

# Oligometastatic Prostate Cancer

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MD Anderson Cancer Center

Location lorem ipsum

[bmuc.be/bmuc2024](https://bmuc.be/bmuc2024)



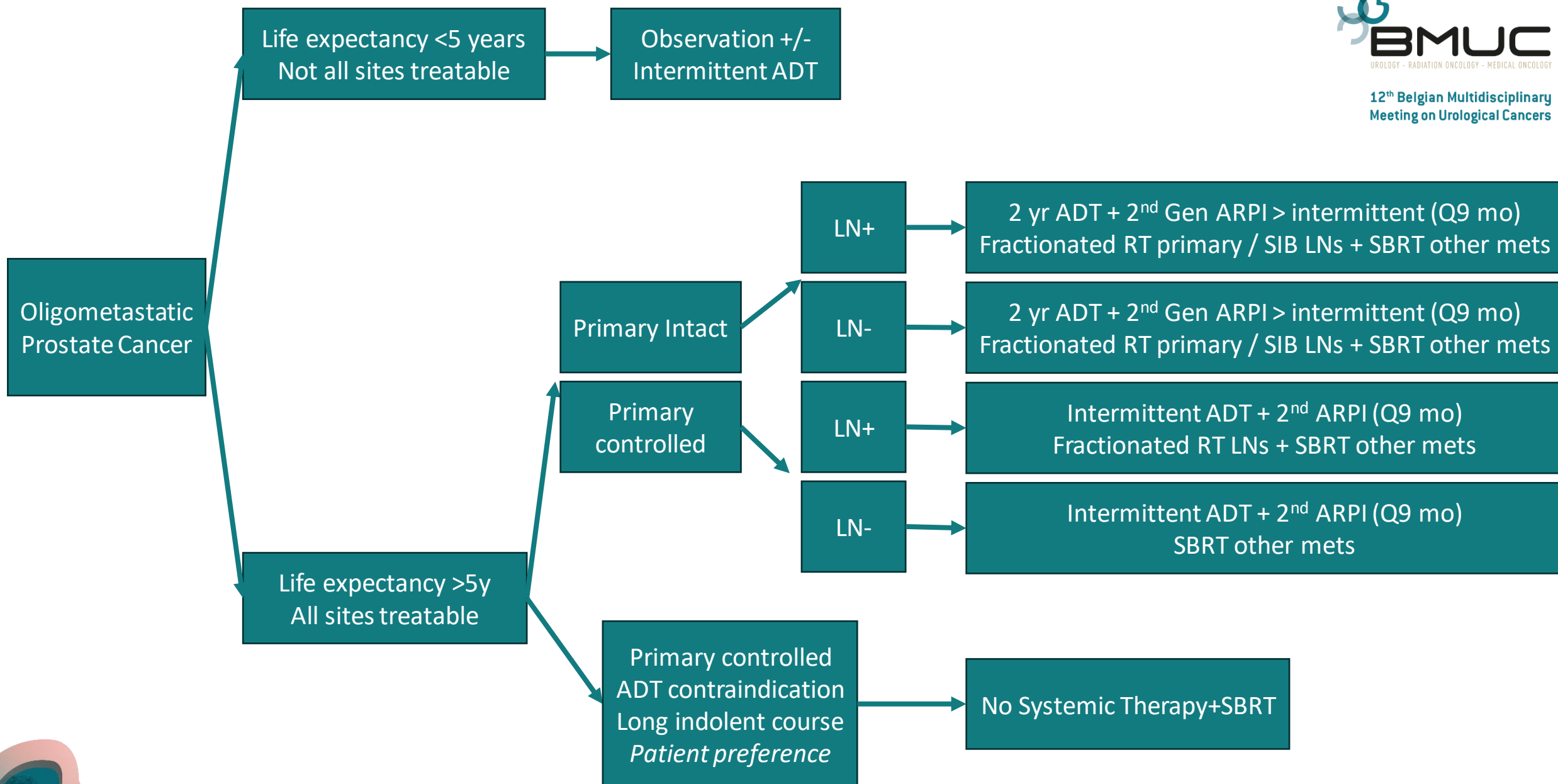
**12<sup>th</sup> Belgian Multidisciplinary  
Meeting on Urological Cancers**

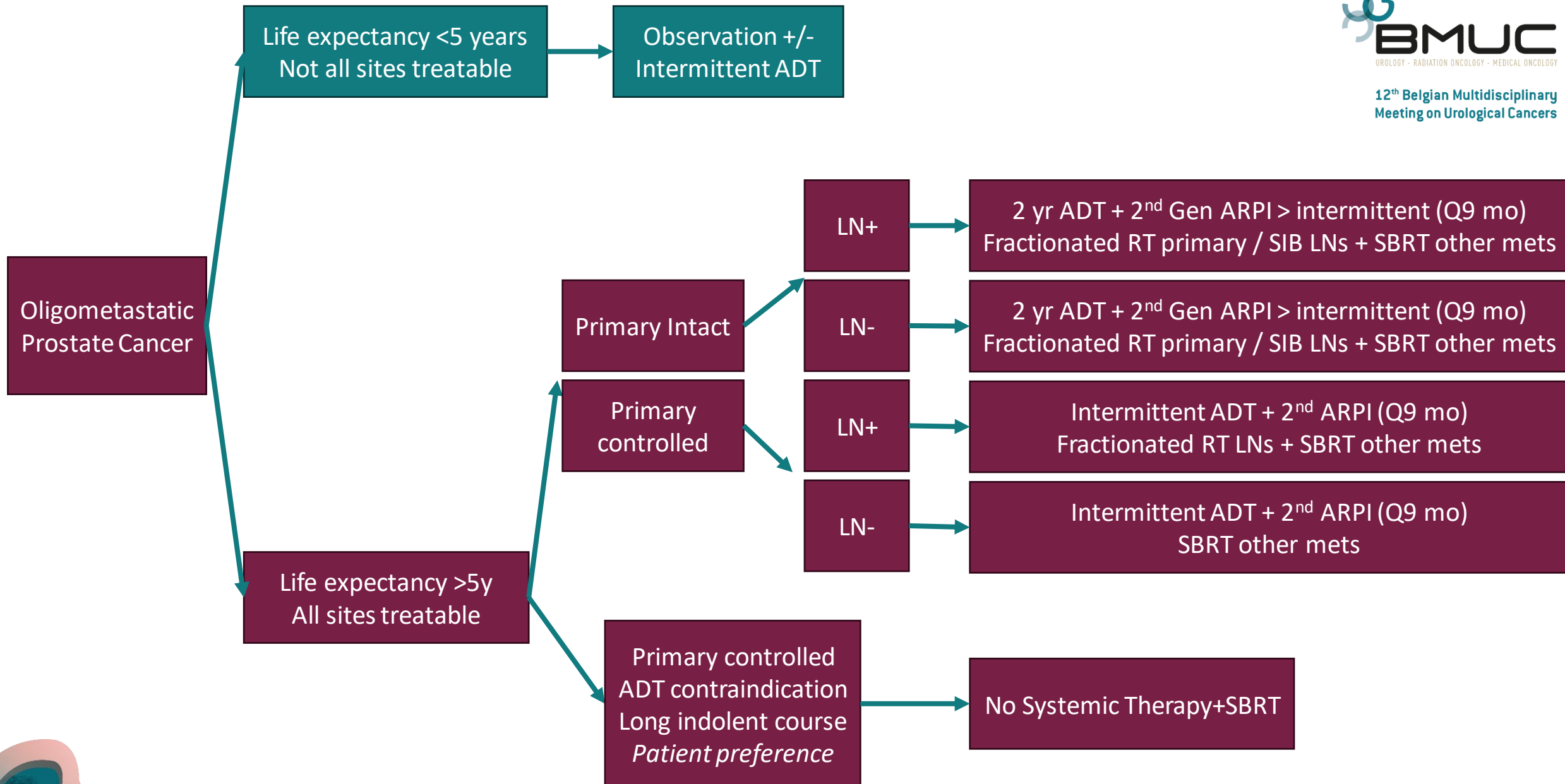
# Conflicts of interest

- I have the following potential conflict(s) of interest to report

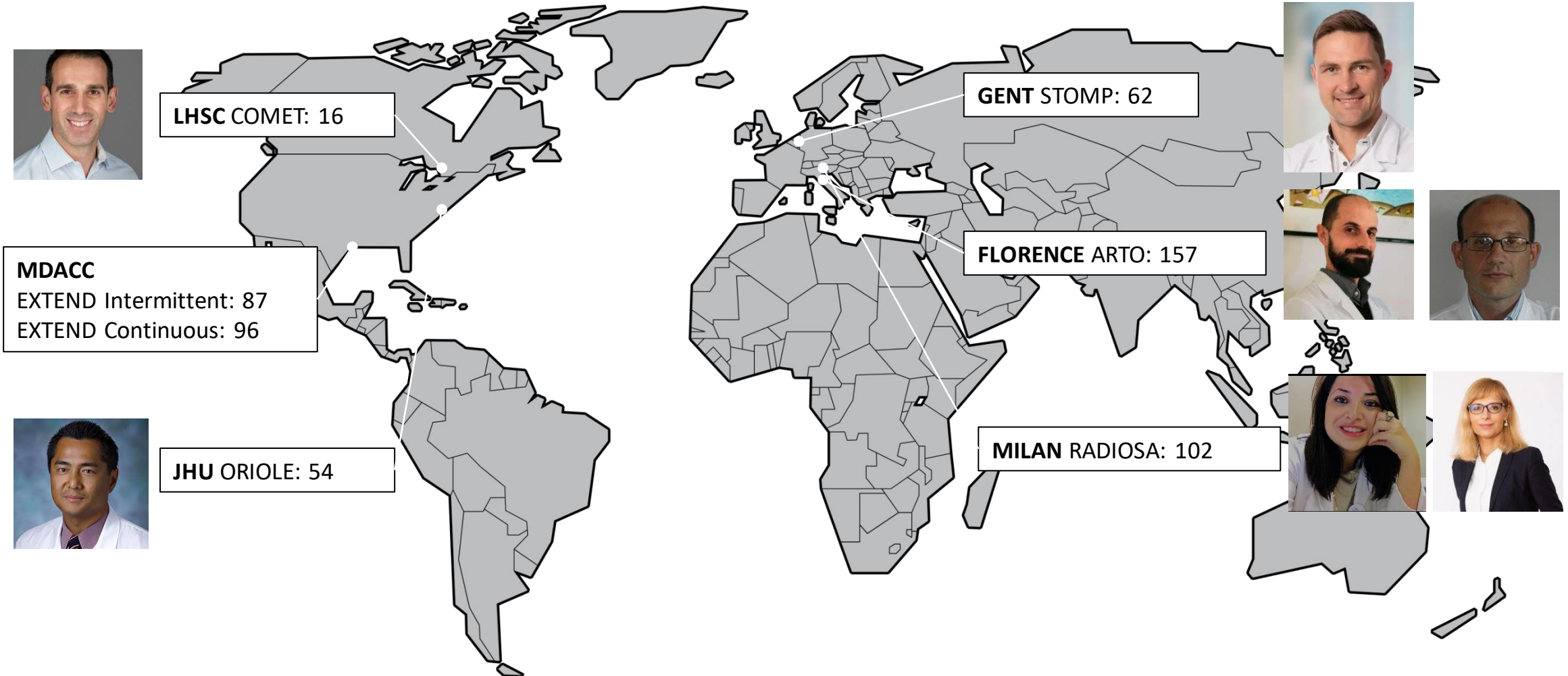
| Type of affiliation / financial interest               | Name of commercial company                                                                                                      |
|--------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Receipt of grants/research supports:                   | Merck, Myriad Genetics                                                                                                          |
| Receipt of honoraria or consultation fees:             | Lantheus, Telix, Boston Scientific, Molli Surgical, Vision RT, Elekta, Bayer                                                    |
| Participation in a company sponsored speaker's bureau: | NA                                                                                                                              |
| Stock shareholder:                                     | NA                                                                                                                              |
| Spouse/partner:                                        | NA                                                                                                                              |
| Other support (please specify):                        | Editor of MD Anderson Handbook of Radiation Oncology, published by Wolter Kluwer (1 <sup>st</sup> and 2 <sup>nd</sup> Editions) |



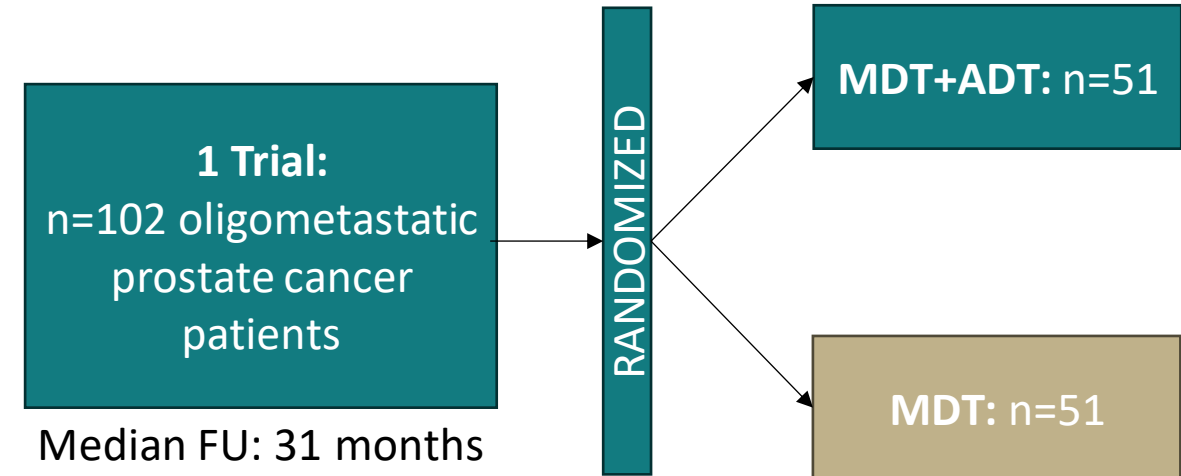
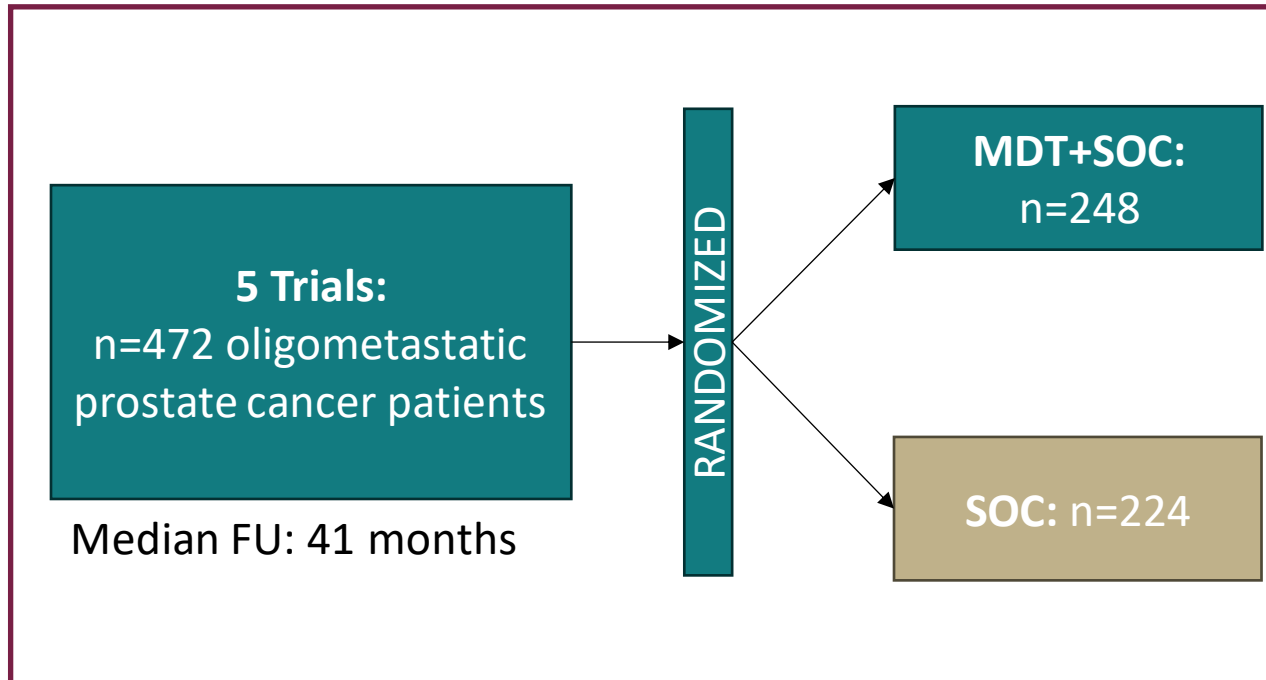




# Should we treat? WOLVERINE-XMET Collaboration



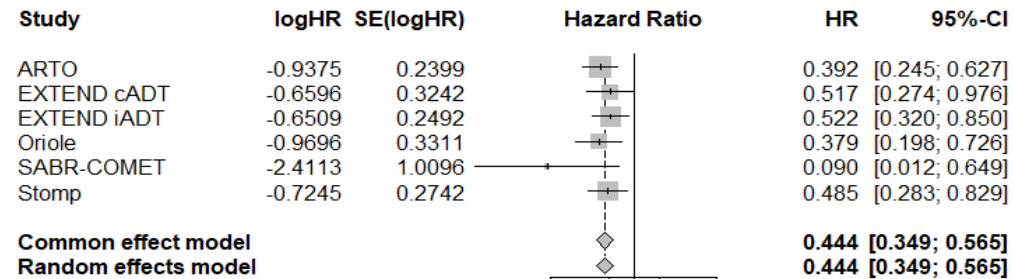
# Randomization Schema



# Progression Free Survival

## Trial Level Analysis:

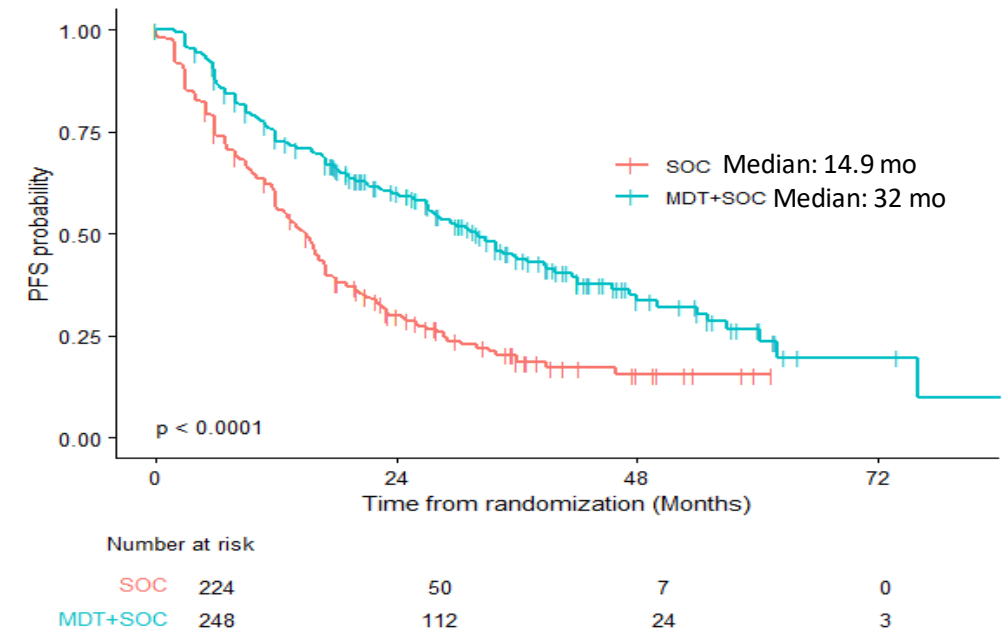
Random effects model  $P < 0.001$



Heterogeneity:  $I^2 = 0\%$ ,  $\tau^2 < 0.0001$ ,  $p = 0.59$

## Cox Regression (Stratified by Trial):

MDT (vs SOC) HR: 0.45 (95% CI: 0.35-0.58),  $P < 0.001$



# Radiographic Progression Free Survival

## Trial Level Analysis:

Random effects model  $P=0.004$

| Study       | logHR   | SE(logHR) | Hazard Ratio                                                                      | HR    | 95%-CI         |
|-------------|---------|-----------|-----------------------------------------------------------------------------------|-------|----------------|
| ARTO        | -0.9558 | 0.2402    |  | 0.384 | [0.240; 0.616] |
| EXTEND cADT | -0.1462 | 0.3488    |  | 0.864 | [0.436; 1.712] |
| EXTEND iADT | -0.4759 | 0.2667    |  | 0.621 | [0.368; 1.048] |
| Oriole      | -0.3878 | 0.3858    |  | 0.679 | [0.319; 1.445] |
| SABR-COMET  | -2.4113 | 1.0096    |  | 0.090 | [0.012; 0.649] |
| Stomp       | -0.1081 | 0.2974    |  | 0.898 | [0.501; 1.608] |

Random effects model

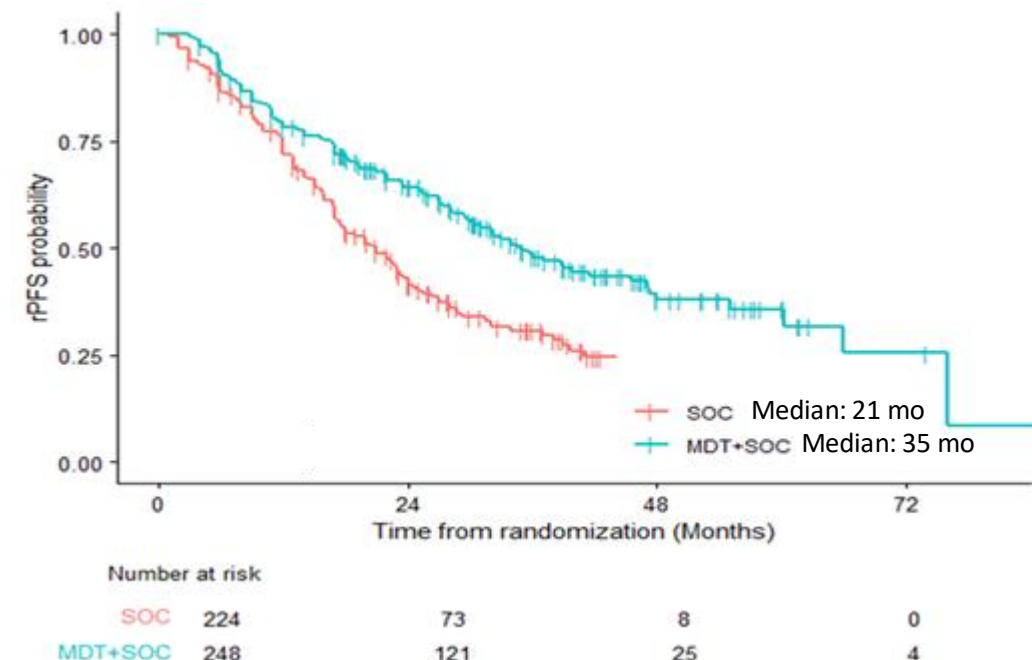
0.600 [0.425; 0.849]

Heterogeneity:  $I^2 = 50\%$ ,  $\tau^2 = 0.0699$ ,  $p = 0.07$

0.1 0.5 1 2 10

## Cox Regression (Stratified by Trial):

MDT (vs SOC) HR: 0.59 (95% CI: 0.46-0.76),  $P < 0.001$



# Freedom from Castration Resistance

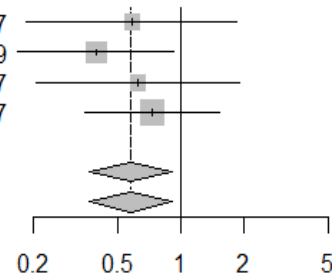
## Castration Sensitive Subset Only (n= 257)

### Trial Level Analysis:

Random effects model  $P=0.019$

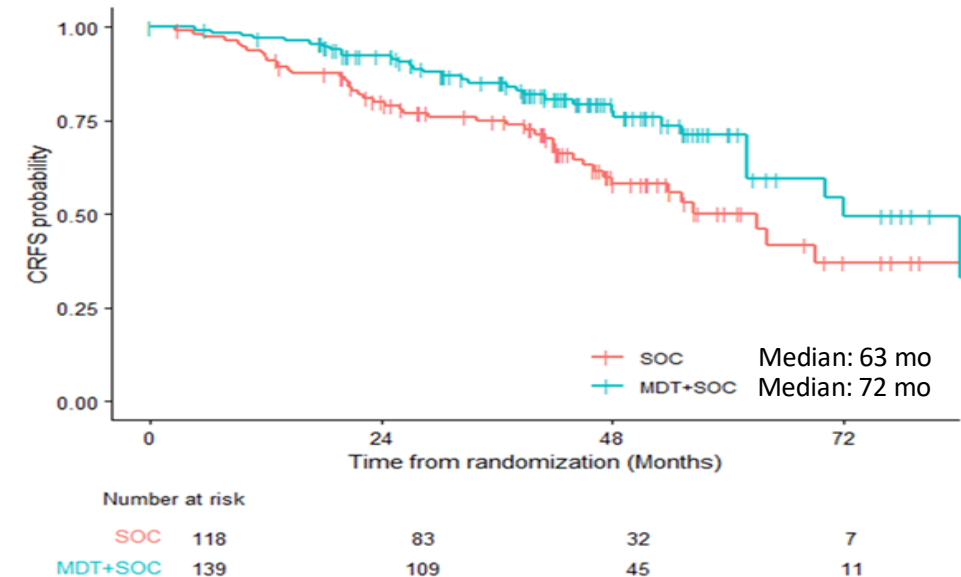
| Study                       | logHR   | SE(logHR) | Hazard Ratio | HR           | 95%-CI                |
|-----------------------------|---------|-----------|--------------|--------------|-----------------------|
| EXTEND cADT                 | -0.5336 | 0.5857    |              | 0.586        | [0.186; 1.848]        |
| EXTEND iADT                 | -0.9218 | 0.4359    |              | 0.398        | [0.169; 0.935]        |
| Oriole                      | -0.4666 | 0.5687    |              | 0.627        | [0.206; 1.912]        |
| Stomp                       | -0.3073 | 0.3747    |              | 0.735        | [0.353; 1.533]        |
| <b>Common effect model</b>  |         |           |              | <b>0.579</b> | <b>[0.367; 0.915]</b> |
| <b>Random effects model</b> |         |           |              | <b>0.579</b> | <b>[0.367; 0.915]</b> |

Heterogeneity:  $I^2 = 0\%$ ,  $\tau^2 = 0$ ,  $p = 0.76$



### Cox Regression (Stratified by Trial):

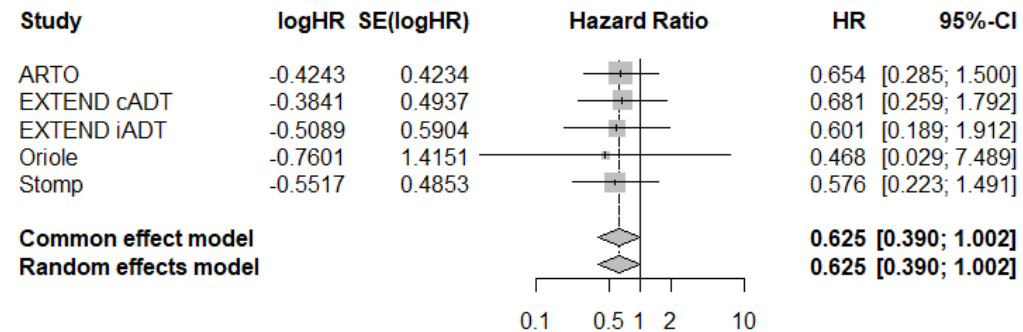
MDT (vs SOC) HR: 0.58 (95% CI: 0.37-0.91),  $P = 0.02$



# Overall Survival

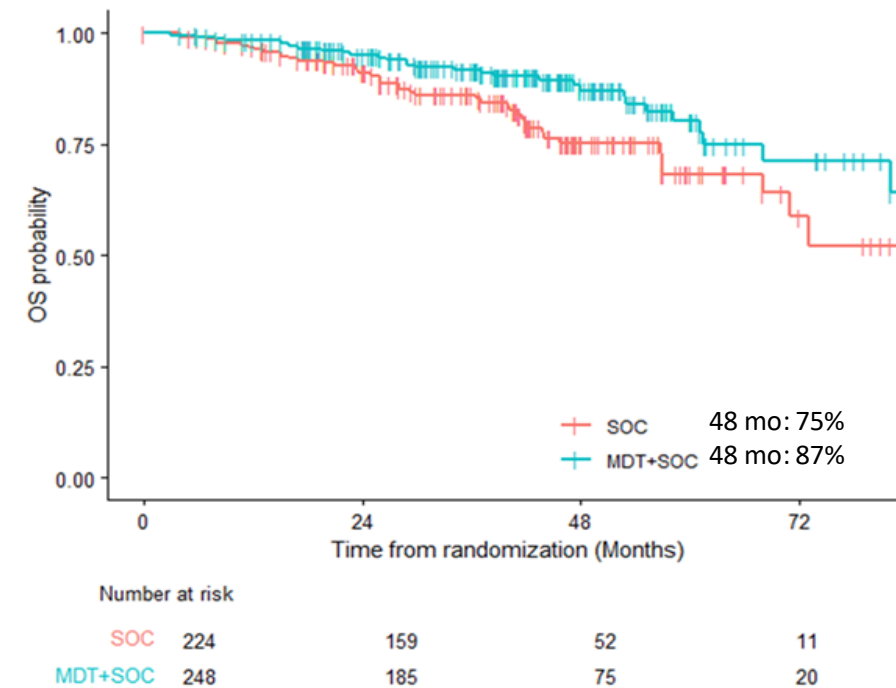
## Trial Level Analysis:

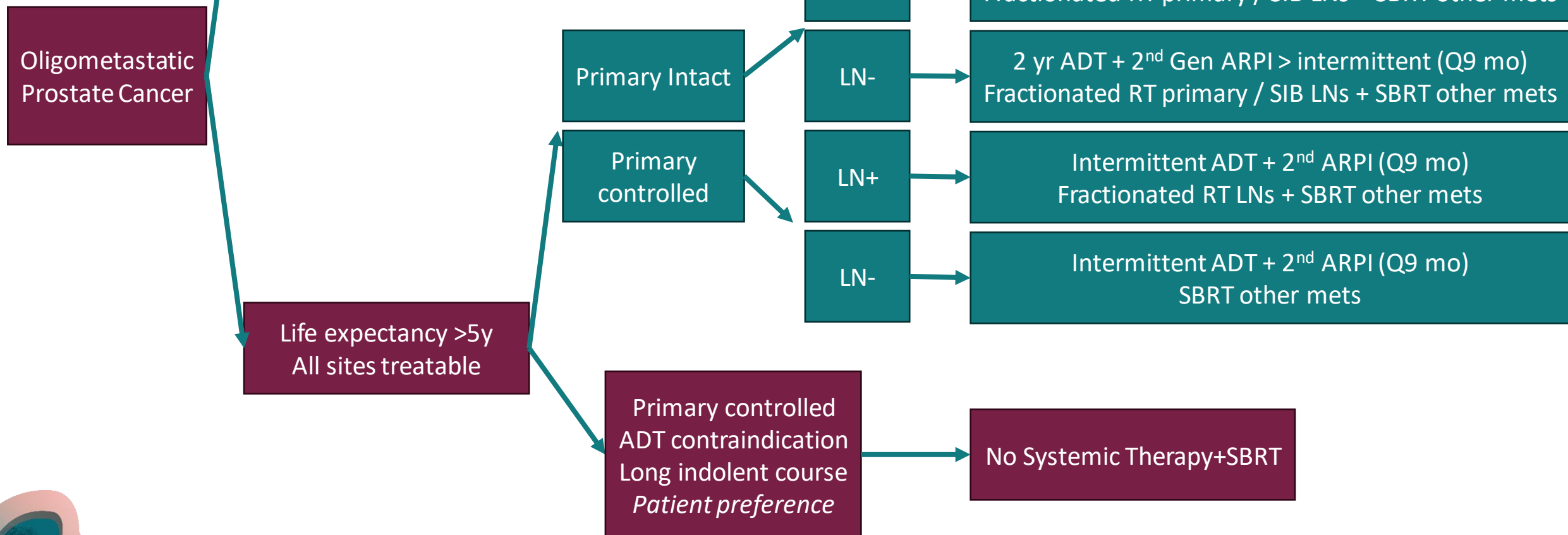
Random effects model  $P=0.051$



## Cox Regression (Stratified by Trial):

MDT (vs SOC) HR: 0.64 (95% CI: 0.40-1.01),  $P = 0.057$





# STOMP

## Initial staging:

1. Choline PET
2. MRI of the prostate/fossa

2012-2015: 62 recurrent with  $\leq 3$   
extracranial metastasis

RANDOMIZED

Metastasis directed therapy

Median FU 3 yrs

Surveillance

# ORIOLE

## Initial staging:

1. CT c/a/p
2. Bone Scan

2016-2018: 54 recurrent disease  
with up 1-3 metastatic lesions,  
hormone naïve for metastatic  
disease

RANDOMIZED

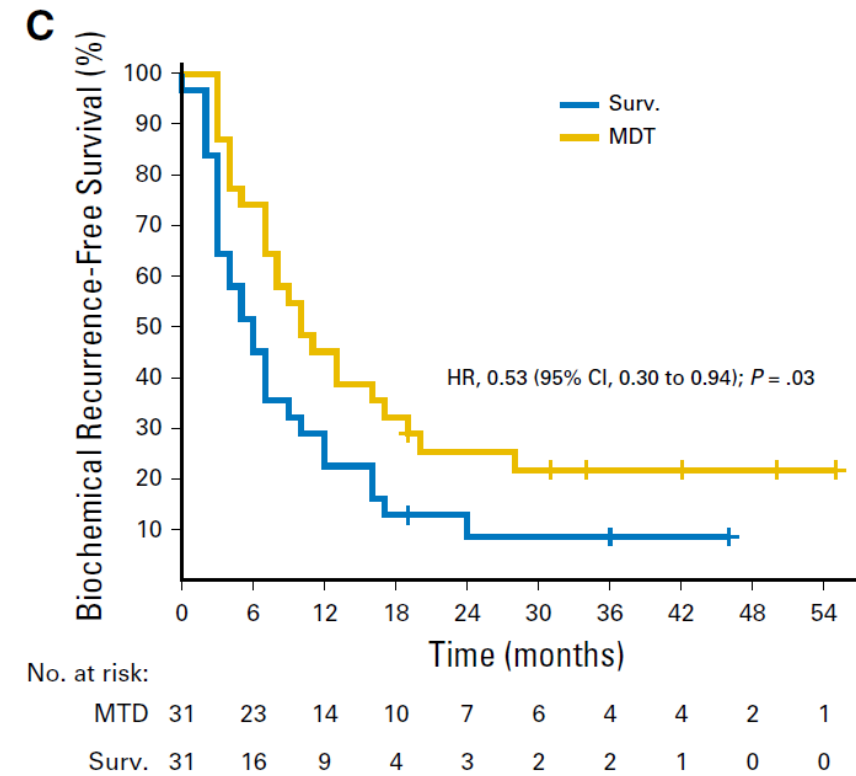
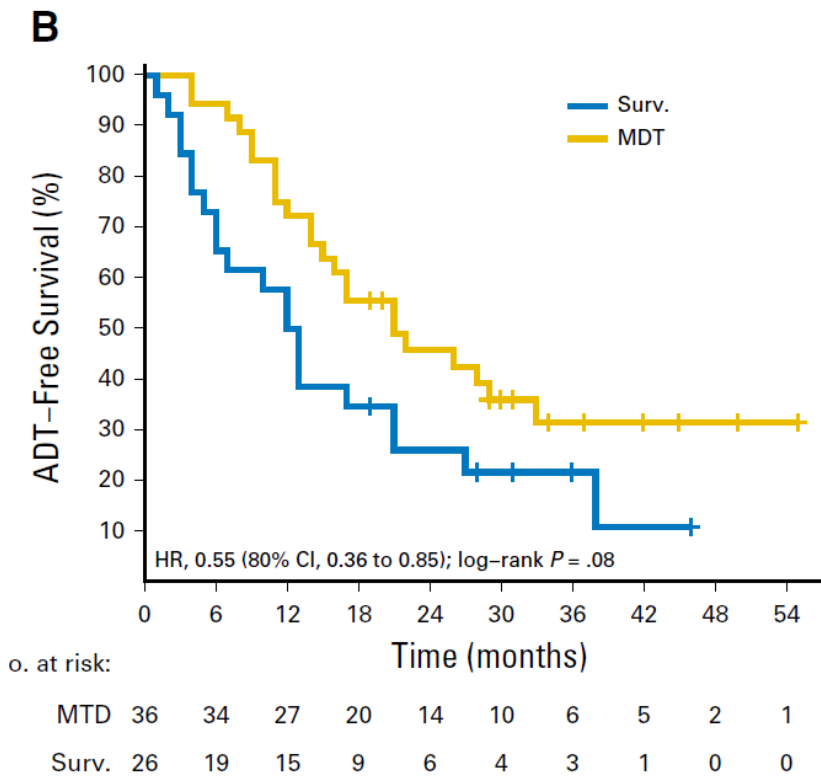
Metastasis directed therapy

Median FU 3 yrs

Surveillance

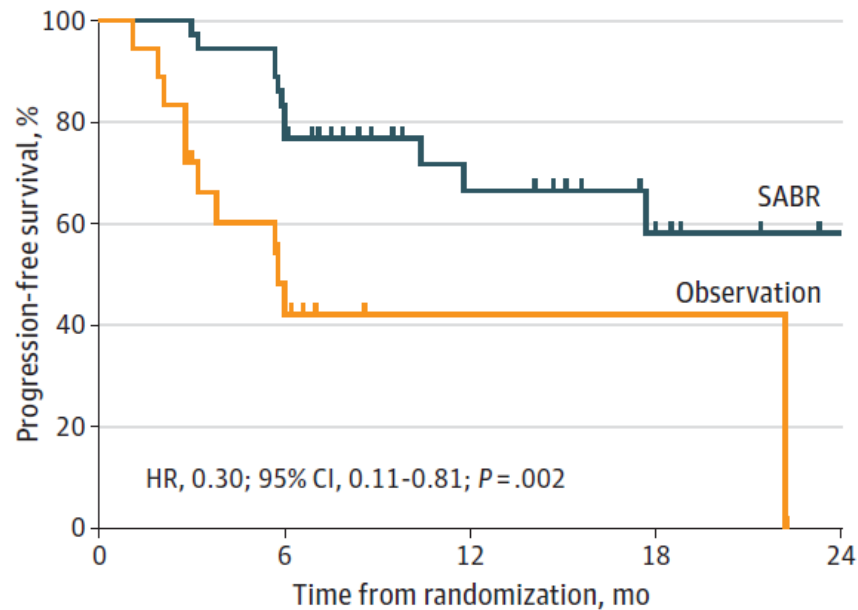
**Primary outcome:** PCWG3 progression (PSA, RECIST,  
or symptomatic decline) at 6 months

# STOMP Results



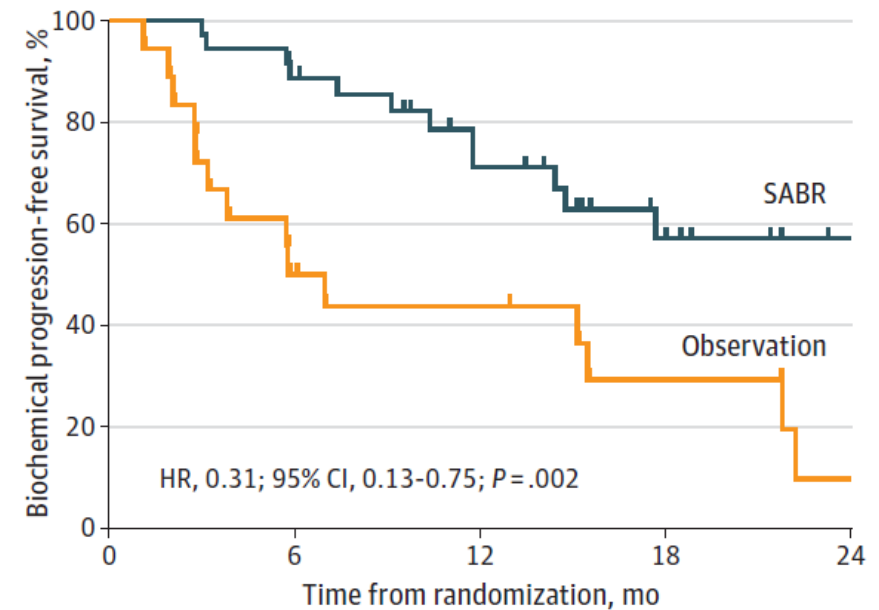
# Oriole Results

**A** Composite PFS stratified by study arm



|             |    |    |    |   |   |
|-------------|----|----|----|---|---|
| No. at risk |    |    |    |   |   |
| SABR        | 36 | 26 | 13 | 7 | 2 |
| Observation | 18 | 8  | 1  | 1 | 0 |

**B** Biochemical PFS stratified by study arm



|             |    |    |    |    |   |
|-------------|----|----|----|----|---|
| No. at risk |    |    |    |    |   |
| SABR        | 36 | 28 | 20 | 10 | 4 |
| Observation | 18 | 9  | 7  | 4  | 1 |

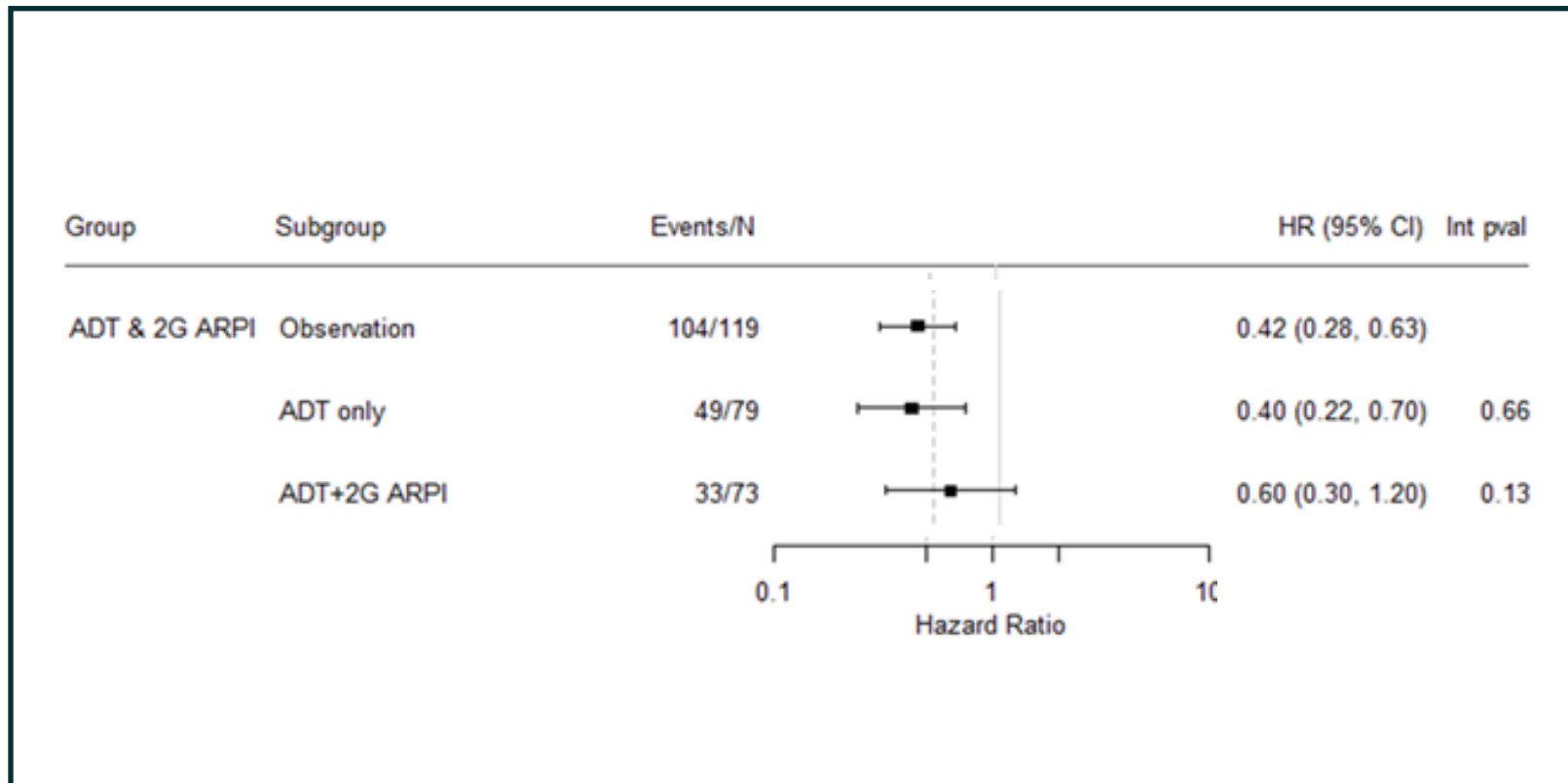
# STOMP-ORIOLE Combined Analysis

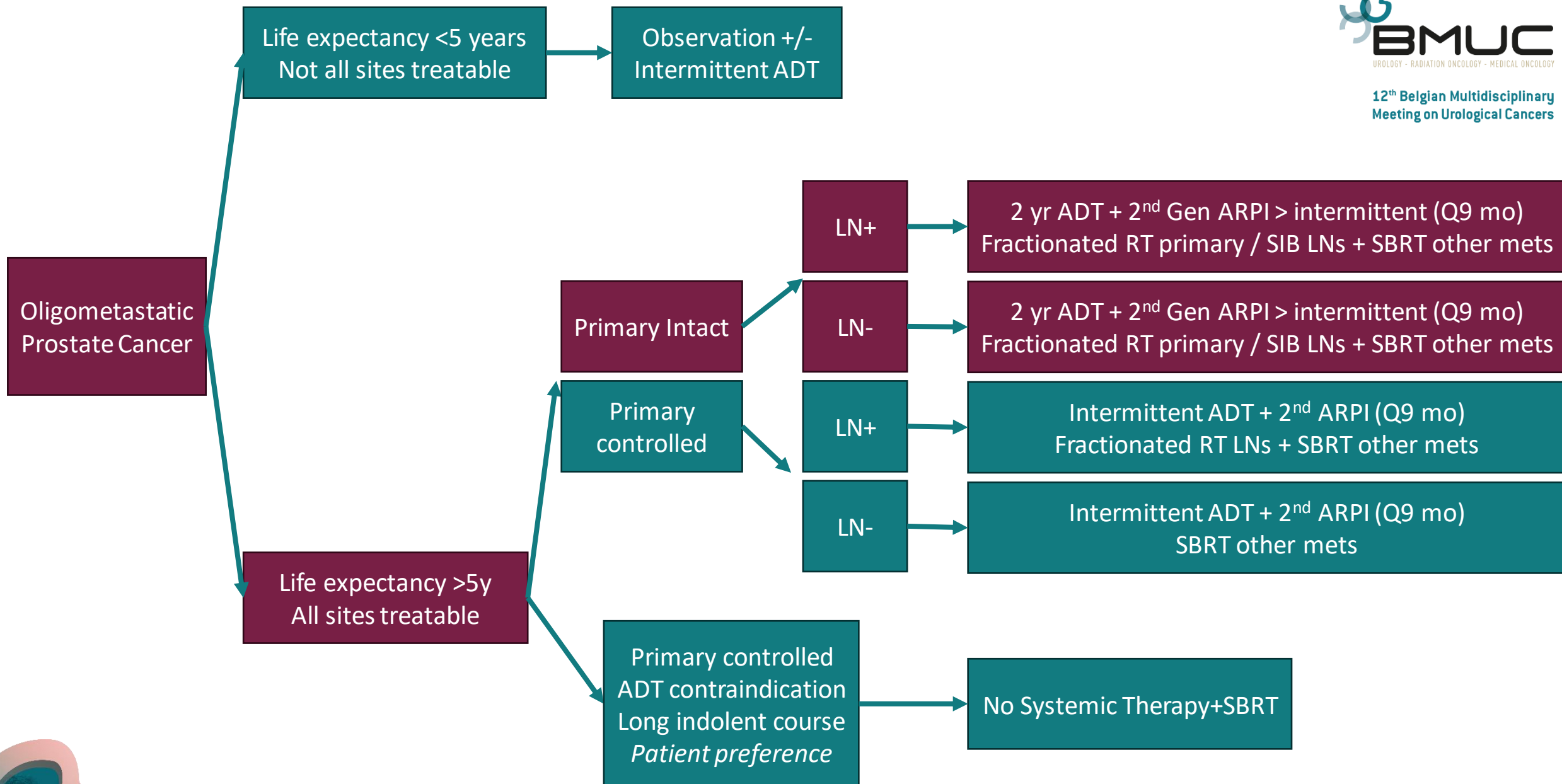
Long-term analysis with median FU of 52.5 Months

| 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    |

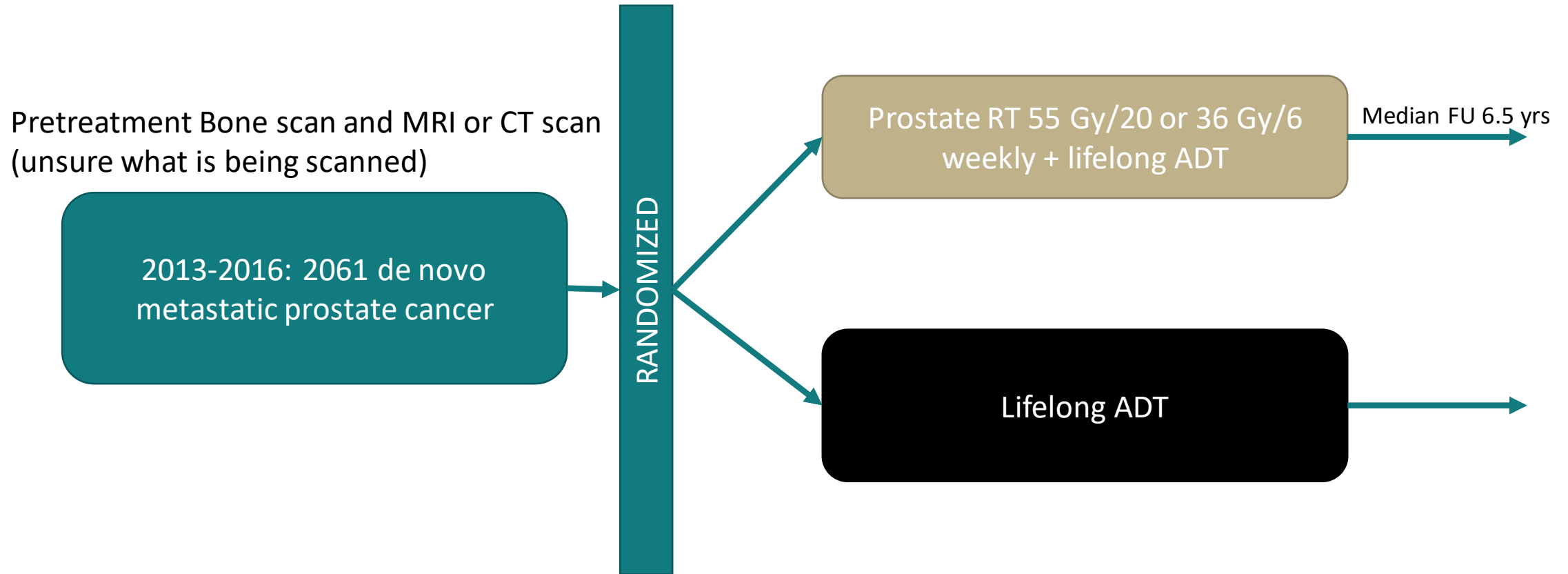
# WOLVERINE: Subgroups

## Benefit of MDT vs no MDT

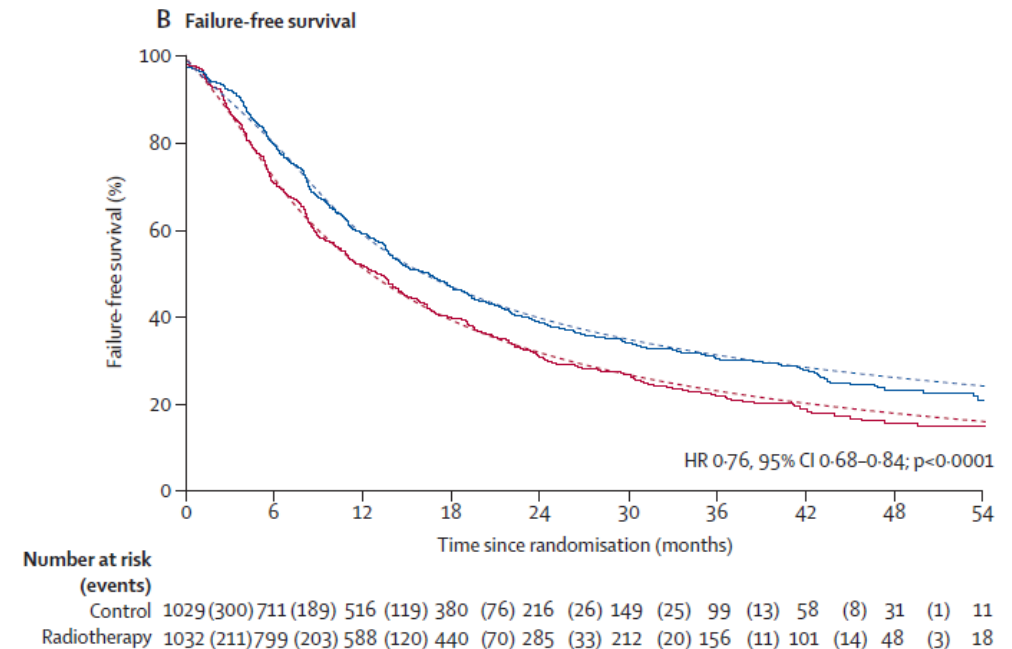
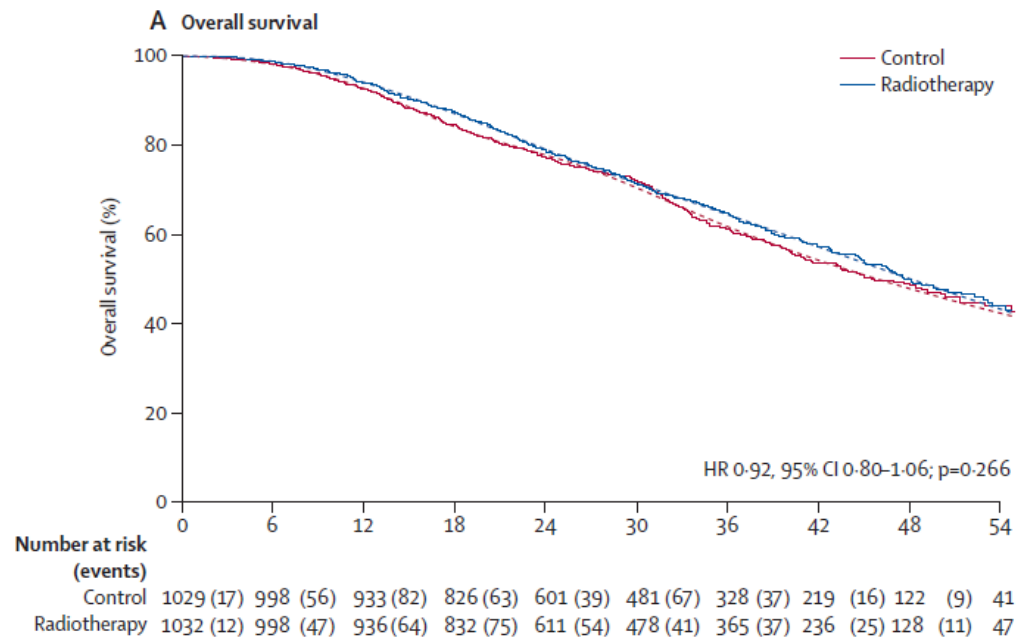




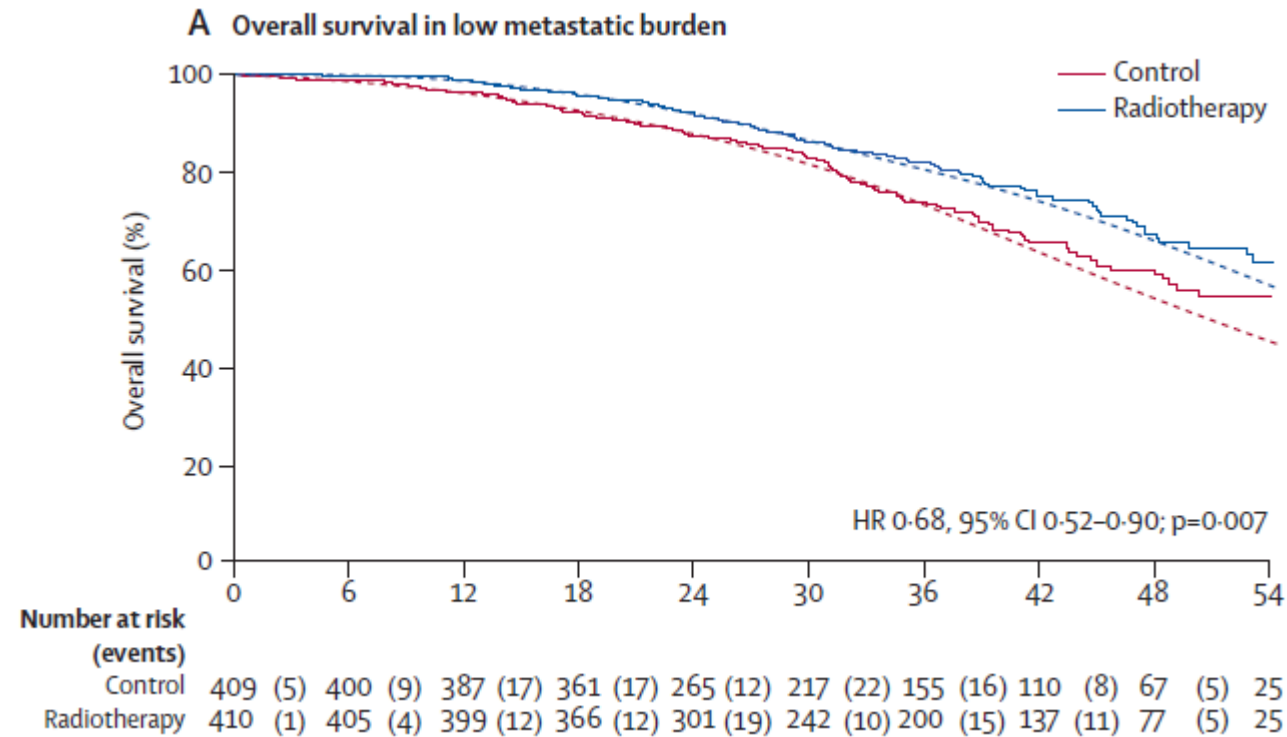
# Prostate Cancer RT: STAMPEDE Arm H



# STAMPEDE Arm H: Primary Outcome



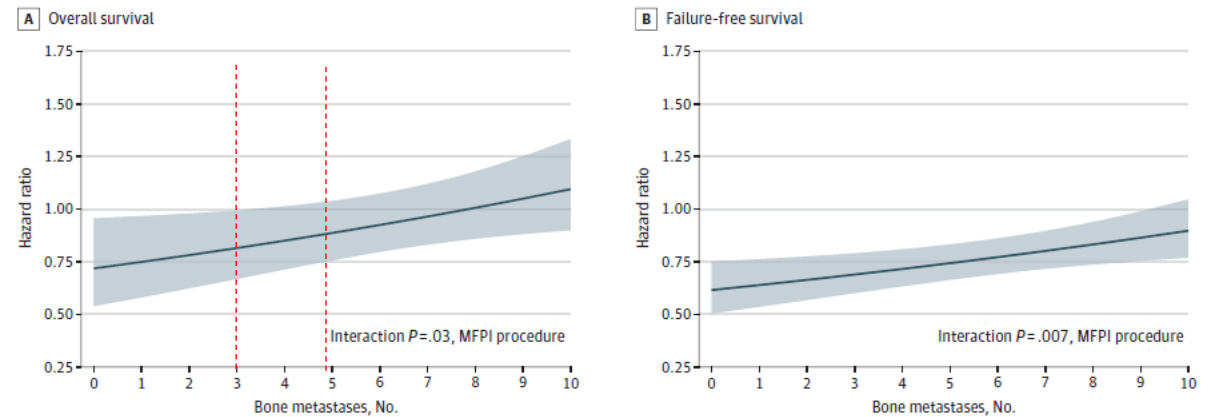
# STAMPEDE Arm H: Low Metastatic Burden



# STAMPEDE Arm H: Subgroup Analysis

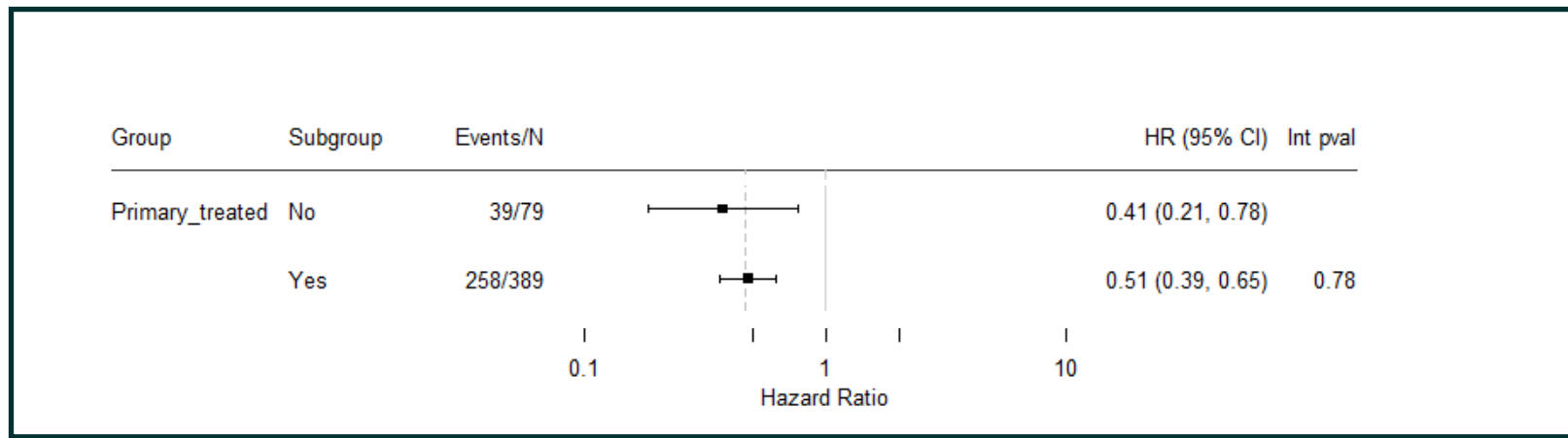
- Significant improvement in OS with  $\leq 3$  bone metastases.
- Survival improved in patients with non-regional lymph node (NRLN) only disease but not in patients with visceral mets.

Figure 2. Treatment Effect Plots for Bone Metastasis Count

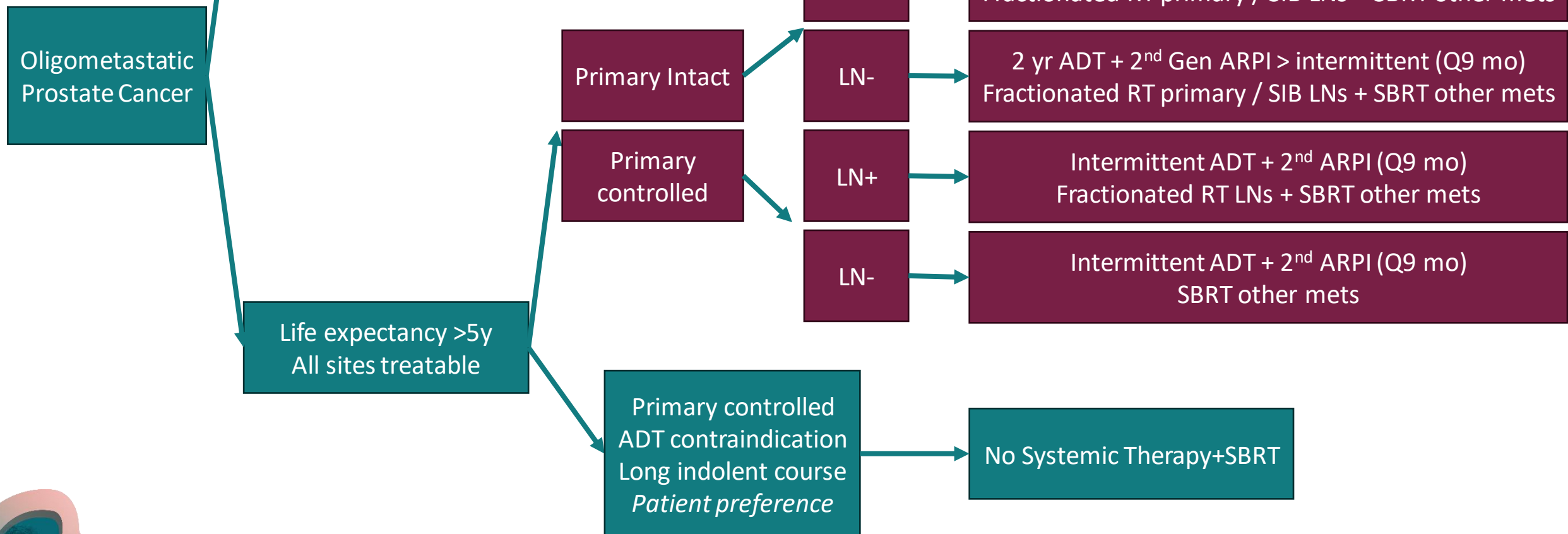


# WOLVERINE: Subgroups

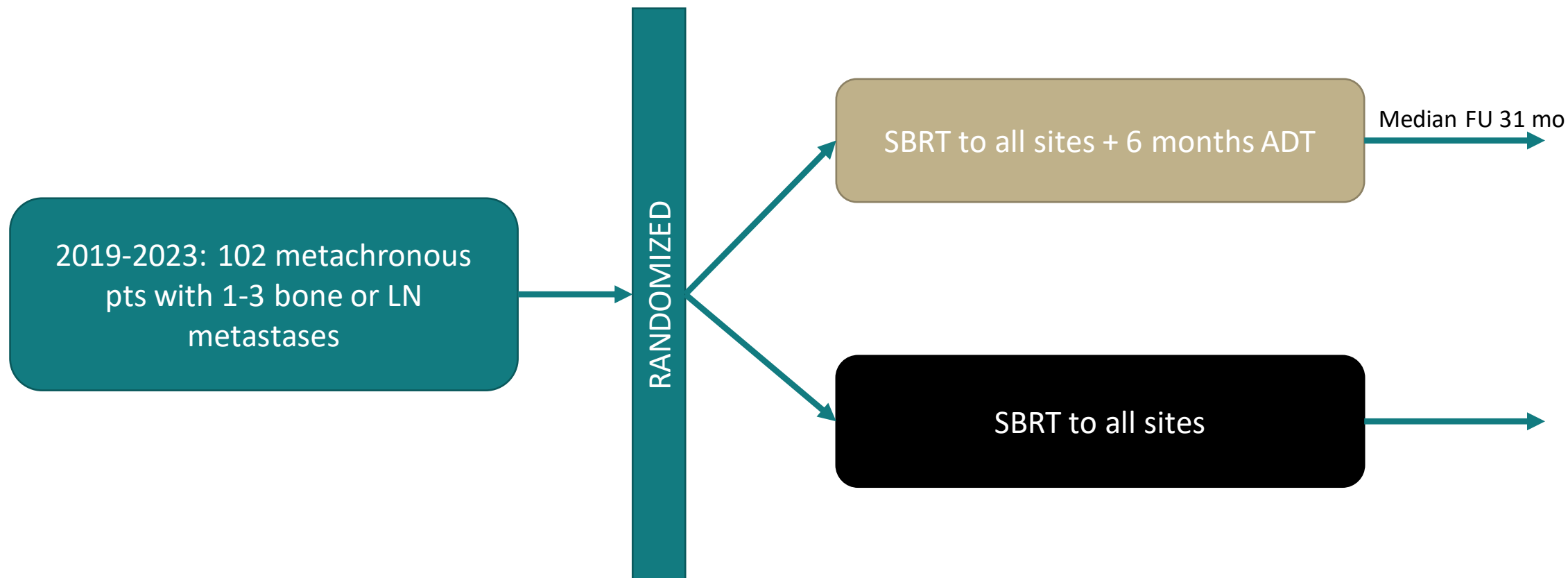
## Benefit of MDT vs no MDT



De novo disease is an area of greater uncertainty, trial enrollment is encouraged



# RADIOSA



# RADIOSA Results

- 6 month ADT improved primary endpoint of clinical progression free survival (~radiographic progression free survival)
- Endpoints such as overall survival and castration resistance free survival immature

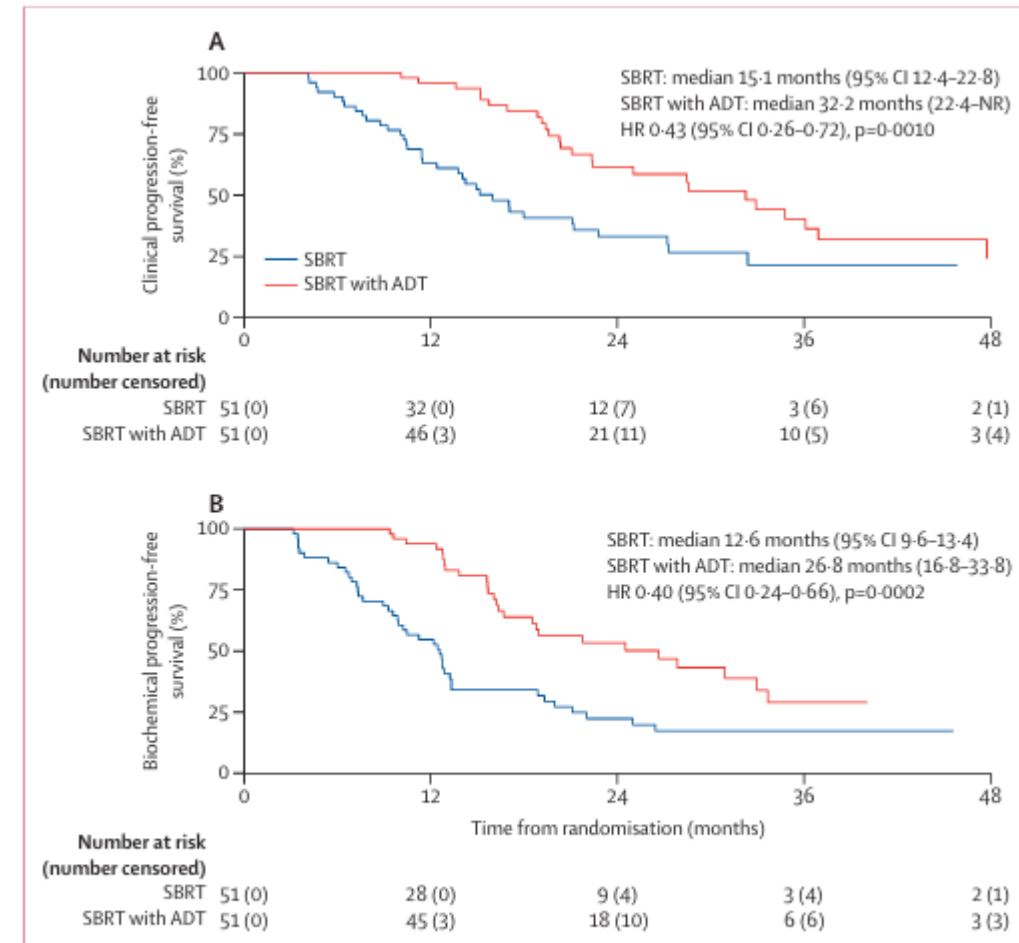
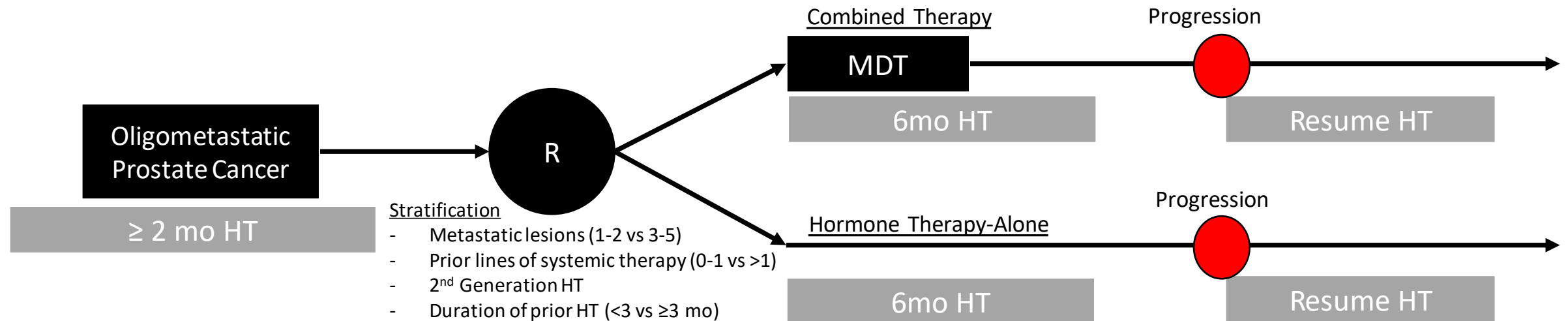


Figure 2: Kaplan-Meier plot of clinical progression-free survival (A) and biochemical progression-free survival (B) by treatment group  
ADT=androgen deprivation therapy. HR=hazard ratio. NR=not reached. SBRT=stereotactic body radiotherapy.

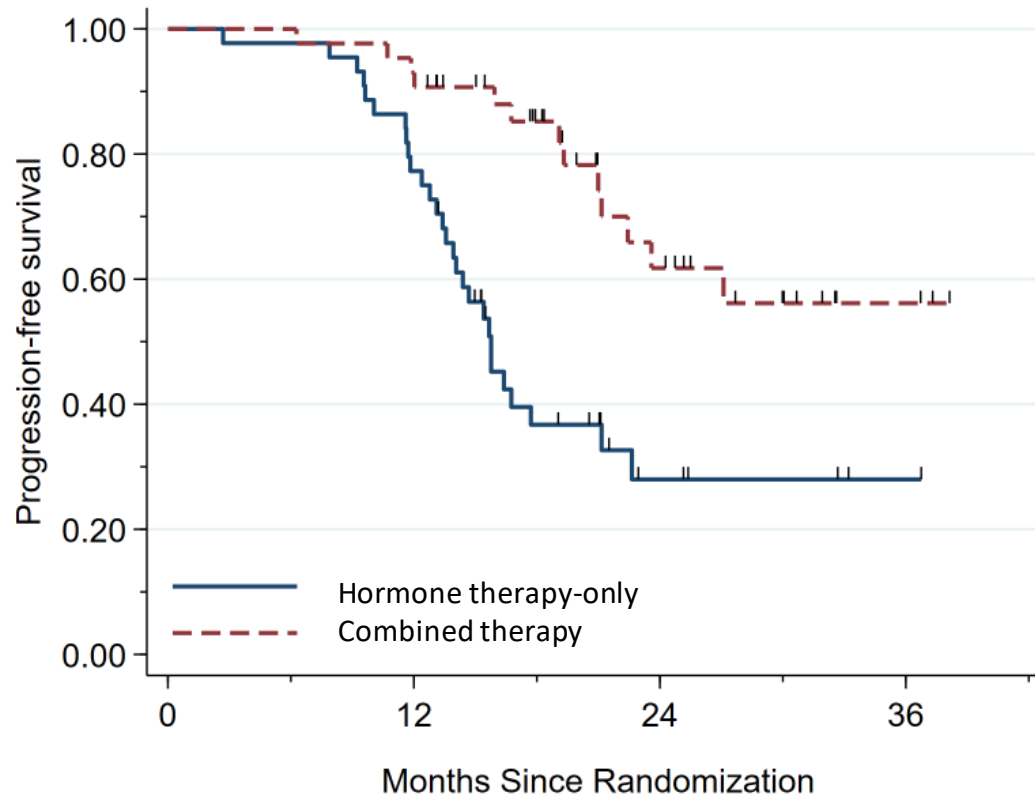
# EXTEND Intermittent ADT Prostate Cancer Basket

## Major Inclusion Criteria

- Histologic diagnosis of prostate cancer
- $\leq 5$  metastases
- $\geq 2$  months of prior HT (either GNRH agonist/antagonist +/- 2<sup>nd</sup> generation HT)
- Untreated primaries were allowed, but must be treated regardless of randomization



# Primary Endpoint: Progression Free Survival



| N at risk (Events)   |    |      |    |      |    |     |   |
|----------------------|----|------|----|------|----|-----|---|
| Hormone therapy-only | 44 | (10) | 34 | (18) | 5  | (0) | 1 |
| Combined therapy     | 43 | (3)  | 40 | (9)  | 15 | (1) | 3 |

**Primary analysis occurred at 41 events**

Median follow: 22.1 mo

Stratified Log Rank:  $P < 0.001$

HR = 0.25 (95% CI: 0.12-0.55)

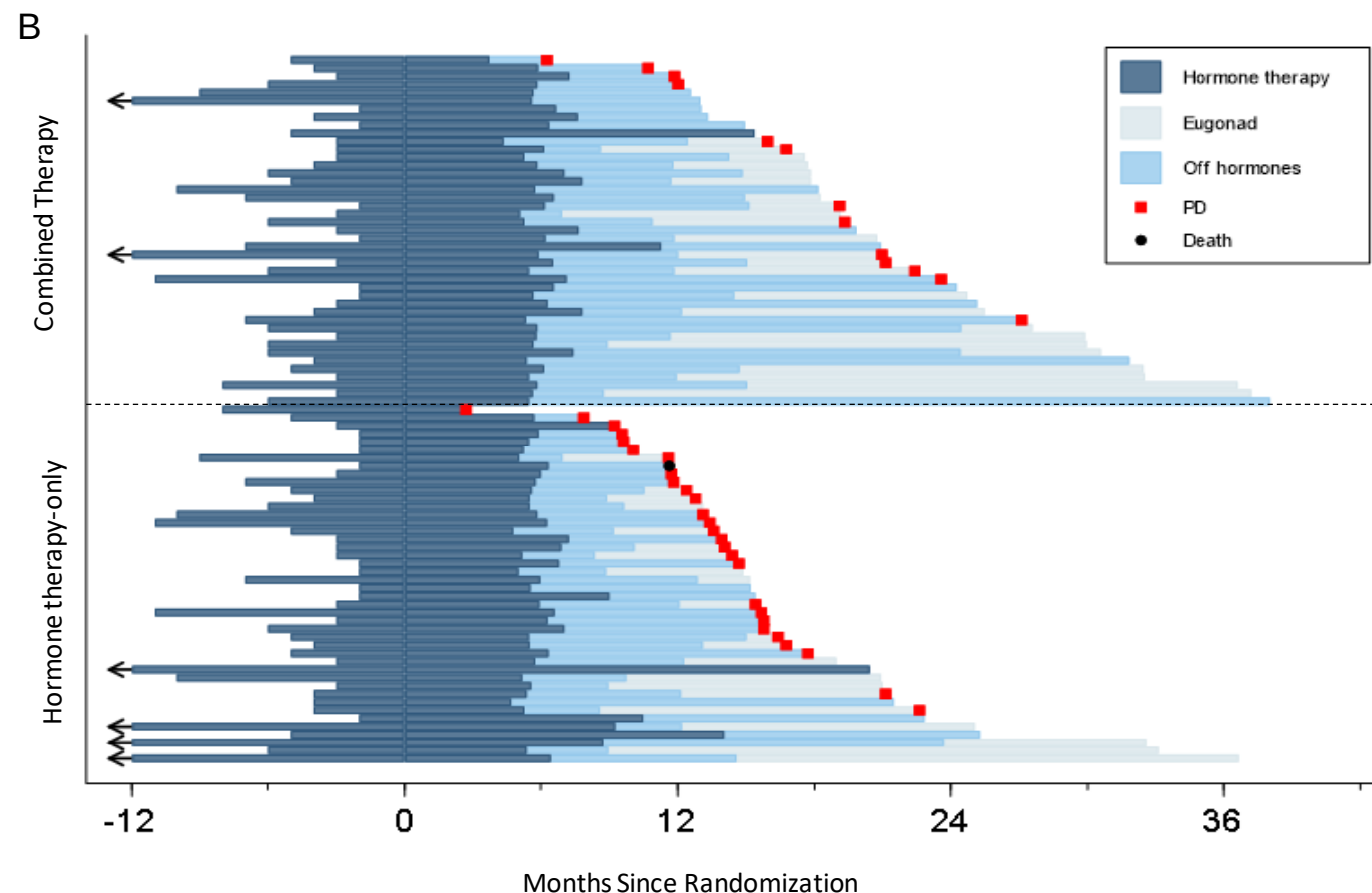
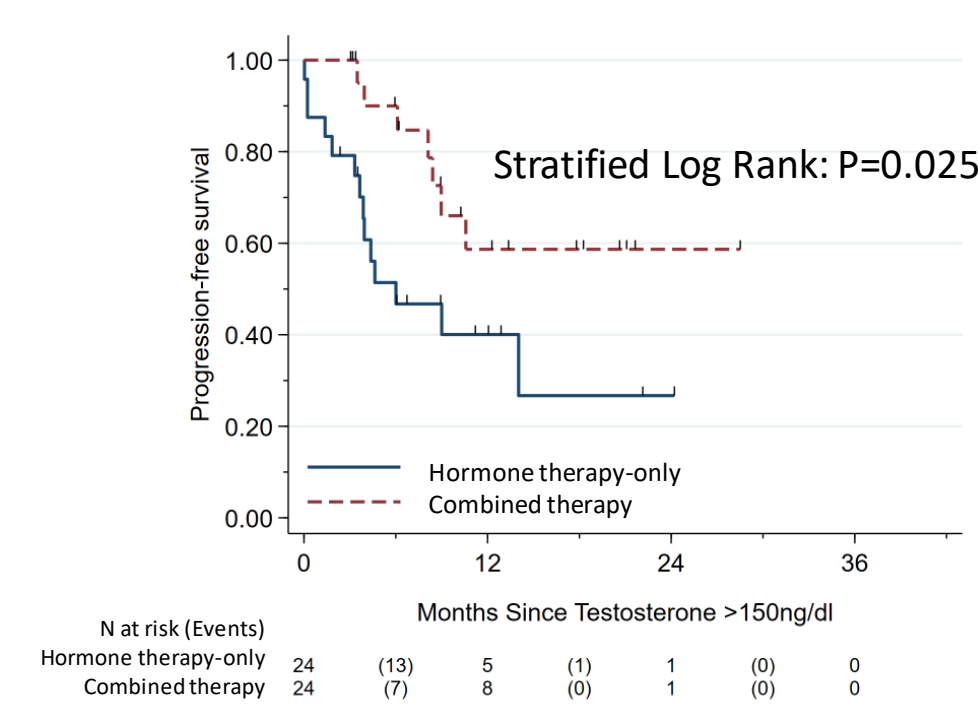
## Median PFS

Hormone therapy-only: 15.8 mo

Combined therapy: not reached

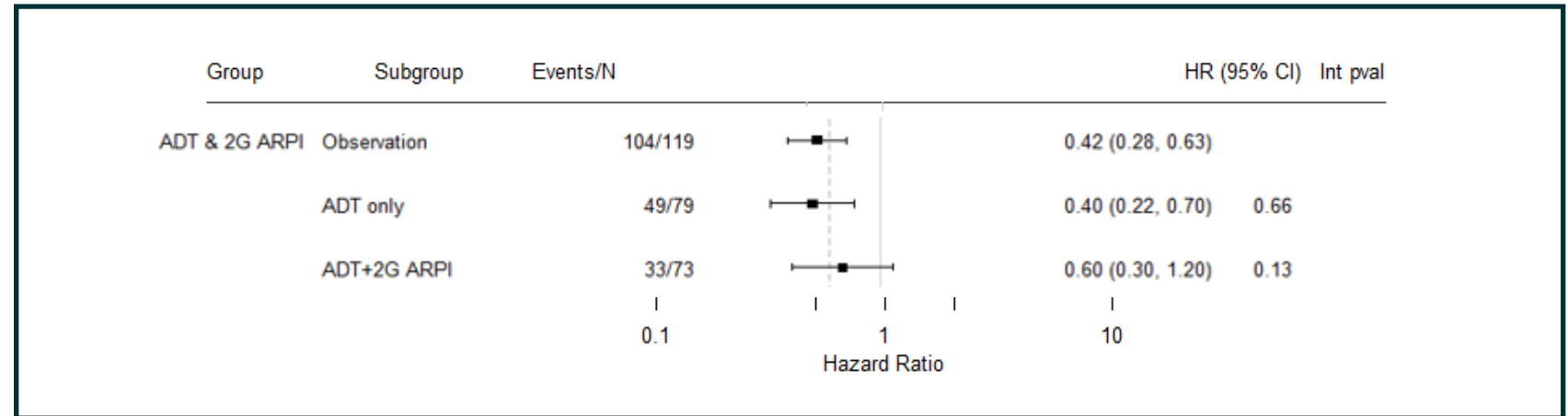
# Secondary endpoint: eugonad progress free survival

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



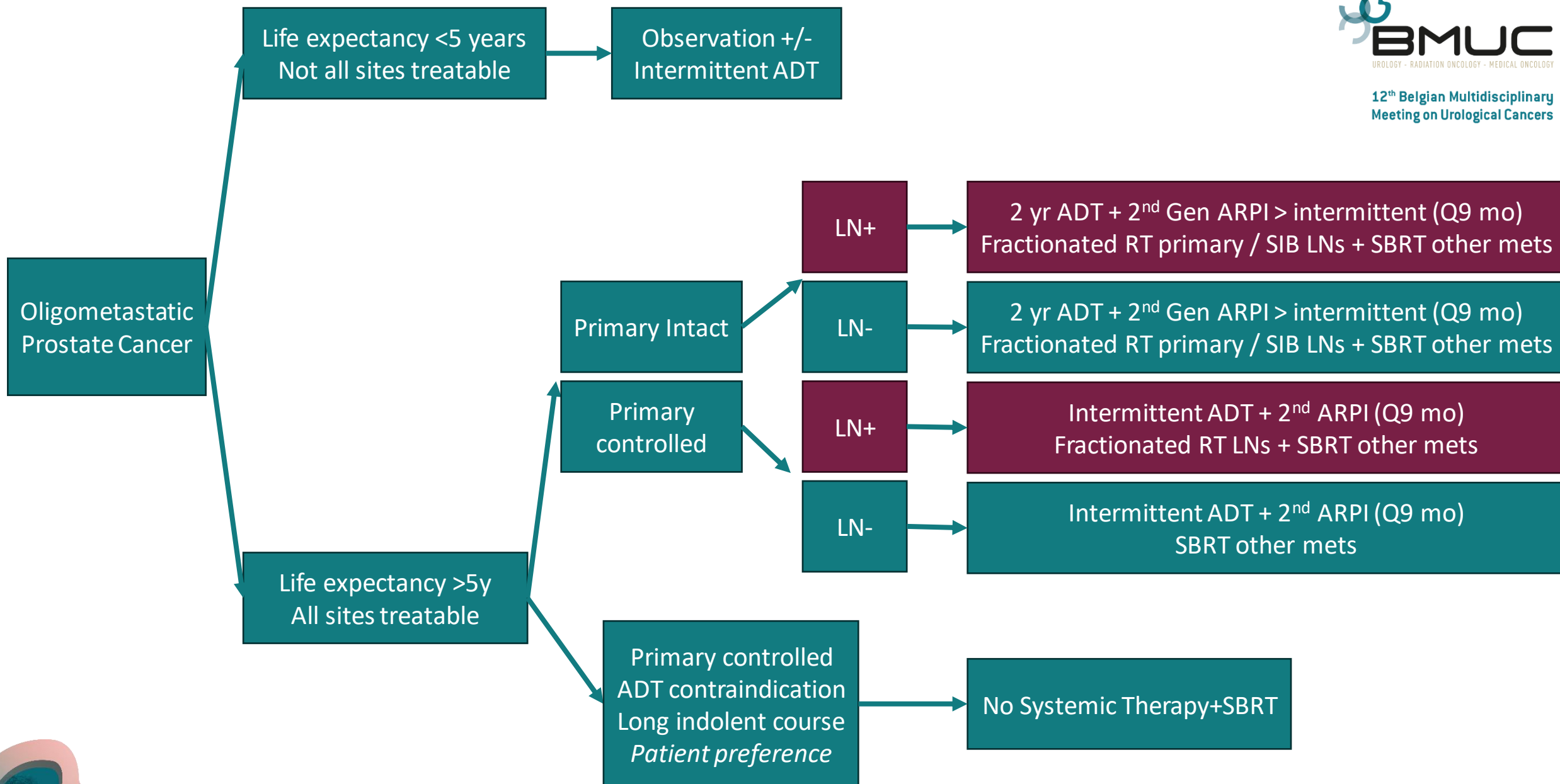
# WOLVERINE: Subgroups Analysis (CSPC Only)

## Benefit of MDT vs no MDT

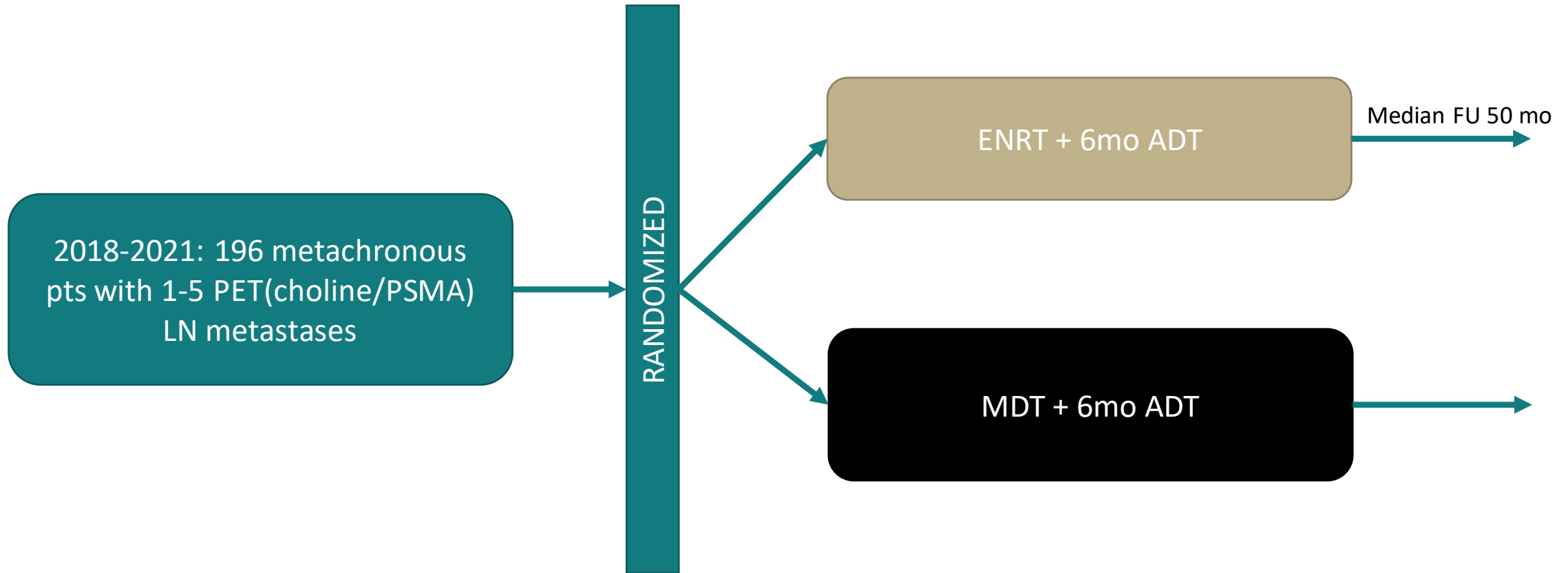


## Prognosis in patients receiving MDT

|                |                  | n_risk | n_events | medians | HR   | Lower CI | Upper CI | P value |
|----------------|------------------|--------|----------|---------|------|----------|----------|---------|
| ADT+ 2Gen ARPI | MDT+ Observation | 120    | 96       | 12      |      |          |          |         |
|                | MDT+ADT only     | 97     | 52       | 28.07   | 0.43 | 0.31     | 0.61     | <.001   |
|                | MDT+ADT+2G ARPI  | 36     | 15       | 38.99   | 0.32 | 0.18     | 0.55     | <.001   |

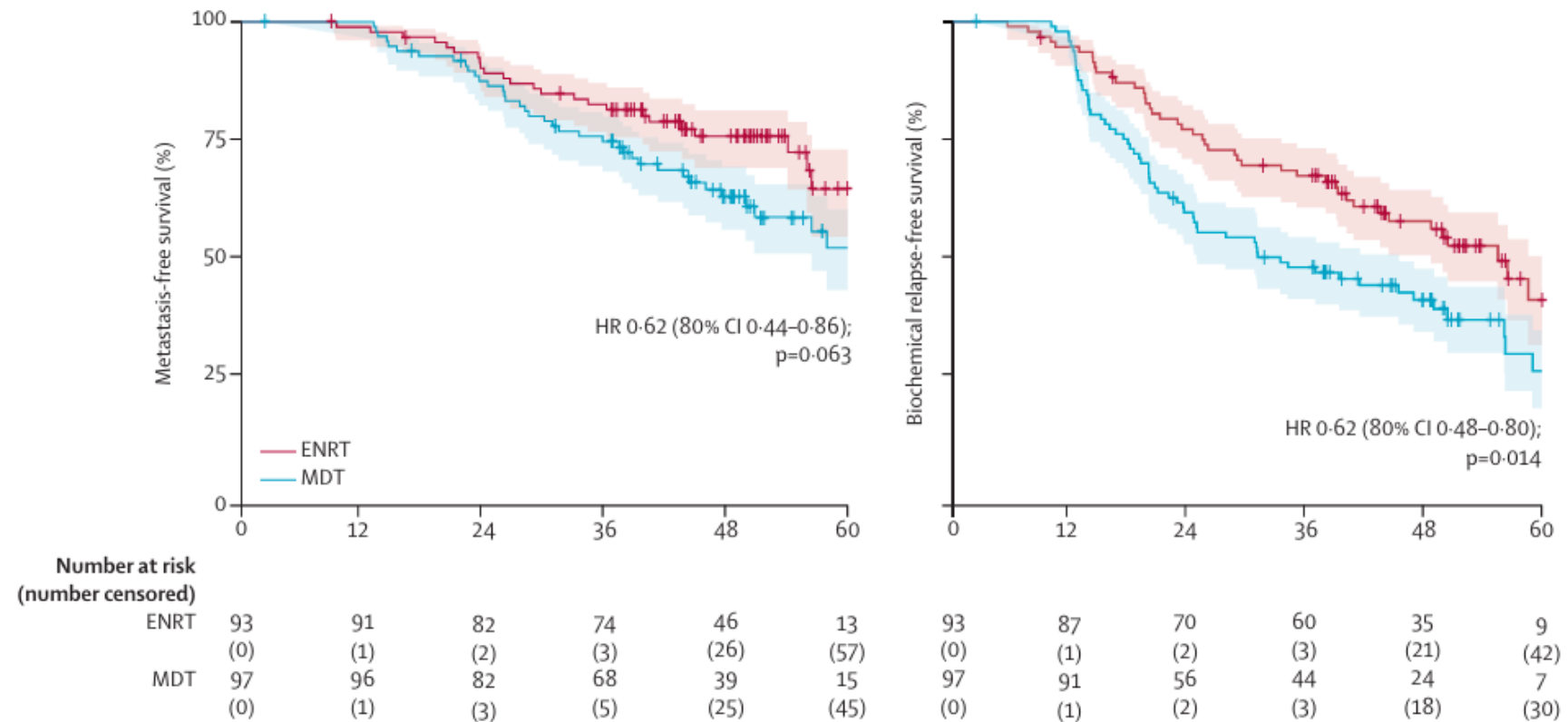


# PEACE V-STORM



# PEACE V-STORM Results

- Primary endpoint metastasis free survival improved with ENRT
- Toxicity not worse with ENRT, toxicity associated with fossa radiation



# Future Phase 3 Trials

| Trial characteristics | PLATON<br>(CCTG PR20)<br>NCT03784755                                                                   | PRESTO<br>(GETUG-PEACE 6)<br>NCT04115007                                                | STARPORT<br>(VA)<br>NCT04787744                                                 | STAMPEDE 2<br>OLIGOMETES     | START-MET<br>NCT05209243                       |
|-----------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------|------------------------------------------------|
| Disease status        | De novo + recurrent                                                                                    | De novo + recurrent                                                                     | Recurrent                                                                       | De novo                      | De novo + recurrent                            |
| Imaging               | Bone scan and CT scan                                                                                  | F- or C-PET/CT,<br>PSMA PET/CT, or<br>whole-body MRI scan                               | Abdomen/pelvis CT/MRI,<br>F- or C- PET/CT, bone<br>scan, or PSMA PET/CT<br>scan | Bone scan and<br>CT/MRI scan | Bone / CT scans +<br>Choline or PSMA<br>PET/CT |
| Oligometes definition | M1 disease with $\leq 5$ metastases<br>(including $\leq 3$ metastases in any<br>non-bone organ system) | M1 disease with $\leq 5$<br>metastases (including $\geq 1$<br>bone or pulmonary lesion) | $\leq 5$                                                                        | $\leq 3^+$                   | $\leq 5$                                       |
| ADT                   | Yes, continuous                                                                                        | Yes, continuous or<br>intermittent                                                      | Yes, continuous                                                                 | Yes, continuous              | yes, continuous                                |
| Primary endpoint      | FFS                                                                                                    | CRPC-free survival                                                                      | CRPC-free survival                                                              | OS                           | rPFS                                           |
| Sample size           | 410                                                                                                    | 550                                                                                     | 464                                                                             | 1939                         | 266                                            |

# Conclusions

- Although phase 3 trials have not reported, aggregated phase 2 data suggests that MDT produces benefits among most endpoints, without substantial adverse events.
- *In de novo patients*: High level evidence support treating the primary in patients with oligometastatic/low volume prostate cancer patients. Limited data treating metastases, but suggestion of benefit exists.
- *In metachronous patients*: Several phase II trials suggest improvement in outcomes with treatment of metastatic sites.
- Hormone therapy is generally given to patients with oligometastatic disease, favoring intermittent ADT.
- Elective LN radiation improves locoregional control over MDT without substantially more adverse events.



# Thank you!

