Patient selection for metastasis directed therapy and Lutetium-177

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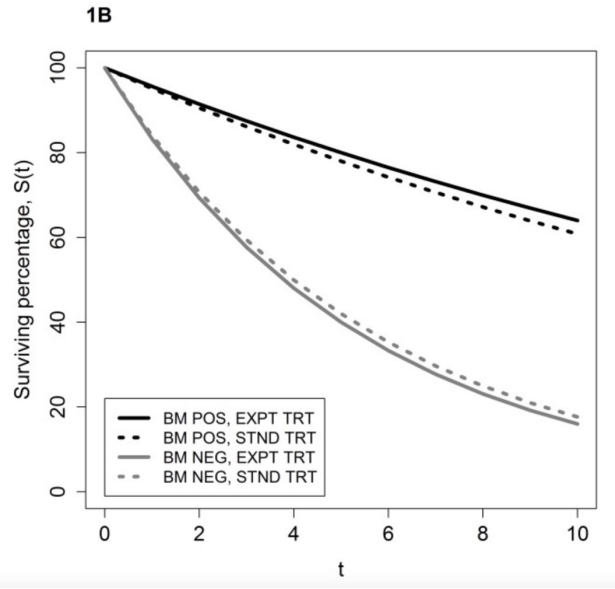
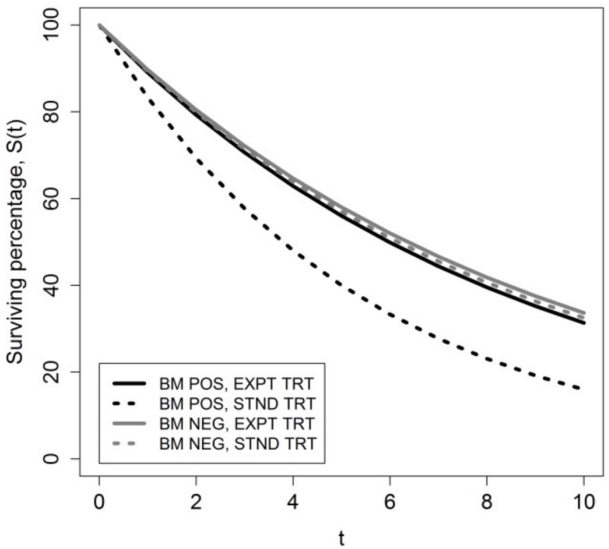
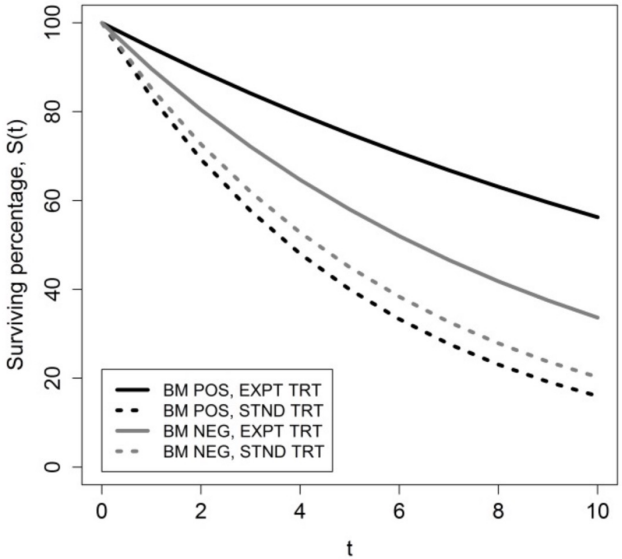
Prognostic vs predictive



Biomarker is prognostic



Biomarker is predictive



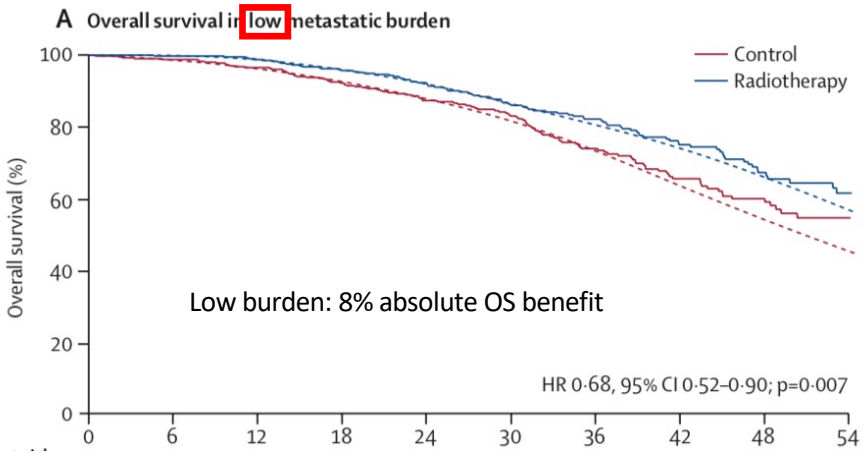
Biomarker is predictive of a differential benefit

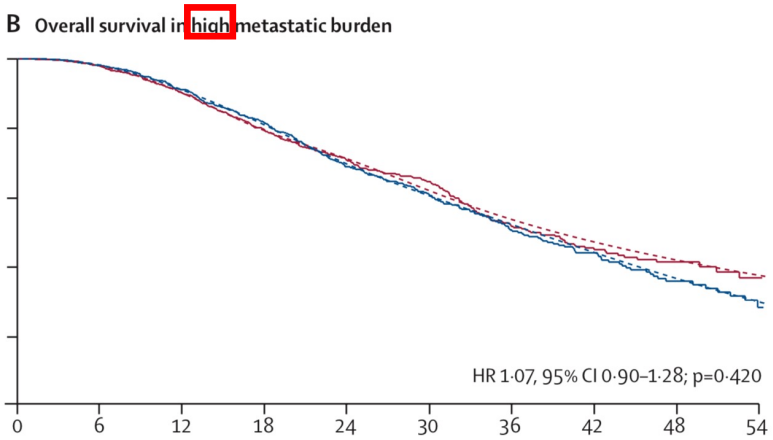
MDT

Synchronous mHSPC

Imaging as a predictor

Which patients need treatment of the primary?





Definition of low burden is predictive of success of radiotherapy to the primary

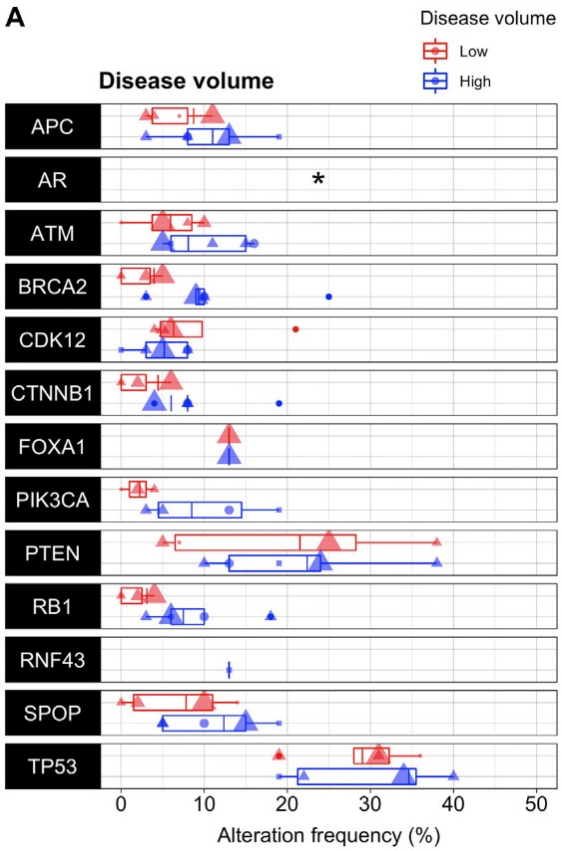
- Low burden is defined as:

Patients with **only NRLN or 3 or fewer bone metastases** with or without NRLN regardless of axial or extra axial location and without any visceral/other metastasis.

C. Parker et al. Lancet 2018

Molecular data as a predictor

Are there molecular differences between high vs low burden?

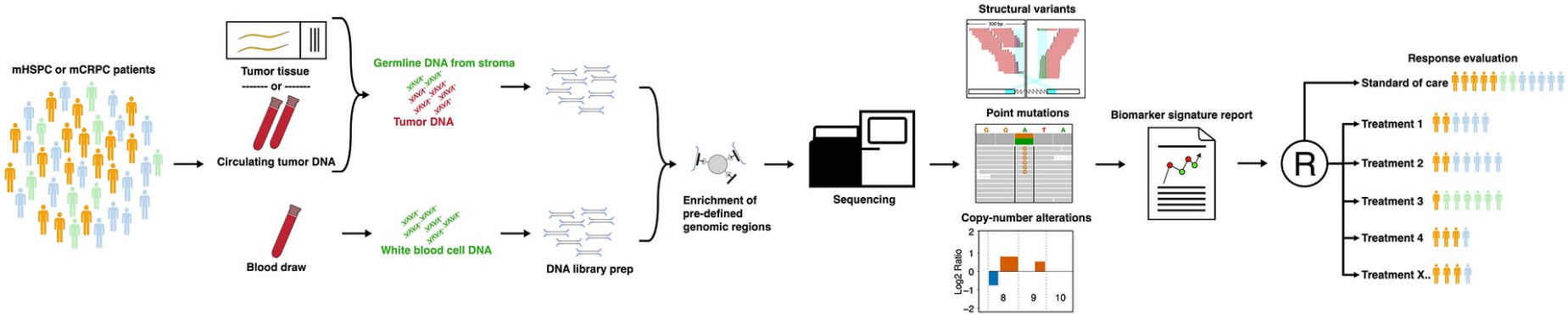


HV vs LV:

- TP53 (35% vs 29%),
- BRCA2 (10% vs 4%),
- PIK3CA (8% vs 2%),
- RB1 (7% vs 3%)
- APC (11% vs 9%)

Vandereecken K et al. Eur Urol Oncol 2021

Future: biology-guided treatment



ProBiotrial.org

MDT

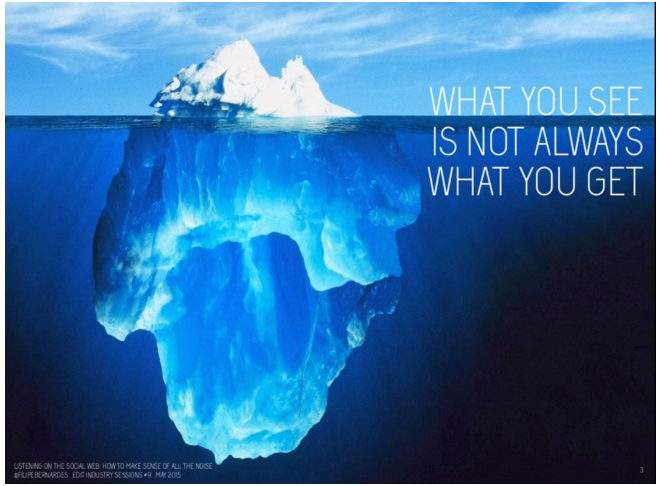
Metachronous mHSPC

Imaging as a predictor

Importance of good imaging

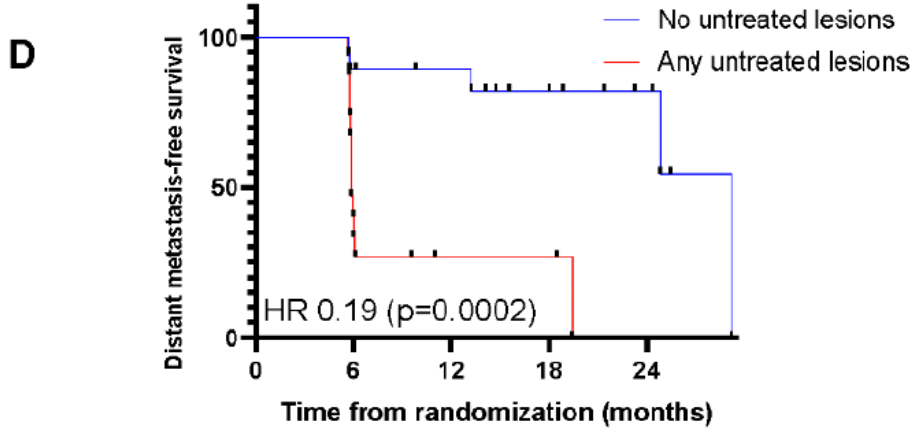
The limited effectiveness of these treatments of oligometastases has been primarily the result of an **inability to recognize all metastases** and the fact that these seemingly limited lesions were too often a manifestation of undetected widespread cancer.

– Weichselbaum 1995-



Importance of good imaging: PSMA

- ORIOLE trial
- SBRT vs observation
- BLINDED PET assessment of metastatic burden
- Untreated lesions drive relapse



Number at risk

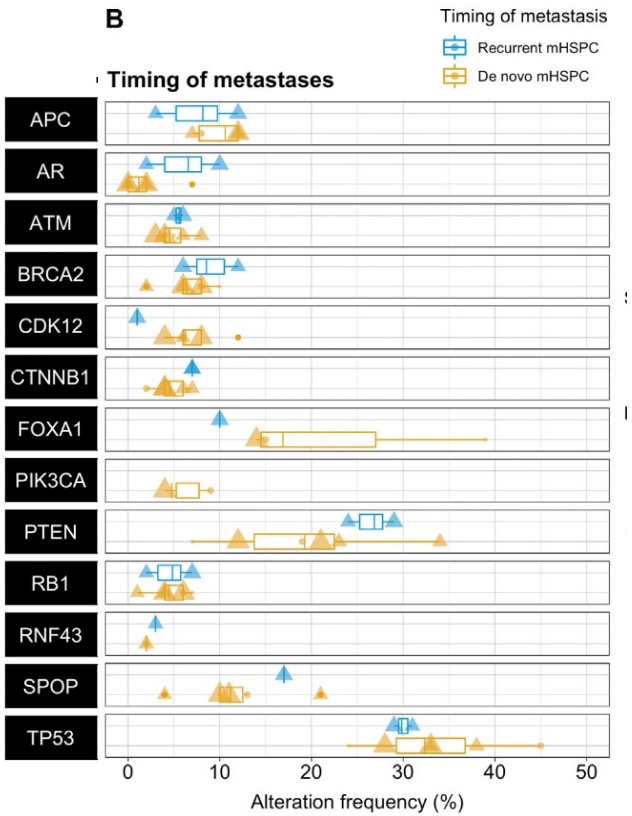
No untreated	19	14	12	8	4
Any untreated	16	6	2	2	0

More sensitive imaging is predictive of outcome.

Phillips et al. JAMA Oncol 2020

Molecular data as a predictor

Are there molecular differences between de novo vs recurrent mHSPC?

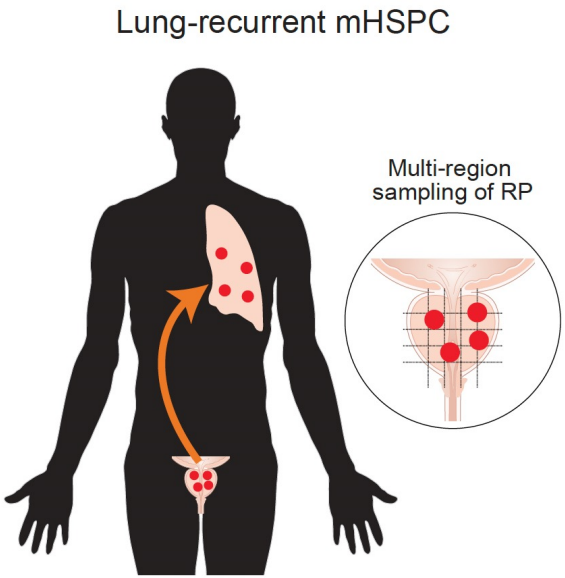


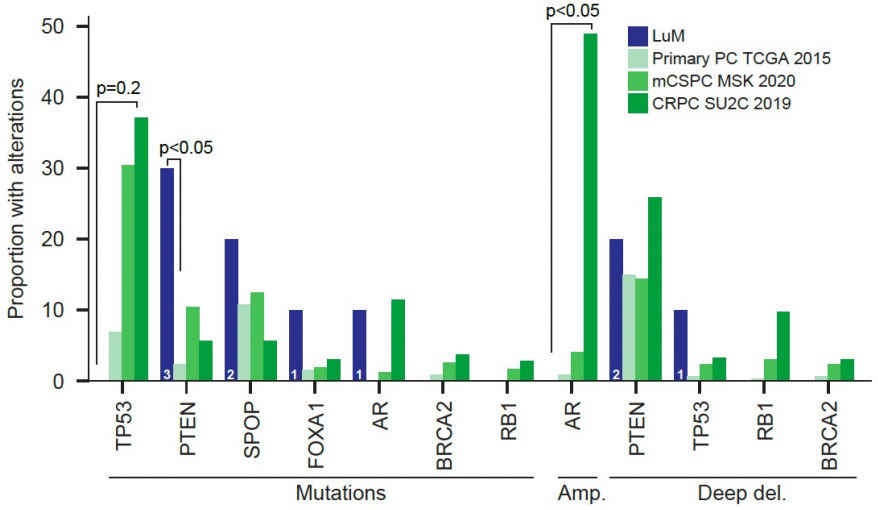
De novo vs Rec:

- CDK12 (6% vs 1%)
- FOXA1 (17% vs 10%)
- Cell cycle signalling
- Wnt pathway
- PTEN
- SPOP

Vandereecken K et al. Eur Urol Oncol 2021

Even within a disease state differences exist.





All patients in this cohort are alive at a FU of >10yrs

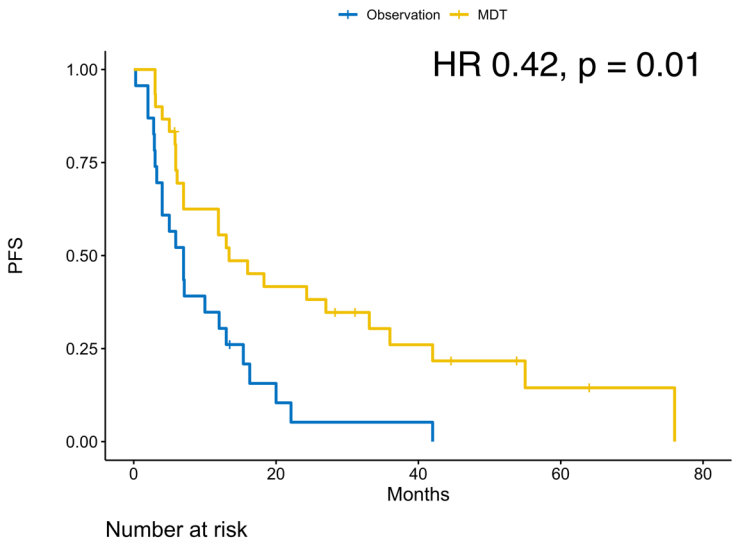
Fosseta, Vandereecken et al. JCO Precision 2022

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

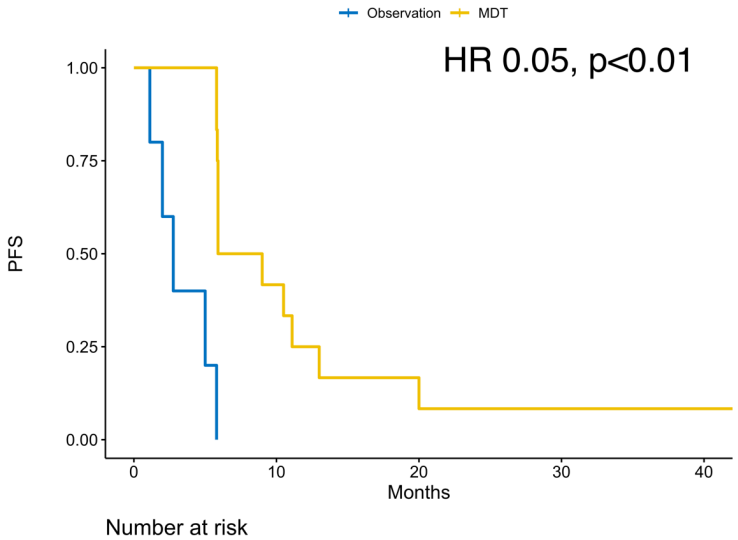
- ORIOLE and STOMP trial
- SBRT vs observation
- Targeted sequencing of the primary or blood
- High risk mutation defined as:
  - Pathogenic somatic or germline mutation in ATM, BRCA1/2, RbA, TP53
- Hypothesis:
  - Patients with a HR mutation do not benefit from SABR/observation
- Primary endpoint: PFS

PFS according to mutation status and treatment arm

No HR mutation



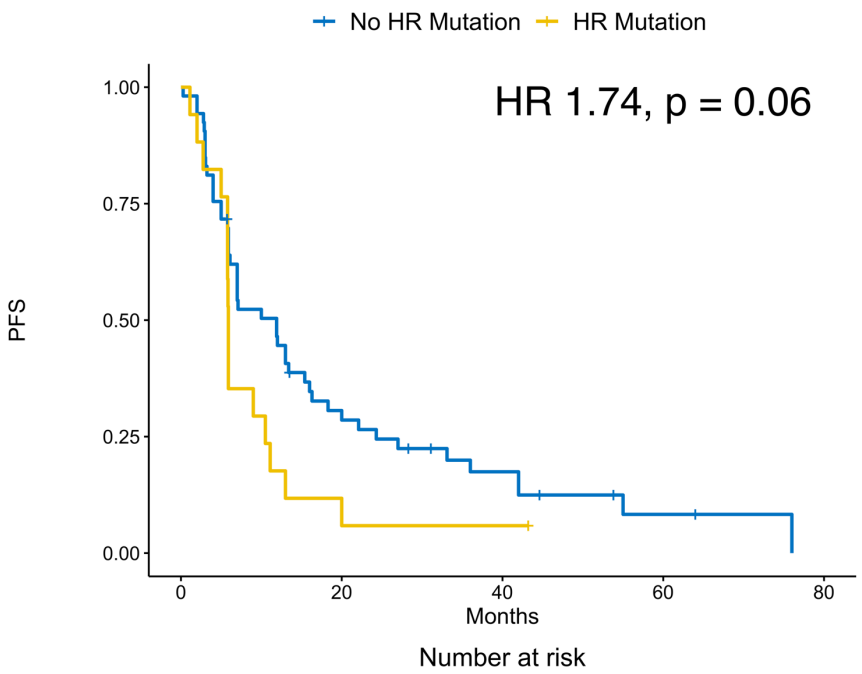
HR mutation



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

Deek M, Ost P, Tran P. submitted

Patients with a HR mutation might need systemic Tx added to SBRT and maybe the others as well!



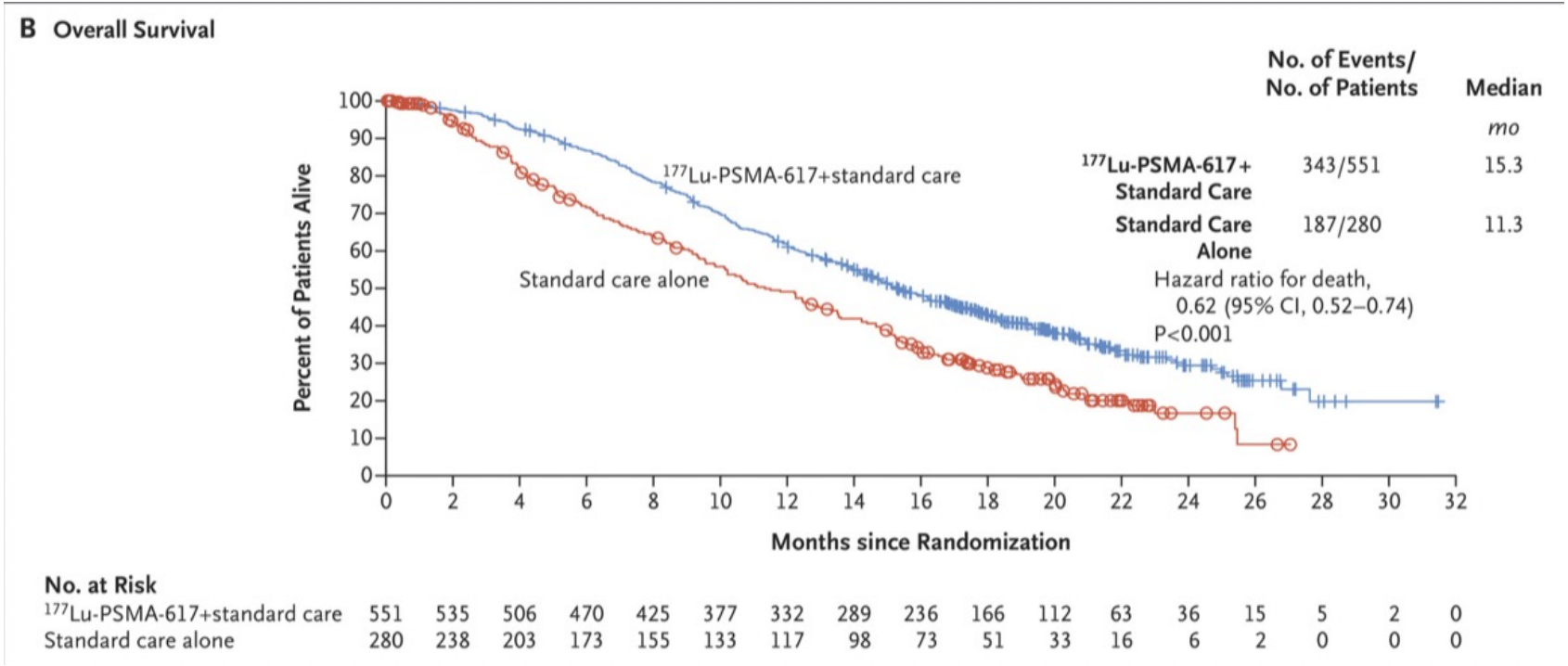
- Almost all patients with a high risk mutation relapse within 2 years

Deek M, Ost P, Tran P. submitted

Lutetium

mCRPC

VISION trial

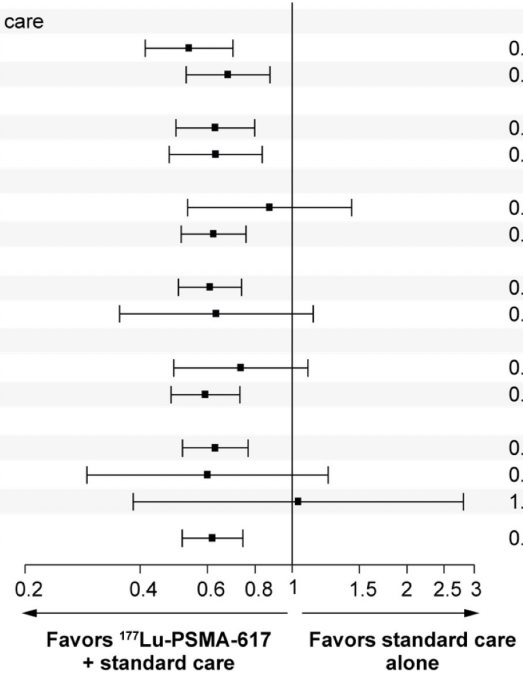


Sartor et al. NEJM 2021

VISION: subgroups

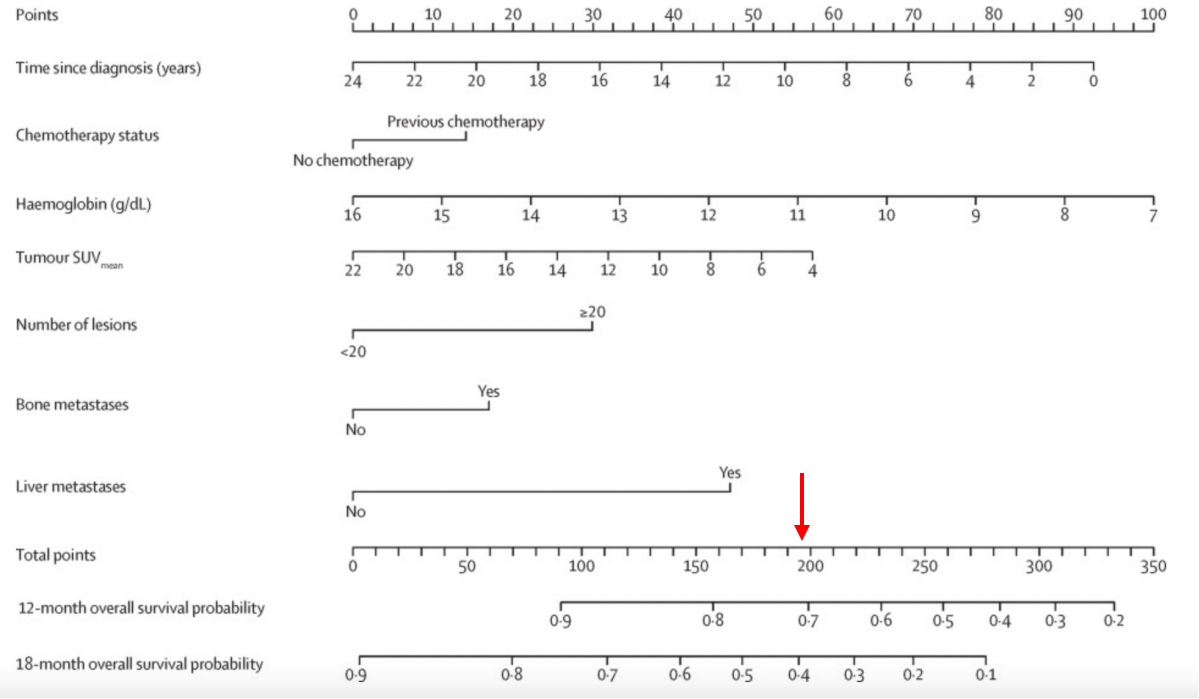
B Overall survival (N=831)

Subgroup	^{177}Lu-PSMA-617 + standard care (N=551) n/N (%)	Standard care alone (N=280) n/N (%)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned standard care			
Yes	135/243 (55.6)	96/146 (65.8)	0.54 (0.41, 0.70)
No	208/308 (67.5)	91/134 (67.9)	0.68 (0.53, 0.87)
LDH			
≤260 IU/L	202/368 (54.9)	107/182 (58.8)	0.63 (0.50, 0.80)
>260 IU/L	140/182 (76.9)	80/97 (82.5)	0.63 (0.48, 0.84)
Liver metastases			
Yes	40/48 (83.3)	28/34 (82.4)	0.87 (0.53, 1.43)
No	303/503 (60.2)	159/246 (64.6)	0.62 (0.51, 0.76)
ECOG score			
0 or 1	305/510 (59.8)	170/258 (65.9)	0.61 (0.50, 0.74)
2	38/41 (92.7)	17/22 (77.3)	0.63 (0.35, 1.13)
Age			
<65 years	82/145 (56.6)	38/60 (63.3)	0.73 (0.49, 1.10)
≥65 years	261/406 (64.3)	149/220 (67.7)	0.59 (0.48, 0.73)
Race			
White	300/486 (61.7)	159/235 (67.7)	0.63 (0.52, 0.77)
African American or Black	20/34 (58.8)	12/21 (57.1)	0.60 (0.29, 1.24)
Asian	9/9 (100)	7/11 (63.6)	1.04 (0.38, 2.81)
All patients	343/551 (62.3)	187/280 (66.8)	0.62 (0.52, 0.74)



Sartor et al. NEJM 2021

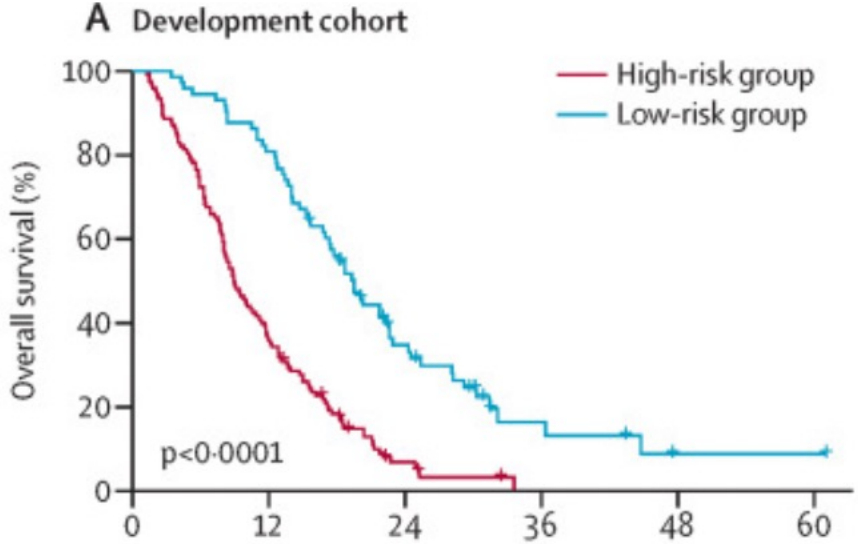
Nomogram developed retrospectively



- All patients in the model got Lu-PSMA
- Cut-off of 197 point of dichotomizing low vs high risk.

Gafita et al. Lancet Oncol 2022

Nomogram “predicts” outcome



Number at risk (number censored)						
High-risk group	123 (0)	48 (0)	6 (5)	0 (7)	0 (7)	0 (7)
Low-risk group	73 (0)	60 (0)	21 (6)	5 (13)	2 (14)	1 (15)

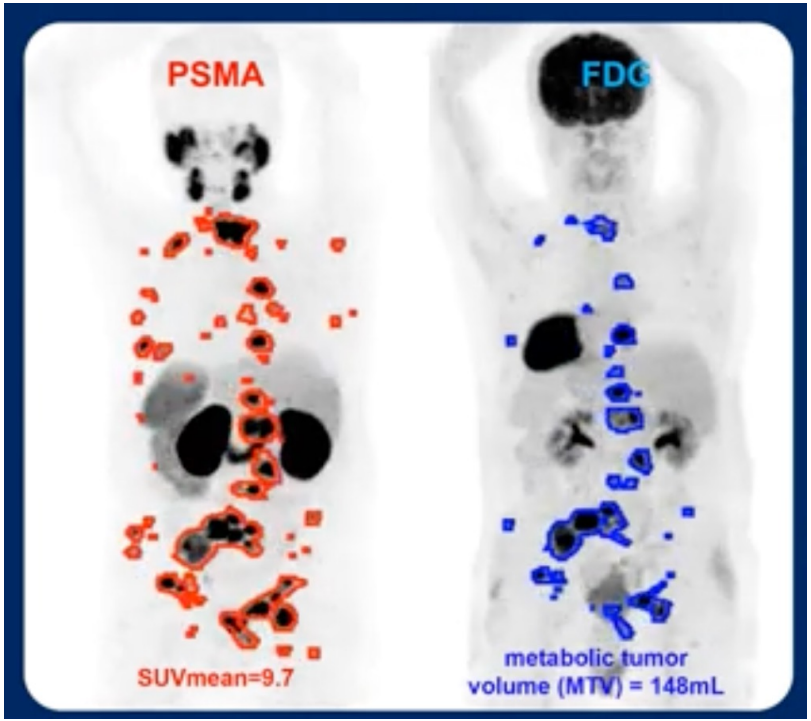
These externally validated **nomograms that are predictive of outcomes** after ^{177}Lu-PSMA in patients with mCRPC might **help in clinical trial design and individual clinical decision making**, particularly at institutions where ^{177}Lu-PSMA is introduced as a novel therapeutic option.

Gafita et al. Lancet Oncol 2022

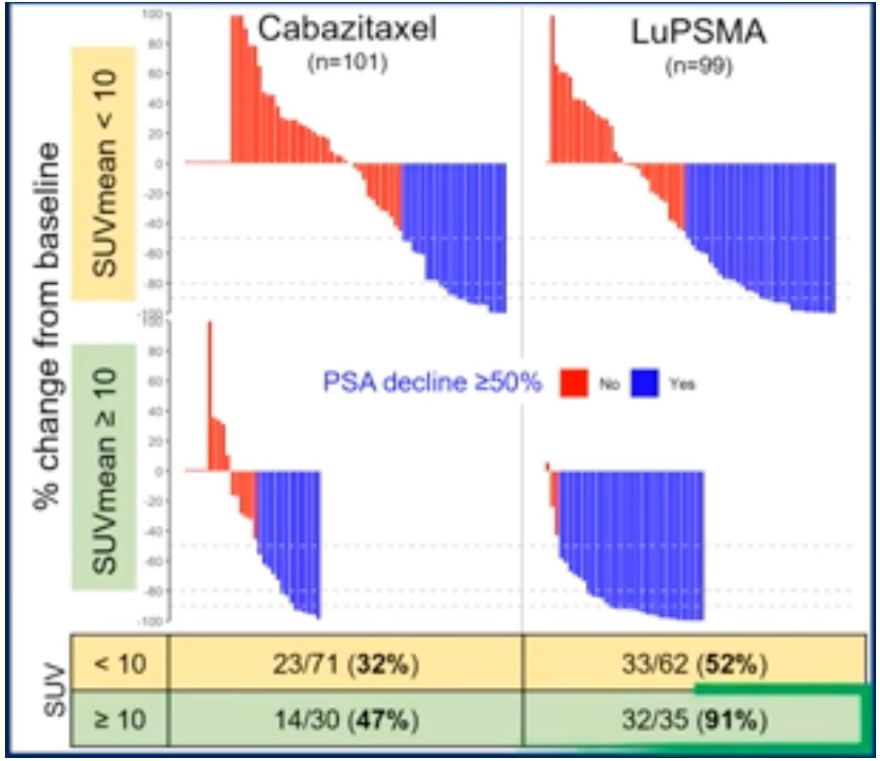
Imaging as a predictor

TheraP trial: Lu-PSMA vs Cabazitaxel

- Hypothesis: PSMA SUV mean of 10 is a prognostic and predictive biomarker



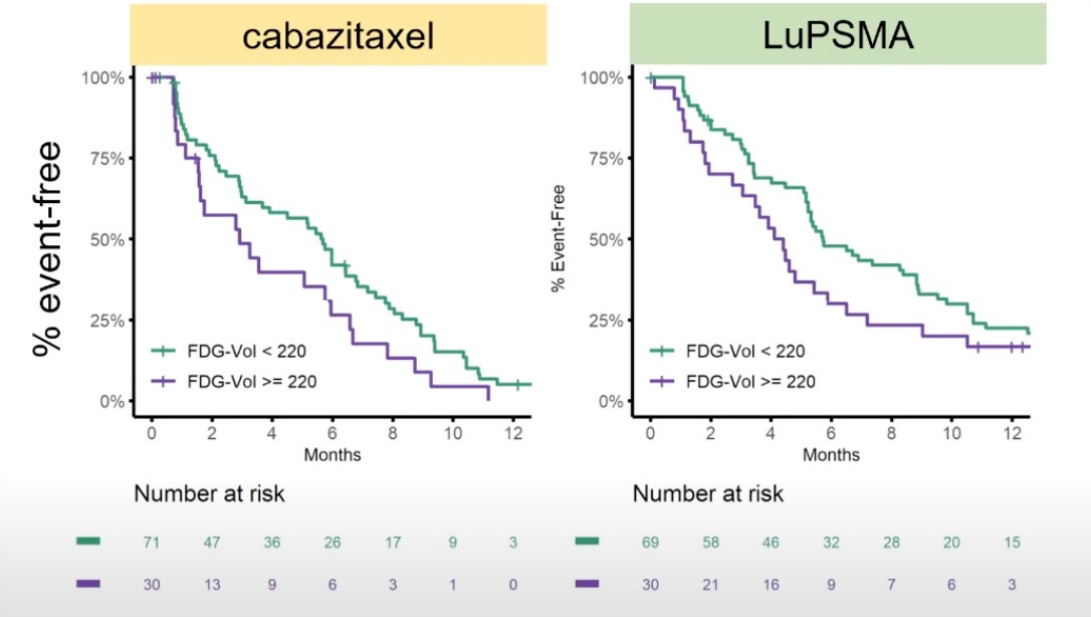
TheraP trial: Lu-PSMA vs Cabazitaxel



- Approximately 1/3 patients has a SUV mean >10.
- The PSMA SUV mean is predictive of a higher likelihood of benefit, but Lu-PSMA is always better than Caba for this endpoint.
- Does this endpoint matter?

Buteau et al. Lancet Oncol 2022

Volume of disease on FDG PET and outcome

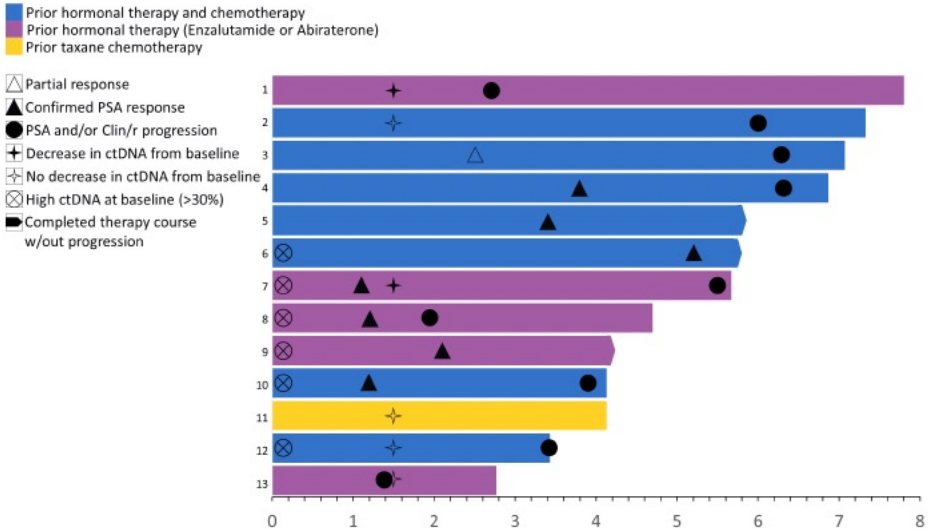


- A high volume of disease on FDG PET is associated with a poor outcome regardless of treatment.

Molecular data as a predictor

ctDNA and PSA response to Lu-PSMA

Swimmer plot showing plasma ctDNA and response to Lu-PSMA treatment over time for each patient



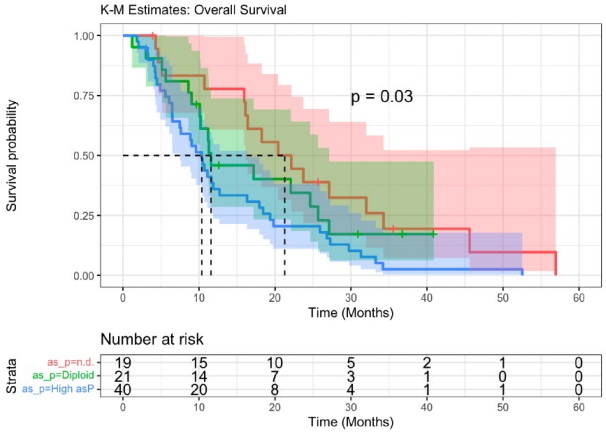
- 89% of pts had detectable ctDNA (N=13)
- **Patients with high pre-treatment ctDNA(>30%) were much more likely to experience a confirmed PSA response (83%vs29%,p=0.1)**
- Data updated at next AACR.

Fettke et al. AACR 2022.

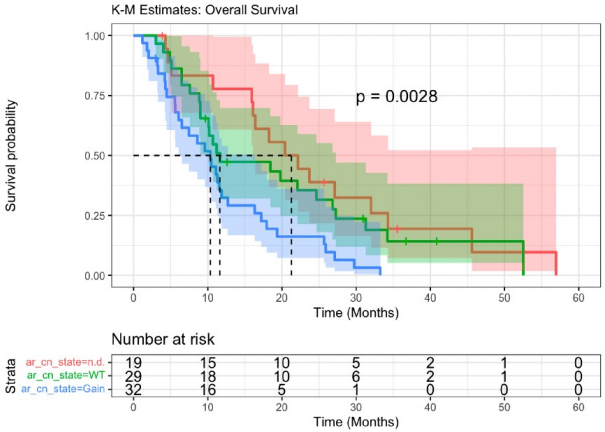
ctDNA a prognostic marker for patients undergoing PSMA targeted Tx

- Patients undergoing Actinium (N=30) or Lutetium PSMA (N=50).
- Assayed using PCF_SELECT platform (AR copy number, HRR gene CN and allele-specific ploidy (asP = metric for genomic instability).

asP and OS



AR status and OS



AR CN gain and high asP are associated with poorer prognosis.

Sun M. ESMO 2022

Conclusion

Predictors of MDT succes

- De novo mHSPC:
  - The definition of “low burden” is predictive of the success of local radiotherapy to the primary.
  - No data on MDT

- Recurrent mHSPC
  - Use the most sensitive imaging available.
  - The genomic profile of the primary is predictive of a differential benefit.

Predictors of PSMA therapy succes

- Imaging:
  - PSMA SUV mean predicts patients with a higher likelihood to respond
  - High FDG tumor load is a negative prognostic factor

- ctDNA:
  - High ctDNA levels yield high response to PSMA
  - AR CN gain and high asP levels result in a poor prognosis