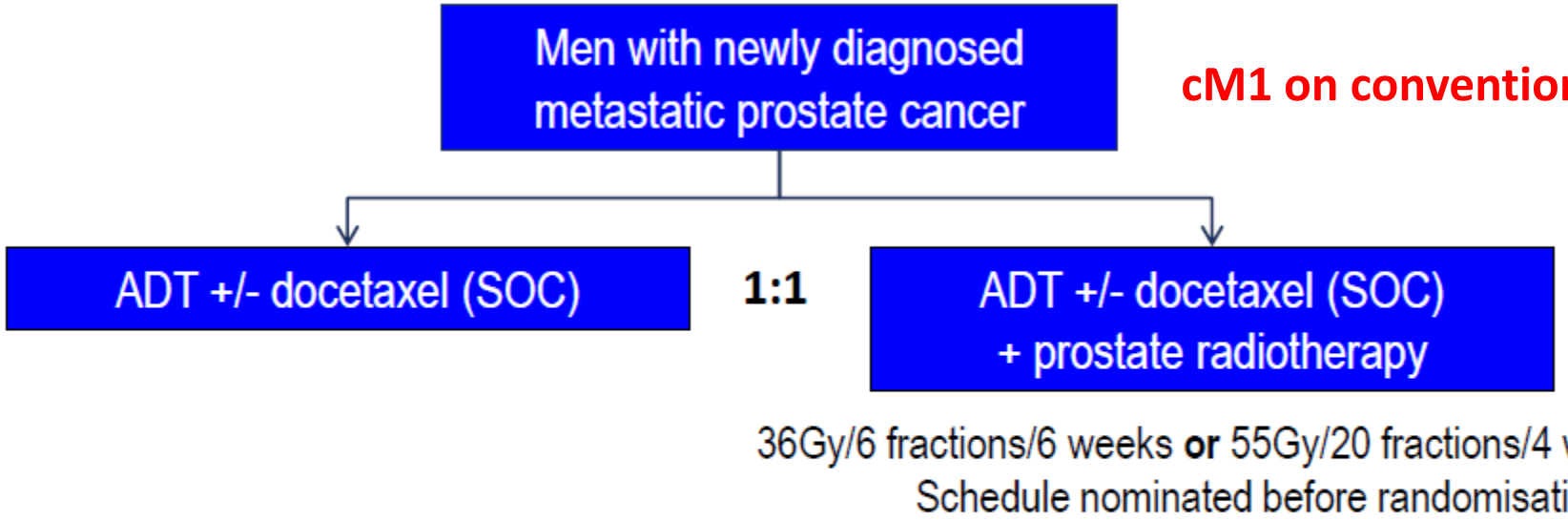


Consensus

Option	Votes
Option 1	0
Option 2	12
Option 3	7
Option 4	85
Abstain	2

NO ARPI added to ADT was included
In the RT to the prostate trials

STAMPEDE: SOC ± RT to the primary



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

Pre-specified subgroup analyses (low *vs* high burden / RT schedule)

Parker CC *et al.* Lancet 2018 and PLOS Medicine 2022

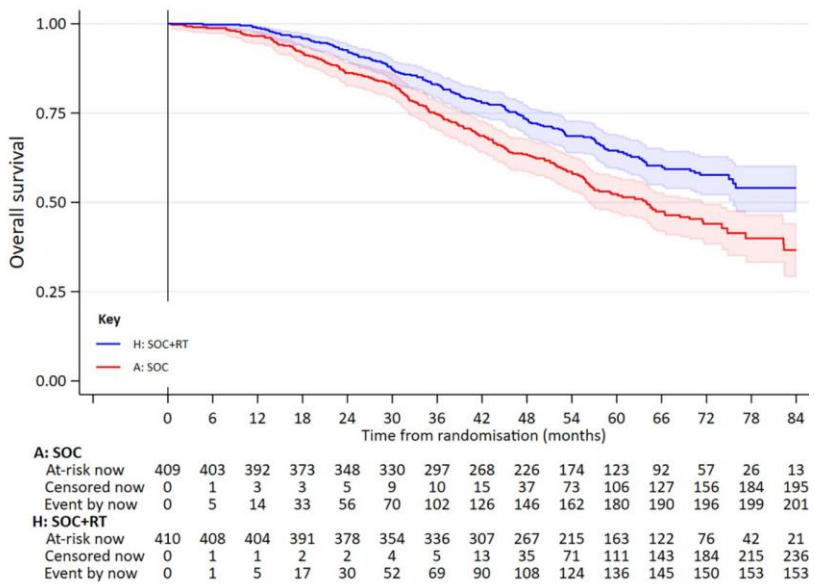
adapted from Zilli, T

STAMPEDE: SOC ± RT to the primary

Low burden

<4 Bone metastasis
AND
No visceral metastasis

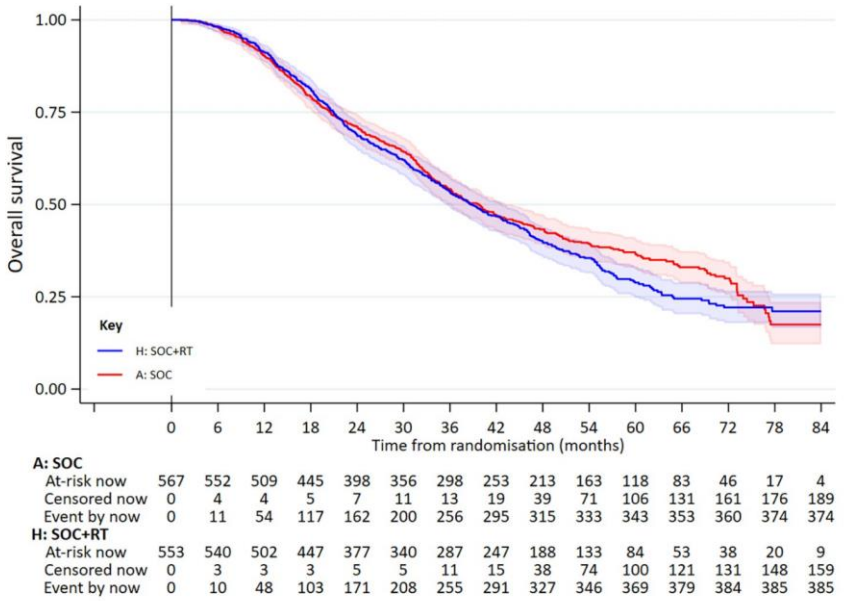
Low burden



	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
A: SOC															
At-risk now	409	403	392	373	348	330	297	268	226	174	123	92	57	26	13
Censored now	0	1	3	3	5	9	10	15	37	73	106	127	156	184	195
Event by now	0	5	14	33	56	70	102	126	146	162	180	190	196	199	201
H: SOC+RT															
At-risk now	410	408	404	391	378	354	336	307	267	215	163	122	76	42	21
Censored now	0	1	1	2	2	4	5	13	35	71	111	143	184	215	236
Event by now	0	1	5	17	30	52	69	90	108	124	136	145	150	153	153

HR: 0.64 (95% CI 0.52-0.79), p <0.001
5-yr OS (%): SOC= 53%
SOC +RT= 65%

High burden



	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
A: SOC															
At-risk now	567	552	509	445	398	356	298	253	213	163	118	83	46	17	4
Censored now	0	4	4	5	7	11	13	19	39	71	106	131	161	176	189
Event by now	0	11	54	117	162	200	256	295	315	333	343	353	360	374	374
H: SOC+RT															
At-risk now	553	540	502	447	377	340	287	247	188	133	84	53	38	20	9
Censored now	0	3	3	3	5	5	11	15	38	74	100	121	131	148	159
Event by now	0	10	48	103	171	208	255	291	327	346	369	379	384	385	385

HR: 1.11 (95% CI 0.96-1.28), p=0.164
5y-r OS (%): SOC= 35%
SOC + RT= 30%

High burden

≥4 Bone metastasis
(≥1 outside vertebral column or spine)
OR
Visceral metastasis

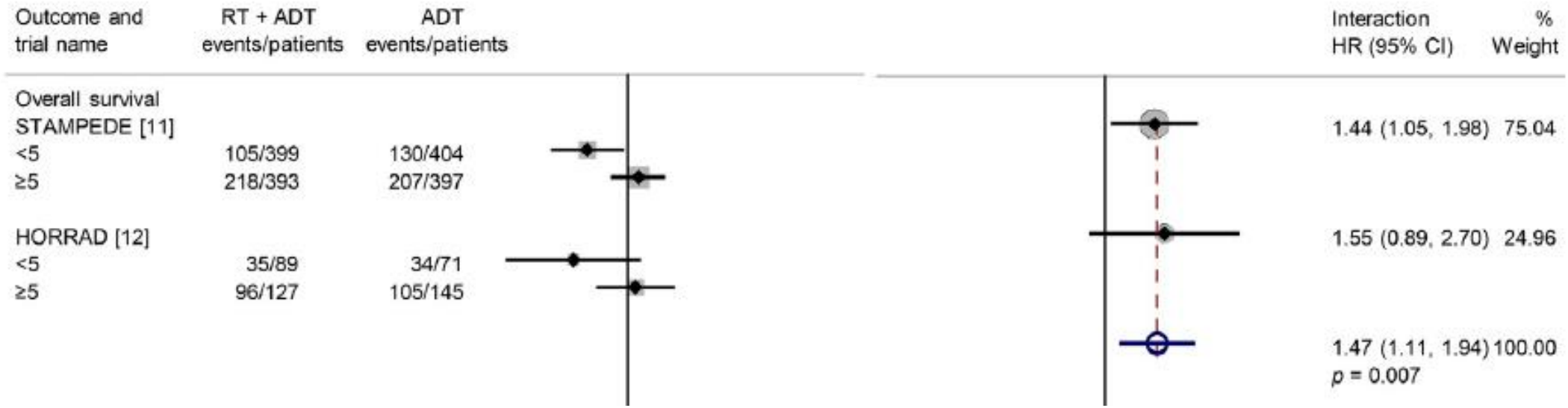
Parker CC *et al.* Lancet 2018 and PLOS Medicine 2022

adapted from Zilli, T

Should we treat the primary in mHSPC?

STOPCAP systematic review and meta-analysis

Effect of adding **prostate RT to ADT w/wt docetaxel** on survival *by the number of bone metastases (conventional imaging)*:



Lifelong ADT + prostate RT improves OS compared to ADT alone in patients with low-volume mHSPC (7% improvement in 3-yr survival)

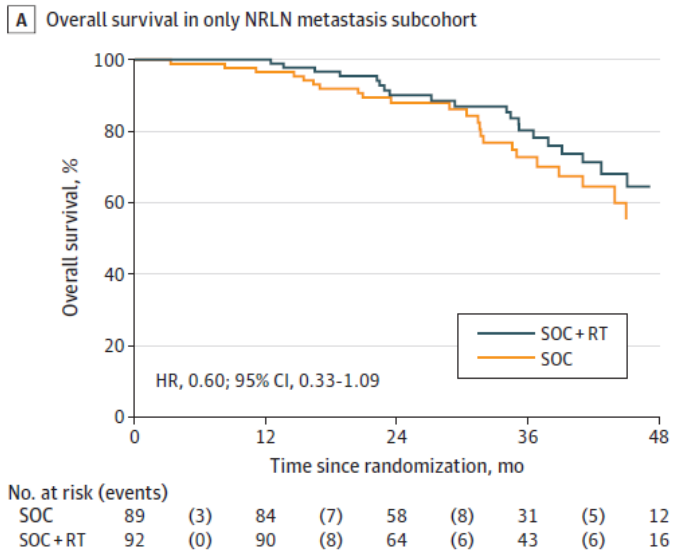
Burdett S *et al.* Eur Urol 2019

adapted from Zilli, T

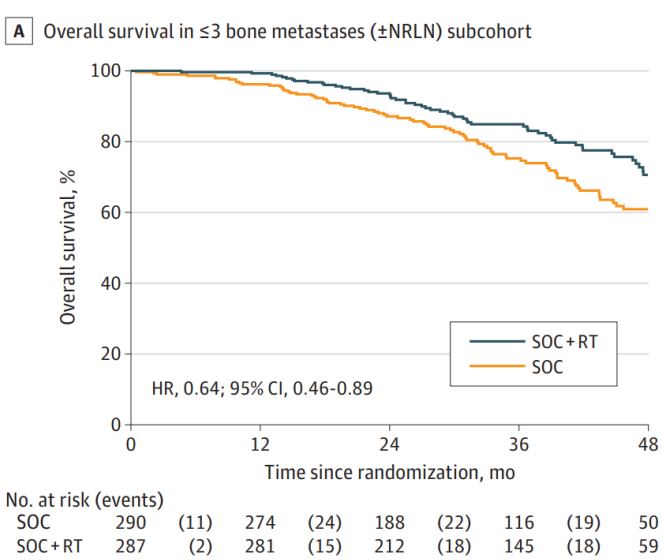
When should we offer the RT to the primary?

STAMPEDE: threshold effect of disease burden

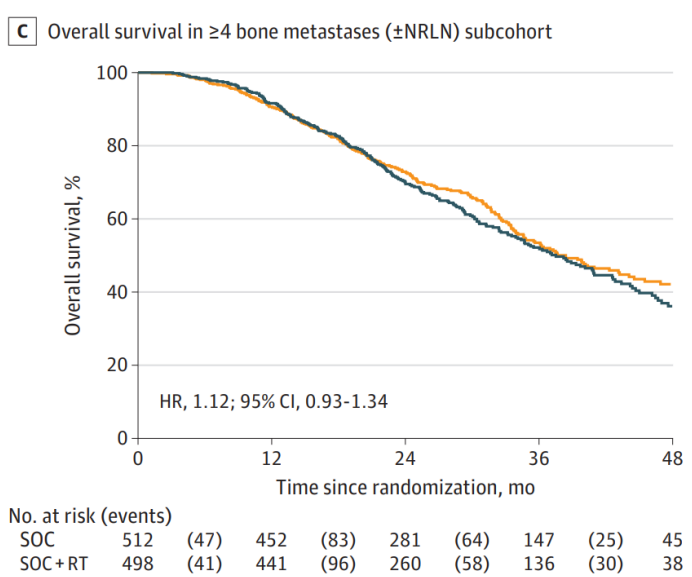
M1a disease



M1b disease ≤ 3 bone mets



M1b disease > 3 bone mets



OS benefit greater in patients with only non-regional lymph nodes (M1a) or ≤ 3 bone metastases without visceral metastasis (HR 0.62; 95% CI, 0.46 – 0.83)

Ali A et al. JAMA Oncol 2021

adapted from Zilli, T

STAMPEDE: toxicity and QoL impact

Table 4. Patients with grade 3/4 worst late RT toxicity score reported over entire time on trial.

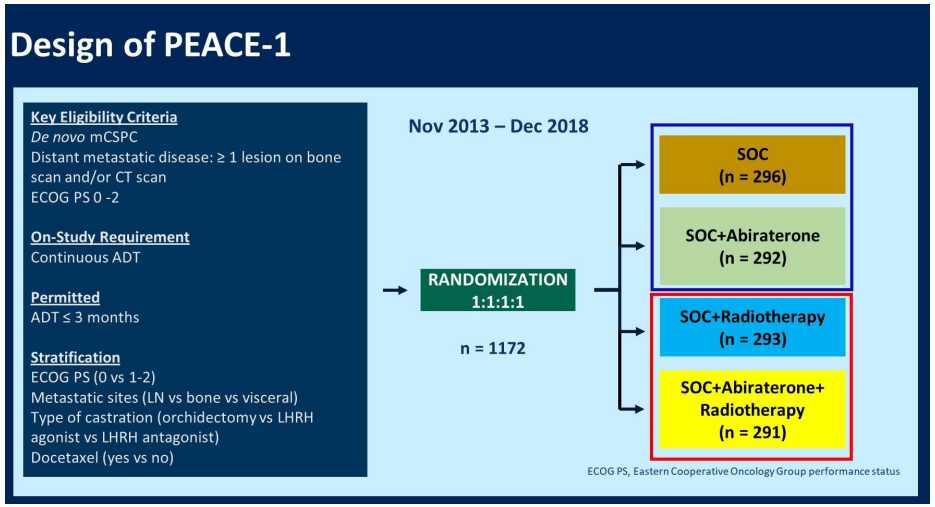
Toxicity area	SOC+RT	
	Weekly, 36 Gy/6 f (*n* = 473)	Daily, 55 Gy/20 f (*n* = 517)
Urinary	**10 (2%)**	**10 (2%)**
Hematuria	4 (1%)	4 (1%)
Urethral stricture	3 (1%)	4 (1%)
Cystitis	3 (1%)	4 (1%)
Bowel	**15 (3%)**	**11 (2%)**
Proctitis	9 (2%)	5 (1%)
Diarrhea	6 (1%)	6 (1%)
Rectal–anal stricture	0 (0%)	0 (0%)
Rectal ulcer	0 (0%)	1 (<1%)
Bowel obstruction	1 (<1%)	1 (<1%)

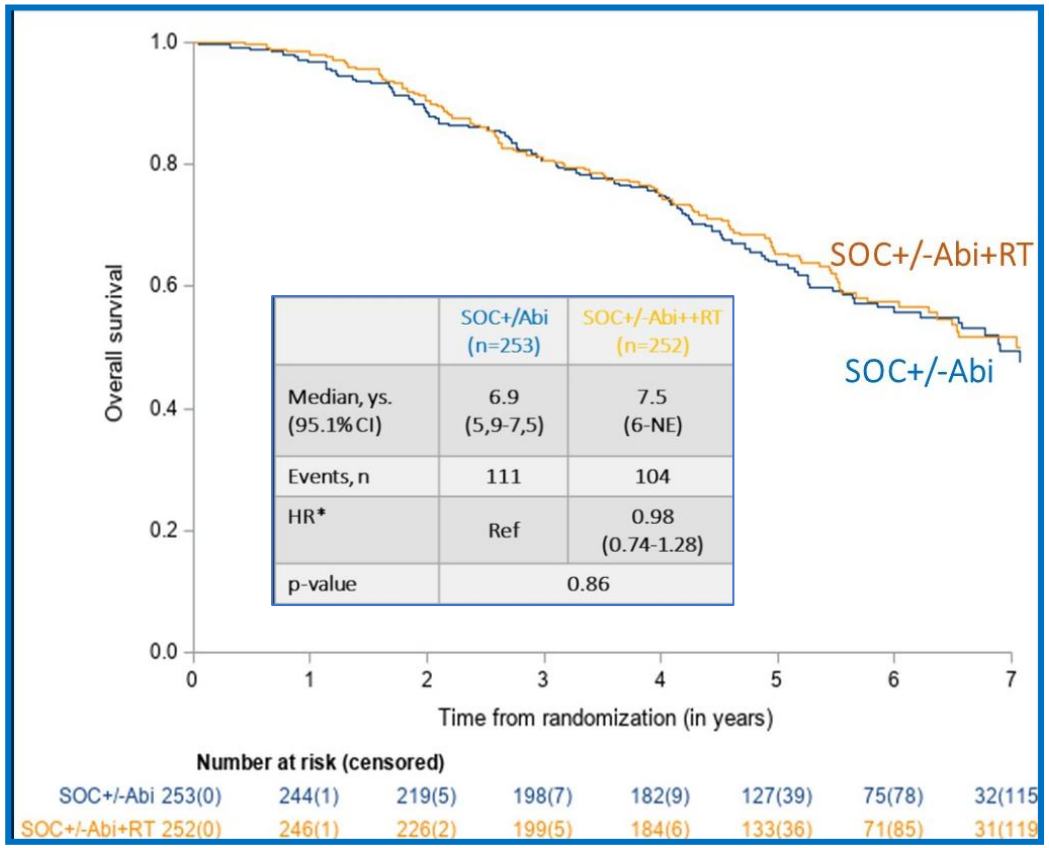
No difference in GU and GI toxicities and QoL scores between SOC vs SOC + RT
No interaction in treatment effect between 36 Gy/6 fx vs 55 Gy/20 fx (≤ 3% of Grade 3-4 toxicities)

Parker CC *et al.* PLOS Medicine 2022

adapted from Zilli, T

mHSPC: local RT and intensified systemic therapy



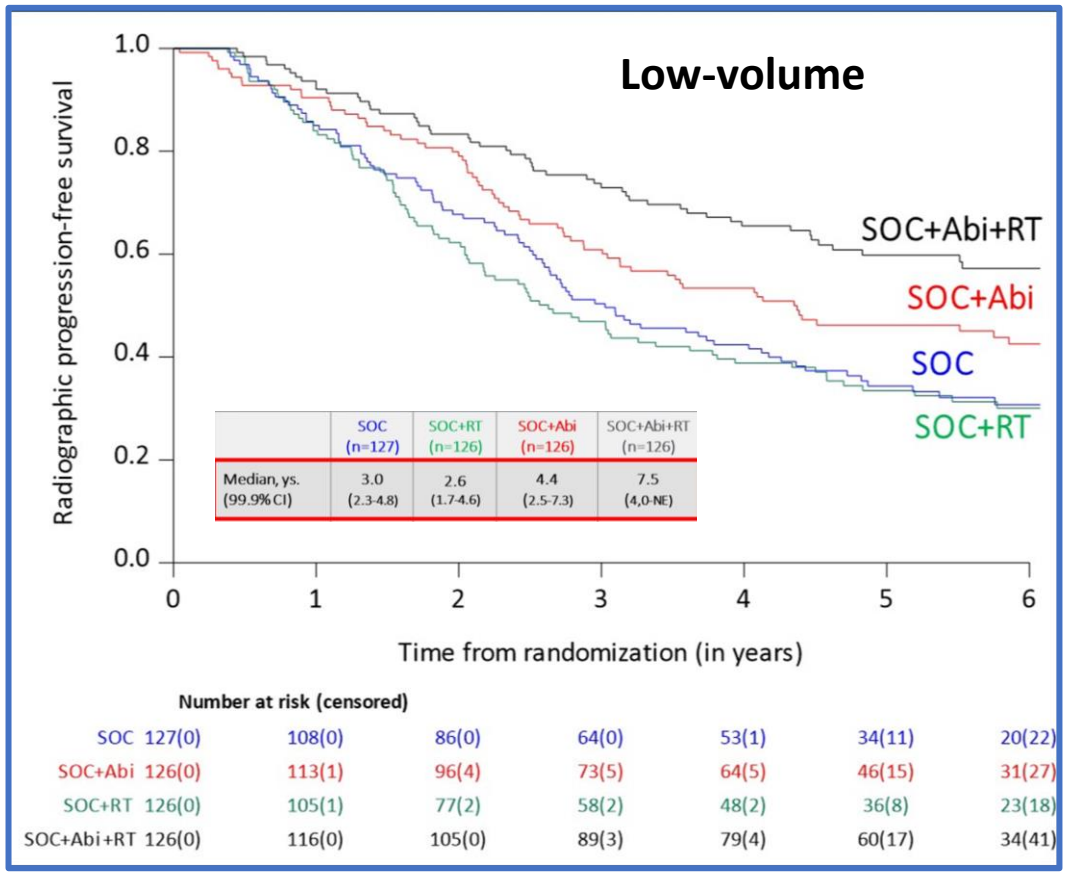


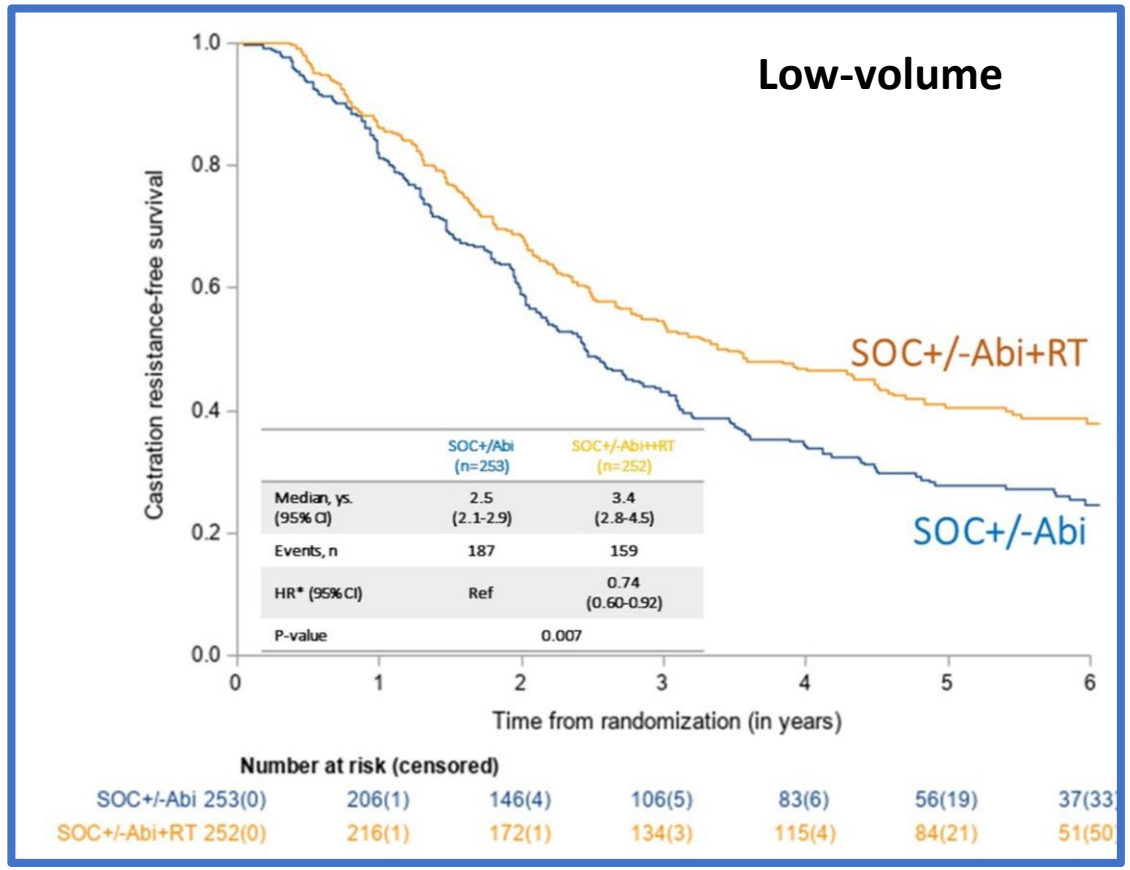
Local RT + intensified systemic therapy (Abiraterone ± docetaxel) does not improve OS in low-volume mHSPC

Bossi A *et al.* ASCO GU 2023

adapted from Zilli, T

mHSPC: local RT and intensified systemic therapy





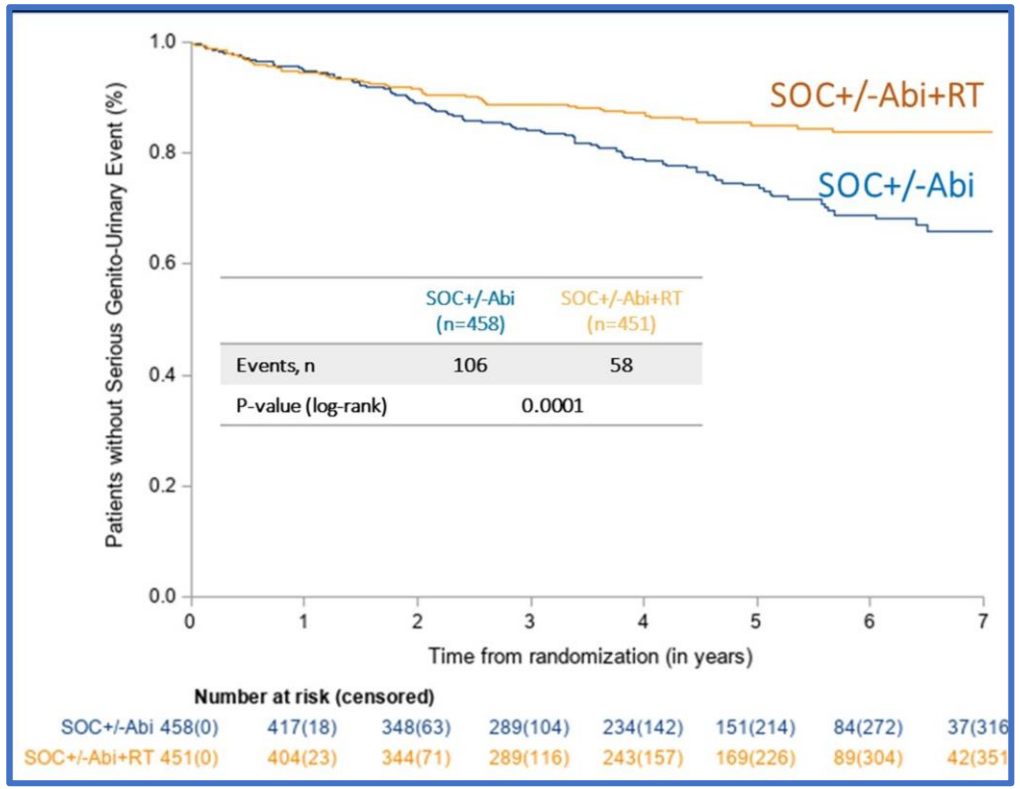
Local RT + intensified systemic therapy (Abiraterone ± docetaxel) improves rPFS and CRPC free-survival in low-volume mHSPC with minimal added toxicity

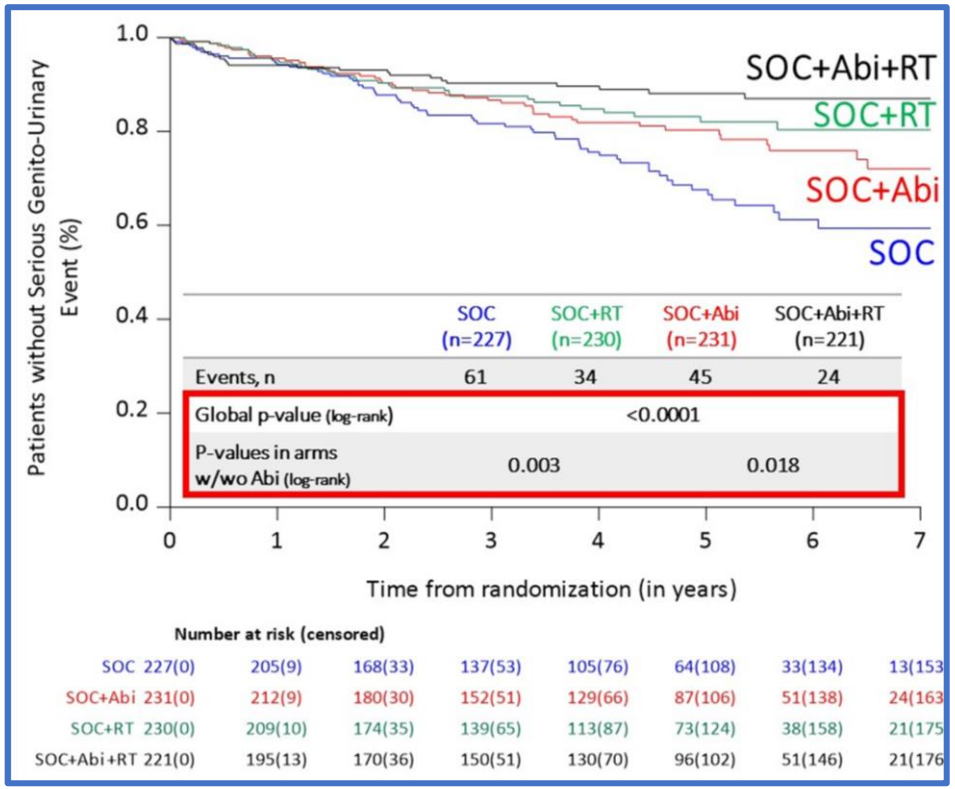
Bossi A *et al.* ASCO GU 2023

adapted from Zilli, T

mHSPC: local RT and intensified systemic therapy

Time to serious genito-urinary events (overall population)





Local RT prevents serious GU events, irrespectively of the disease burden (low vs high volume)

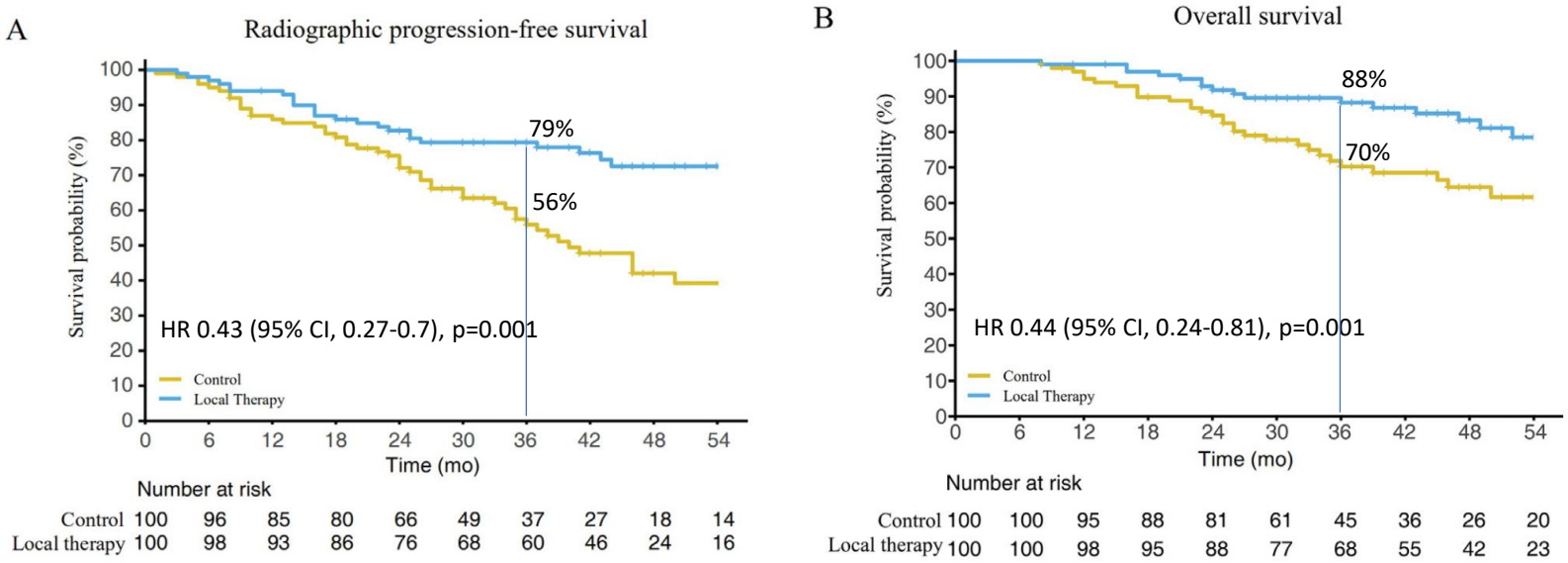
Bossi A *et al.* ASCO GU 2023

adapted from Zilli, T

Is there a role for cytoreductive prostatectomy?

Combination of Androgen Deprivation Therapy with Radical Local Therapy Versus Androgen Deprivation Therapy Alone for Newly Diagnosed Oligometastatic Prostate Cancer: A Phase II Randomized Controlled Trial

- Phase II RCT: ADT *vs* ADT + local treatment
- 200 pts with oligoM+ disease (≤ 5 lesions) on standard imaging
- Exp arm: 85 pts radical prostatectomy
  11 pts EBRT
- Primary endpoint: rPFS
- Secondary endpoints: OS, bRFS



ADT + radical local treatment (mainly radical prostatectomy) improves rPFS and OS in oligometastatic PCa patients compared to ADT alone (with 28% of perioperative complications and no Clavien IVb events)

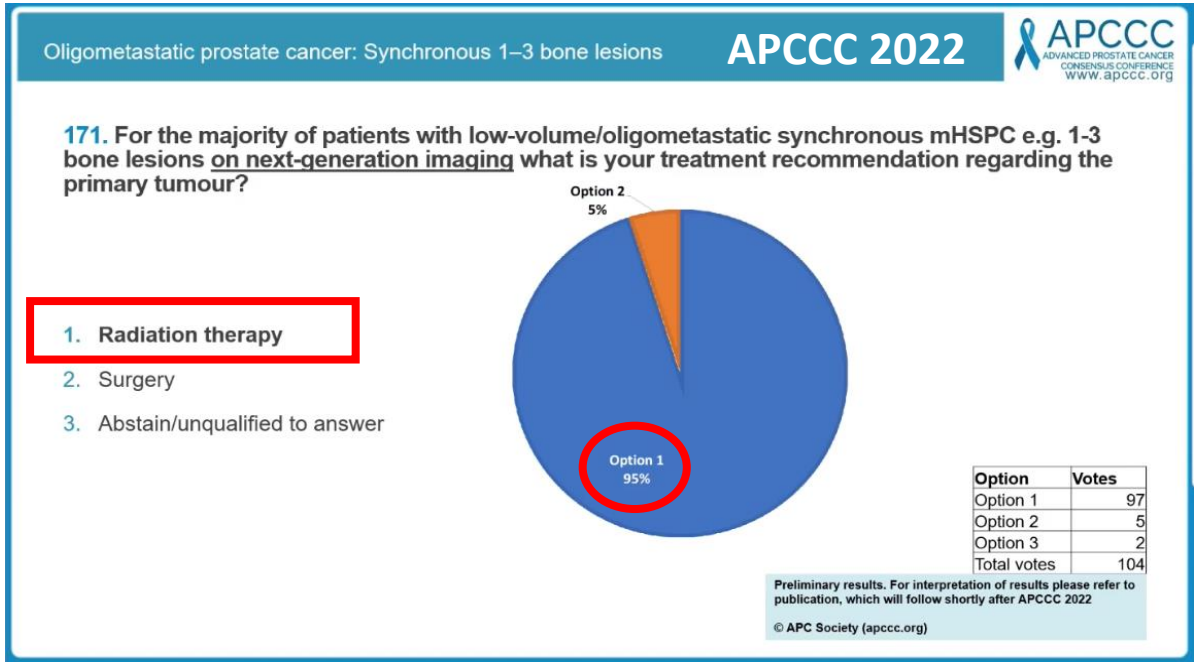
Dai Bo *et al.* Eur Urol Oncol 2022

cM1: cytoreductive prostatectomy

Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong

EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on

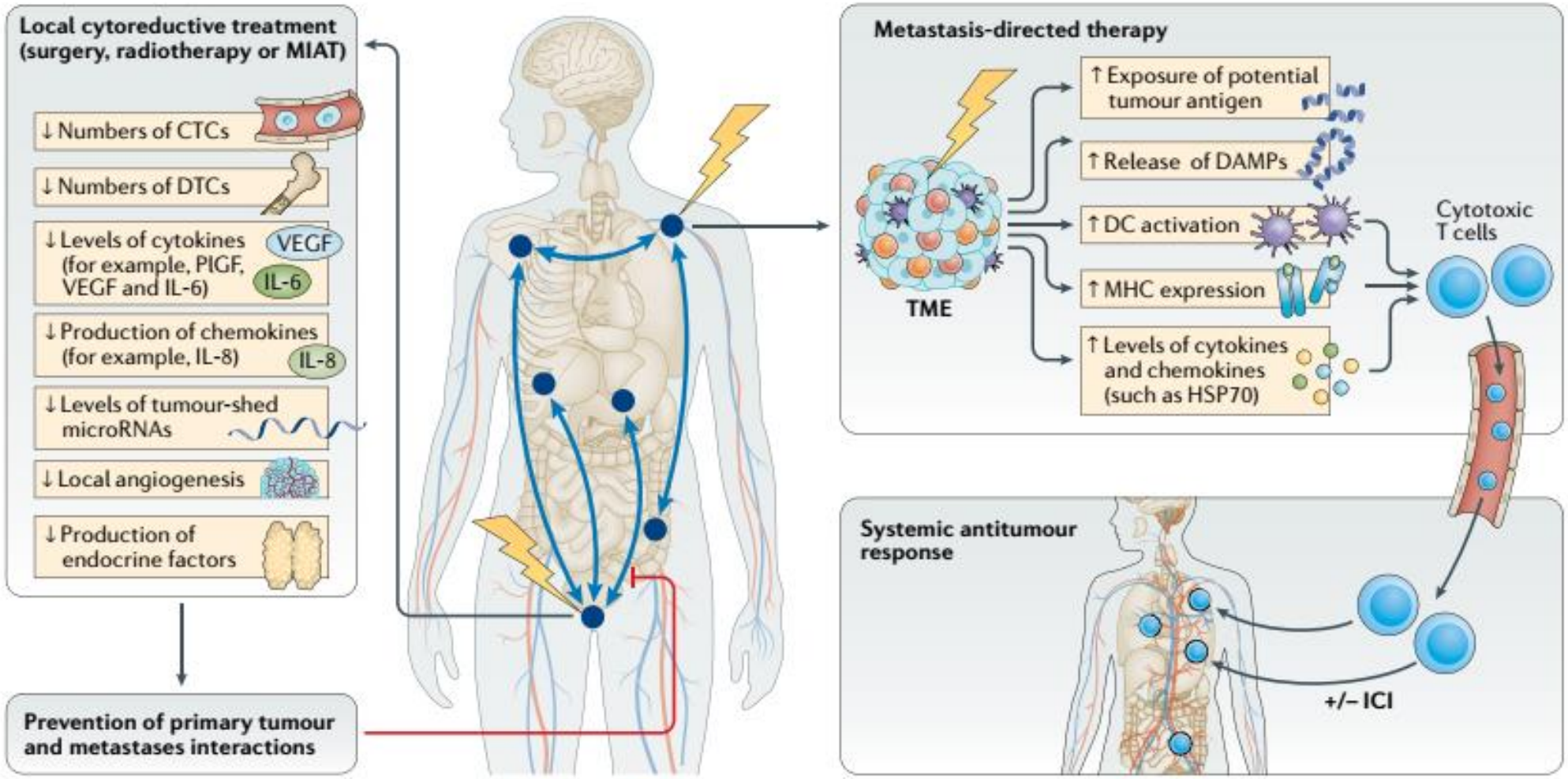
Prostate Cancer



Ongoing clinical trials of best systemic therapy ± definitive primary treatment (RP vs RT) (SWOG/NRG 1802 and MDACC Phase II NCT01751438) will probably help to define the best local strategy

adapted from Zilli, T

Is there a rationale to treat all metastatic sites?

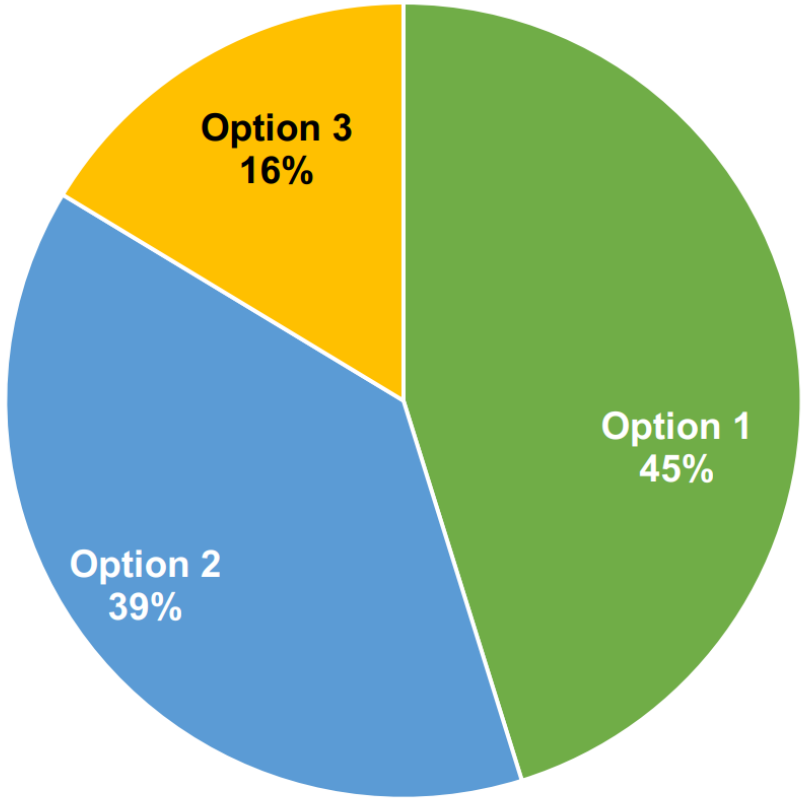


Connor MJ *et al.* Nat Rev Clin Oncol 2020

adapted from Zilli, T

77. In patients with synchronous low-burden mHSPC on next-generation imaging and negative on conventional imaging, do you recommend additional metastases directed therapy (if technically feasible) of all lesions?

1. Yes, in the majority of patients
2. Yes, but only in selected patients
3. No
4. Abstain/unqualified to answer



Option	Votes
Option 1	47
Option 2	40
Option 3	17
Abstain	2

Comprehensive RT: non-randomized evidence

MSKCC

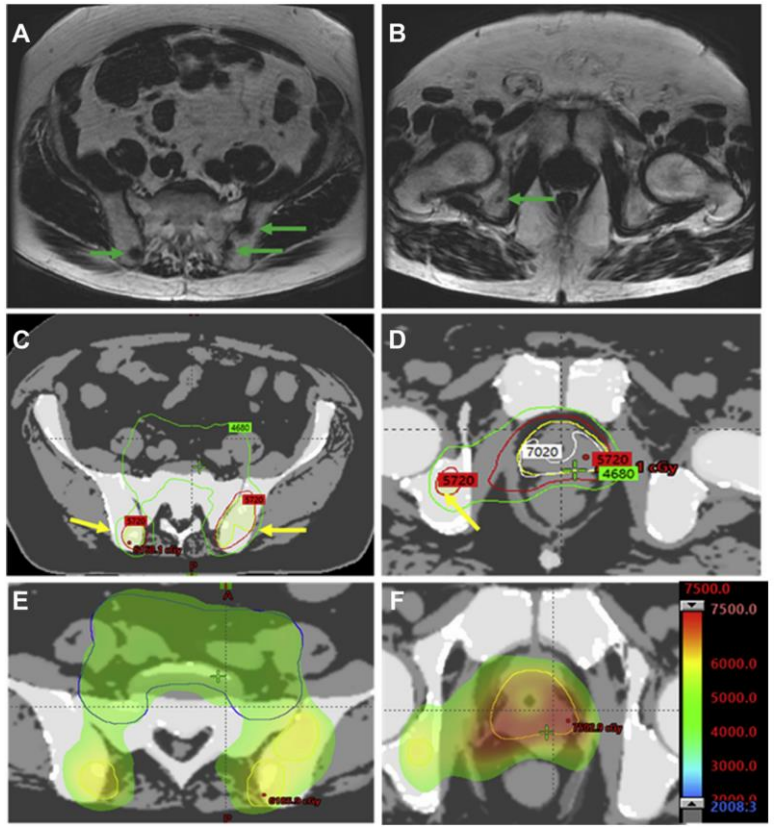
- N=47 men with de novo oligomets PCa
- Treatment including local RT, ADT and MDT to all M+ sites (up to 6)
- ***70% of patients achieved undetectable PSA after testosterone recovery***

John Hopkins

- N=12 men with de novo oligomets PCa (≤ 5 lesions)
- Treatment including local RT, chemo + ADT and SBRT to all M+ sites
- ***67% of patients achieving undetectable PSA after testosterone recovery at 3-yr***

San Raffaele

- N=39 men with de novo oligomets PCa (≤ 2 lesions)
- Treatment including local RT, ADT + SBRT to all M+ sites
- ***4-yr: 47% recurrence, 27% with new M+, 35% with CRCP disease***



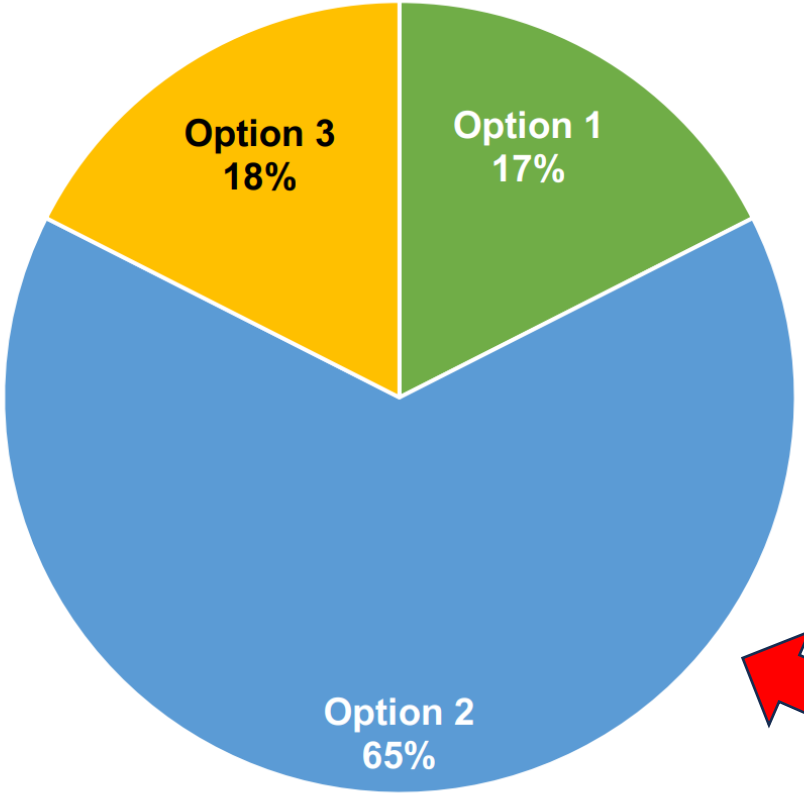
Loco-regional RT with SBRT to all PET+ metastatic sites is feasible with promising disease control rates

Imber *et al.* Advances Radiat Oncol 2020; Reyes *et al.* Med Oncol 2020; Deantoni *et al.* Br J Radiol 2020

adapted from Zilli, T

79. In patients with synchronous low-burden mHSPC on next-generation imaging and negative on conventional imaging and if you use metastases-directed therapy what is your recommendation regarding the duration of systemic therapy?

1. Continuous lifelong treatment of ADT ± ARPI
2. Continuous treatment of ADT ± ARPI for 2-3 years
3. Intermittent (e.g., interrupt after 6-12 months if PSA <0.2 ng/mL)
4. Abstain/unqualified to answer (including I did not vote for metastases-directed therapy or I do not use systemic therapy in this situation)



Option	Votes
Option 1	17
Option 2	63
Option 3	17
Abstain	9

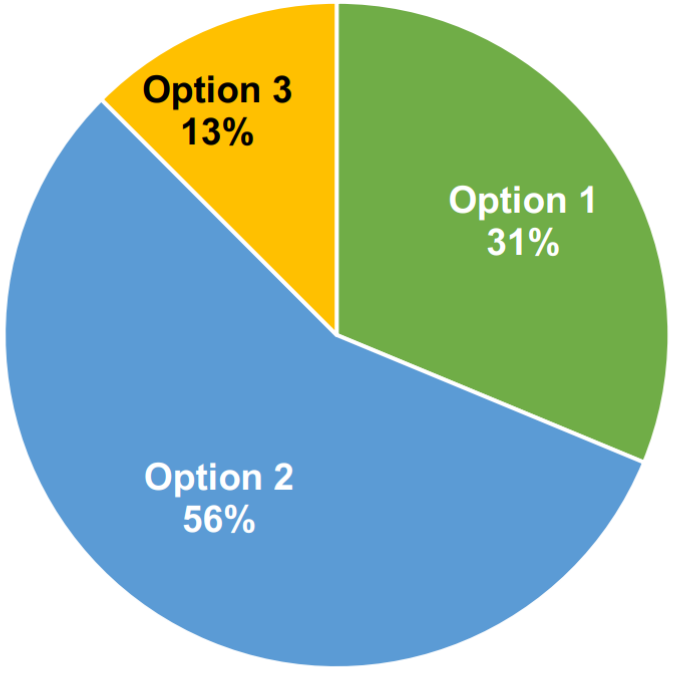
Experts vote for **De-escalation (duration)**

SOC would be until progression or toxicity

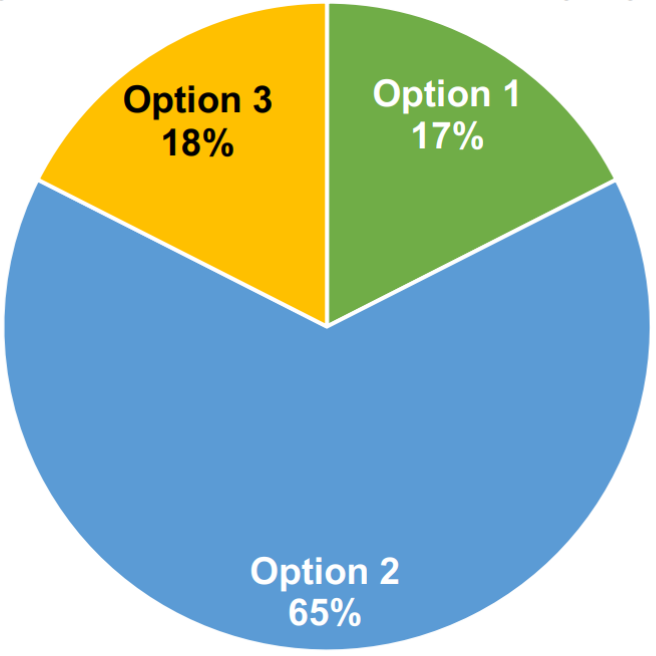
78.+ 79. In patients with synchronous low-burden mHSPC and if you use metastases-directed therapy what is your recommendation regarding the duration of systemic therapy?

1. Continuous lifelong treatment of ADT ± ARPI
2. Continuous treatment of ADT ± ARPI for 2-3 years
3. Intermittent (e.g., interrupt after 6-12 months if PSA <0.2 ng/mL)
4. Abstain/unqualified to answer (including I did not vote for metastases-directed therapy or I do not use systemic therapy in this situation)

Conventional imaging low burden



Next-generation imaging low burden, negative on conventional imaging



78 + 79

Comprehensive RT: prospective evidence

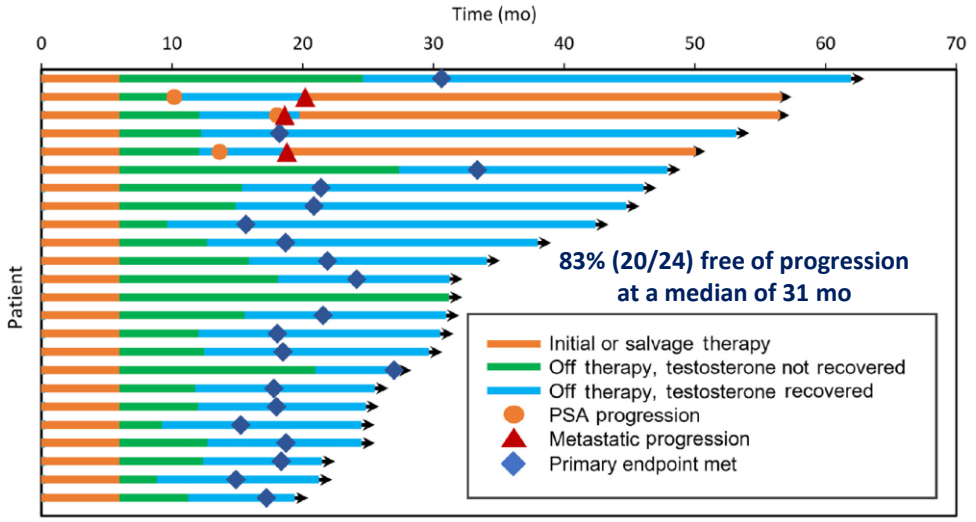
Systemic and Tumor-directed Therapy for Oligometastatic Prostate Cancer: The SOLAR Phase 2 Trial in De Novo Oligometastatic Prostate Cancer

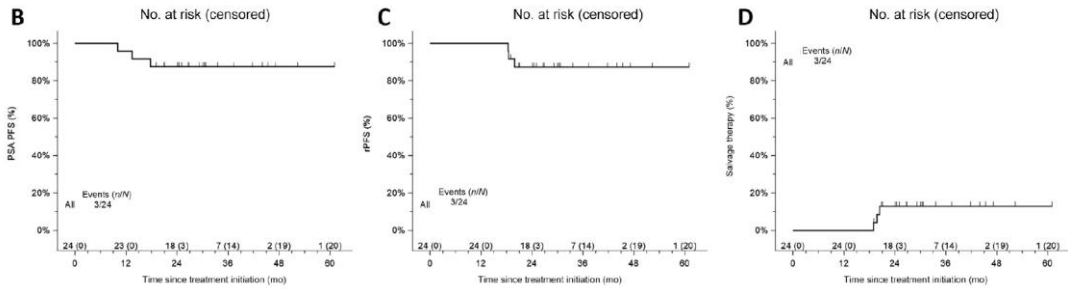
- **Prospective**: 28 de-novo mHSPC patients (2018-2022)

- PSMA PET (89%); Fluciclovine (3.5%), NaF (7%)
- M1a: 29%; M1b: 71%
- N0: 36%; N1: 64%
- ISUP GG 4-5: 61%
- Number of mets: 1 - 42%; 2 - 21%; 3-5: 38%

- **Treatment**: ADT + Abi + Apa **for 6 mo** + RP with LND or RT with WPRT + MDT to all metastatic sites

- **Primary endpoint**: testosterone recovery and controlled PSA at 6 mo after recovery (PSA <0.2 ng/ml after RP ad <2 ng/ml after RT)



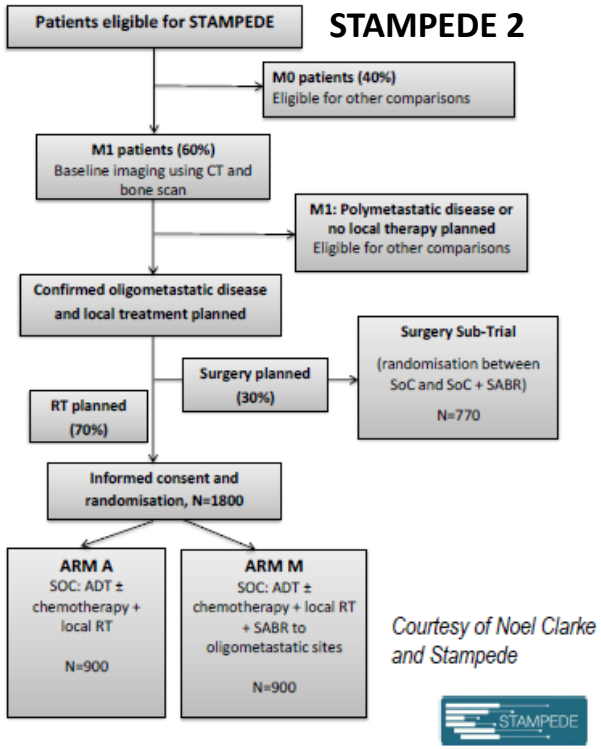


Loco-regional treatment with SBRT to all PET+ metastatic sites + 6 months of intensified systemic therapy achieves lasting remission without ongoing castration in de-novo oligometastatic mHSPC

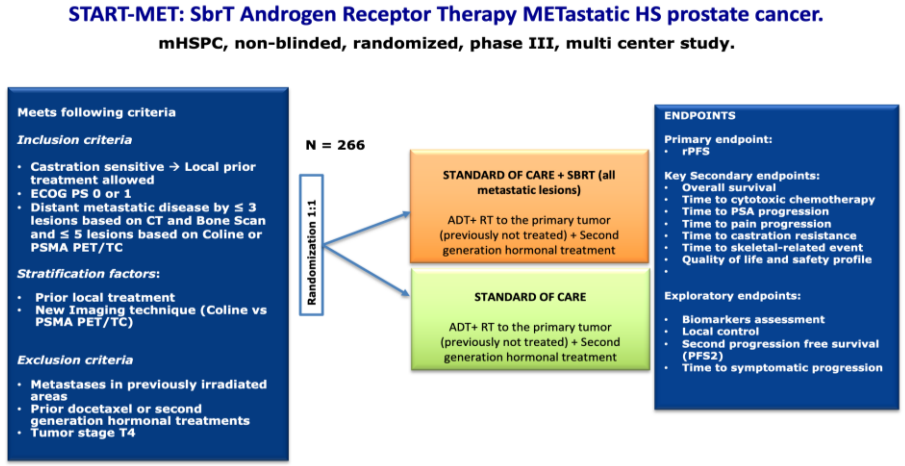
Nickols NG *et al.* Eur Urol 2024 in press

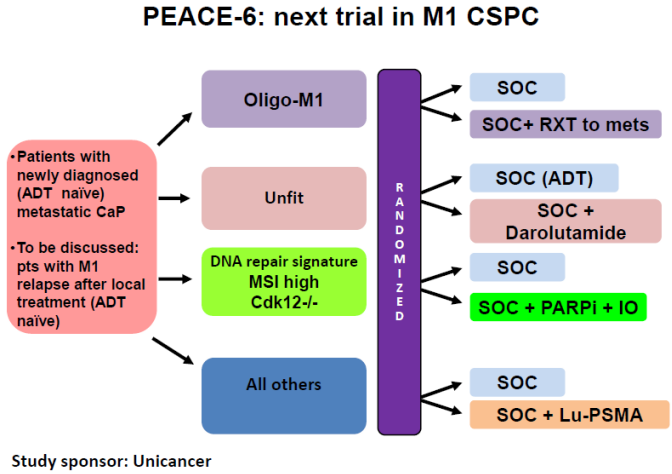
adapted from Zilli, T

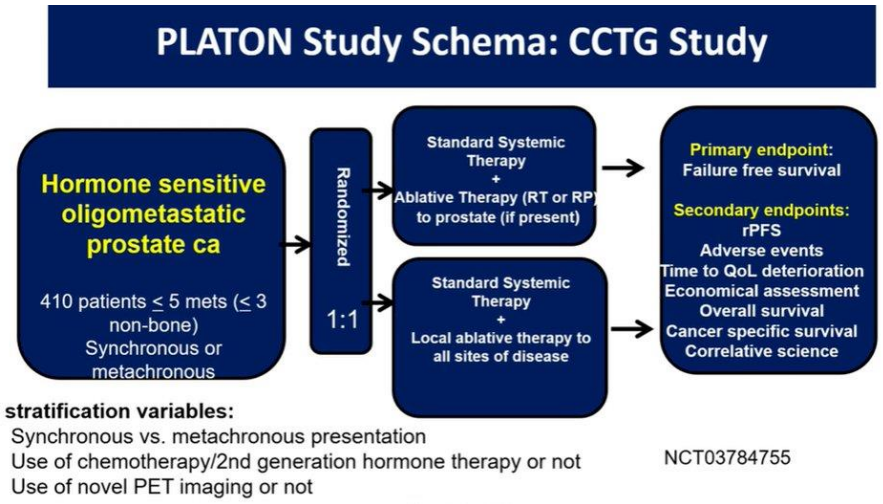
Comprehensive RT: randomized trials will shed light

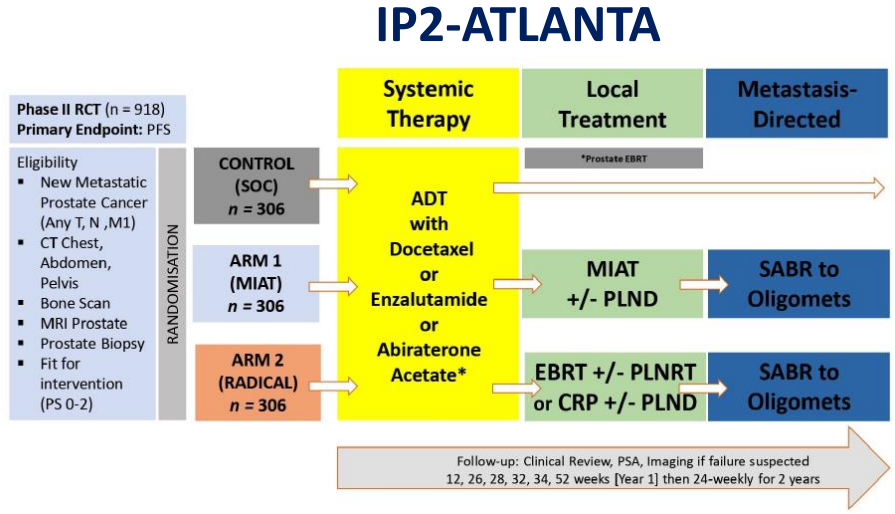


Courtesy of Noel Clarke and Stampede







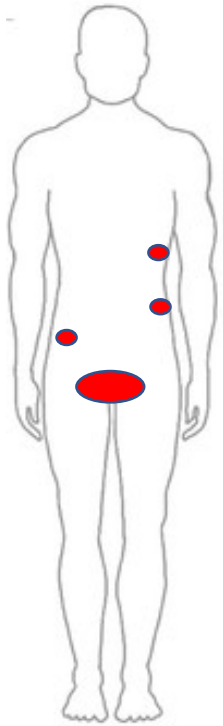


adapted from Zilli, T

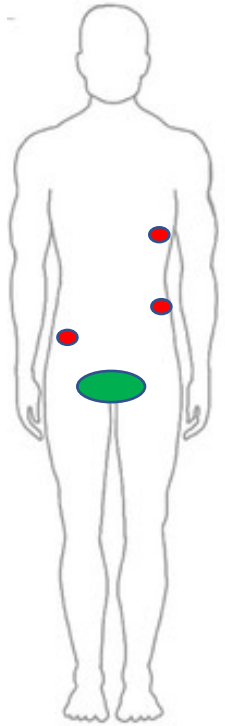
The oligometastatic PCa landscape

Uncontrolled lesion

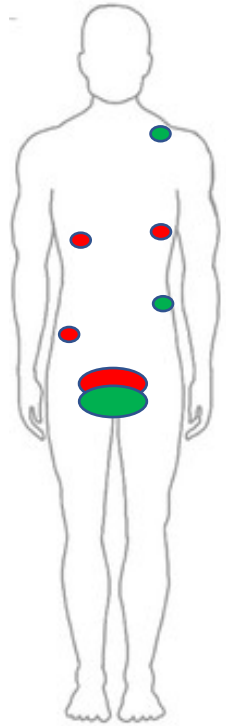
Controlled lesion



***De novo* oligometastases mHSPC (synchronous oligoM)**



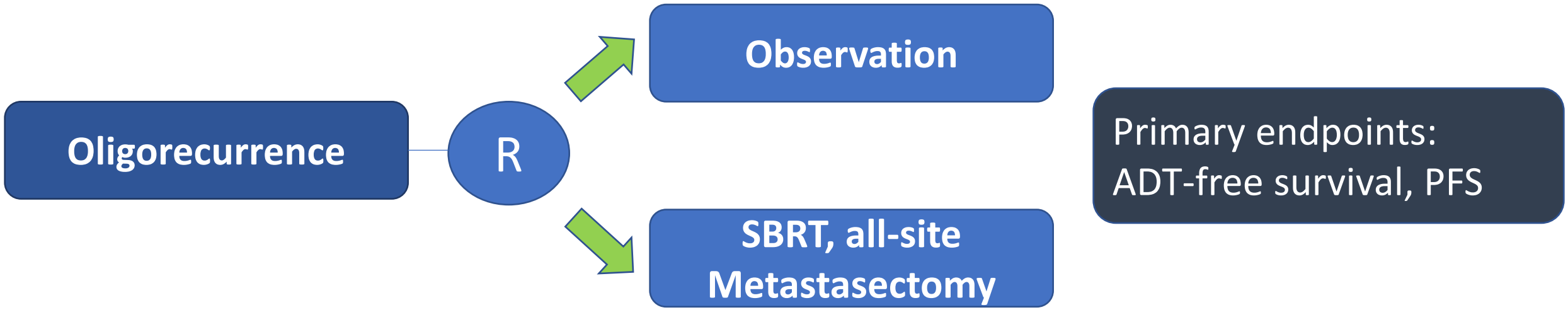
Oligorecurrent mHSPC (metachronous oligoM)



Oligometastatic CRPC (≤ 5 mets)
Oligoprogressive (induced oligoM)

Metastasic directed therapy (MDT) as a form of **de-escalation**
→ delay of ADT +/- ARPI start (SOC) ?

Prospective data on MDT

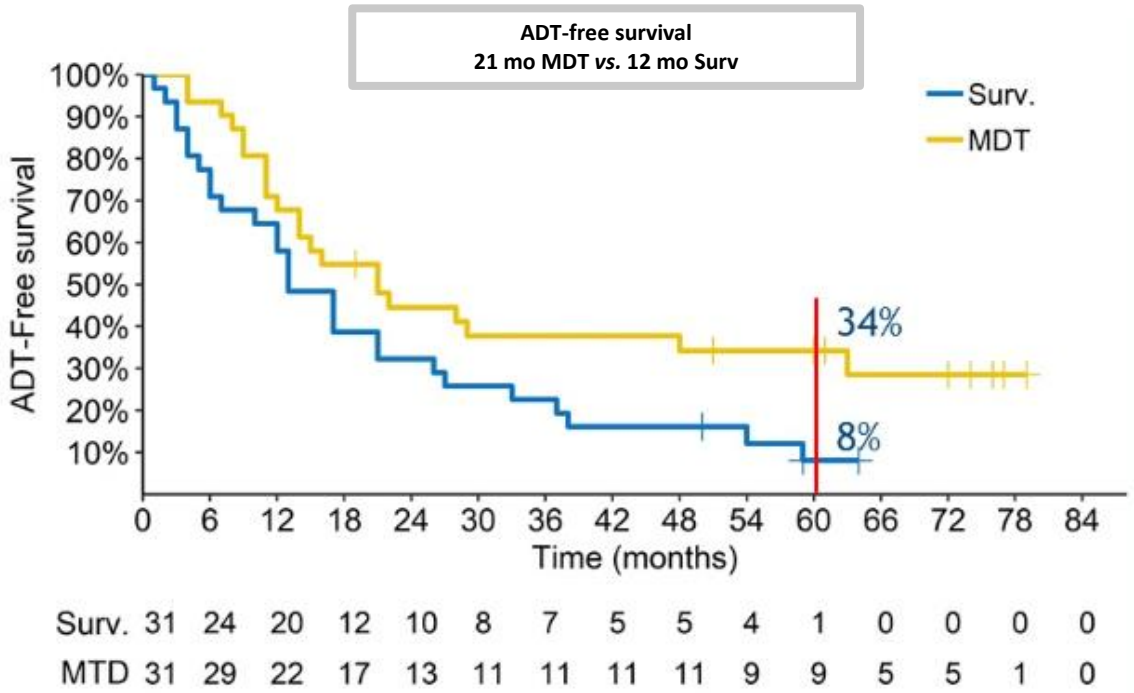


- **Two prospective, randomized, phase II trials (STOMP and ORIOLE) + SABR-COMET**
- **Four prospective single-arm trials (POPSTAR, PSMA MgRT, TRANSFORM, OLI-P)**

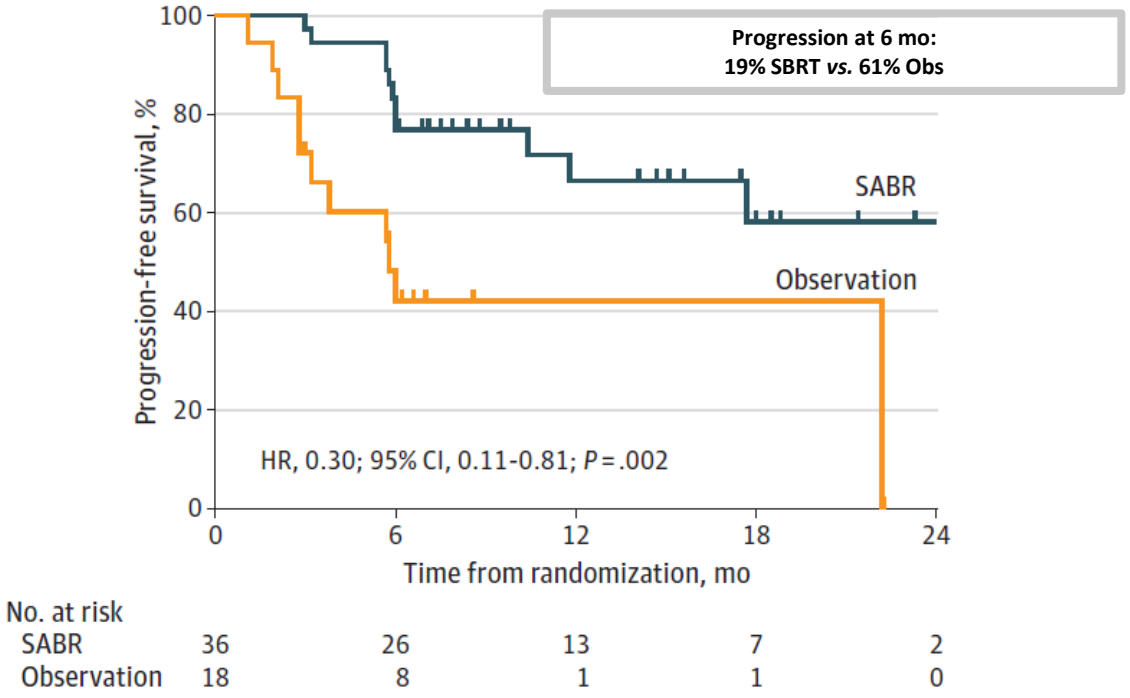
adapted from Zilli, T

Oligorecurrent PCa: observation *vs* MDT

STOMP trial (n=62)



ORIOLE trial (n=54)

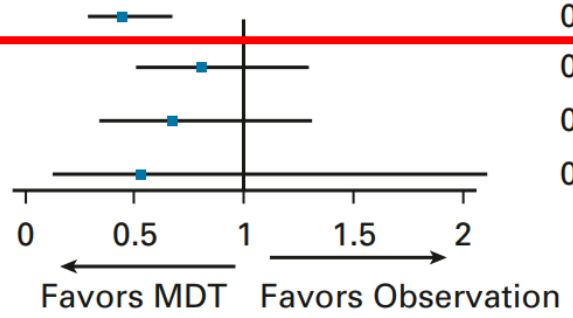


Ost *et al.* JCO 2018 – ASCO GU 2020; Philips R *et al*. JAMA Oncol 2020

Oligorecurrent PCa: observation *vs* MDT

Long-term outcomes of MDT *vs* observation: STOMP and ORIOLE trials

Outcome	MDT Median Time to 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



Median FU: 52.5 mo

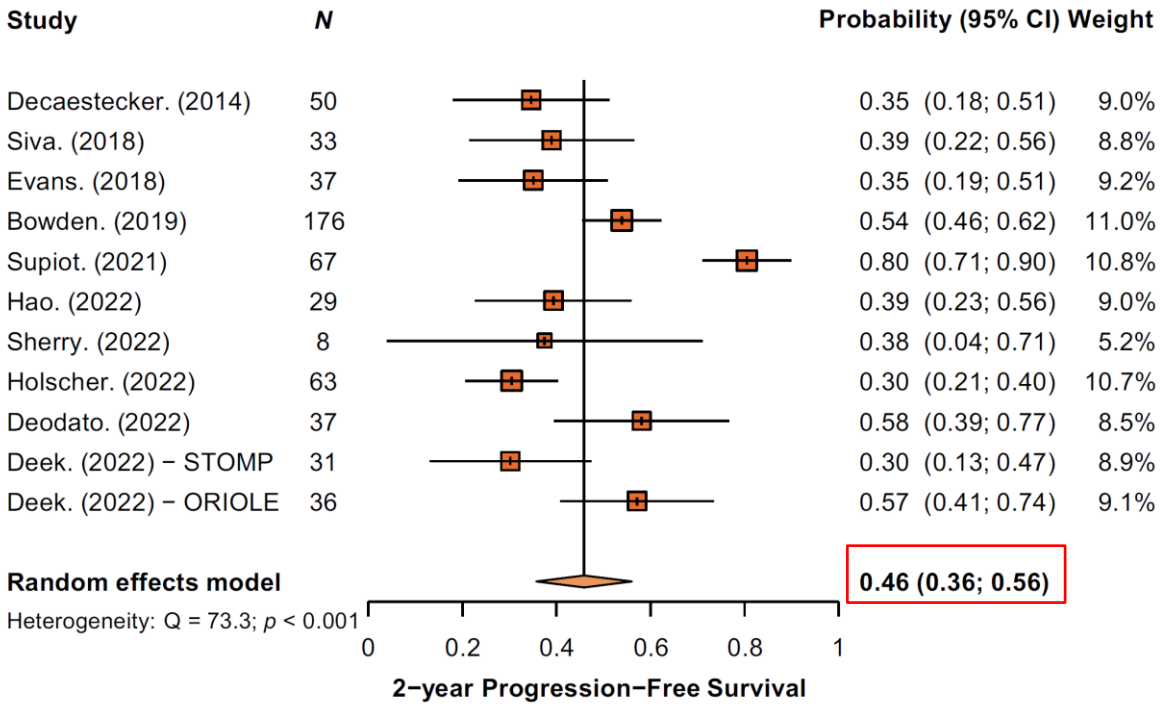
Sustained clinical benefit of MDT over observation in terms of PFS (but not for OS and time to CRPC)

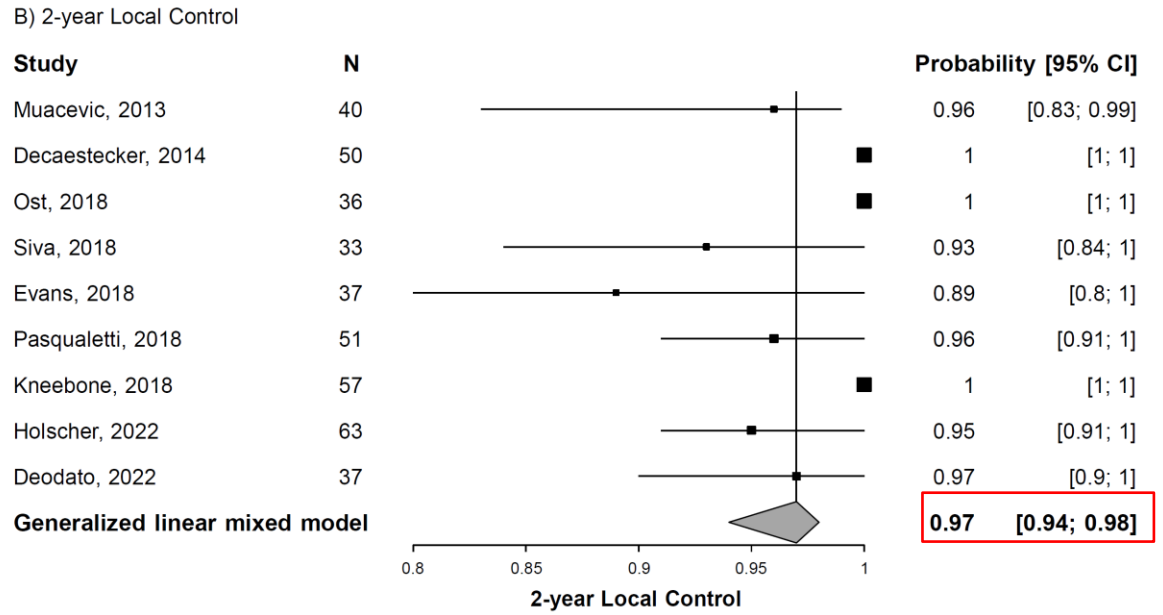
Deek *et al.* JCO 2022

adapted from Zilli, T

MDT can achieve durable disease control

Systematic review and meta-analysis: 22 prospective studies (2 RCT), 1137 patients





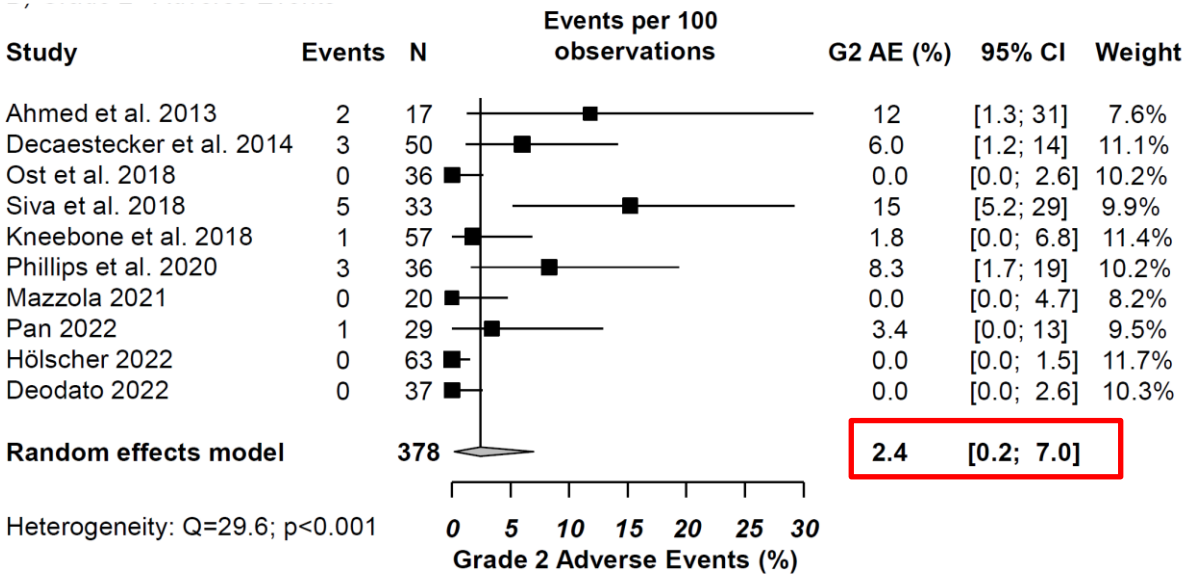
MDT is associated with promising PFS benefit and excellent local control rates

Miszczyk M *et al.* Eur Urol 2023

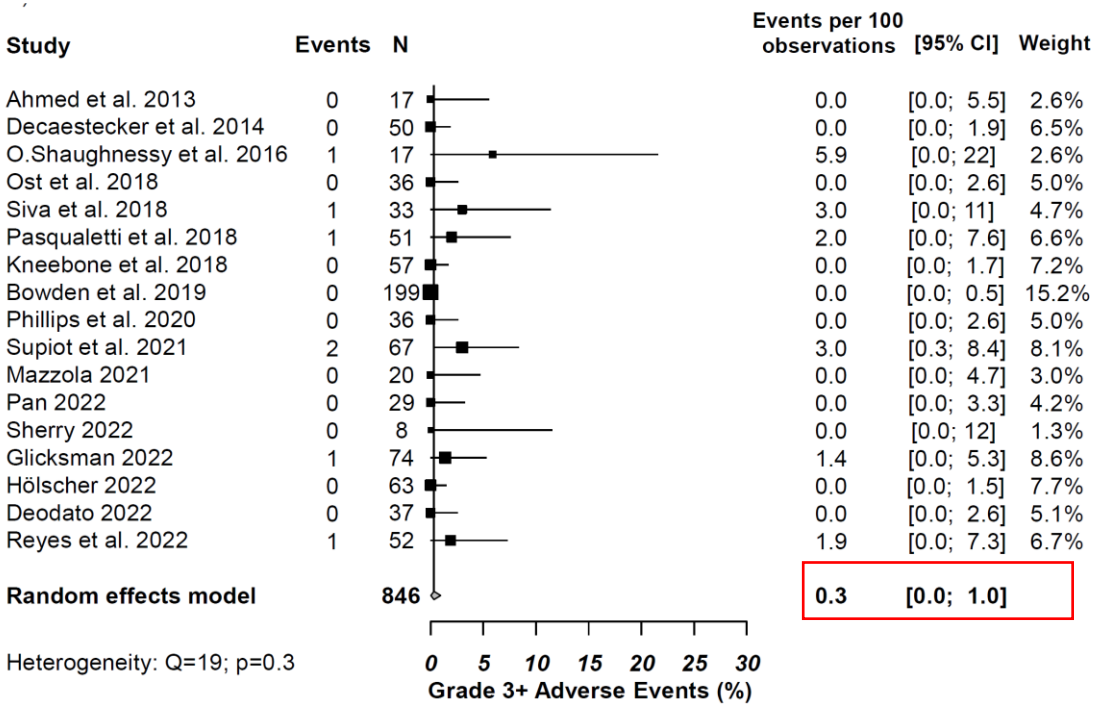
adapted from Zilli, T

MDT is not toxic

Grade 2 adverse events



Grade 3 adverse events



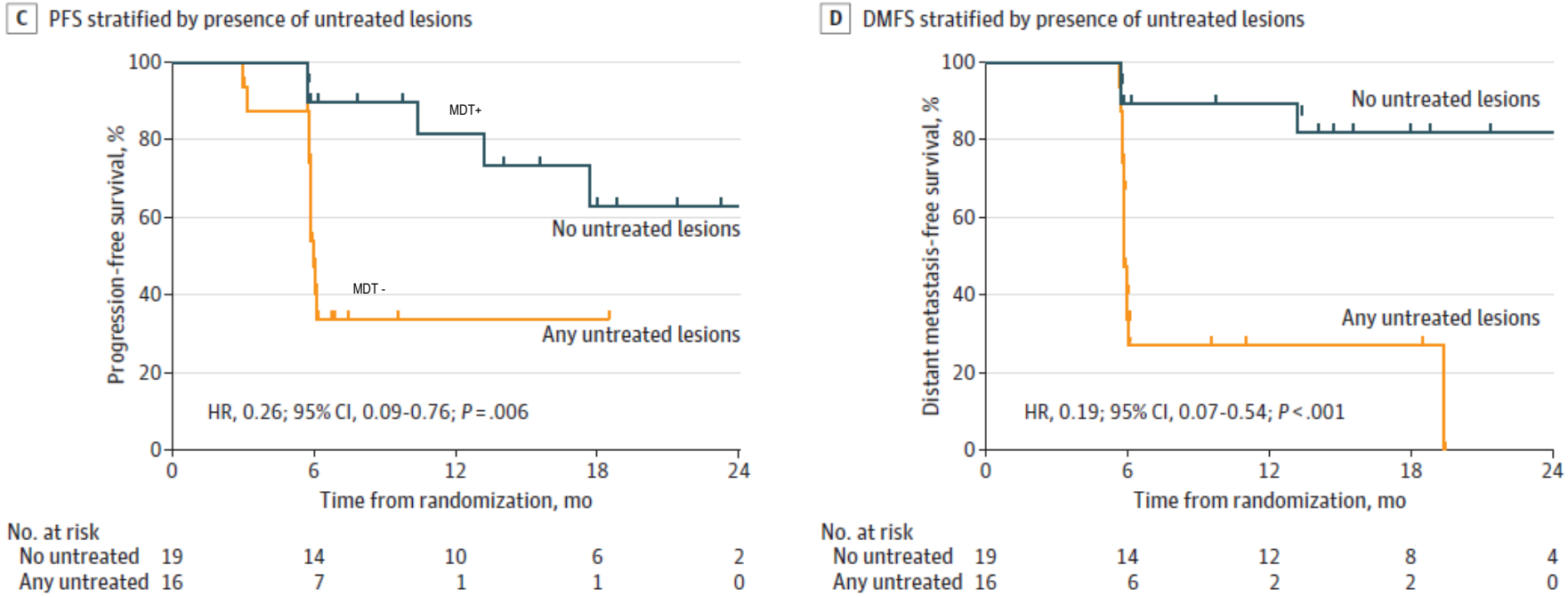
MDT is well tolerated with minimal G2+ toxicity (<3%)

Miszczyk M *et al.* Eur Urol 2023

adapted from Zilli, T

Total SBRT consolidation of PSMA+ lesions

ORIOLE trial



Patients with progression at 6mo: 5% with no untreated lesions vs 38% with any untreated lesions
Median DMFS: 29mo with no untreated lesions vs 6mo with any untreated lesions

Philips R *et al.* JAMA Oncol 2020

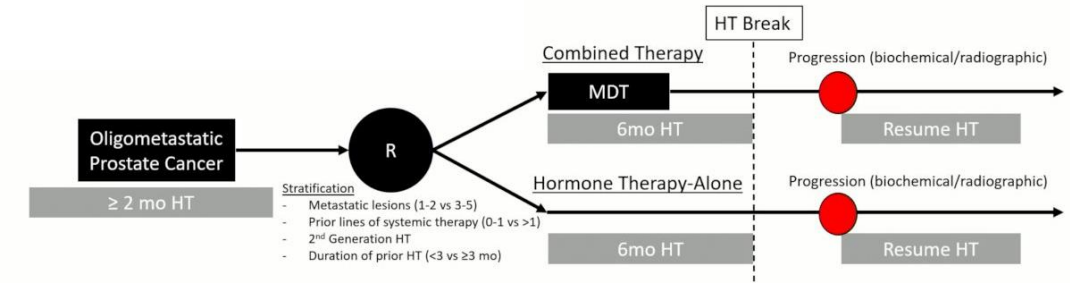
adapted from Zilli, T

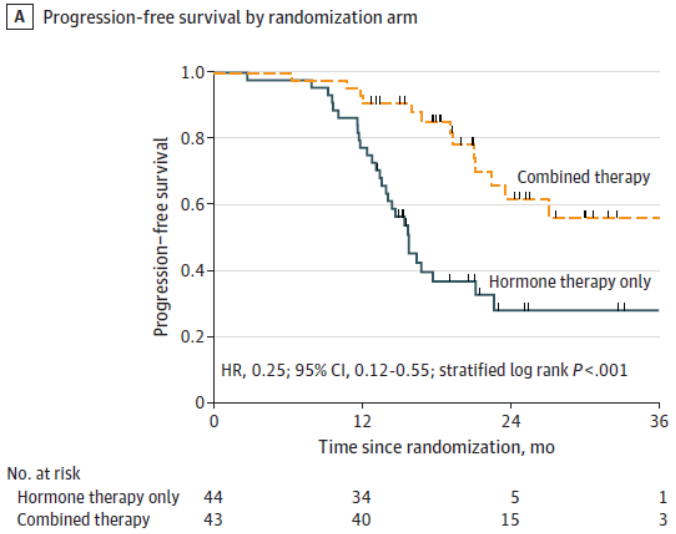
MDT can improve the outcome of systemic therapy

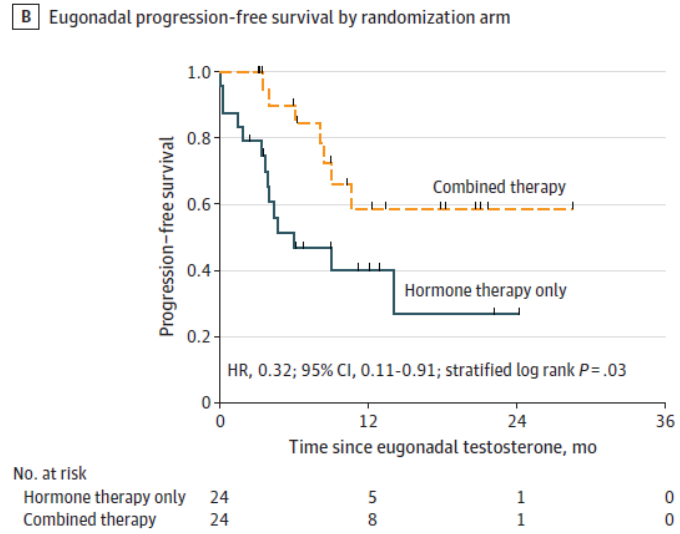
EXTEND trial

- Prospective, randomized Phase II, single center
- **87 oligorecurrent men, low-volume, mostly HSPC** (>90%)
- **≤ 5 metastases** (conv. imaging 75%; fluciclovine PET/CT 25%)

- Randomization 1:1: **intermittent HT** *vs* **HT + MDT** (~40% ARPI)
- Median FU: 22 mo





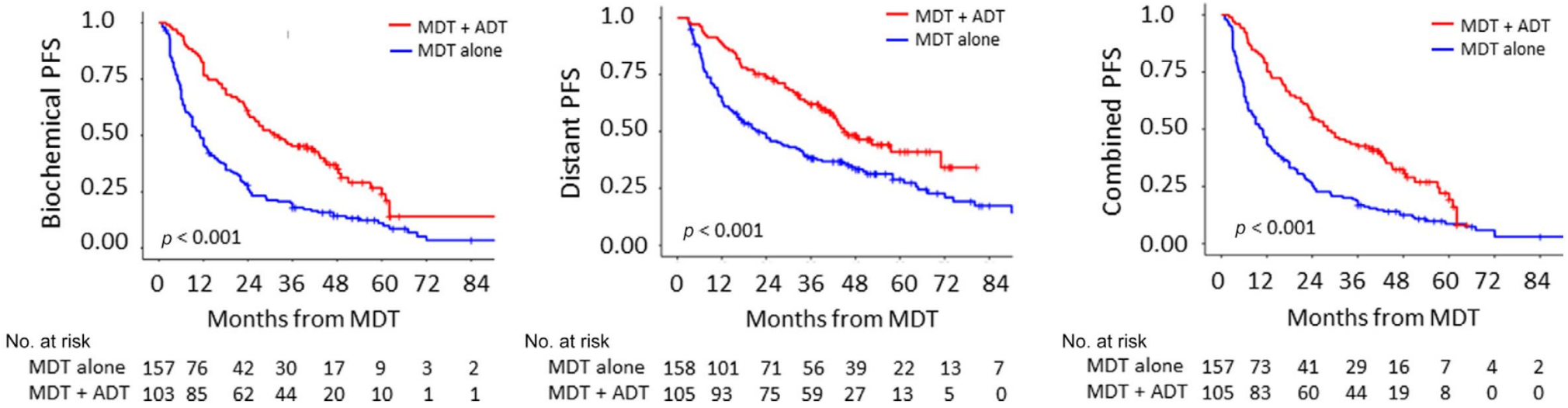


MDT + ADT ± ARPI as part of an intermittent regimen improves PFS and thus time off hormone therapy

Tang C *et al.* JAMA Oncol 2023

Systemic therapy improves the outcome of MDT

- Retrospective, multicenter
- **263 oligorecurrent men, low-volume HSPC,** mostly metachronous (90.5%)
- MDT + ADT: 105; MDT alone: 158
- Median ADT prescription: 21 mo (IQR 12-32 mo)



MDT + ADT is associated with improved PFS compared to MDT alone

Deek M *et al.* Eur Urol Oncol 2024

adapted from Zilli, T

Ongoing trials testing systemic therapies and MDT

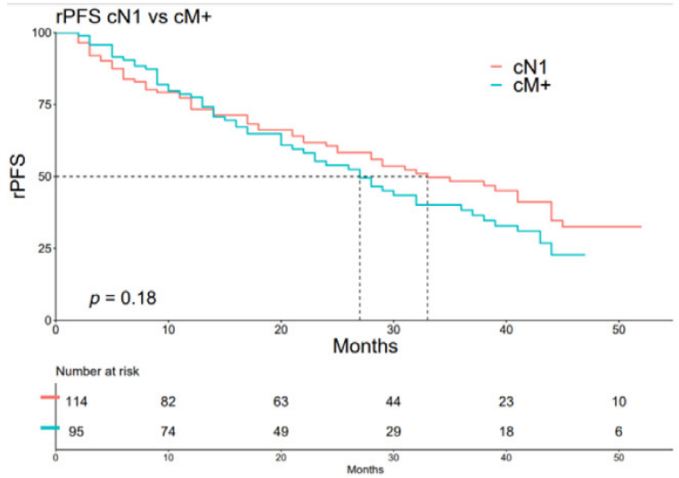
Trial	OligoM setting	Number of mets	Imaging	Design	Primary endpoint	Therapy
PLATON (CCTG PR20) NCT03784755	De novo Metachronous	≤5	Conventional	RCT phase III	PFS	SOC continuous ± SBRT
PRESTO (GETUG-PEACE 6) NCT04115007	De novo Metachronous	≤5	Conventional and NGI	RCT phase III	CRPC-free survival	SOC continuous / intermittent ± SBRT
START-MET NCT05209243	De novo Metachronous	≤5	Conventional and NGI	RCT phase III	rPFS	SOC continuous ± SBRT
VA STARPORT NCT04787744	Metachronous	≤5	Conventional and NGI	RCT phase III	CRPC-free survival	ADT continuous ± SBRT
RADIOSA NCT04641078	Metachronous	≤3	Choline PET	RCT phase II	PFS	SBRT ± 6 mo ADT
ADOPT NCT04302454	Metachronous	≤4	PSMA PET	RCT phase III	MFS	SBRT ± 6 mo ADT
PROMETHAN NCT05053151	Metachronous	≤5	Fluciclovine/PSMA PET	RCT phase II	rPFS	SBRT ± relugolix
DART NCT04641078	Metachronous	≤5	PSMA PET	RCT phase II	MFS	SBRT ± darolutamide
SPARKLE NCT05352178	Metachronous	≤5	PSMA PET	RCT phase III	Polymetastatic-free survival	MDT *vs* MDT 1 mo ADT *vs* MDT + 6 mo ADT + enzalutamide
POSTCARD NCT03795207	Metachronous	≤5	Choline / PSMA PET	RCT phase II	PFS	SBRT ± durvalumab
RAVENS NCT04037358	Metachronous	≤3	Conventional or NGI	RCT phase II	PFS	SBRT ± radium 223

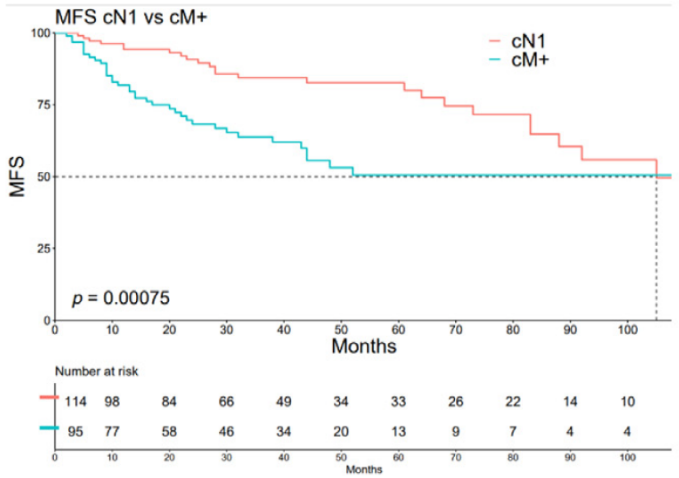
NGI: next-generation imaging; RCT: randomized clinical trial; PFS: progression-free survival; CRPC: castration resistant prostate cancer; rPFS: radiological progression-free survival; MFS: metastasis-free survival; SOC: standard of care; SBRT: stereotactic body radiotherapy; MDT: metastasis-directed therapy; ADT: androgen deprivation therapy

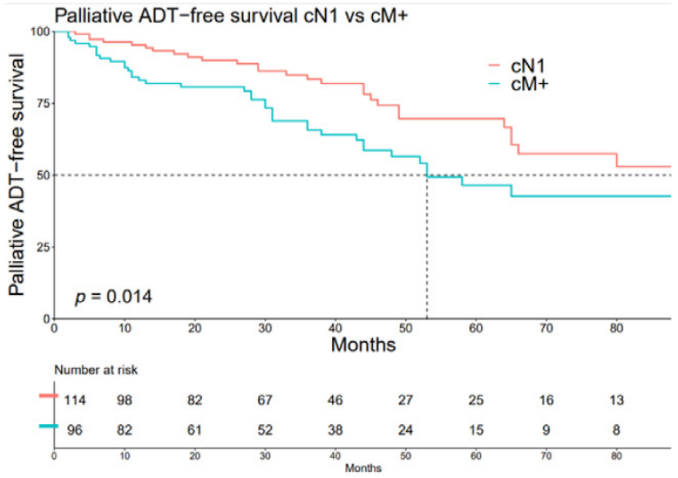
adapted from Zilli, T

What are the patient who progress and are not best treated with MDT only postponing ADT – not every patient ideal for de-escalation

- Retrospective, bicentric
- **211 oligorecurrent men, low-volume HSPC,** metachronous after RP – cN1: 54%; cM1: 46% (63% on PSMA)
- **MDT alone (no ADT)**: SBRT (23%), sLND (56%), ENRT (15%), metastasectomy (5%)







- **Predictors for MFS for cN1**: iPSA at RP, pN stage at RP, persistent PSA after RP, PSA at MDT, number of nodes +
- **Predictors for MFS for cM1**: high pathological GS (Gleason score), number of lesions, cM1b-cM1c (non-nodal)

Oligorecurrent cM1b-cM1c men with high pGS and high tumor burden have the worse outcome after MDT

Milenkovic U *et al.* Eur Urol Oncol 2023

adapted from Zilli, T

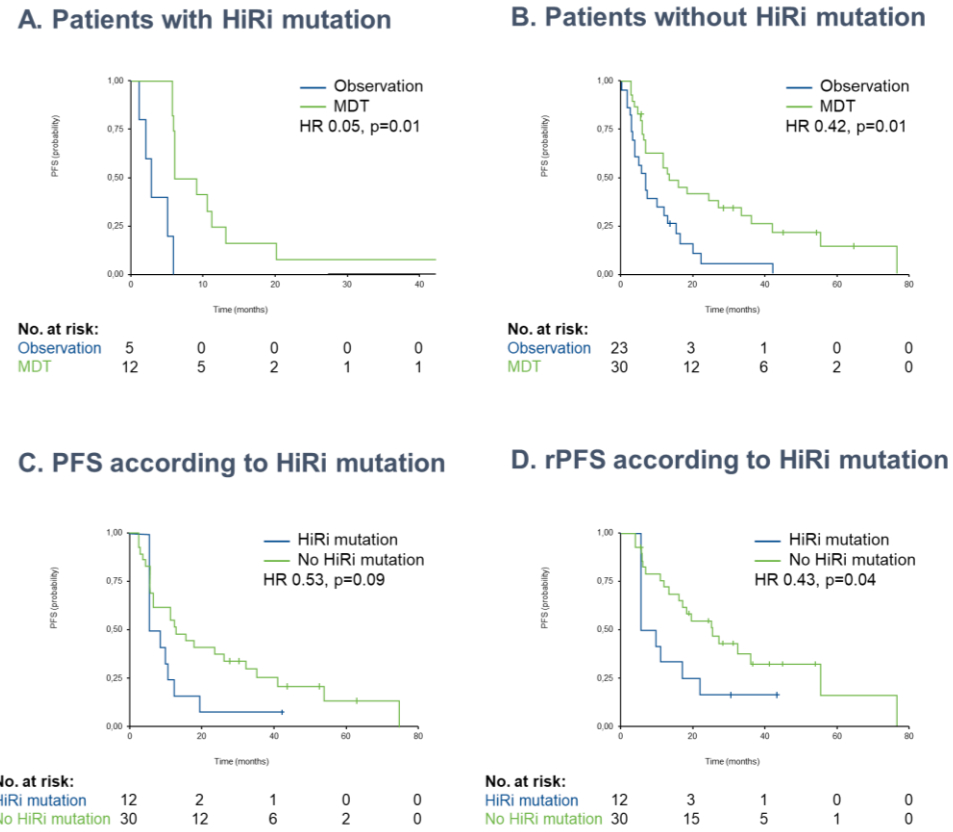
Molecular phenotype: a further stratification?

Long-Term Outcomes and Genetic Predictors of Response to Metastasis-Directed Therapy Versus Observation in Oligometastatic Prostate Cancer: Analysis of STOMP and ORIOLE Trials

70 pooled **oligorecurrent** men from **STOMP** and **ORIOLE** with genomic data available

High-risk (HiRi) mutations: ***ATM, BRCA1/2, Rb1, or TP53***

Primary endpoint: PFS
Median FU: 52.5 mo



MDT in men without HiRi mutations has the best outcome (median PFS 13.4 vs 7.5 mo with observation)
Observation in men with HiRi mutations has the poorest outcome (median PFS 2.8 mo)

Deek M et al. J Clin Oncol 2020

adapted from Zilli, T

The guidelines

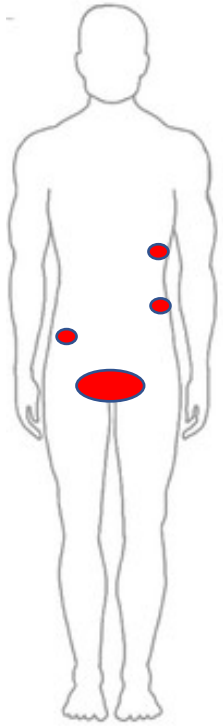
EAU – EANM – ESTRO – ESUR – ISUP – SIOG Guidelines on **Prostate Cancer**

Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

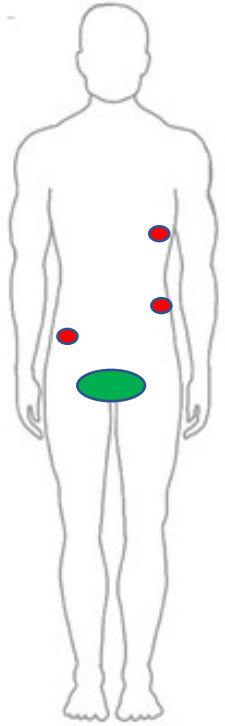
The oligometastatic PCa landscape

Uncontrolled lesion

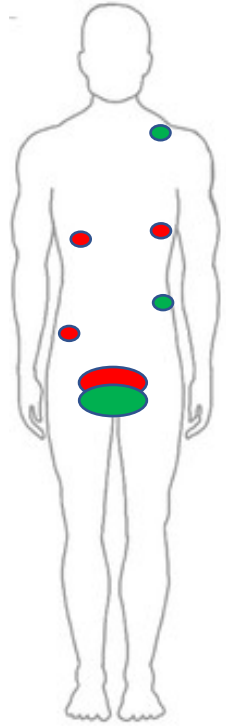
Controlled lesion



***De novo* oligometastases mHSPC (synchronous oligoM)**



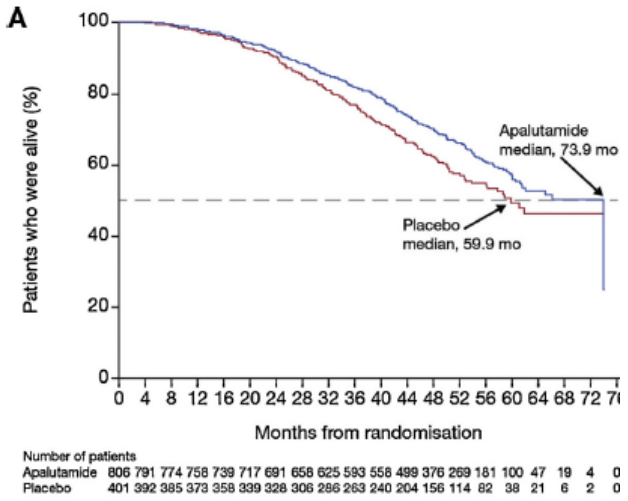
Oligorecurrent mHSPC (metachronous oligoM)



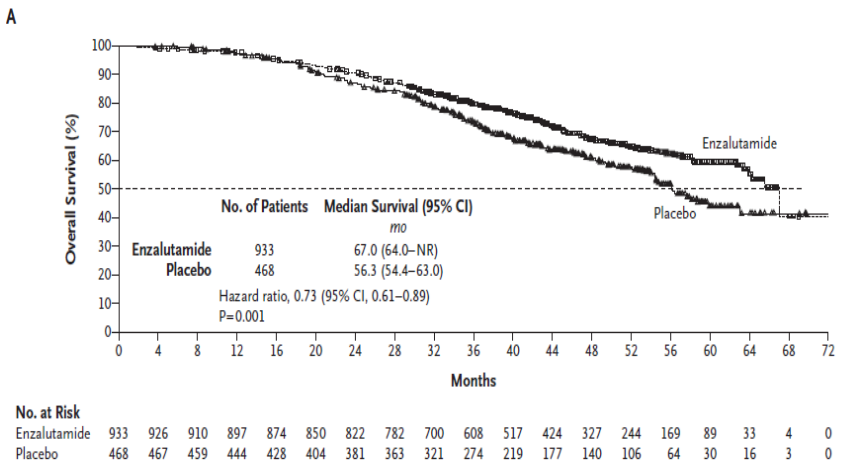
Oligometastatic CRPC (≤ 5 mets)
Oligoprogressive (induced oligoM)

nmCRPC: the «SPA» treatment

SPARTAN TRIAL



PROSPER TRIAL



ARAMIS TRIAL

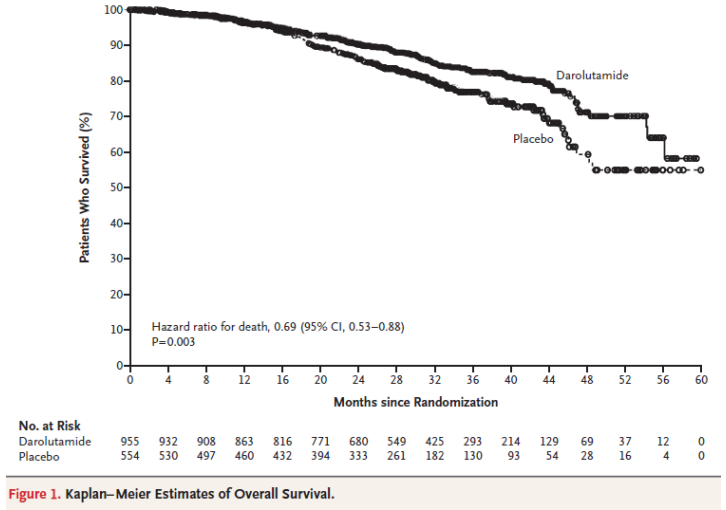


Figure 1. Kaplan–Meier Estimates of Overall Survival.

29% of these patients are oligometastatic when restaged with PSMA PET/CT

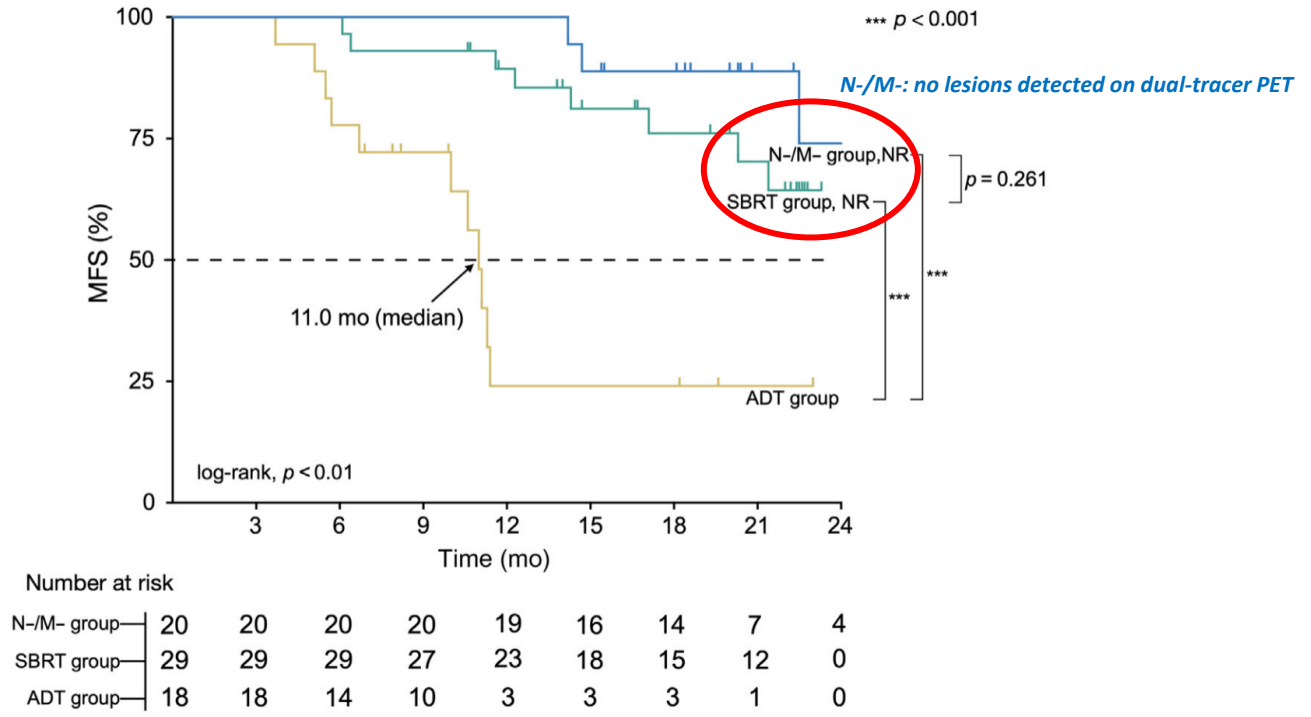
Smith *et al.* Eur Urol 2021; Sternberg *et al*. NEJM 2020; Fizazi *et al.* NEJM 2020; Fendler WP *et al.* Clin Cancer Research 2019

Università della Svizzera italiana

nmCRPC: SBRT

Stereotactic Radiotherapy for Lesions Detected via ^{68}Ga-Prostate-specific Membrane Antigen and ^{18}F-Fluorodexyglucose Positron Emission Tomography/ Computed Tomography in Patients with Nonmetastatic Prostate Cancer with Early Prostate-specific Antigen Progression on Androgen Deprivation Therapy: A Prospective Single-center Study

- *47 nmCRPC pts on standard imaging restaged with PSMA and FDG PET*
- *Median PSA: 0.59 ng/mL*
- *SBRT for 1-5 PET+ detected mets*



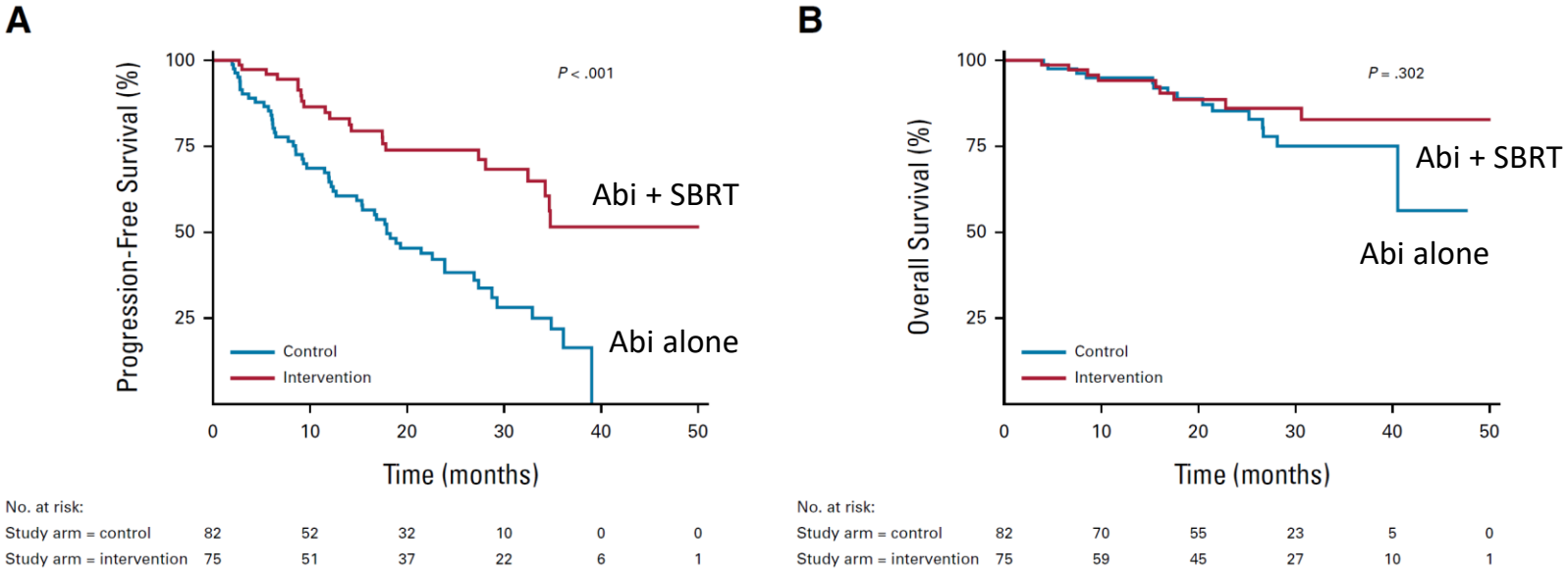
nmCRPC patients on standard imaging with 1-5 PET+ lesions treated with SBRT had similar MFS compared to patients with nmCRPC disease on dual-tracer PET imaging (and better than patients continuing ADT)

Pan J *et al.* Eur Urol Oncol 2022

mCRPC: SBRT in the 1st line

ARTO trial

- **157 oligometastatic mCRPC** pts
  (1-3 non-visceral lesions on NGI)
- Phase II RCT:
  Abiraterone *vs* Abiraterone + SBRT
- Primary endpoint:
  PSA response (decrease ≥ 50% at 6 mo)
- Secondary endpoints:
  Complete biochemical response
  (PSA <0.2 ng/mL at 6 mo); PFS



- ***PSA response: 68.3% Abi vs 92% Abi + SBRT***
- ***Complete PSA response: 23.2% Abi vs 56% Abi + SBRT***

Addition of SBRT to 1st line abiraterone MDT improves biochemical response and PFS in oligoprogressive mCRPC patients

ESCALATION

Francolini G *et al.* JCO 2023

Ongoing prospective trials

Trial	Title	Phase	Design
PILLAR (NCT03503344)	Apalutamide With or Without SBRT in Treating Participants With CRCP	II	Randomized, open label
PCS IX TRIAL (NCT02685397)			omized, open label
PCS X (NCT04070209)			omized, open label
DECREASE (NCT04319783)			omized, open label
TRAP (NCT03644303)			arm, prospective interventional t study
FORCE (NCT03556904)	FOcal Radiation for Oligometastatic Castration-rEsistant Prostate Cancer (FORCE)	II	Randomized, open label
MEDCARE (NCT04222634)	Metastasis-directed Therapy in Castration-refractory Prostate Cancer MEDCARE : a Non-randomized Phase 2 Trial	II	Single arm interventional study

Major limitations:

- Small trials
- Majority single center
- PSA-based endpoints (vs MFS/OS for ARPI)

APCCC 2024 and ESTRO-ACROP: expert consensus

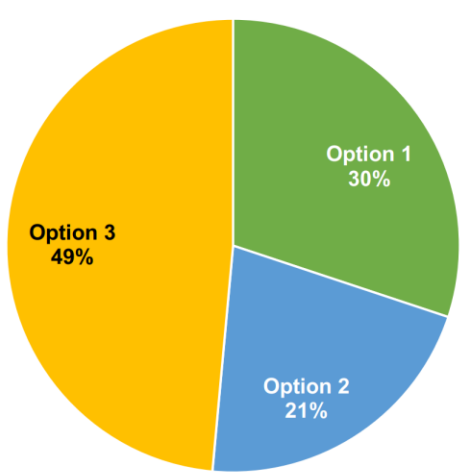
APCCC ADVANCED PROSTATE CANCER CONSENSUS CONFERENCE

4. mCRPC

Consensus questions APCCC 2024

133. For the majority of patients with multiple metastases and only oligoprogressive mCRPC (max. 3 progressing lesions) what do you recommend?

1. Switch systemic therapy
2. Switch to another systemic therapy **and** perform MDT of all progressing lesions
3. Do not change systemic therapy; perform MDT of all progressing lesions
4. Abstain/unqualified to answer



Option	Votes
Option 1	31
Option 2	22
Option 3	50
Abstain	3

Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2024 © APC Society (apccc.org)

ESTRO

ACROP- Advisory Committee on Radiation Oncology Practice

23. For patients with oligoprogressive PCa (with no visceral metastases), which treatment do you recommend?

MDRT of all lesions without switch of systemic therapy

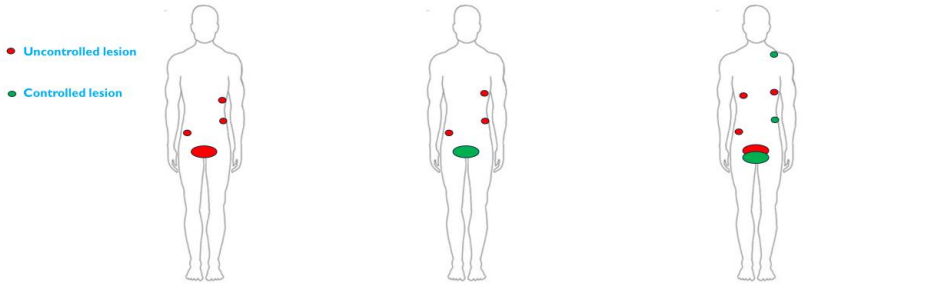
Consensus Round 1: 56%; round 2: 76%; round 3: 84%

Gillessen S *et al.* Eur J Cancer 2023; Zilli T *et al.* Radiother Oncol 2022

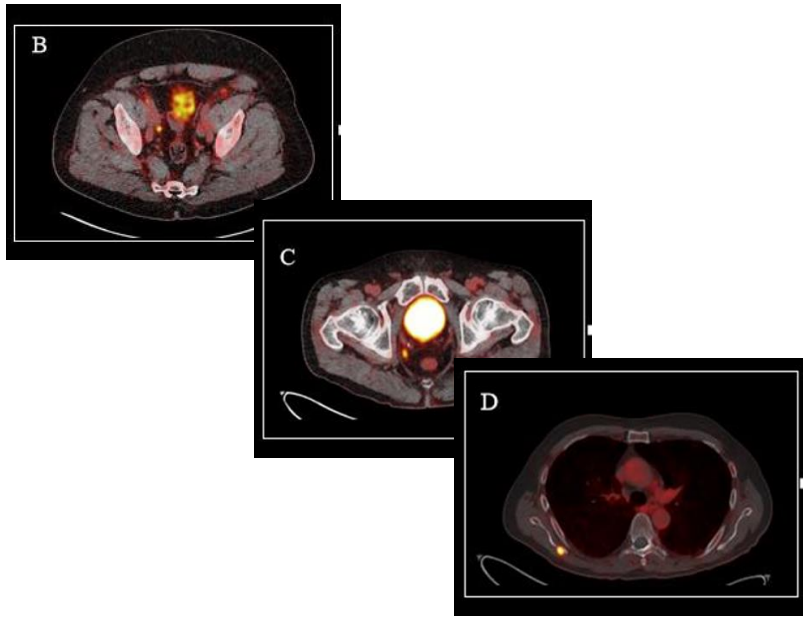
Università della Svizzera italiana

The future of oligometastases: a mix of…

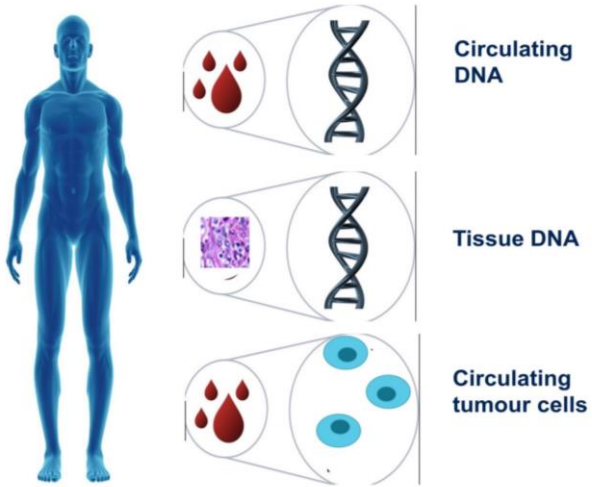
CLINIC



MOLECULAR IMAGING



TUMOR BIOLOGY



CLINICAL TRIALS!

DE-ESCALATE Intermittent Androgen Deprivation Therapy in the era of AR pathway inhibitors; a phase 3 pragmatic randomized trial (EORTC 2238)

Progression (defined as investigator decision to start next OS prolonging drug)

n (estimated)= 1600 patients

mHNPC
PSA ≤ 0.2 ng/dl after 6 to 12 months of ADT + ARPI
Docetaxel
Stratification
- ADT + ARPI
- ADT+ ARPI+ radiotherapy
- ADT+ ARPI+ chemotherapy

Randomized 2:1

MAB

MAB → MAB → MAB

✓ Treatment reinitiate at investigator discretion
✓ Suspended at 6 months if PSA< reached

Subsequent 2nd, 3rd, 4th line

Death

Endpoints:

Co-Primary (hierarchical):

1. proportion of patients without iADT treatment at one year
2. Overall survival at 3 years

Secondary

- Overall survival
- Time to next systemic prostate cancer therapy
- Proportion of patient having received next systemic prostate cancer therapy at 24, 36 and 52 months.
- Toxicity with CTCAE v5
- Quality of life with QLQ-C30/PR-25
- Health economics parameters (e.g. Incremental cost effectiveness ratio)

Stratification
- 2:1 ratio,
- stratified by country and
- ARPI alone, ARPI + docetaxel, ARPI + radiotherapy
- PSA ≤0.1 vs >0.1 - ≤ 0.2 ng/dl

mHNPC: metastatic hormone naïve prostate cancer patients; PSA90%: decrase in PSA from baseline by 90%); MAB Maximum androgen blockade

Courtesy of Turco, F

The future of cancer therapy

Take home points
Das oligometastasierte Prostakarzinom – Zeit zur De-Eskalation

1. De-escalation strategies are in progress, though yet lacking evidence

- Duration of systemic treatment in mHSPC with optimal PSA response (<0.2 ug/L) to prevent long-term metabolic events (cardiovascular, bone loss…)

- **Metastases directed therapy (MDT) can postpone disease progression** and **delay the use of long-term ADT** or **even cure** in the **oligorecurrent metachronous** setting (phase 2 evidence only)
- **MDT** can **delay time to PSA failure, PFS** and **time to next intervention** in the **oligoprogressive CRPC setting**

2. Escalation strategies are evolving still in the de-novo high-volume patients (triplet therapy)

- Treating the primary in low volume de-novo mHSPC is SOC in combination with ADT
- Total therapy (ADT+RT to the primary + ARPi) in de-novo low volume patients has reached consensus at APCCC (though lacking evidence)

Multidisciplinary discussion and inclusion in **clinical trials** or **registries** is recommended

Thank you for your attention!

Mail: ursula.vogl@eoc.ch @UrsulaVogl