Local therapy optimisation: metastasis-directed therapy +/- systemic treatment

Is delaying systemic therapy meaningful or wishful thinking?

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Conflicts of interest

Receipt of grants/research supports: Bayer

Receipt of honoraria or consultation fees: Bayer, Janssen, MSD, Novartis

Metachronous mHSPC

Goals of treatment

Improve

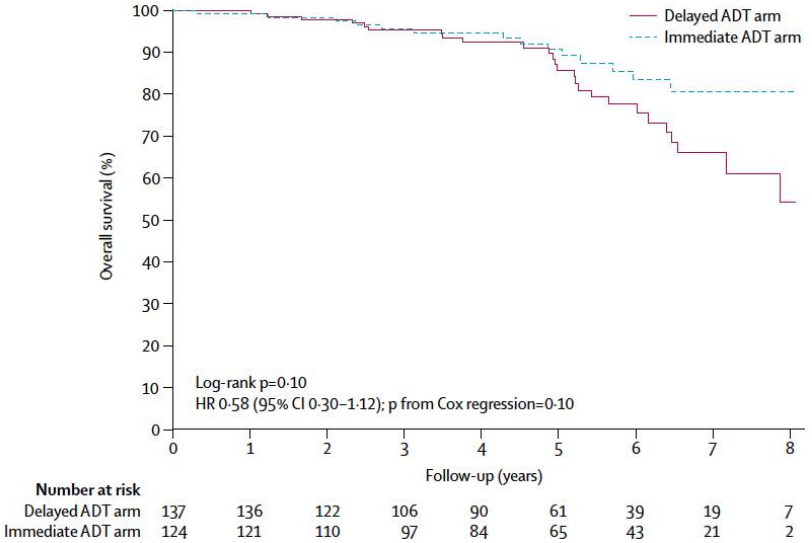
SURVIVAL
and/or
QUALITY OF LIFE

Is postponing systemic Tx really a goal for SBRT?

- Postponing should not be detrimental for survival
- Postponing should improve QoL

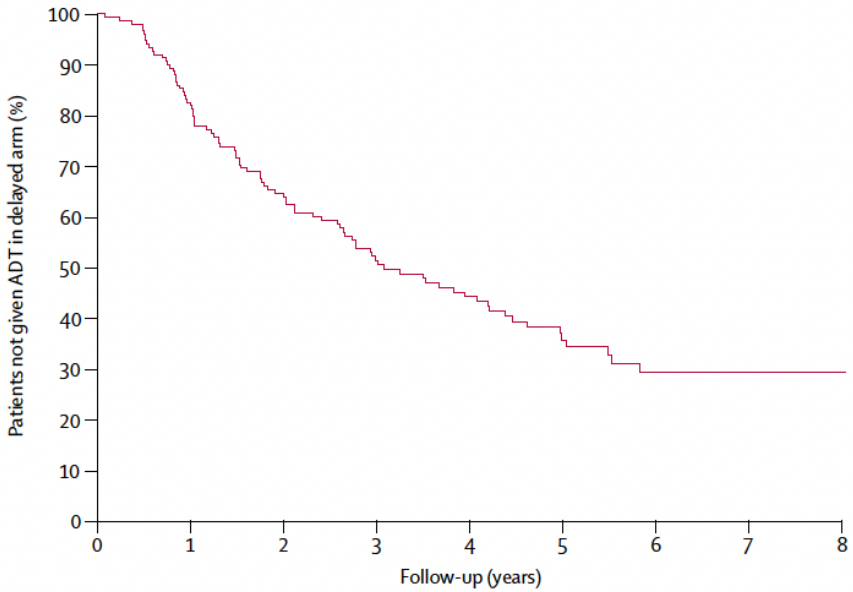
ADT for rising PSA?

- Past decade: immediate or delayed ADT
  - Delayed ADT means observation of your patients with starting of ADT at time of symptomatic progression or fast PSA DT.
  - ADT could be continous or intermittent



Duchesne et al. Lancet Oncol 2016

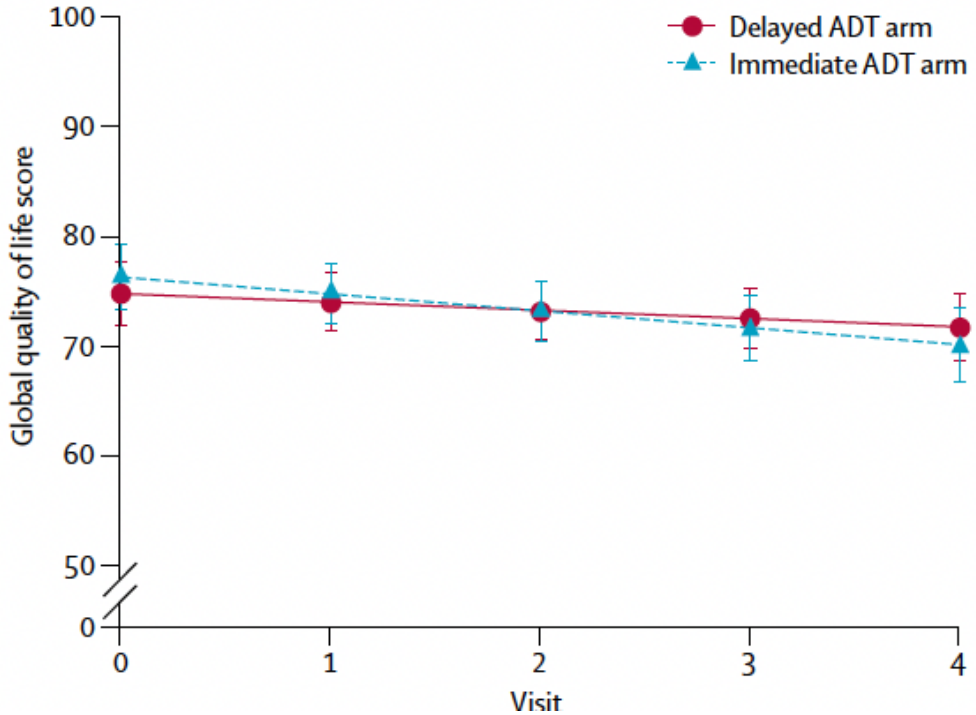
How long can ADT be postponed?



Trigger to start ADT: development of symptoms or metastases, or PSA doubling times decreased to 6 months or less

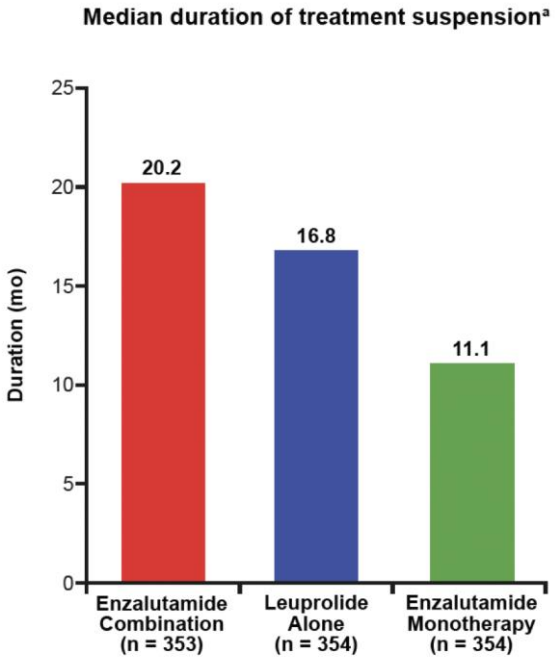
- In the PSA-relapse group within this arm, for those who did commence androgen-deprivation therapy, **the median delay was 1·58 years** (IQR 0·93–2·93).
- Early start of therapy was more common in men who had relatively poor risk features at the time of PSA relapse, with a **median delay of 12·3 months** (IQR 9·4–17·9) for these men.

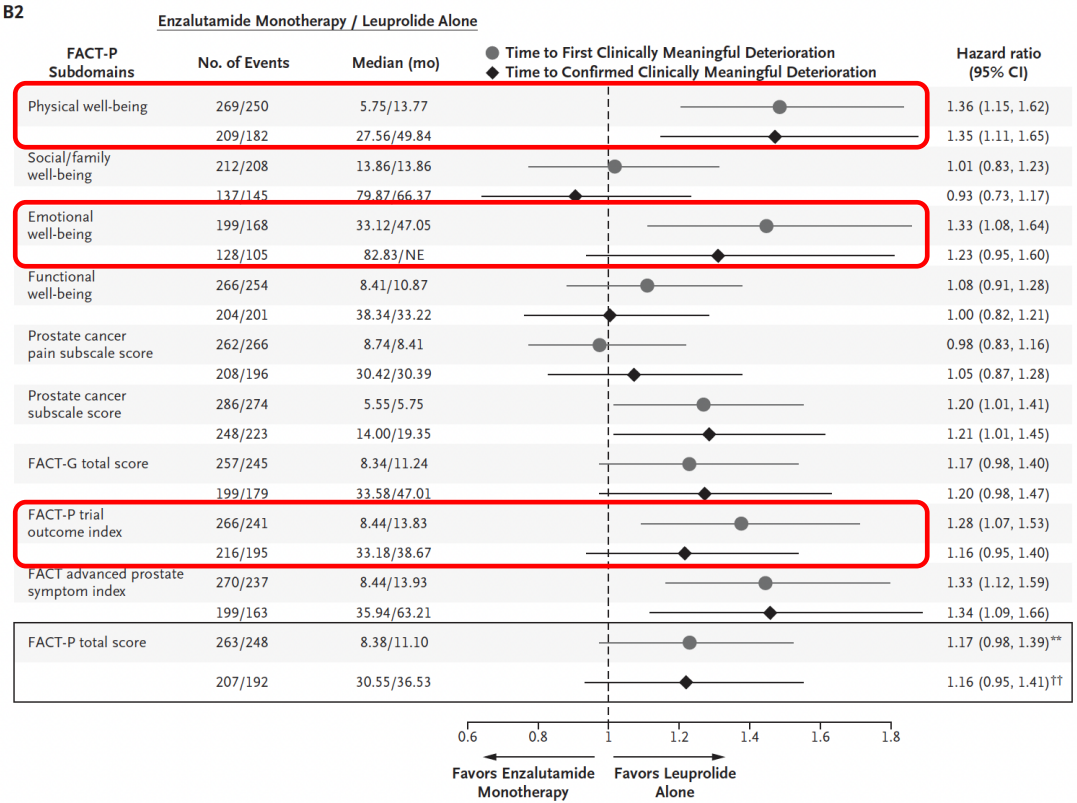
Does postponing ADT improve QoL?



Duchesne et al. Lancet Oncol 2016

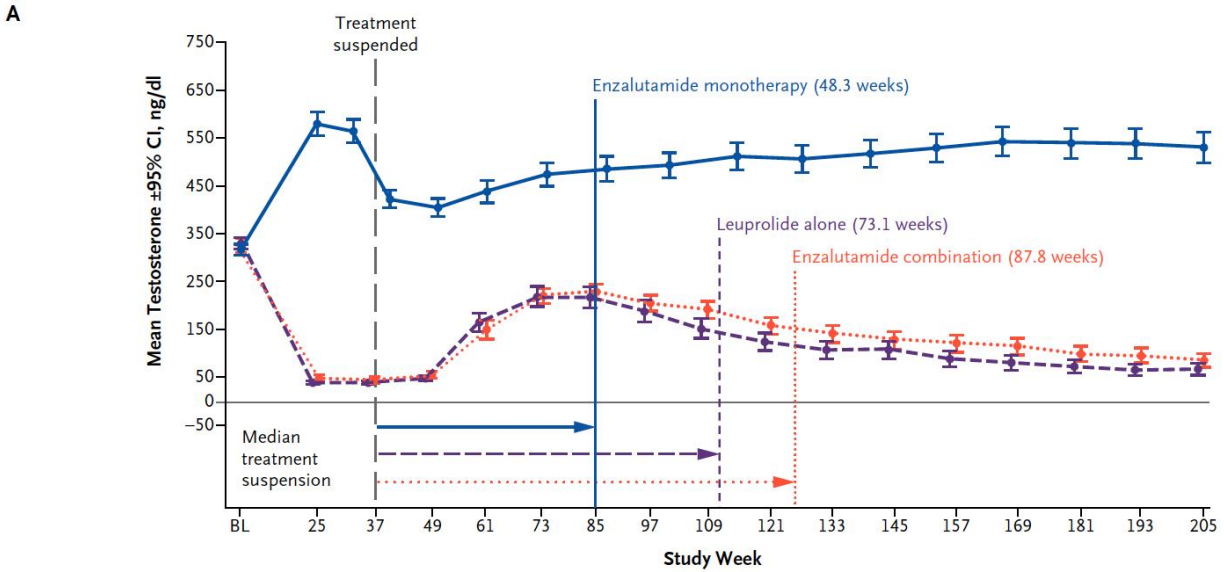
EMBARK:





Freedland et al. NEJM 2023

Evolution of Testosterone over time

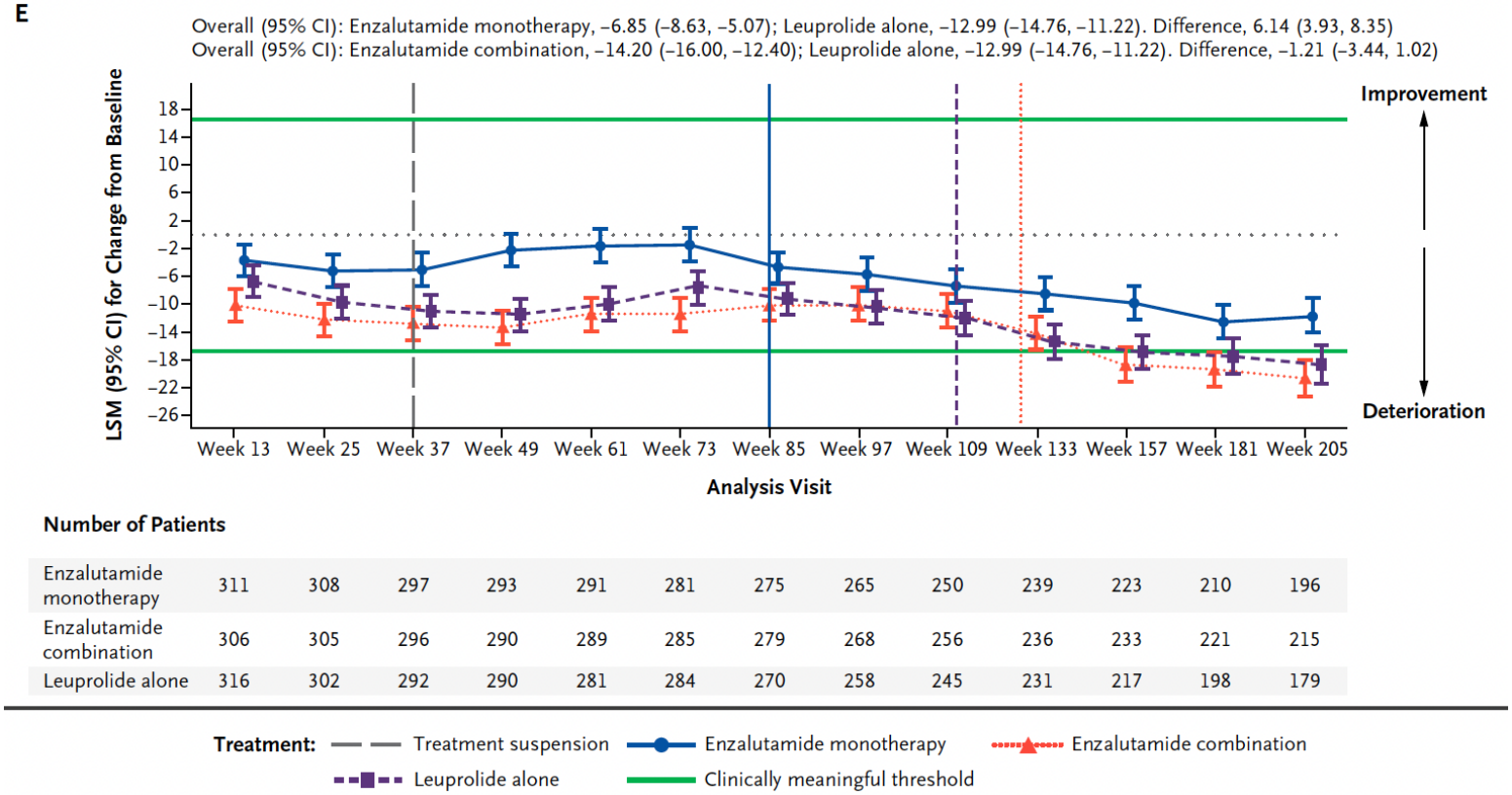


Number of Patients

Enzalutamide monotherapy	354	333	314	305	303	296	298	287	279	268	265	258	243	251	233	234	219
Enzalutamide combination	351	328	294	278	281	278	273	272	268	257	250	249	251	243	234	241	231
Leuprolide alone	354	329	304	291	286	281	266	253	247	238	232	222	219	213	210	192	193

Treatment: Treatment suspension; Enzalutamide monotherapy; Enzalutamide combination; Leuprolide alone; Clinically meaningful threshold

Sexual functioning over time



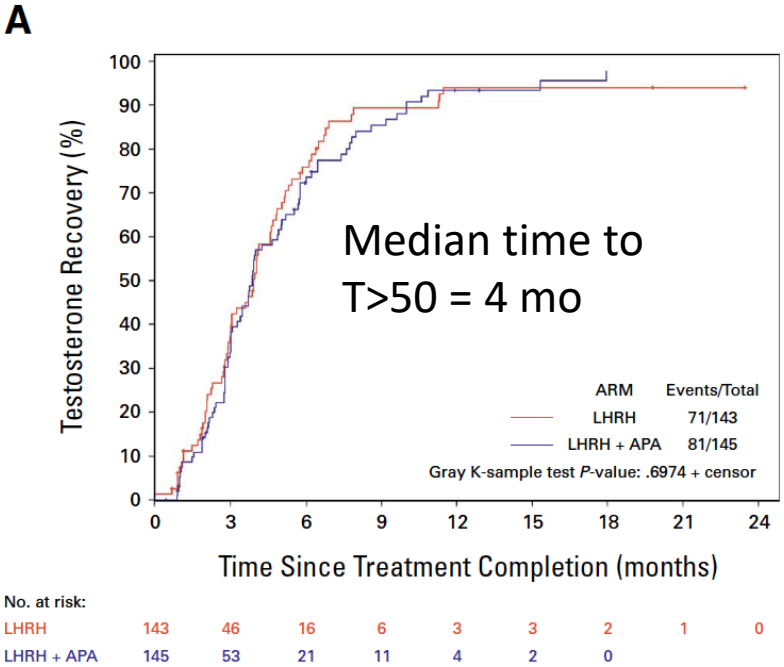
Number of Patients

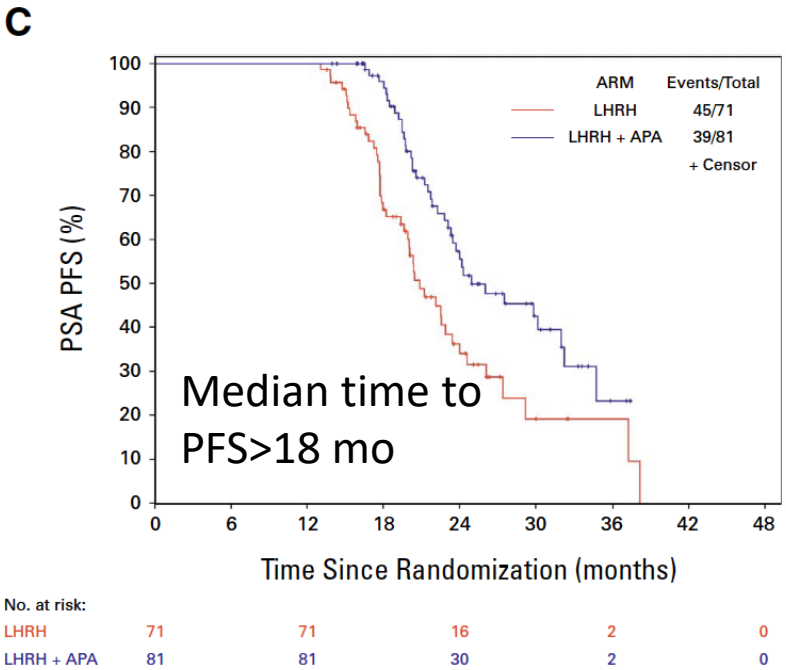
Enzalutamide monotherapy	311	308	297	293	291	281	275	265	250	239	223	210	196
Enzalutamide combination	306	305	296	290	289	285	279	268	256	236	233	221	215
Leuprolide alone	316	302	292	290	281	284	270	258	245	231	217	198	179

Treatment: Treatment suspension; Enzalutamide monotherapy; Enzalutamide combination; Leuprolide alone; Clinically meaningful threshold

Cave: most patients already had sexual dysfunction at baseline

PRESTO:

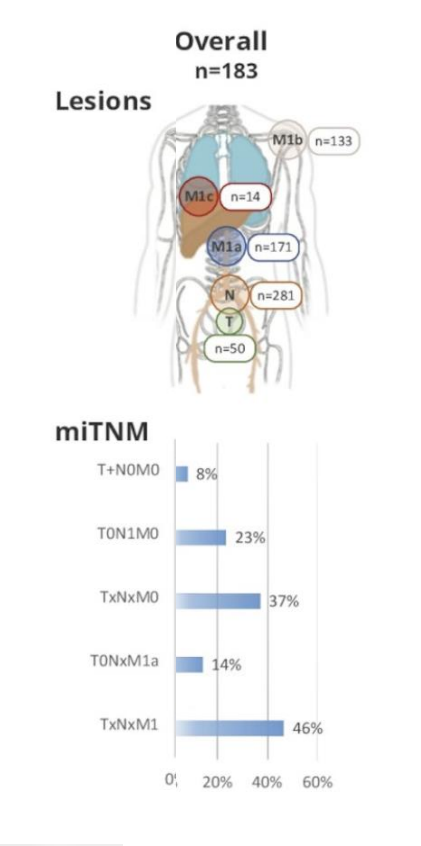




In this testosterone recovered subgroup, the addition of apalutamide to ADT significantly prolonged PSA-PFS compared with ADT alone (HR, 0.53 [95% CI, 0.34 to 0.82]

Aggerwal et al. JCO 2024

PSMA results of an EMBARK-like population



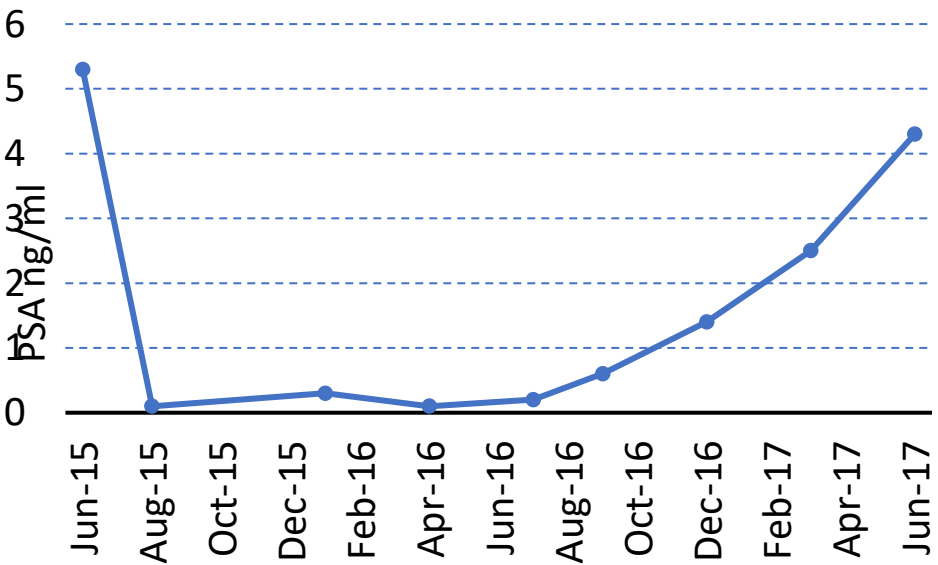
- PET-positive: 85%
  - Non-metastatic: 58%
  - Oligometastatic: 34%
  - Polymetastatic 8%

Armstrong et al. ASCO 23

Distant recurrences

A FAMILIAR TALE

- 61 year old male; PSA 5.3ng/ml
- MRI and biopsy: Gleason 3+4=7 in 6/21 cores
- RARP: pT3a 4+3=7; N0; neg margin
- Salvage radiotherapy
- Rising PSA, DT<12mo, PET negative



PSA DT calculated on
https://www.mskcc.org/nomograms/prostate/psa_doubling_time

Proposed treatment for EMBARK high-risk ?

A. Observation with ADT at time of progression
B. Immediate ADT
C. Immediate ARTA
D. ADT+ARTA

A FAMILIAR TALE

- 61 year old male; PSA 5.3ng/ml
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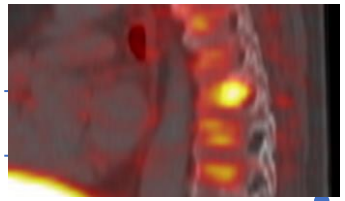
- Salvage radiotherapy
- Rising PSA, DT<12mo, PET positive



PSA DT calculated on
https://www.mskcc.org/nomograms/prostate/psa_doubling_time

Proposed treatment for EMBARK high-risk ?

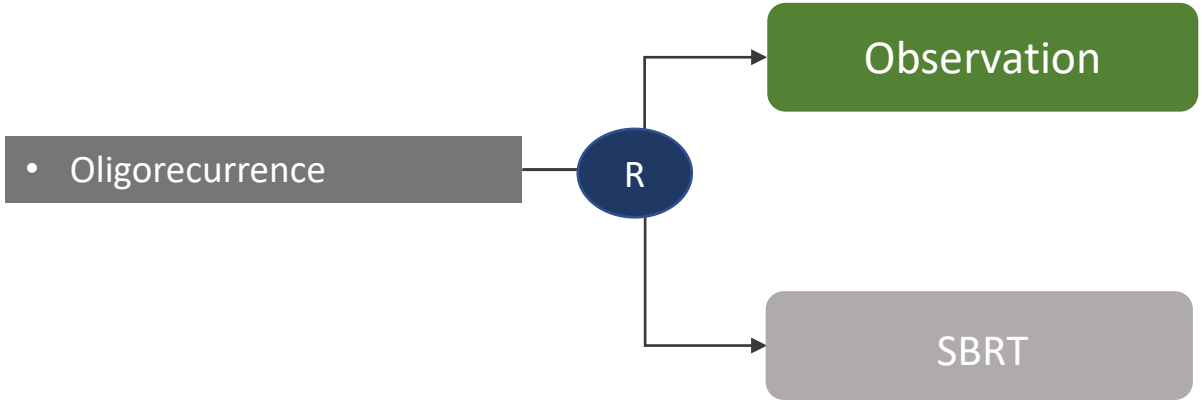
A. Observation with ADT at time of progression

B. Immediate ADT or ARTA or ADT+ARTA

C. MDT

D. MDT + systemic therapy of choice

STOMP and ORIOLE



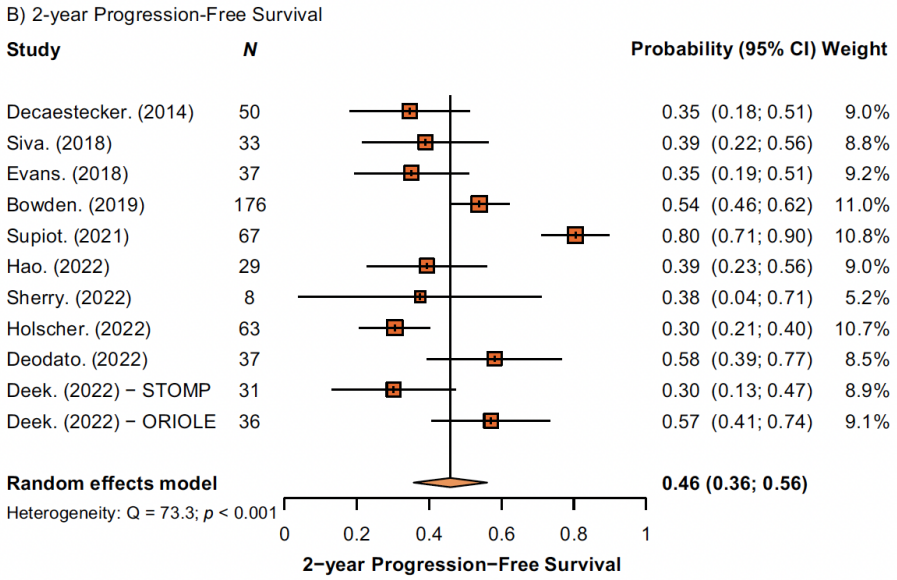
Primary endpoint:
- ADT-free survival or PFS

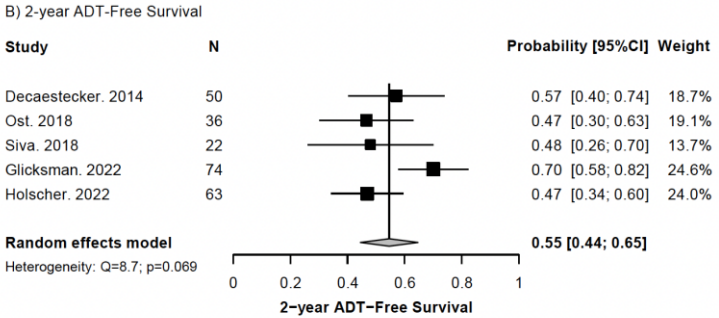
Toxicity of SBRT (STOMP/ORIOLE)

CTCAE toxicity	MDT (%)	Observation (%)	p value
0	41 (61.2)	45 (91.8)	0.001
1	24 (35.8)	4 (8.2)	
2	2 (3)	0 (0)	
3 or higher	0 (0)	0 (0)	

Deek M, Ost P, Tran P. JCO 2023

Average ADT-free survival with MDT





TOAD trial: median ADT-FS = 1 year

SABR studies: median ADT-FS = 2 year

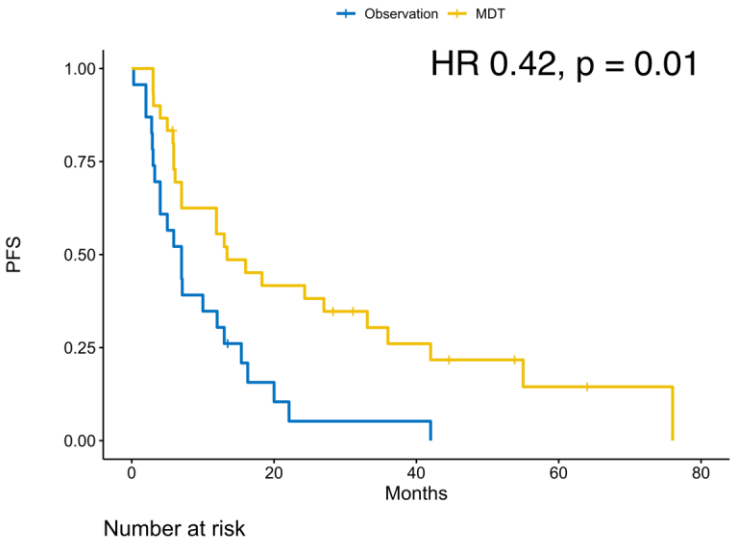
Miszcyk et al. Eur Urol. 2023

Is there a subset of patients that does not benefit from SBRT/observation?

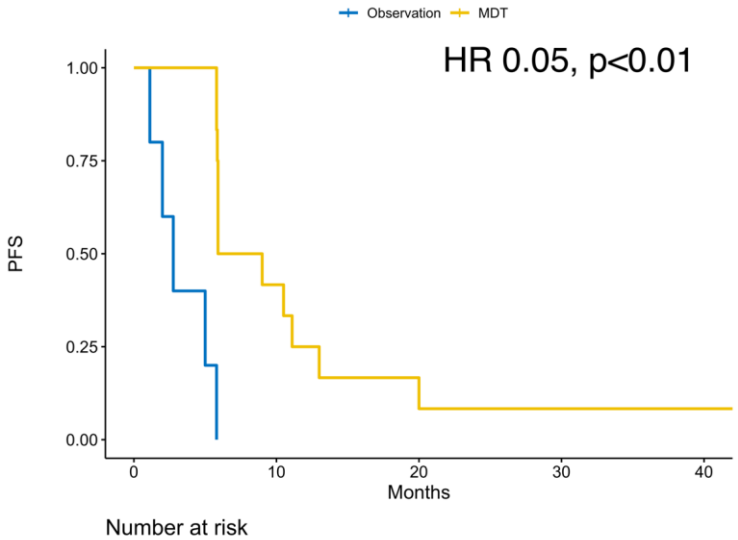
- ORIOLE and STOMP trial
- SBRT vs observation
- Targeted sequencing of the primary or blood
- High risk mutation defined as:
  - Pathogenic somatic or germline mutation in ATM, BRCA1/2, RbA, TP53
- Hypothesis:
  - Patients with a HR mutation do not benefit from SABR/observation
- Primary endpoint: PFS

PFS according to mutation status and treatment arm

No HR mutation



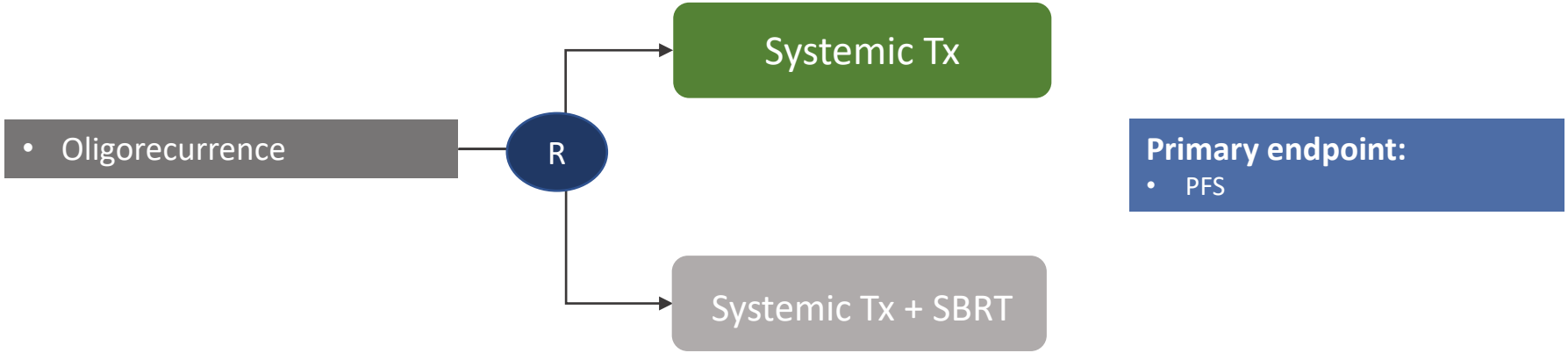
HR mutation



MDT is always better than observation,
but patients with a high risk mutation benefit even more, but might require something more!

Deek M, Ost P, Tran P. JCO 2023

Newer trials



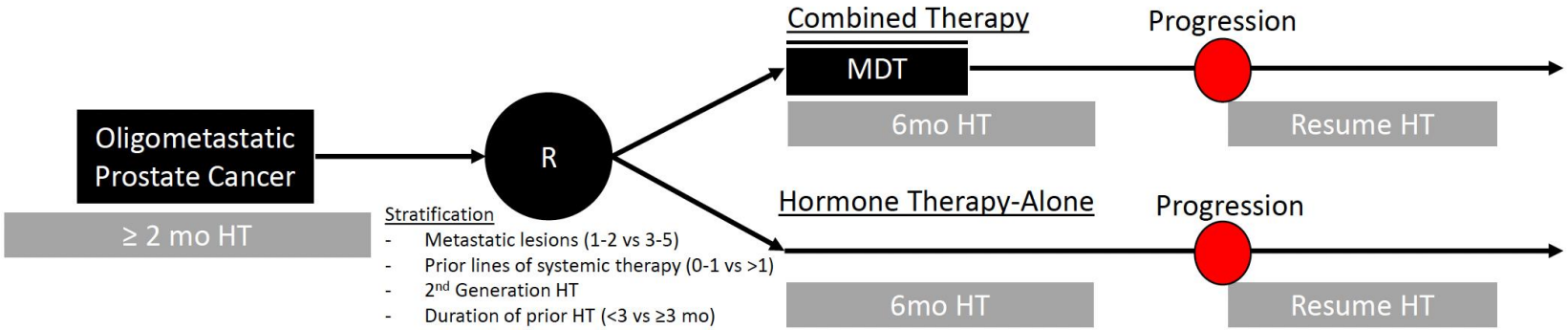
EXTEND trial: design

Major Inclusion Criteria

- Histologic diagnosis of prostate cancer
- ≤5 metastases
- ≥2 months of prior HT (either GNRH agonist/antagonist +/- 2nd generation HT)
- Untreated primaries were allowed, but must be treated regardless of randomization

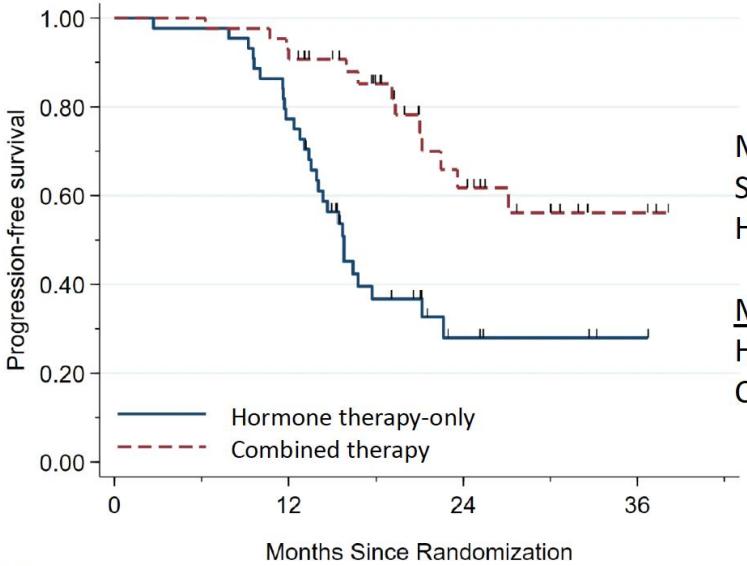
Primary Endpoint: Progression

- Biochemical progression (≥2 ng/mL or ≥25% increase above nadir)
- Clinical progression (symptoms or need to restart HT)
- RECIST 1.1 radiographic progression
- Death



Slides Chad Tang.

EXTEND trial: progression-free survival



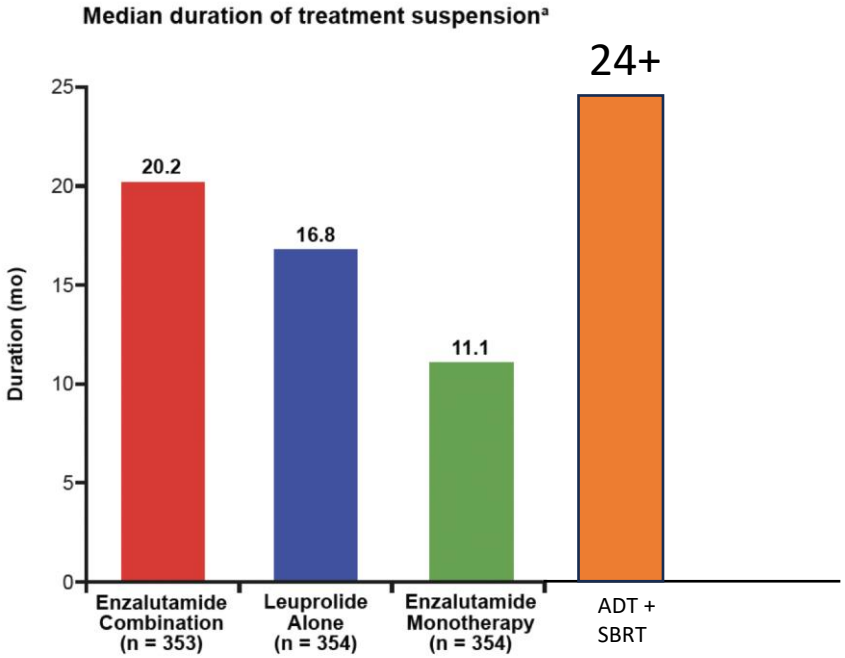
Median follow: 22.1 mo
Stratified Log Rank: P<0.001
HR = 0.25 (95% CI: 0.12-0.55)

<u>Median PFS</u>
Hormone therapy-only: 15.8 mo
Combined therapy: not reached

EMBARK median treatment suspension for ADT = 17 months in the ADT arm!

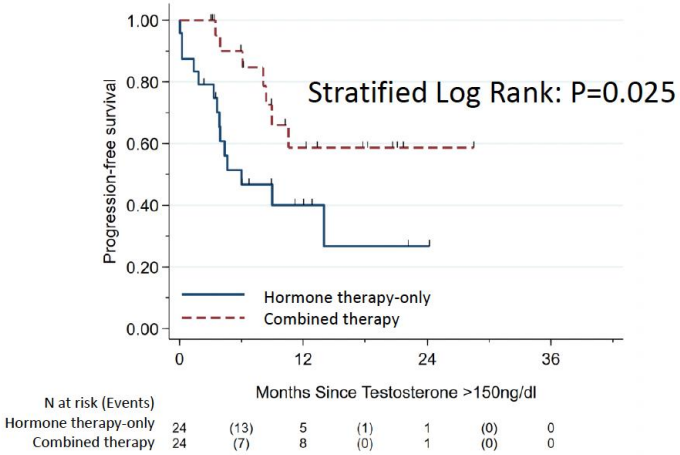
Slides Chad Tang.

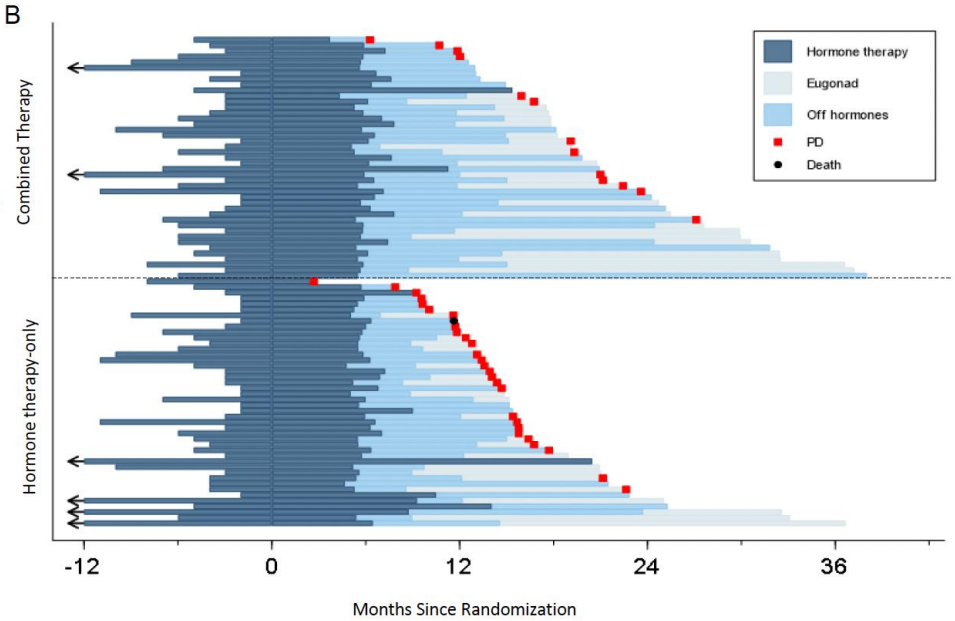
Can we further “EXTEND” treatment-free period?



EXTEND trial: Eugonad PFS.

Time-to-event analysis starting from eugonad testosterone (>150 ng/dL) to progression





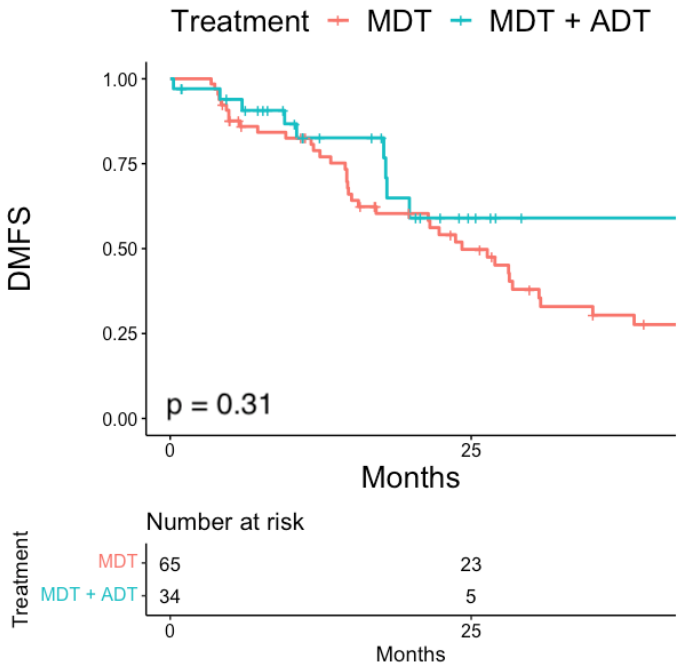
Median time to T-level >150:

- EMBARK: 5 months
- EXTEND control arm: 5 months
- EXTEND SBRT arm: not reached

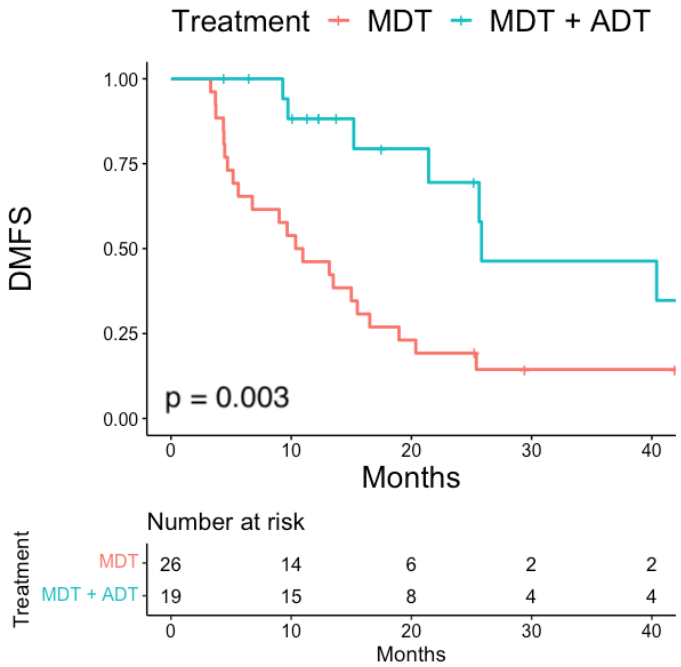
Slides Chad Tang.

Who benefits most of adding ADT

No HR mutation



HR mutation



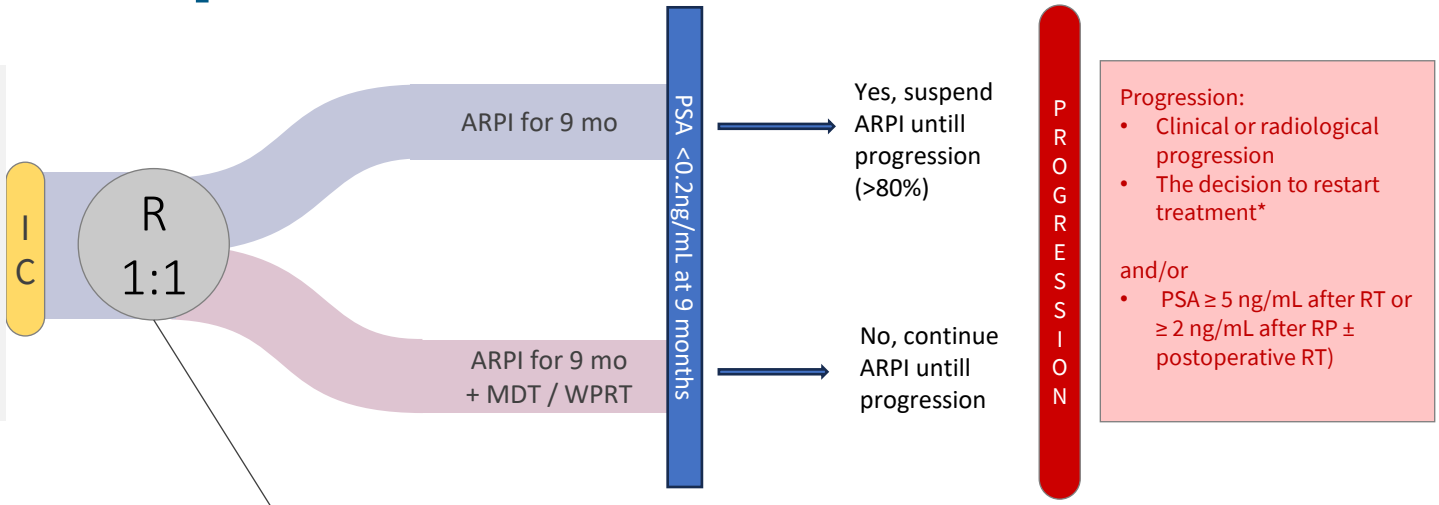
Sutera et al. (unpublished data)

What do experts recommend with SBRT?

- APCCC 2017:
  - 30% would not add a drug to MDT
  - 52% would add a temporary systemic drug to MDT
- APCCC 2019:
  - 75% suggests to go for local treatment of all lesions
  - Of those 33% would not add a drug
  - 67% would add a drug

New trial concept: Re-escalate

High-risk hormone-sensitive prostate PCa
- PSA ≥ 0.2 ng/mL after RP± postoperative RT or ≥ 2 ng/mL after RT
- PSADT ≤ 9 months
- Testosterone > 150 ng/dL
- On PSMA PET/CT restaging presence of:
  - 1 to 5 metastases that are amenable to MDT (M1) and/or pelvic nodes (N1)



Stratification factors:
- PSMA N1 vs PSMA M1
- Previous prostate bed radiotherapy or not
- PSA doubling time (≤3 mo vs. >3 to ≤9 mo)

At progression a new MDT and/or WPRT is allowed in both arms

1st endpoint
Time to disease progression

Slide Thomas Zilli, Piet Ost, Bertrand Tombal, Silke Gillissen

Conclusion

Conclusion

- Recurrent mHSPC
  - Observation alone: ADT-free survival 1 year
  - ADT alone: time off treatment: 1.5 yrs
  - SBRT alone: ADT-free survival 1.5 - 2 years
  - SBRT + 6mo ADT: ADT-free survival >2 years
  - A proportion of patients will require at least temporary syst Tx

- Enroll in trials!