Multidisciplinary Approaches to Cancer Symposium

Metastasis-Directed Treatment in Prostate Cancer: Are We Delaying ADT or Improving Outcomes?

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Disclosures

- Grant Research Support from Blue Earth Diagnostics, RefleXion & Varian

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *How does clinical heterogeneity in prior treatment course and willingness to undergo recommended treatments impact outcome?*
- *Which patients are the least likely to understand the implications of these findings and why?*

Definition of oligometastatic disease

- An intermediate state of cancer spread between localized disease and widespread metastases
- Proposed as a distinct clinical state by S Hellman and R Weichselbaum in 1995
- Many studies have shown that, across different cancers, patients with oligometastatic disease have better outcomes than those with widespread disease

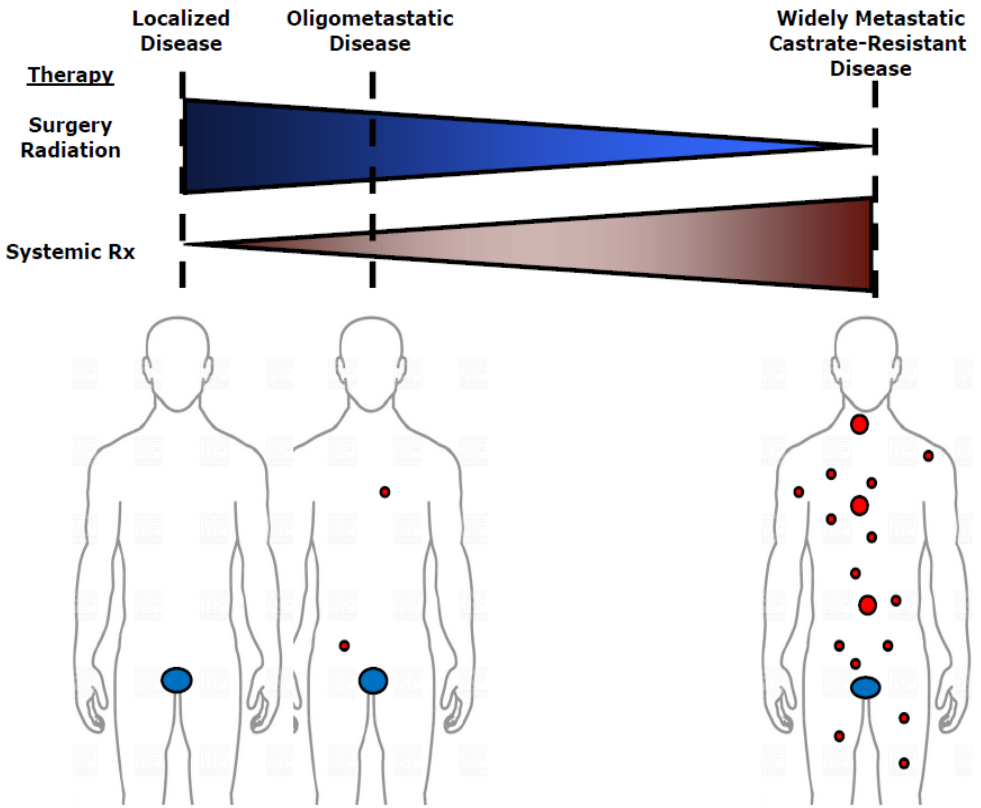


Figure courtesy of Dr. Phuoc Tran

Which of the following is the best current definition of oligometastatic prostate cancer?

A. ≤ 3 lesions outside of the pelvis

B. ≤ 5 lesions limited to lymph nodes or bones

C. ≤ 5 total lesions without visceral organ involvement

D. The definition is evolving and dependent upon imaging modality

Definitions of oligometastatic disease is not clear

Study (year)	n (cohort)	Oligometastasis definition	Sites allowed	Imaging modality
STOMP — Ost et al (2018)	62	≤ 3	Any (bone, LN, soft tissue)	11C-choline PET/CT
ORIOLE — Phillips et al (2020)	54	1–3	Bone, LN, soft tissue	Conventional imaging +/- PSMA PET for analysis
Siva et al (prospective / SBRT series)	33	≤ 3	Bone, LN	Conventional + (choline PET)
Franzese et al (2023)	163	Up to 5 lesions, ≤2 organs	Bone, LN	Choline or PSMA PET
Pastorello et al (2023)	164	≤ 3–5 (varied)	Bone, LN	68Ga / 18F PSMA PET/CT

The role of MDT in PCa has evolved

2000 → 2014 → 2021

SYMPTOM CONTROL

LOCAL CONTROL

DELAY ADT

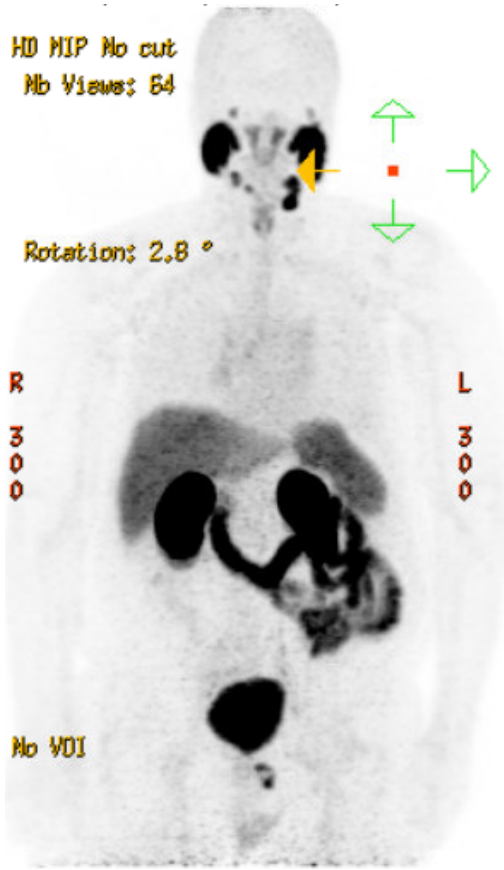
ENHANCE ADT

IMPROVE PFS

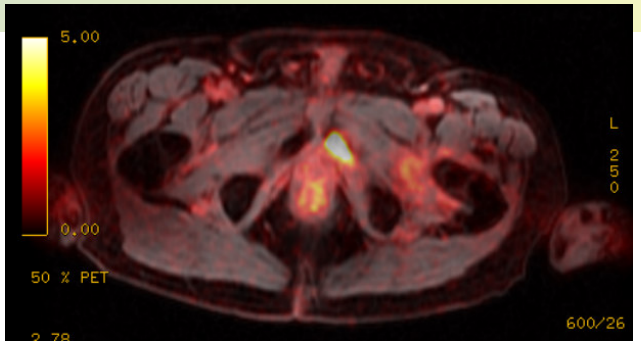
A CHANCE OF CURE…?

A tale of two patients: Patient 1

- Prostatectomy in 2007 for a pT3bN0 (0/13 LNs), (-)M, pG4+3+5 disease, iPSA 15, post-op PSA initially undetectable
- PSA recurrence in 2010 (0.03), by 2012 rose to 0.133 (TRUS bx-)
- Treated with salvage WPRT (50Gy in 25) +PB (20Gy in 10) + 4 months of ADT with PSA nadir=0.03
- In 2021 at age 78, presents with a slowly rising PSA to 1.2
- Ga-68 PSMA PET/CT shows solitary oligometastatic disease in L pubic ramus.
- KPS=90, no major comorbidities, works fulltime



A tale of two patients: Patient 1



- Prostatectomy in 2007 for a pT3aN0 (0/9 LNs), (-)M, pG4+3+5 disease, iPSA 15, post-op PSA initially undetectable
- PSA recurrence in 2013 rising to 0.8
- Treated with salvage WPRT (45Gy in 25)/PB boost (20Gy in 5 fractions) + 4 months of ADT
- In 2017 at age 65, presents with a slowly rising PSA to 1.3
- Ga-68 PSMA PET/CT shows solitary oligometastatic disease in L pubic ramus.
- KPS=90, no major comorbidities
- **What do you recommend? His SHIM is 21 with Cialis and notes that his quality of life is very important to him.**

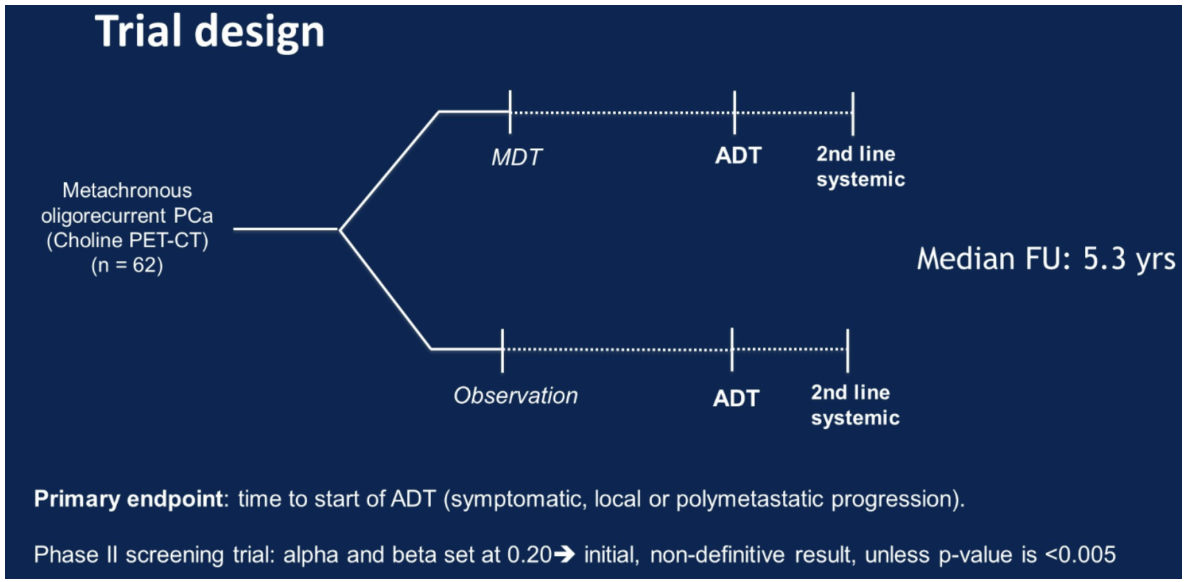
Phase II study (STOMP): early innovation in MDT

- Primary endpoint: ADT-free survival
- Stratification: PSA DT & Location of mets
- 3 asymptomatic metastases detected on Choline PET
  - Symptoms
  - Local progression
  - Polymetastatic progression

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

Piet Ost, Dries Reynders, Karel Decaestecker, Valérie Fonteyne, Nicolaas Lumen, Aurélie De Bruycker, Bieke Lambert, Louke Delrue, Renée Bultijnck, Tom Claeys, Els Goetghebeur, Geert Villeirs, Kathia De Man, Filip Ameye, Ignace Billiet, Steven Joniau, Friedl Vanhaverbeke, and Gert De Meerleer

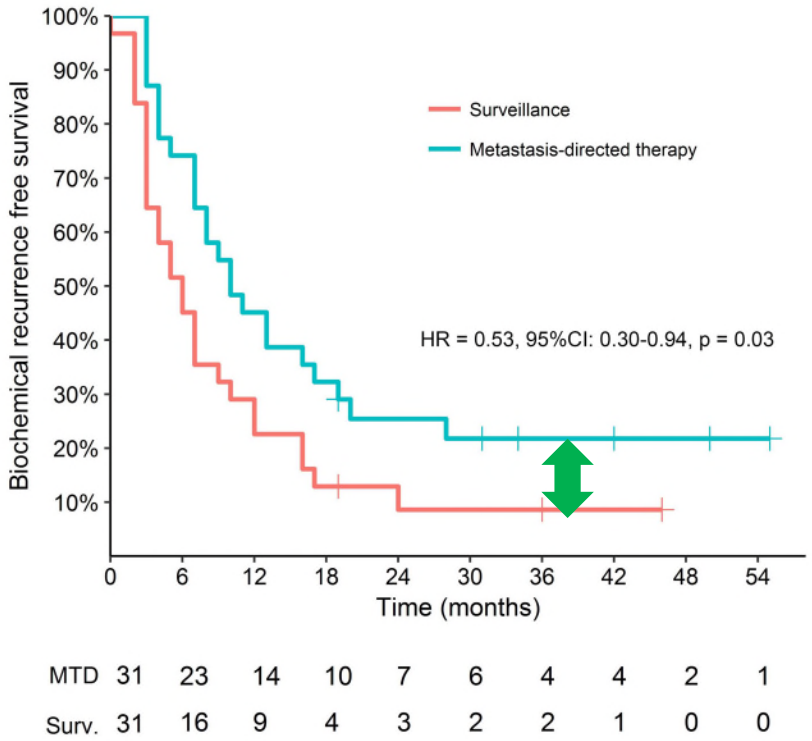


Ost et al, JCO 2017

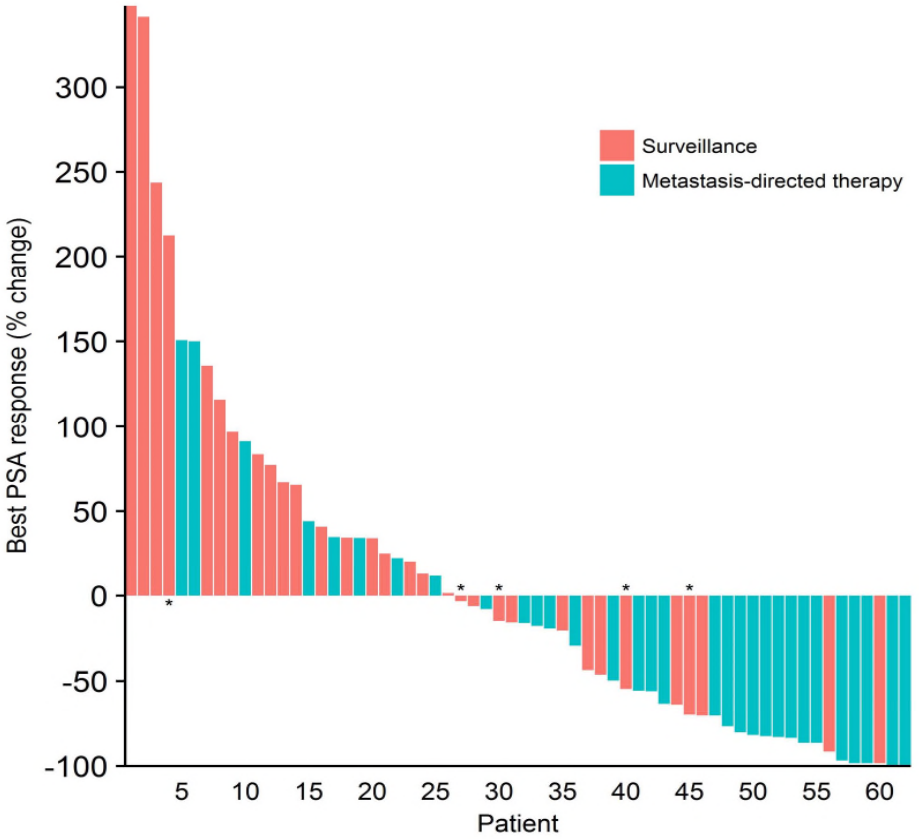
Metastases-directed therapy for mHSPC is safe

Study (year)	Setting	n	SBRT regimen (typical)	Grade ≥3 toxicity (reported)	Median FU
ORIOLE — Phillips et al. (2020)	Randomized phase II, oligorecurrent HSPC	107	MDT SBRT to 1–3 lesions (various regimens)	0% grade ≥3	6–18 mo
STOMP — Ost et al. (2018)	Randomized phase II, oligorecurrent HSPC	62	MDT: surgery or SBRT to ≤3 lesions	0% grade ≥2–5	3 years
POPSTAR / Siva et al. (2018)	Prospective single-arm (single-fraction SABR series)	33	Single-fraction SABR for bone/nodal metastases (e.g., 20 Gy ×1 or similar)	rare ≥3 events	2 years

Some patients derive long term benefits from MDT



About 20% free of PSA recurrence at 3 years after txt



Are we just delaying ADT or improving outcomes?

If you proceed with SBRT alone, what is the chance that the patient has no evidence of disease at 3 years without any further treatment?

A) 80%

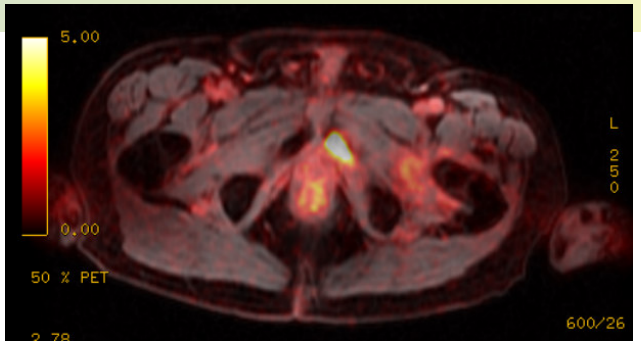
B) 60%

C) 40%

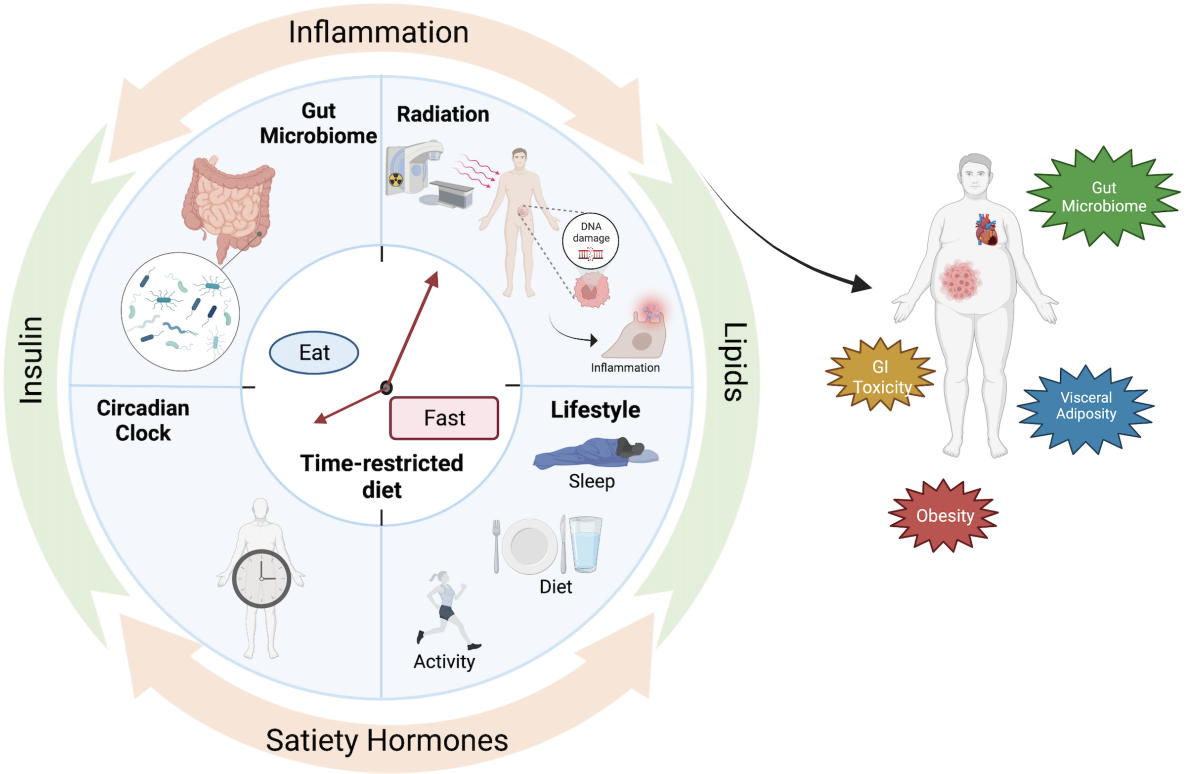
D) 20% or less

A tale of two patients: Patient 1

- Prostatectomy in 2007 for a pT3aN0 (0/9 LNs), (-)M, pG4+3+5 disease, iPSA 15, post-op PSA initially undetectable
- PSA recurrence in 2013 rising to 0.8
- Treated with salvage WPRT (45Gy in 25)/PB boost (20Gy in 5 fractions) + 4 months of ADT
- In 2017 at age 65, presents with a slowly rising PSA to 1.3
- Ga-68 PSMA PET/CT shows solitary oligometastatic disease in L pubic ramus.
- KPS=90, no major comorbidities
- **SBRT monotherapy to L pubic ramus (outside of prior salvage field) 35Gy in 5 fractions.**
- **At 3 years, patient was progression-free with PSA stable at ~0.05**



“Omitting” ADT leads to better health outcomes

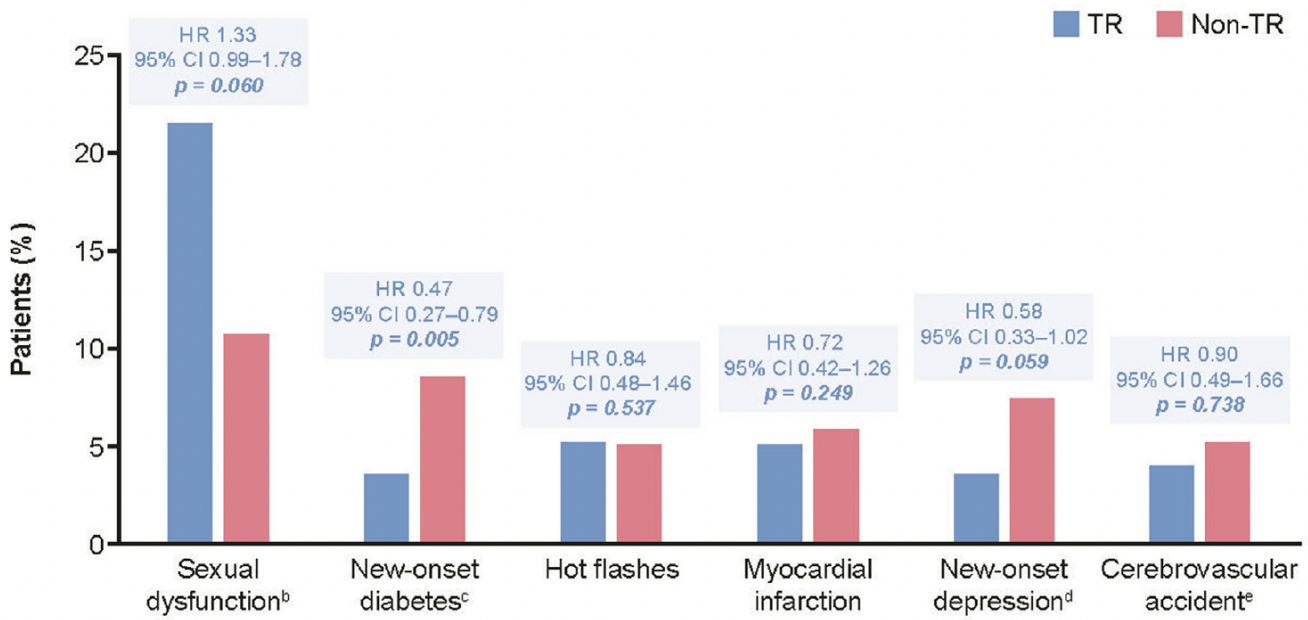


	PCa	Non-PCa
Age (Median)	62.7	43.8
Hispanic/Latino (%)	33.3%	25.0%
Receiving T2D medications (%)	11.1%	0.0%
Fasting Blood Glucose Baseline (Median)	104.9	95.7
A1c Baseline (Median)	5.9	5.6
A1c at 6 months (Median)	6.2	5.2
BMI Baseline (Median)	30.4	28.5
BMI 6 month follow up (Median)	30.8	28.5
Visceral Adiposity Ratio Baseline (visceral:subcutaneous) (Mean)	0.49	0.38

Table 1: Differences in prevalence of ACMD clinical risk factors in PCa patients (n=32 PCa, n=9 non-PCa) as compared to other participants in NCT05722288.

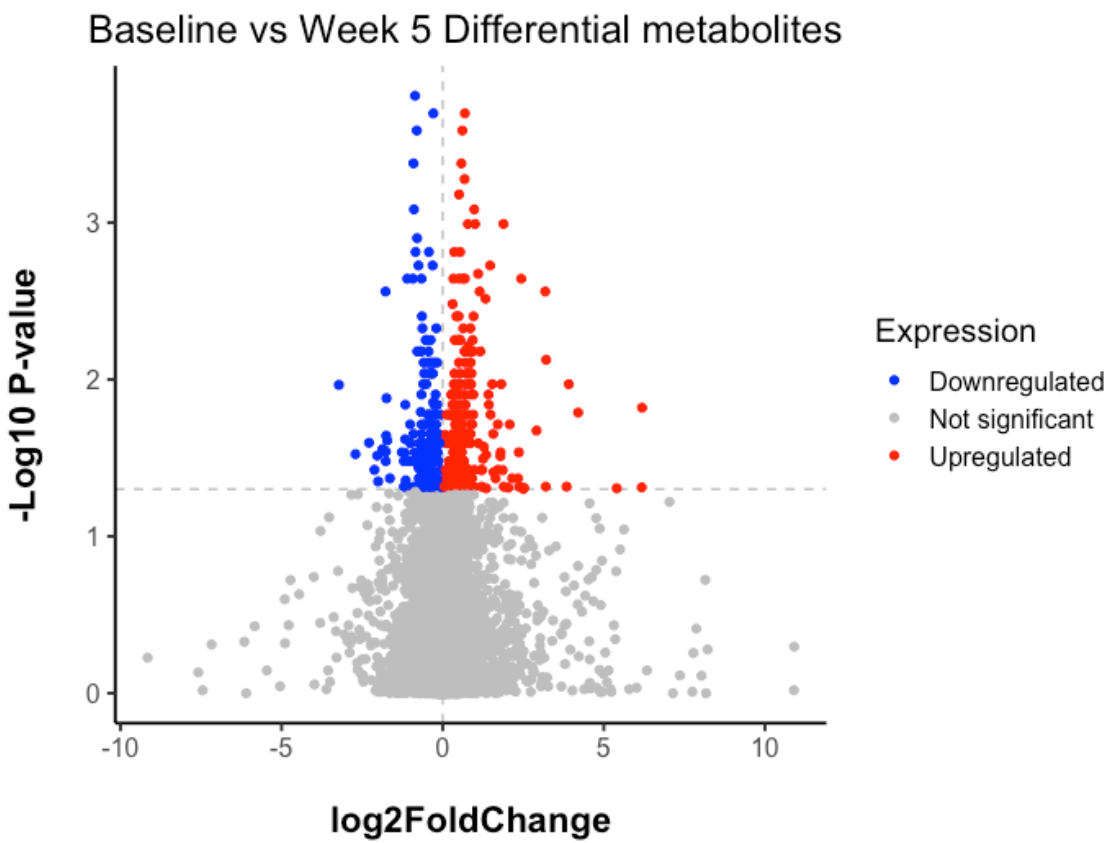
Reducing ADT can improve outcomes

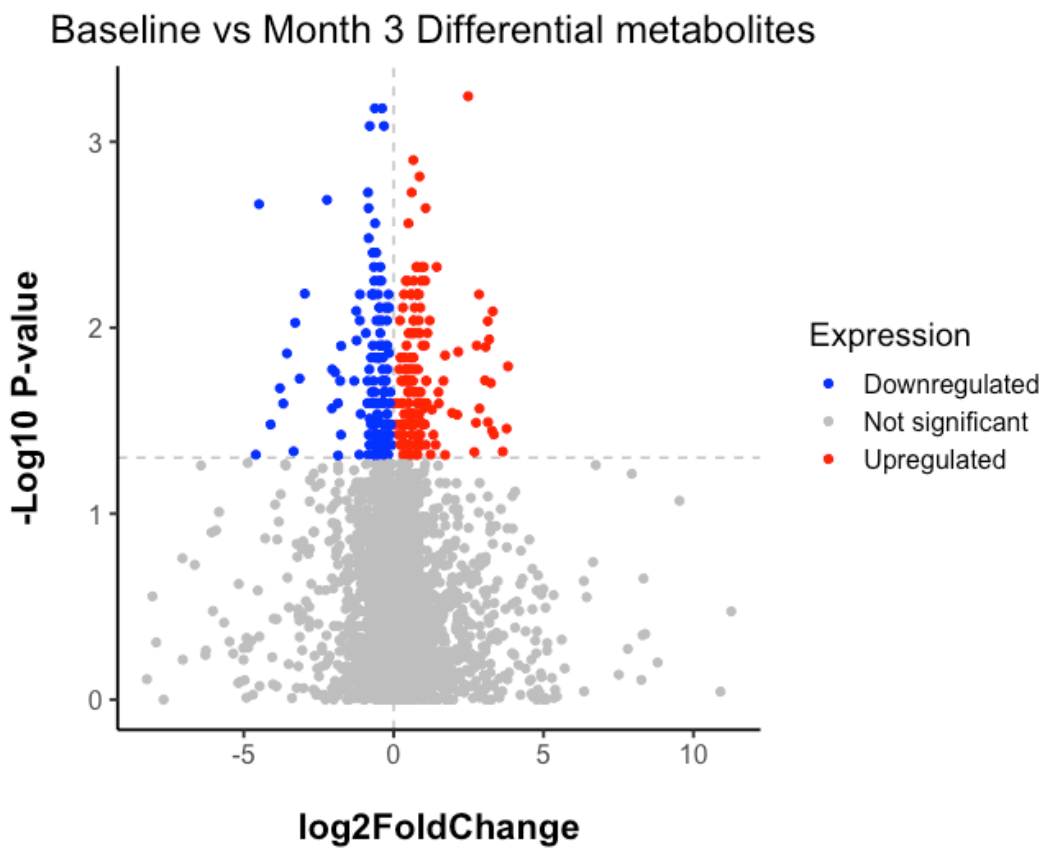
- ADT is a broad range of physiologic changes and consequent comorbidities
- Cardiometabolic toxicities include metabolic impairments, including insulin resistance, dyslipidemia, weight gain, and visceral adiposity.
- CVD remains a common cause of mortality among men with localized prostate cancer



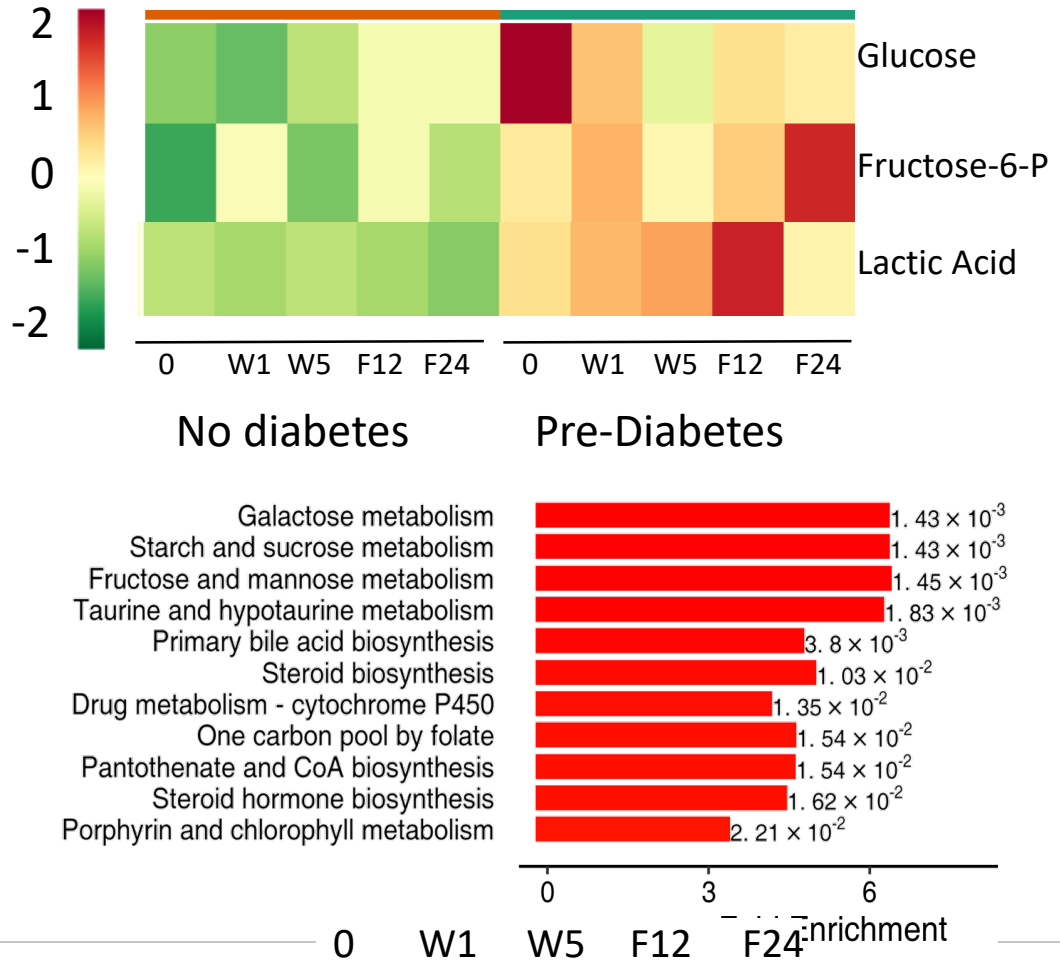
Liu, Prevalence and prognosis significance of cardiovascular disease in cancer patients: a population-based study, *Aging*, 2019

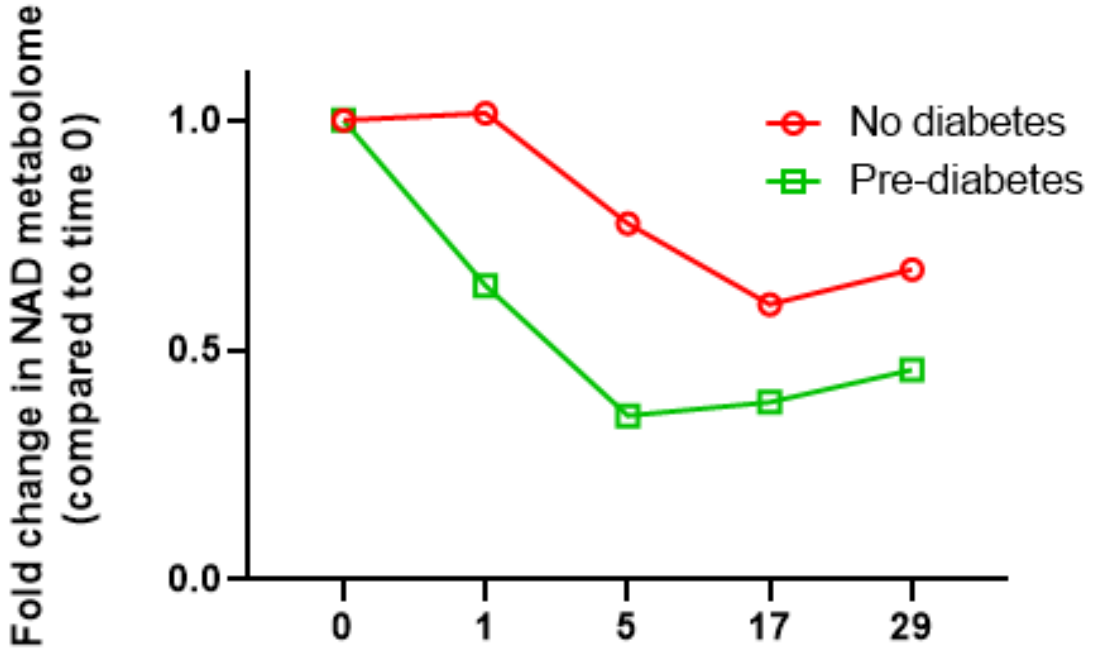
How does ADT impact metabolic health?





Metabolic derangements in glucose and NAD metabolism correlates with poor ADT tolerance





Can prophylactic interventions mitigate risks of ADT related cardiometabolic dysfunction?

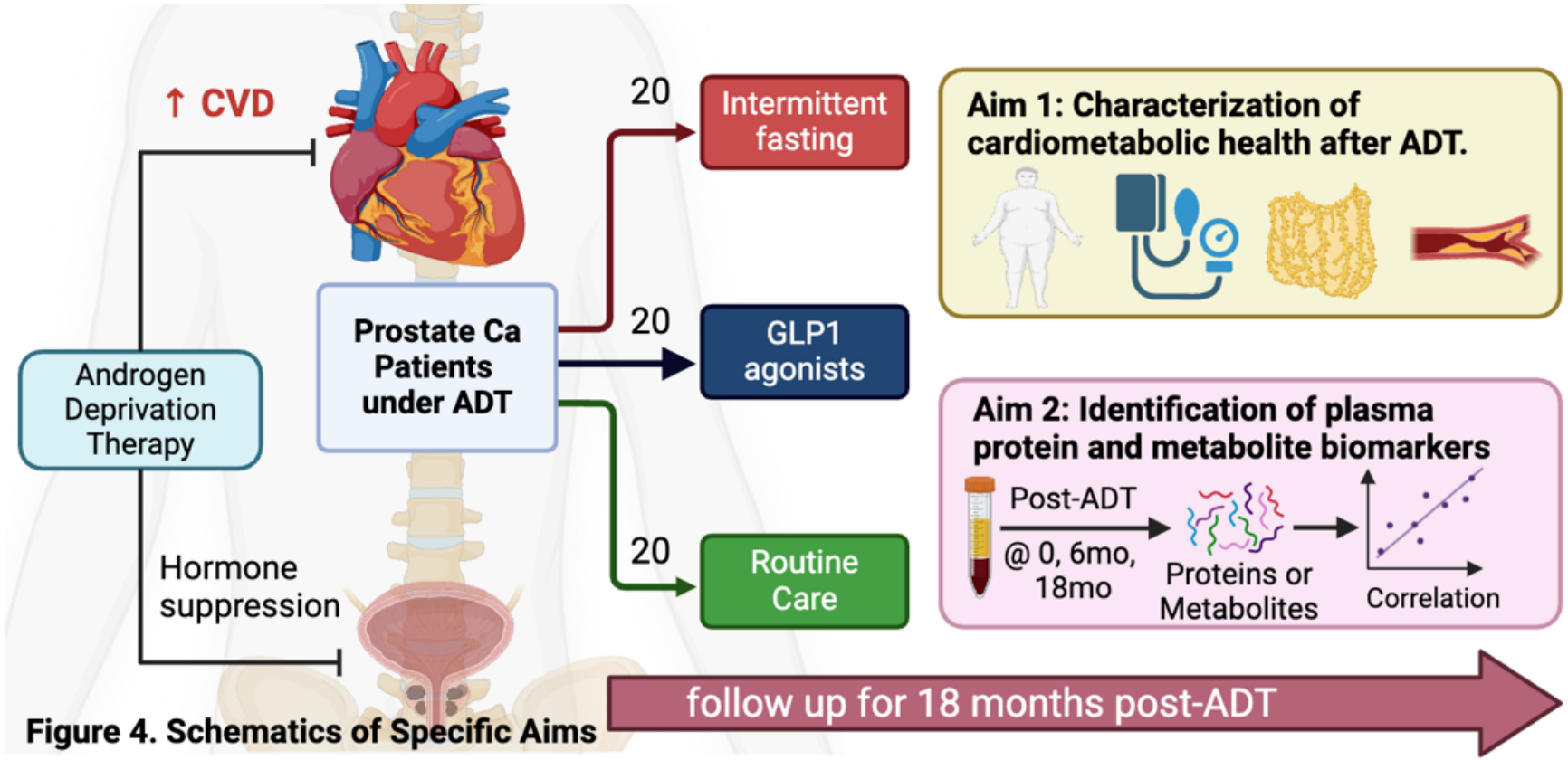


Figure 4. Schematics of Specific Aims

In collaboration with Dr. June Rhee
Support from AHA Collaborative Sciences Award

A tale of two patients: Patient 2

- pT3aN0 cancer with focal (+)M, 0/10 LN, iPSA 11, pG4+3, s/p RP in 2012
- Subsequent PSA undetectable
- Treated in 2/2015 with salvage PBRT + short term ADT for PSA recurrence up to 0.8
- In 1/2020 presented with rising PSA to 0.5; PSMA PET shows also a solitary L pubic ramus met
- He undergoes SBRT monotherapy 35Gy in 5 fractions

A tale of two patients: Patient 2

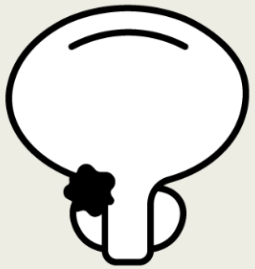
PSMA PET scan from 1/2020 **PSMA PET scan from 2/2020**

- pT3aN0 cancer with focal (+)M, 0/10 LN, iPSA 11, pG4+3, s/p RP in 2012
- Subsequent PSA undetectable
- Treated in 2/2015 with salvage PBRT + short term ADT for PSA recurrence up to 0.8
- In 2020 presented with rising PSA to 0.5; PSMA PET shows also a solitary L pubic ramus met
- He undergoes SBRT monotherapy 35Gy in 5 fractions
- **No PSA response, repeat PSMA PET shows new nodal conglomerate 1 month after SBRT**

Phase II ORIOLE Trial showing benefit of MDT + ADT

POPULATION

54 Men



Adult men with recurrent, hormone-sensitive prostate cancer and 1-3 metastases detectable by conventional imaging

Median age: 68 y

SETTINGS / LOCATIONS

3 Radiation treatment facilities in 2 US locations

INTERVENTION

54 Patients randomized

36 Stereotactic radiotherapy

Stereotactic ablative radiotherapy (SABR) to all metastases

18 Observation

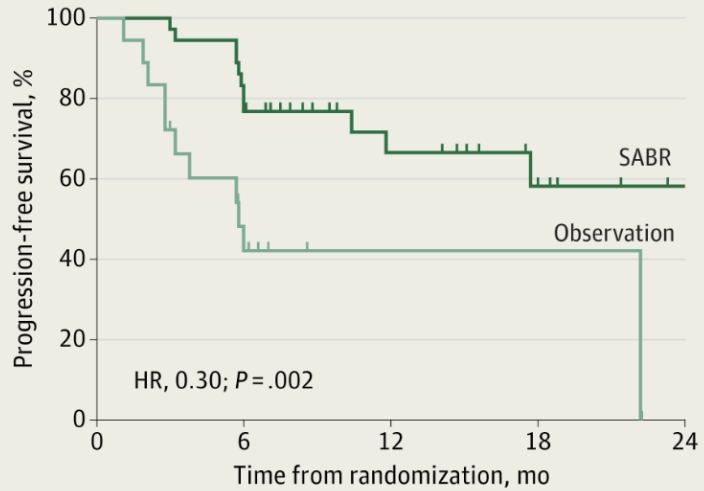
Observation only for 6 mo

PRIMARY OUTCOME

Progression of disease measured by any of the following: prostate-specific antigen testing, conventional imaging, symptomatic progression, androgen deprivation therapy initiation for any reason, death

FINDINGS

Progression of disease at 6 mo was less common with SABR compared with observation (19% vs 61%; *P* = .005)



Proportion of patients with progression at 6 mo

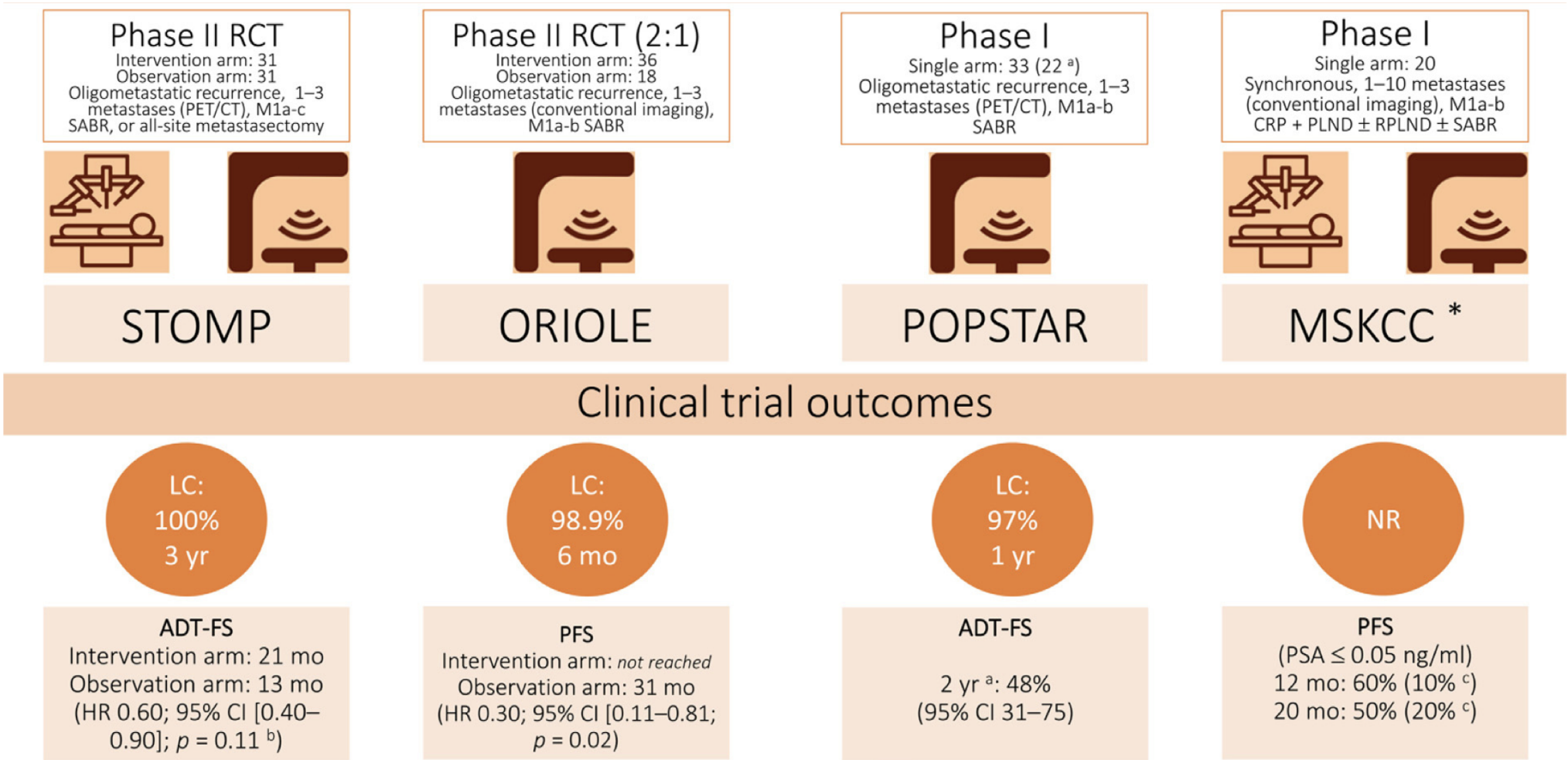
Stereotactic radiotherapy: **19%**

Observation: **61%**

PFS: prostate-specific antigen level increase, progression detected by conventional imaging, symptomatic progression, ADT initiation, or death

Phillips, *JAMA Onc*, 2020

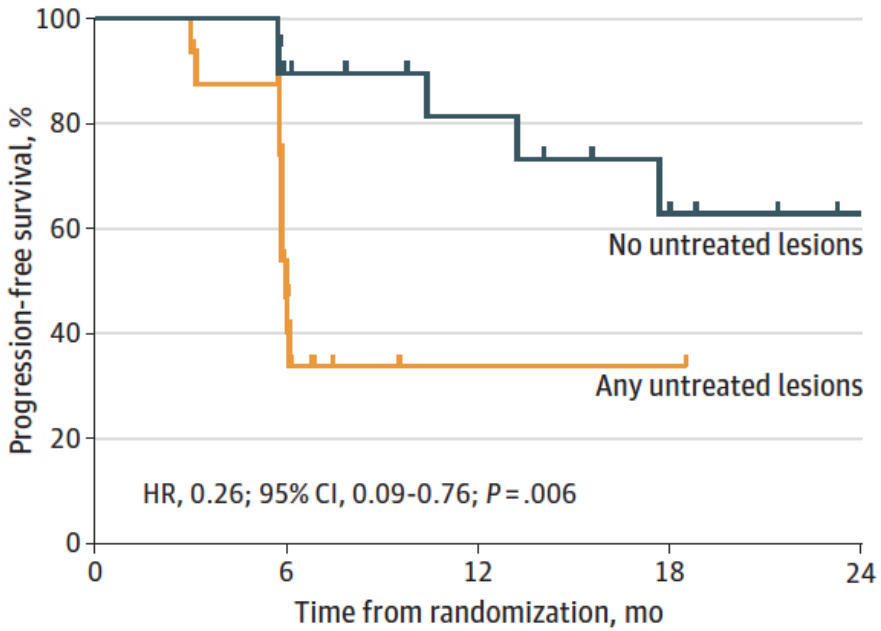
MDT is associated with excellent local control



Connor et al, Eur. Ur. Onc. 2020

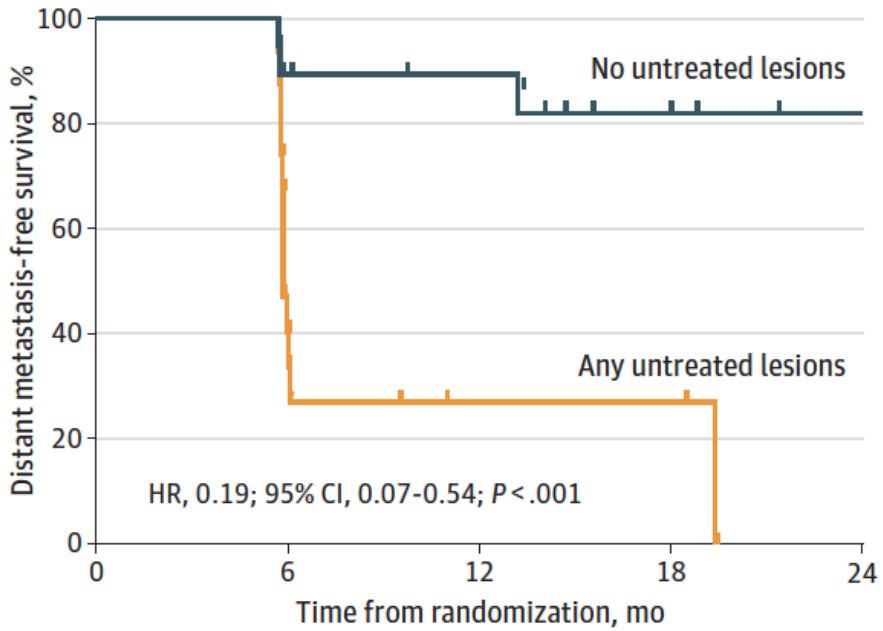
MDT works *much* better if you ablate all lesions

C PFS stratified by presence of untreated lesions



No. at risk					
No untreated	19	14	10	6	2
Any untreated	16	7	1	1	0

D DMFS stratified by presence of untreated lesions



No. at risk					
No untreated	19	14	12	8	4
Any untreated	16	6	2	2	0

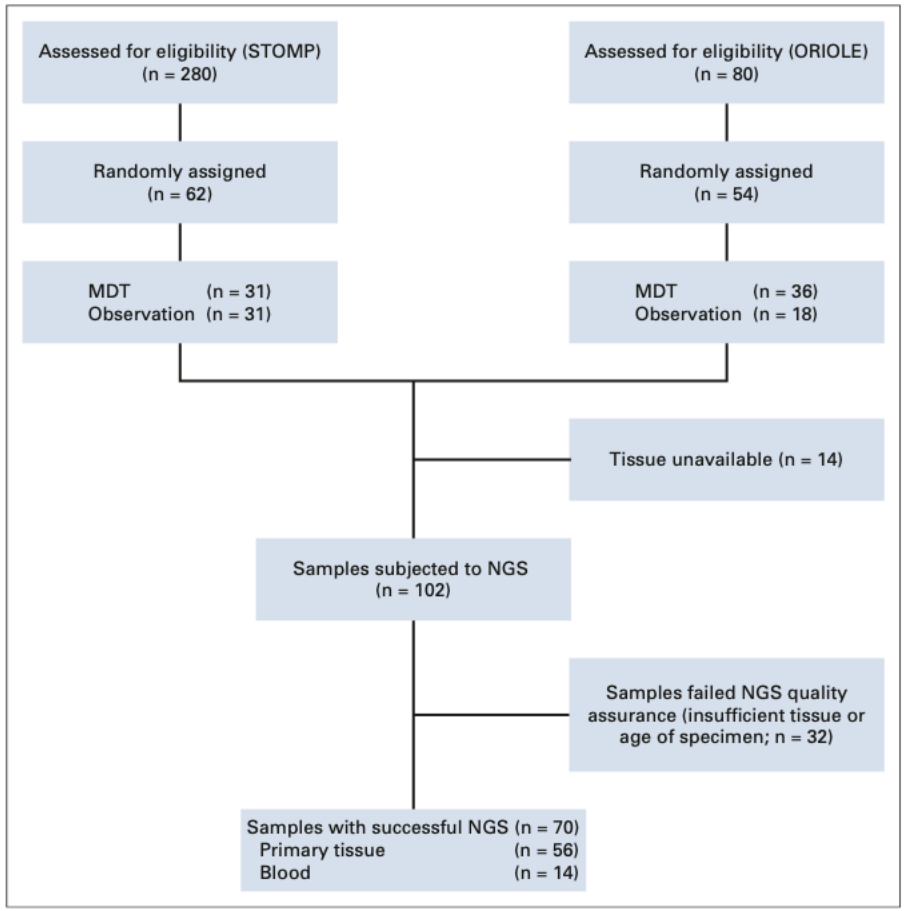
Who will benefit from MDT alone?

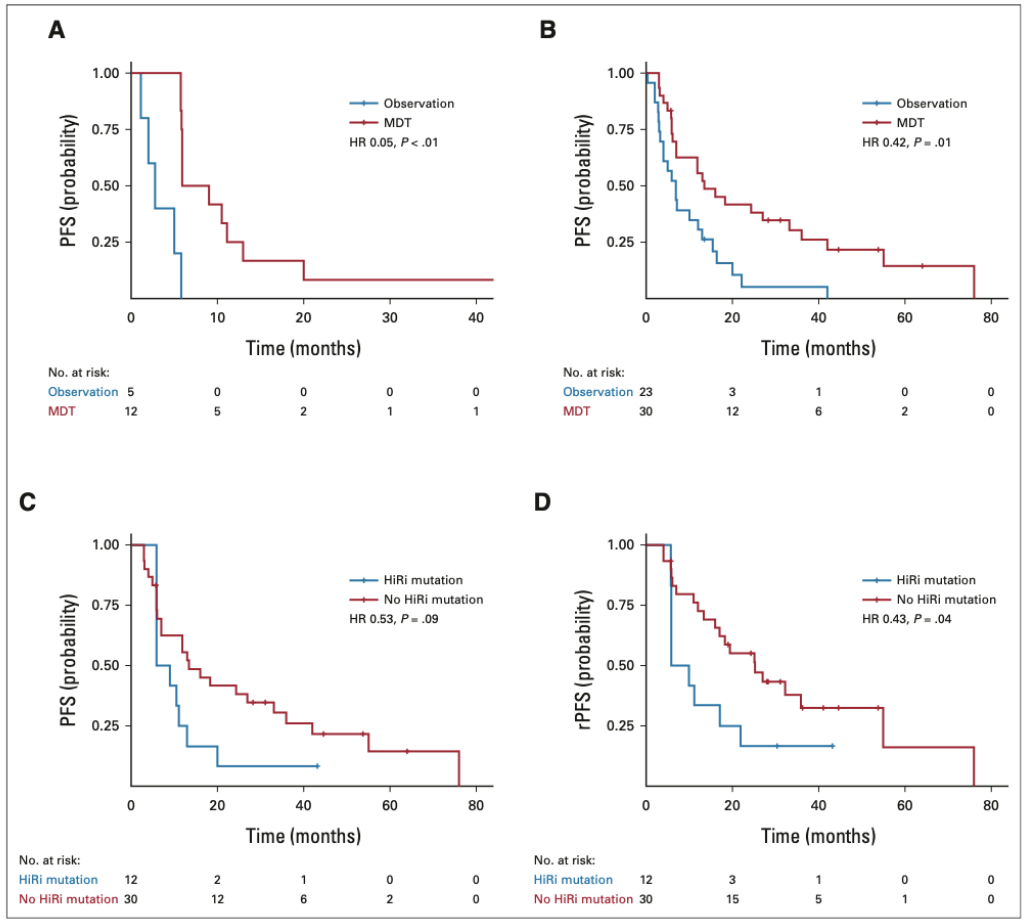
High risk mutations: ATM, BRCA1/2, RB1, TP53

clinical trial update

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

Matthew P. Deek, MD[1,2]; Kim Van der Eecken, MD, PhD[3]; Philip Sutera, MD[2]; Rebecca A. Deek, MS[4]; Valérie Fonteyne, MD, PhD[5]; Adrianna A. Mendes, MD[6]; Karel Decaestecker, MD, PhD[7]; Ana Ponce Kiess, MD, PhD[2]; Nicolaas Lumen, MD, PhD[5];

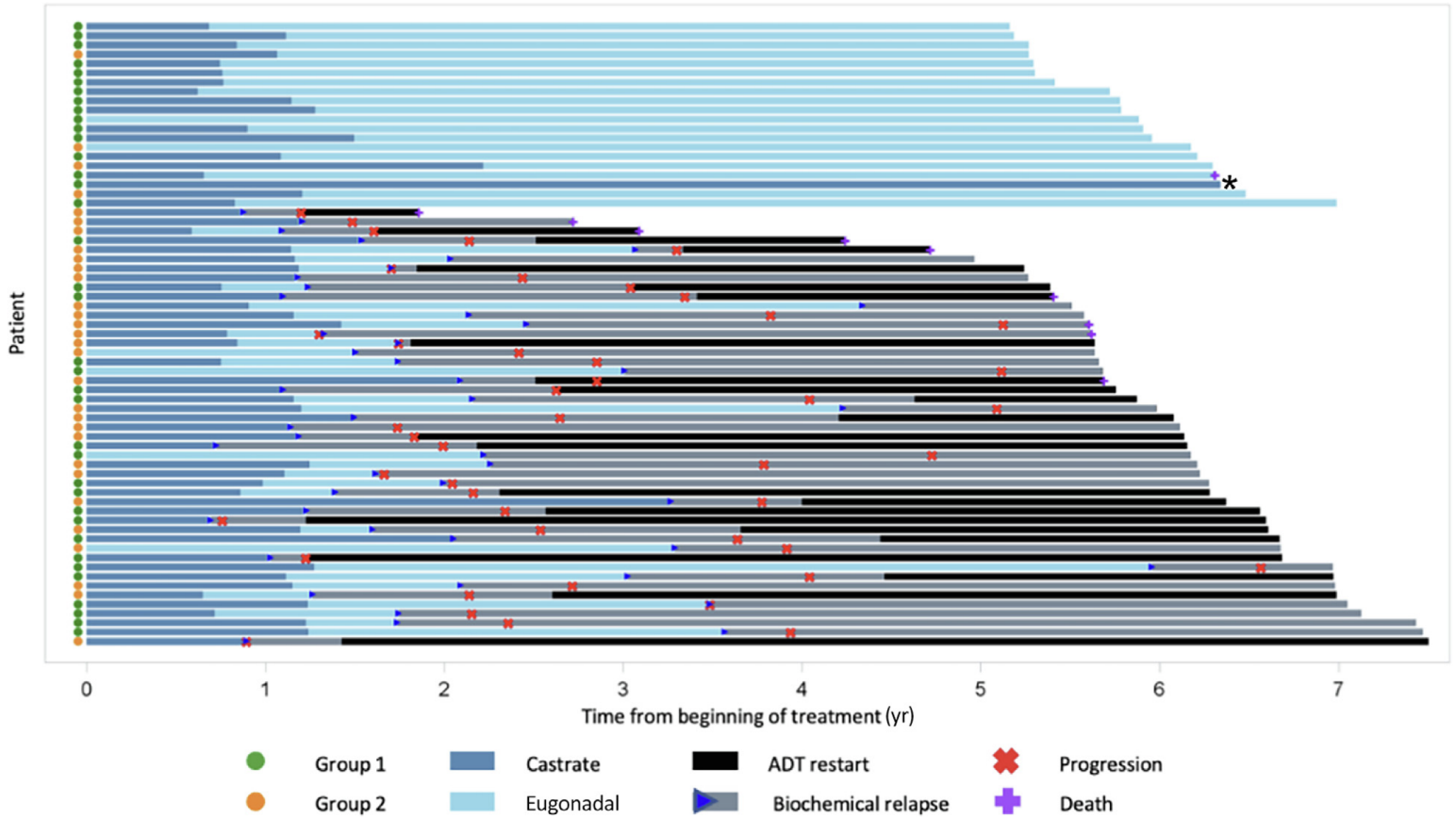




When MDT alone is not enough…

- Multiple studies have evaluated benefit of adding ADT or ADT/ARSI to MDT
    - ADT/ARSI sensitize prostate cancer to radiation
- However, ADT and AR-directed therapies have side effects
- Addition of MDT to ADT/ARSI can thus reduce duration of ADT and possibly prevent the need for lifelong androgen ablation

Elective nodal RT may be needed for oligo N+ progression



Group 1: no prior BCR
Group 2: prior BCR

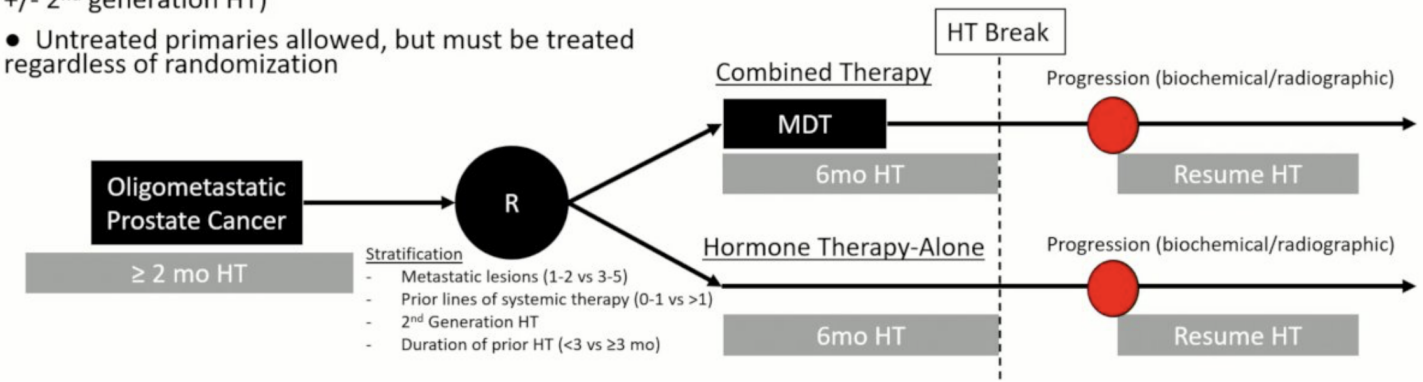
Vaugier, GETUG-P01 (OLIGOPELVIS)

MDRT can reduce duration of ADT use and T recovery

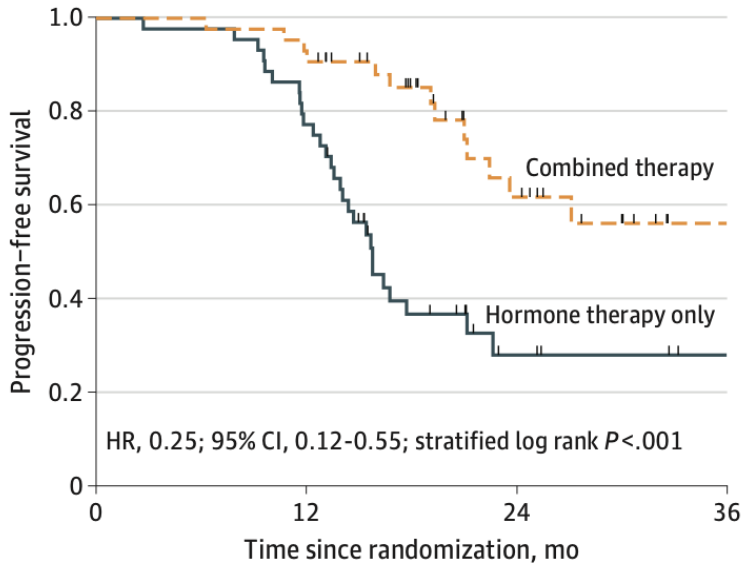
EXTEND intermittent prostate cancer

Major Inclusion Criteria

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



A Progression-free survival by randomization arm

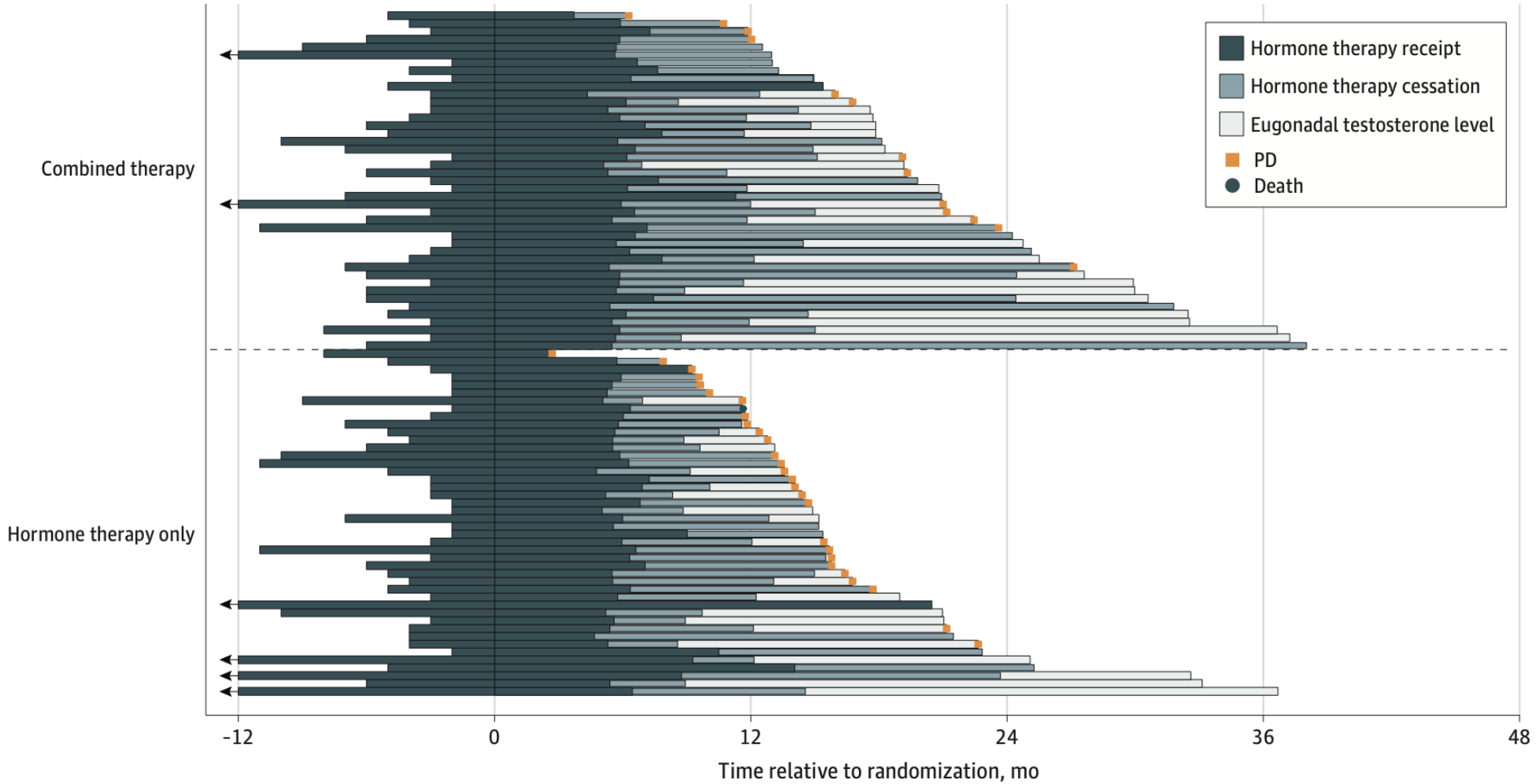


No. at risk

Hormone therapy only	44	34	5	1
Combined therapy	43	40	15	3

Tang et. al, JAMA Onc, 2023

MDRT can reduce duration of ADT use and T recovery

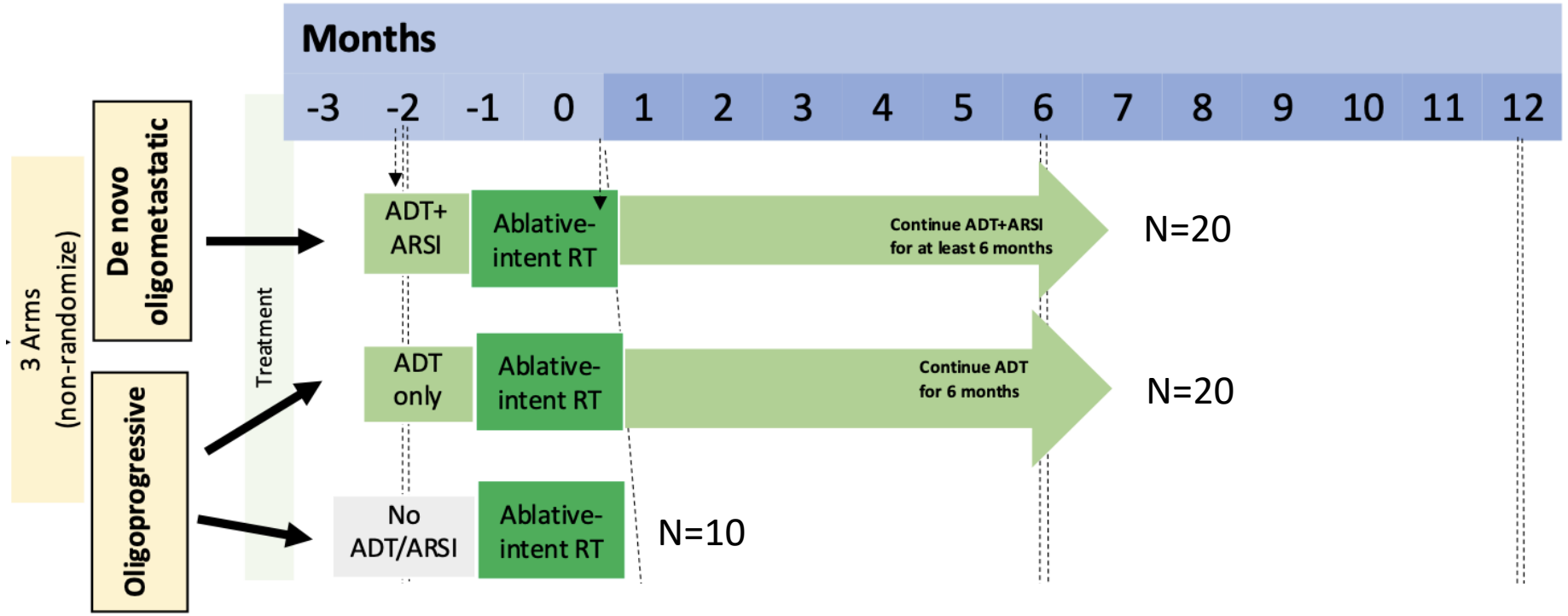


Tang et. al, JAMA Onc, 2023

How can we improve MDT outcomes?

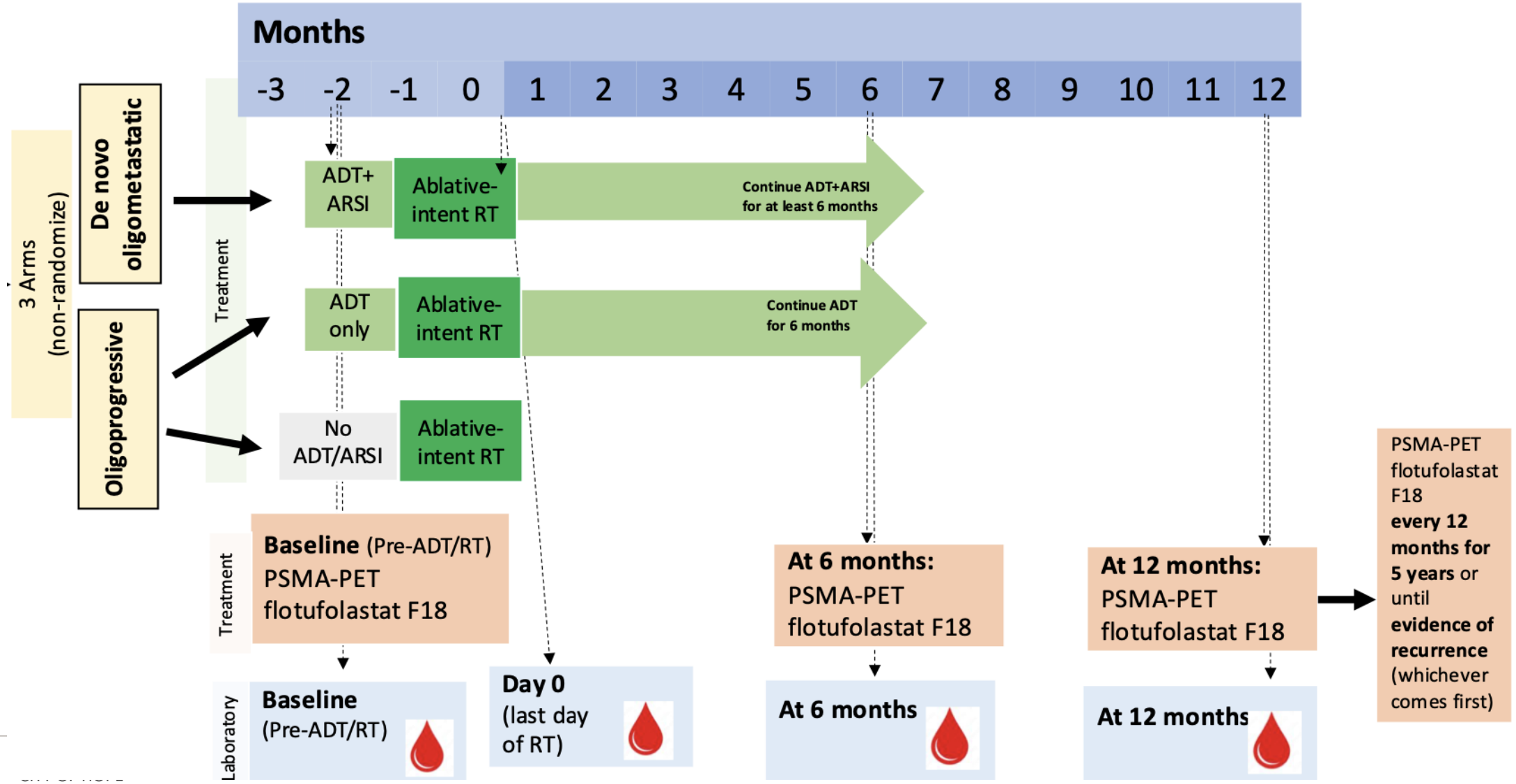
- Ultimately, MDT may not provide sufficient durable control alone
- LC is excellent but systemic control after MDT is difficult to assess during ADT
  - Accurate and sensitive imaging to identify who truly has oligometastatic disease
  - Validated imaging to evaluate systemic outcomes
  - Imaging or liquid biomarkers to capture early systemic progression or predict efficacy

Phase II Study of POSLUMA-PSMA PET Response after Oligo-Metastatic/Progressive-directed Treatment with Radiotherapy (PROMPT-R)



In collaboration with Dr. Tanya Dorff
IIT supported from Blue Earth Diagnostics

IRB25339: PROMPT-R Study Schema



Conclusions: MDT for oligometastatic HSPC

- No precise definition for “oligo”, most studies use <=3-5 sites, stage patients with PSMA PET CT
- MDT prolongs PFS, bPFS (possibly OS) and improve QoL by omitting, reducing or delaying ADT
    - With more patients and longer follow up, MDT may show improved OS
- MDT with SBRT is well-established to be safe with excellent LC (>95%)
- If MDT is planned, you must treat ALL sites to ABLATIVE doses
- Randomized evidence support ADT+SBRT over ADT or SBRT alone for oligometastatic patients
    - No comparison of SBRT vs SBRT+ADT+ARSI thus far available
    - Can SBRT delay need for ARSI and/or ARSI resistance?
- Early data suggests a role for CD8+ tumor-reactive T-cells and T cell clonal expansion in mediating SBRT response

And a few commentaries

- With clinical experience, MDT can be safely delivered to multiple sites concurrently and/or sequentially as long as dose constraints are met for normal organs across ALL courses
- Patients MUST understand there is a possibility of limited/no benefit and accept the risks of MDT
- Ere on the side of offering MDT in "gray zone scenarios":
    - multiple nodes in a station count as "1" site (but the whole pelvis should be treated)
    - benefit of doubt for unclear lesions >3-5 (eg. low SUV rib met is possibly false positive)
- Most studies use short term (6 months) ADT in combination with MDT. LT-ADT is strongly recommended for de novo disease oligometastatic presentation

Thank you for listening

Thank You For Your Support

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