

Genomic evaluation of prostate cancer: what, how and when?

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bmuc.be/bmuc-2026



**13th Belgian Multidisciplinary
Meeting on Urological Cancers**

Conflicts of interest

- I have no potential conflict of interest to report



~~Genomic~~ evaluation of prostate cancer: what,
how and when?

Molecular evaluation of prostate cancer: what,
how and when?



Agenda

- What, how and when?
 - The “minimum” standard: what to do and how to interpret the results.
 - Additional analyses with low “opportunity cost”
 - Future perspectives
- More insights on How and When?
 - Archival versus fresh
 - Liquid biopsy: is it PRIME time?



Germline Testing

NCCN Guidelines

TESTING CRITERIA FOR PROSTATE CANCER SUSCEPTIBILITY GENES
(Genes such as *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13*, *PALB2*, and *TP53*) (*GENE-A*)^{a,gg,hh}

Testing is clinically indicated in the following scenarios:
• See General Tumor Criteria on CRIT-1. • Personal history of prostate cancer at any age with: ▸ Metastatic^q (Stage IVB) or node-positive (Stage IVA) prostate cancer ▸ Very high-risk or high-risk disease (See Initial Risk Stratification and Staging Workup [PROS-2] - NCCN Guidelines for Prostate Cancer) ▸ Ancestry: Ashkenazi Jewish ▸ Family history^c ◊ ≥1 close blood relative^p with ANY: – breast cancer at age ≤50 y – male breast cancer – ovarian cancer – pancreatic cancer – metastatic,^q node positive, or very high-risk or high-risk prostate cancer ◊ ≥3 close blood relatives^p with prostate cancer (any grade) and/or breast cancer on the same side of the family including the patient with prostate cancer ◊ For additional family history considerations, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric • Family history criteria: unaffected; or affected but does not meet criteria above ◊ Individual with a first-degree or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making)^r
Testing may be considered in the following scenario:
• Personal history of prostate cancer ≤55 yⁱⁱ not meeting any of the above criteria • Personal history of prostate cancer with intermediate-risk prostate cancer with intraductal/cribriform histology (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer) at any age
Refer for genetic testing in the following scenario:
• Biochemical recurrence ▸ For this heterogeneous disease state, refer for genetic testing if: 1) Very high-risk or high-risk disease at diagnosis (see above), 2) family history of cancer criteria met, or if (and at time of) progression to metastatic disease

Germline Testing for PCa patients

- Any patient with Metastatic or high/very high-risk disease
- Any patient with intermediate risk prostate cancer with a cribriform/intraductal histology
- Any patient with a personal history of PCa before the age of 55
- Any patient for whom a somatic test reported a BRCA mutation



Metastatic PCa patients should be offered somatic genomic testing



6.7.2.a. Molecular diagnostics

Metastatic patients should be offered somatic genomic testing for homologous repair and MMR defects early on.

Testing can be performed on more recently collected primary tumour tissue or on tissue from metastases.

Alternatively, but still less common, genetic testing on circulating tumour DNA (ctDNA) is an option and has been used in some trials. One test, the FoundationOne[®] Liquid CDx, has been FDA approved [1292]. Defective *MMR*

assessment can be per

generation sequencing

recommended for patie



NCCN Guidelines Version 5.2026) and/or by next
Prostate Cancer and *MMR* is

• Testing

► Somatic testing for alterations in DNA damage response:

- ◊ Multigene tumor testing for alterations in HRR genes, including but not limited to *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12*, is recommended in patients with metastatic prostate cancer. This testing can be considered in patients with regional prostate cancer.
 - Loss of *BRCA1* and *BRCA2* may be especially associated with response to PARP inhibitor therapy compared to other HRR gene alterations.
- ◊ Tumor testing for MSI-H or dMMR is recommended in patients with mCRPC and may be considered in patients with regional or castration-sensitive metastatic prostate cancer.
- ◊ TMB testing is recommended in patients with mCRPC.

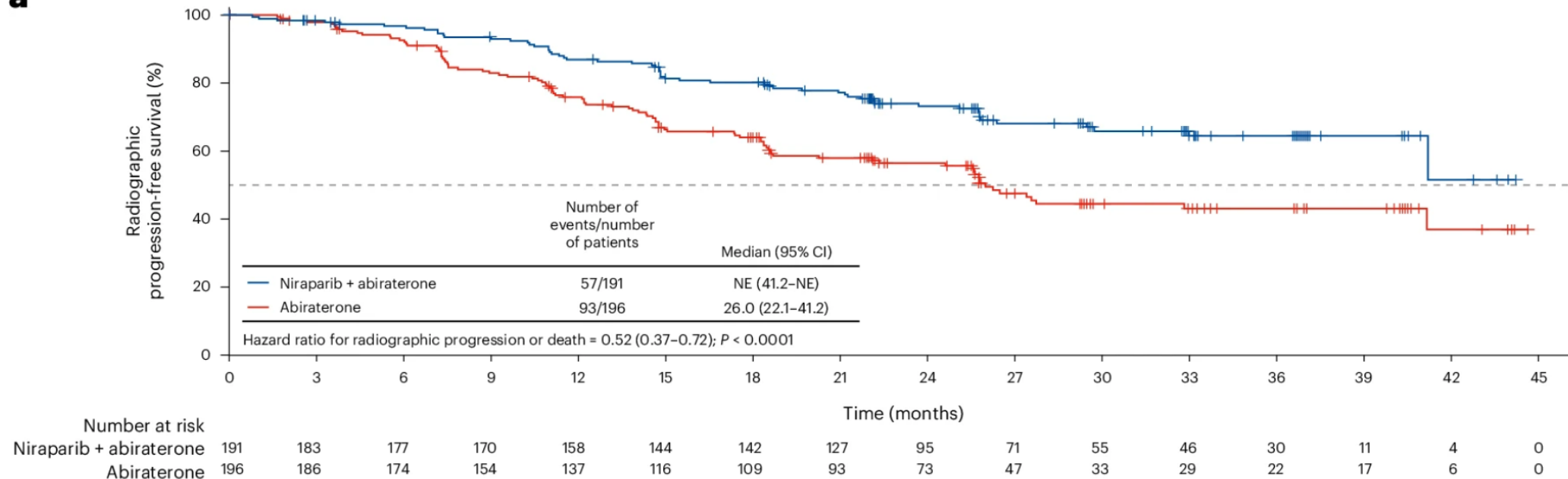
The “minimum” standard: HRR

- **Homologous recombination repair (HRR) genes**

- **Highly relevant:** BRCA2, BRCA1, PALB2, BRIP1 ...
- **Others:** CDK12, **ATM**, CHECK2, FANCA ...

AMPLITUDE trial

a

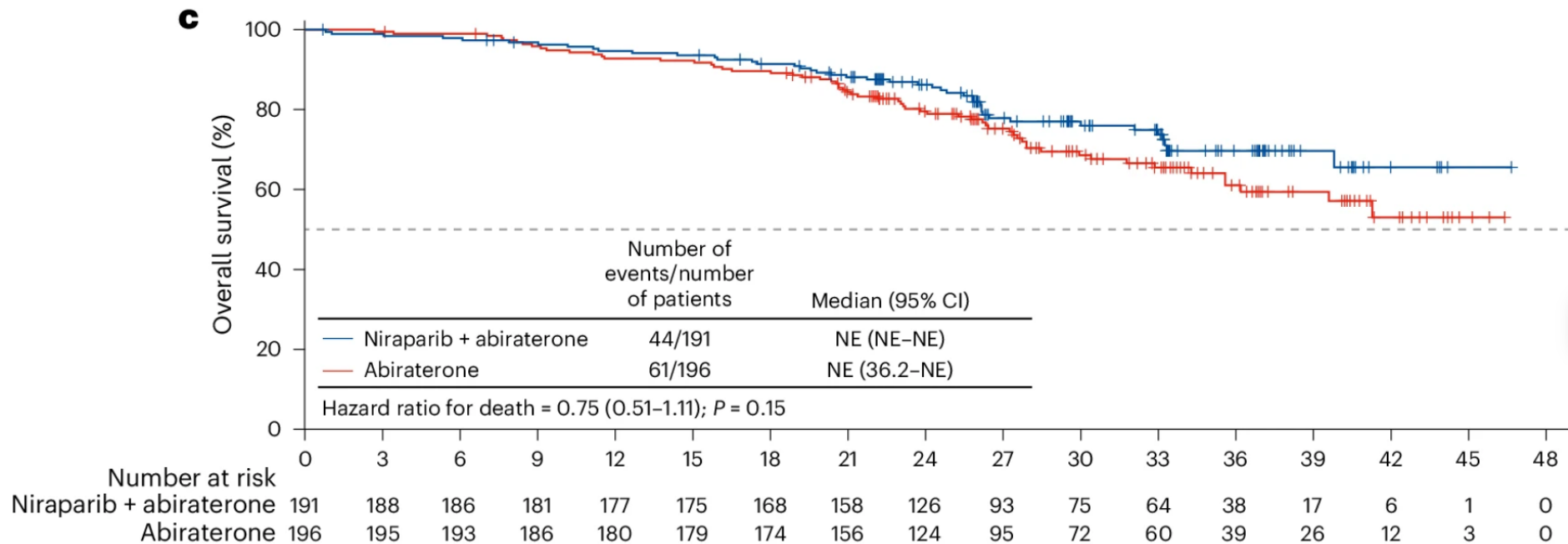


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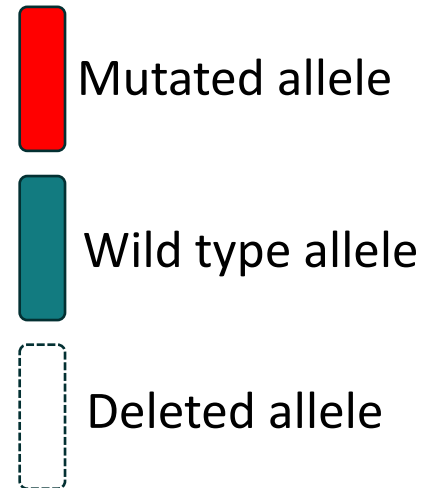
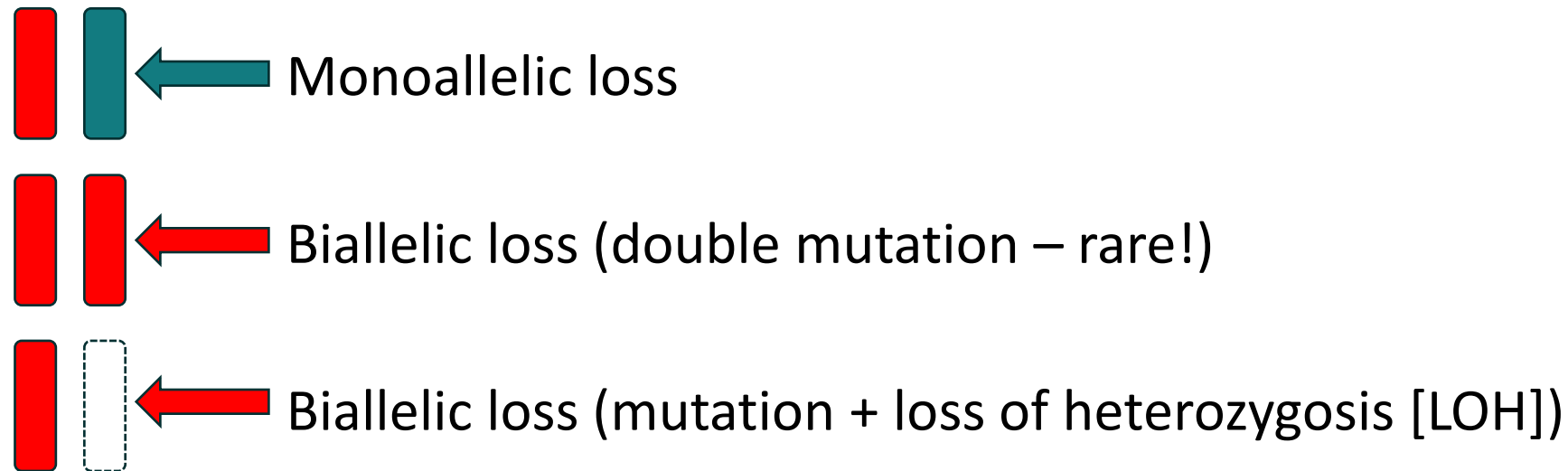
**Even within a HRR gene
not all alterations are the same**



Biallelic versus monoallelic mutations

Detection of a pathogenic mutation in a HRR gene suggests that one copy of the gene is “dysfunctional”.

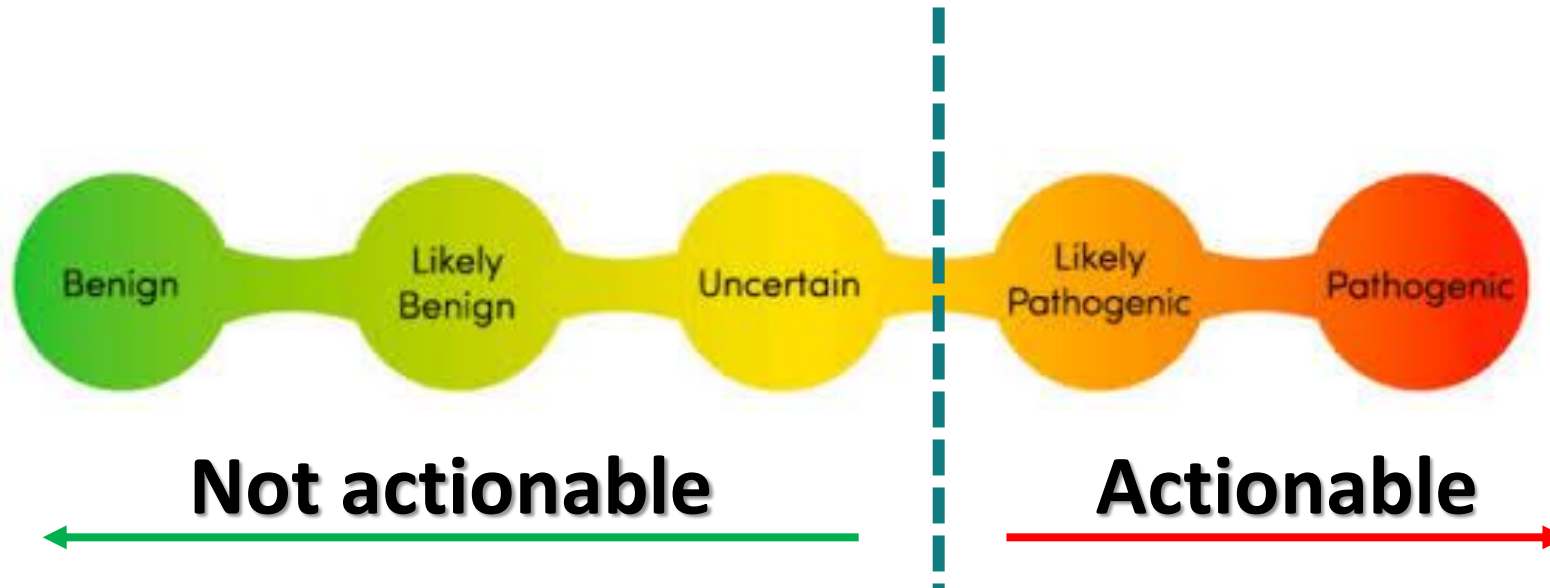
What about the other copy?



Biallelic versus monoallelic mutations

- Synthetic lethality of PARPi is much higher when both copies of the HRR gene are lost/dysfunctional.
- In TRITON2, biallelic mutations were associated with a higher PSA response rate (75%) versus monoallelic mutations (11%)
- Higher motivations to offer PARPi for PCa patients with tumours harbouring a confirmed biallelic HRR gene alteration.
- Most NGS panels used in clinical practice cannot discriminate between monoallelic and biallelic mutations (cannot call LOH or deletions in general)

ACMG/AMP Guidelines



Are Variants of Uncertain Significance (VUS) to be ignored?



ACMG/AMP Guidelines

For a variant to be classified as “likely pathogenic”, the likelihood of pathogenicity of the variant should be >90%

- A BRCA2 mutation that has an 80-90% likelihood of being pathogenic **is still** a VUS
- Patients with VUS in HRR genes were mostly excluded from PARPi trials, but some left room for interpretation.
- ORR for BRCA1/2 mutant tumours to PARPi monotherapy was 30-43% in monotherapy trials in mCRPC setting.

Variant classification	VUS temperature scale	Posterior probability
Pathogenic		99%
Likely pathogenic		90%
Uncertain significance	Hot	81.2%
	Warm	67.5%
	Tepid	50%
	Cool	32.5%
	Cold	18.8%
	Ice cold	10%
Likely benign		0.1%
Benign		

VUS – General consensus

- Do NOT offer PARPi to patients with HRR gene VUS
- Whenever possible discuss the findings at a tumour molecular board
- Stay updated as VUS are reclassified over time

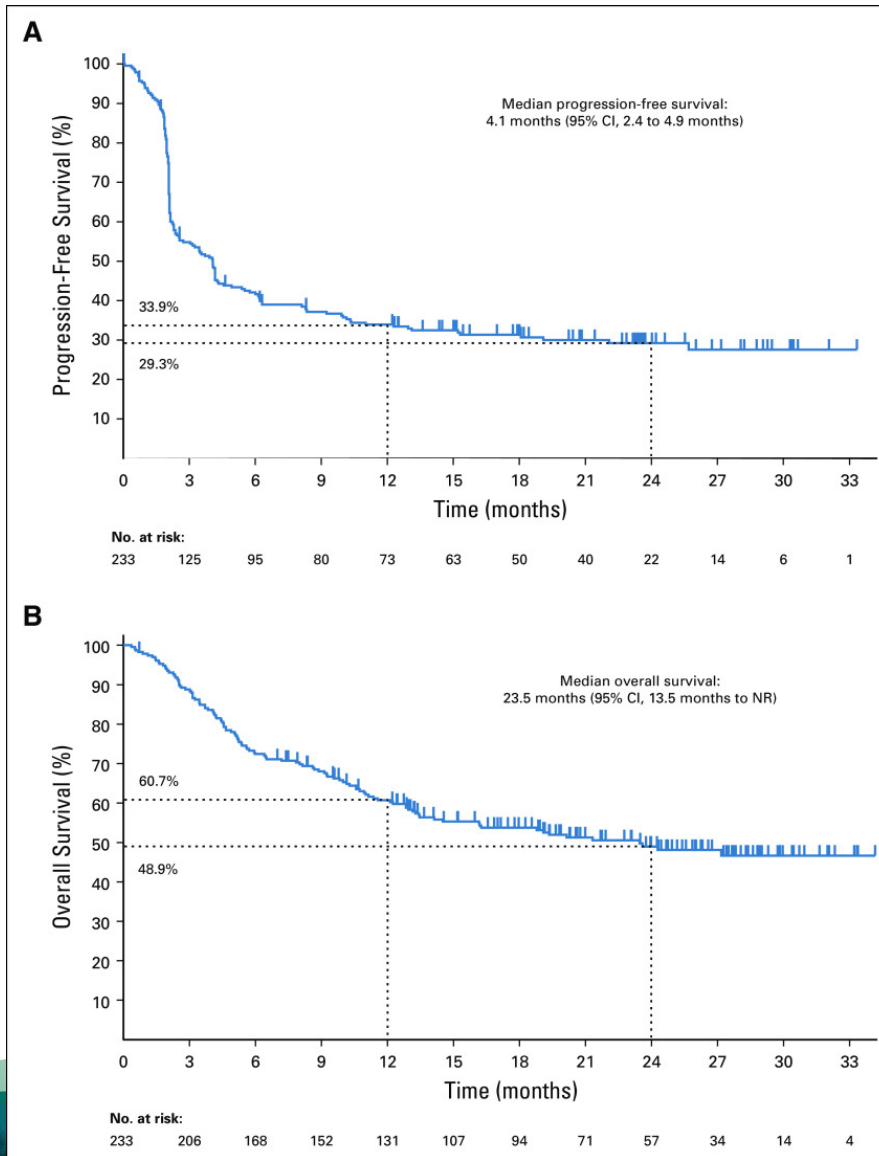


The “minimum” standard

- **Homologous recombination repair (HRR) genes**
 - **Highly relevant:** BRCA2, BRCA1, PALB2, BRIP1 ...
 - **Others:** CDK12, ATM, CHECK2, FANCA ...
- **Mismatch Repair deficiency (MMRd)**
 - IHC and NGS: MSH2, MSH6, MLH1 and PMS2
 - NGS: Microsatellite instability (MSI)

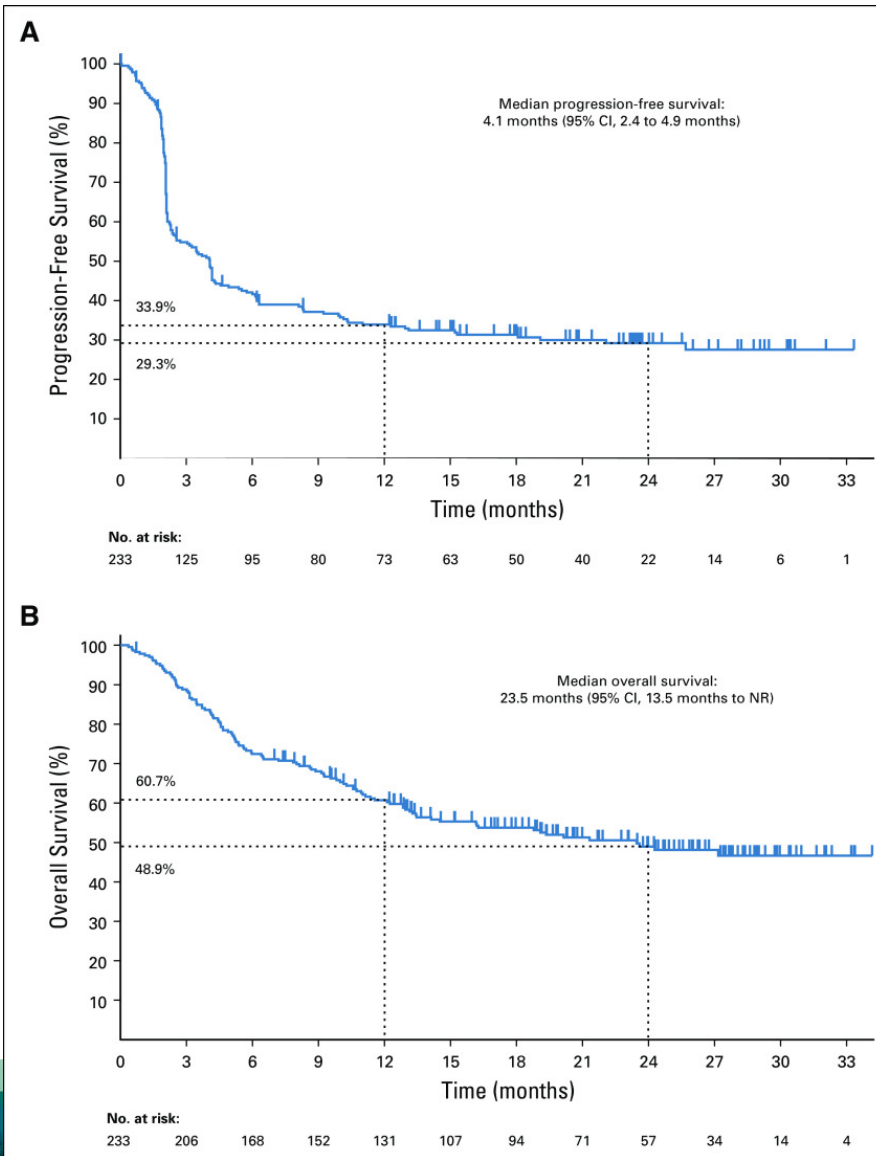


Microsatellite instability



- KEYNOTE-158 trial → Pembrolizumab works!
- However, only 6 PCa patients were included
- Some additional evidence from single institute cohorts.
- Only for mCRPC, but why wait to test?

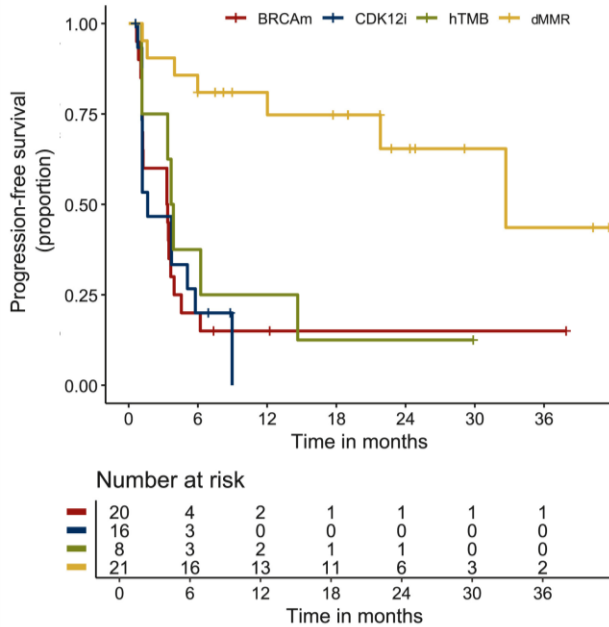
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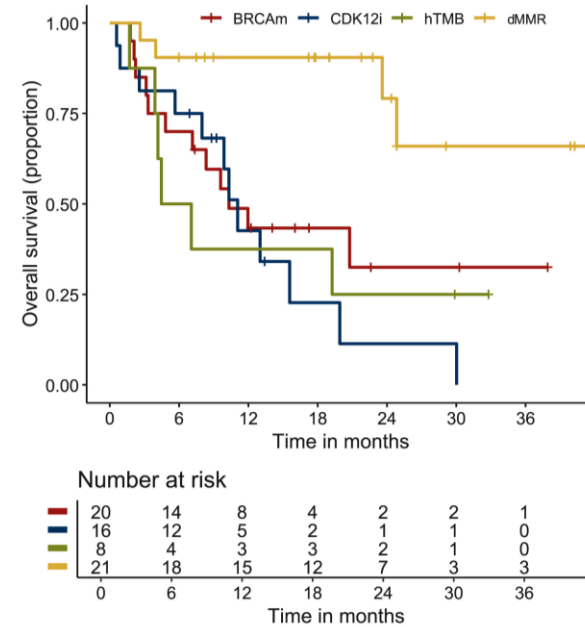
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Immunotherapy beyond MSI-H PCa

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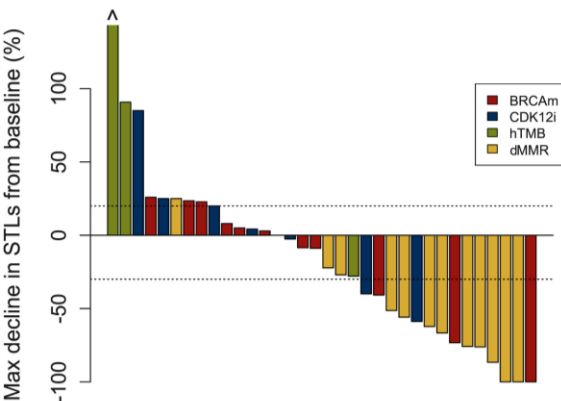


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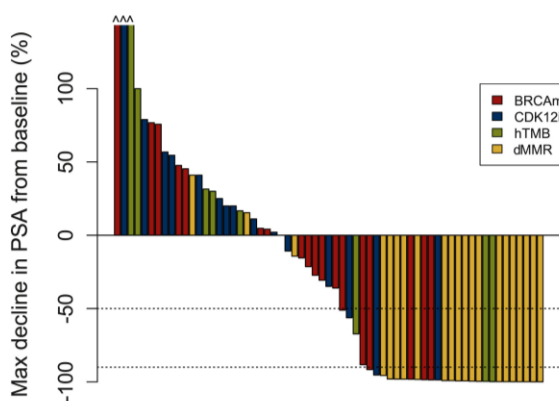


- INSPIRE Trial: High TMB and HRR gene-mutant tumours
- Some responses for hTMB and BRCA2 mutant tumours observed, but not sustained responses.

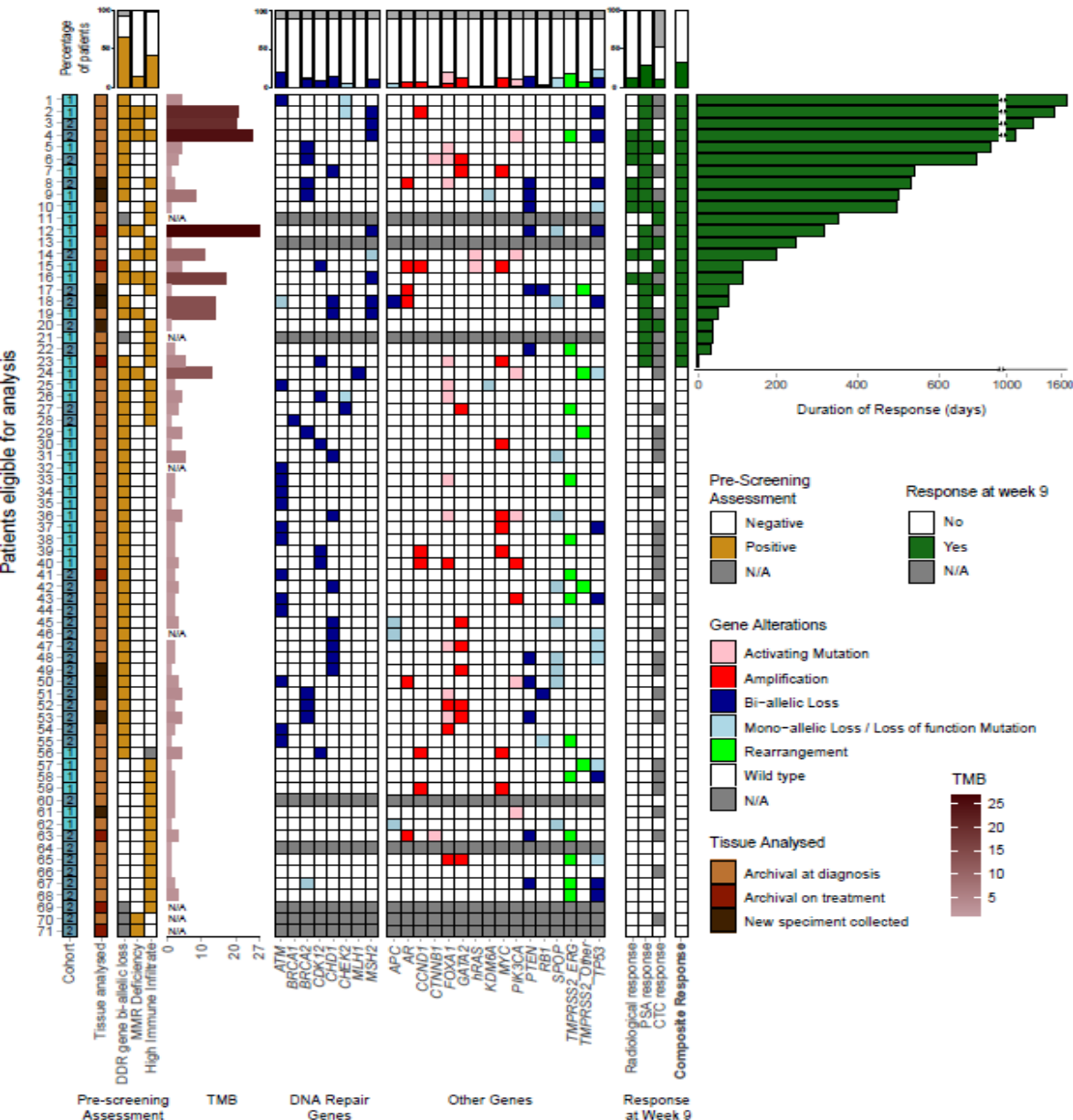
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Immunotherapy beyond MSI-H PCa

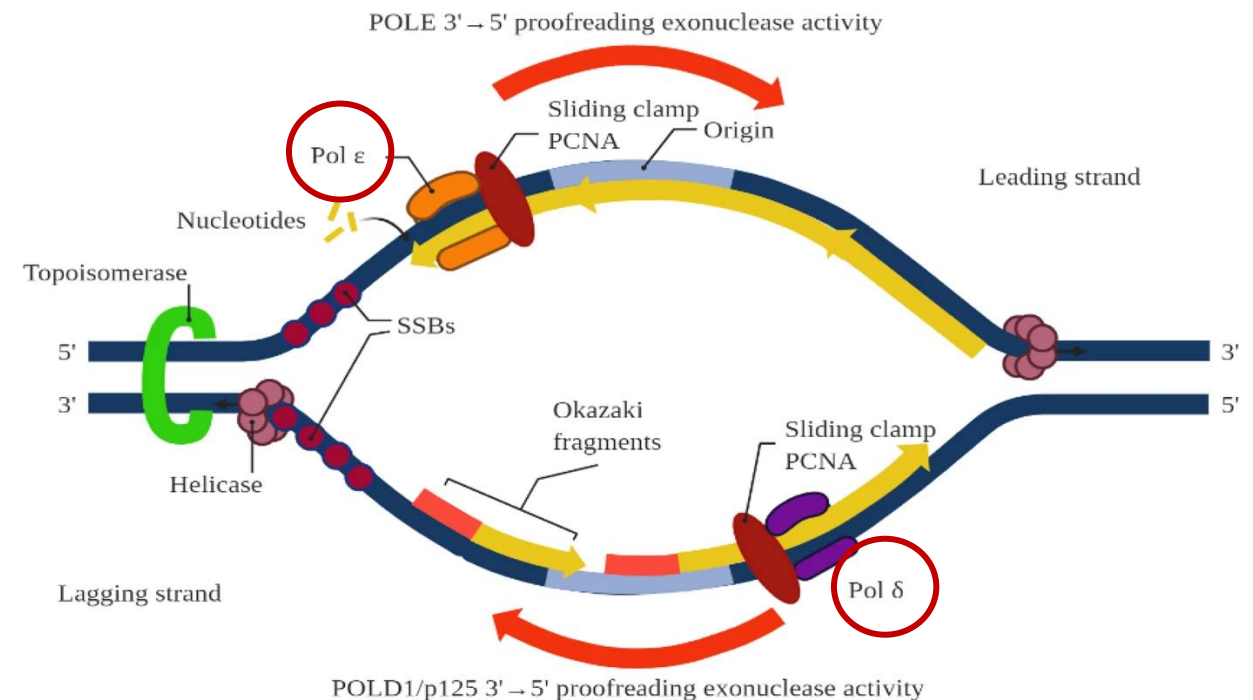


- NEPTUNES Trial: HRR-gene mutations (only biallelic) and high TILs (>20%).
- Better responses in the HRD cohort (e.g., BRCA2 4/8 responses).
- Patients selected only on the basis of high TILs did not respond or had short duration of response for the most part.

Immunotherapy beyond MSI-H PCa

POLE and POLD1: extremely rare, but game changing!

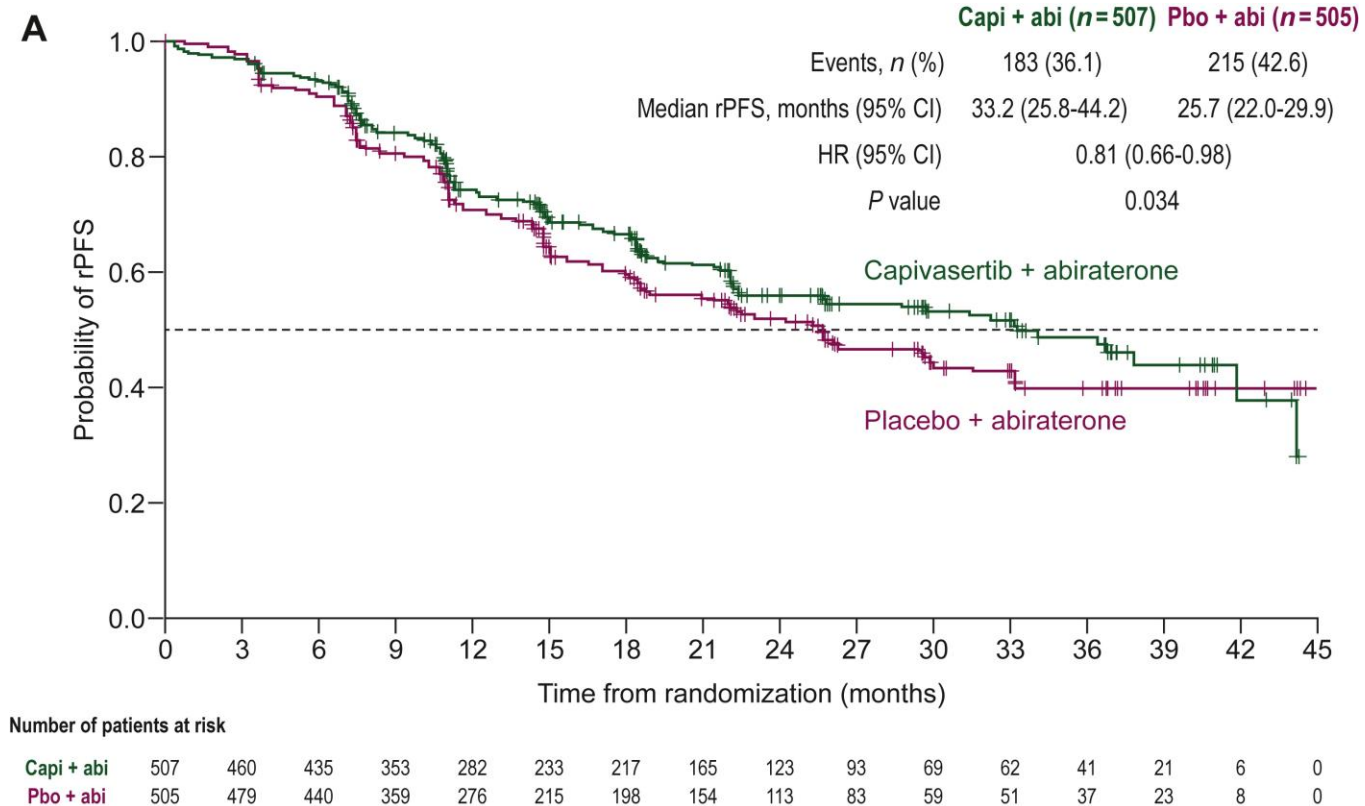
- Often included in commercial NGS panels
- Lead to ultra-hypermutated phenotype (TMB > 100 Mut/Mb)
- But characteristically MSS!!!
- Dramatic responses to immunotherapy reported



New: PTEN IHC Loss

Capitello-281 Trial

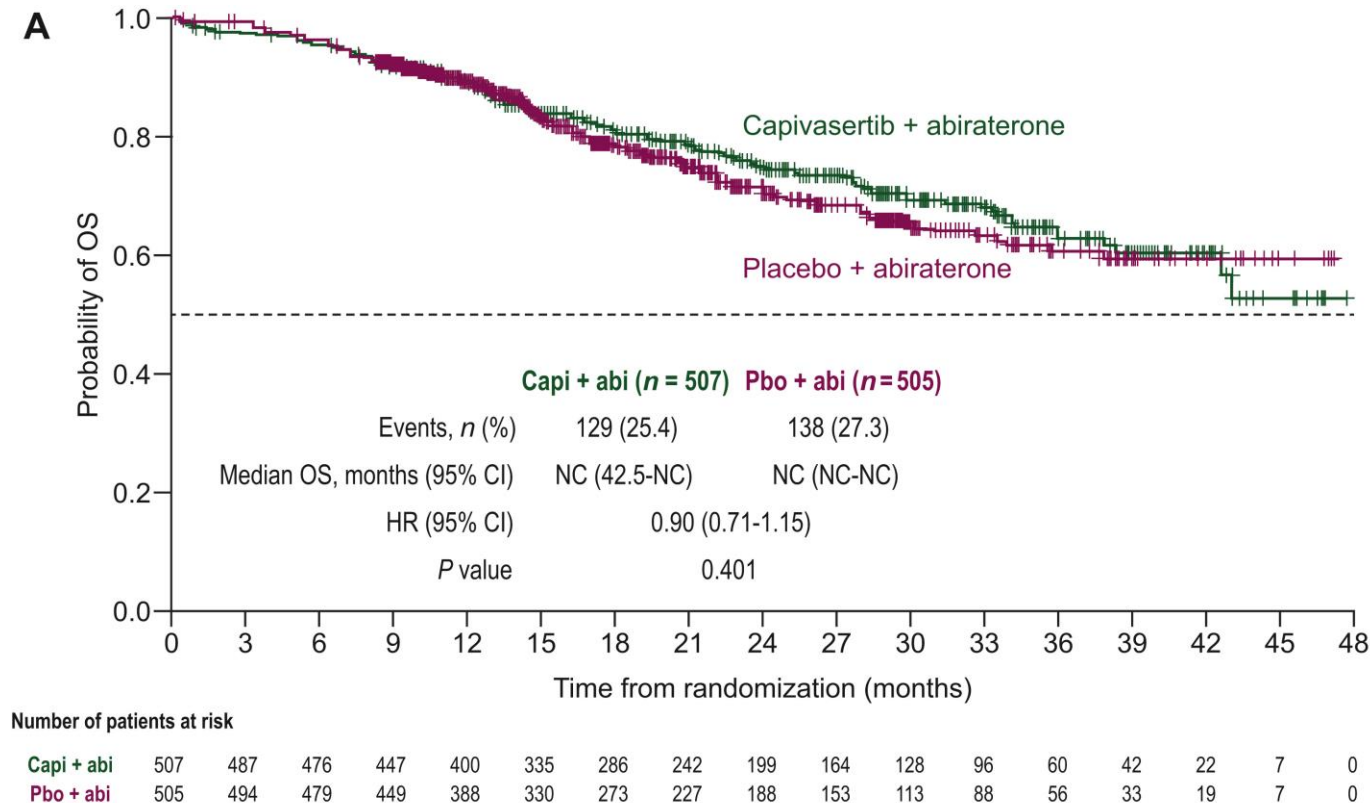
- PFS Benefit, OS data immature
- Subgroup analyses suggest higher efficacy for tumours with higher % of PTEN loss
- Findings of PTEN mutations in NGS or high score in PTEN-loss signature (transcriptomic) are NOT equivalent to IHC loss



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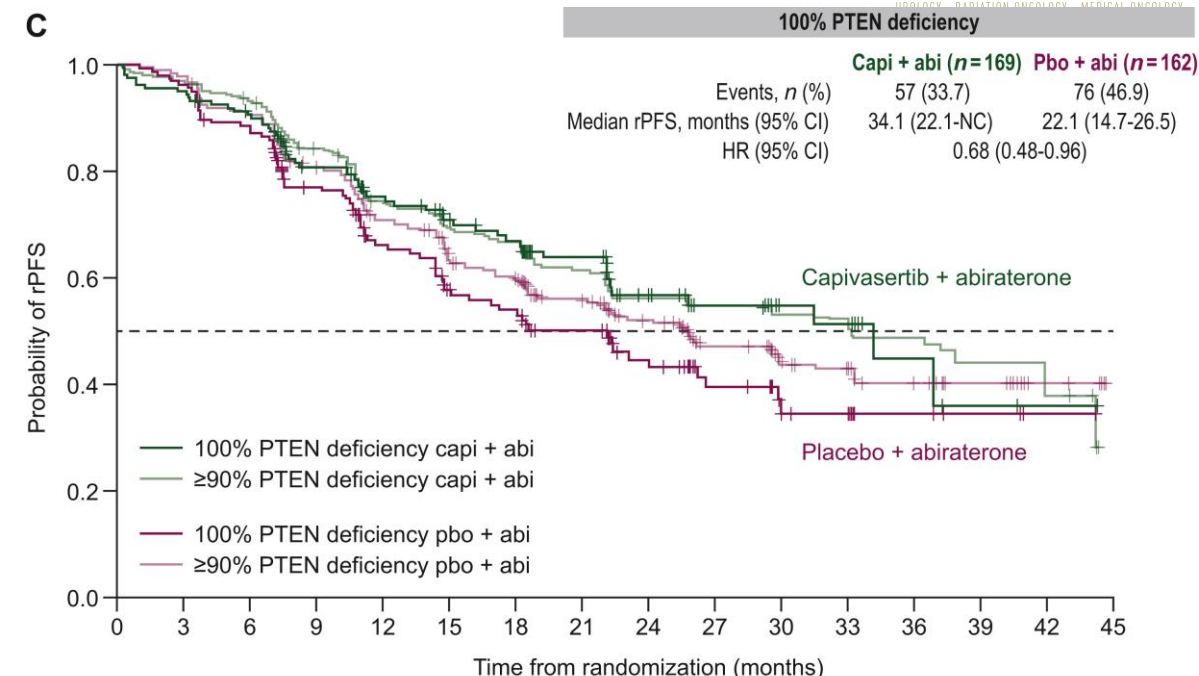
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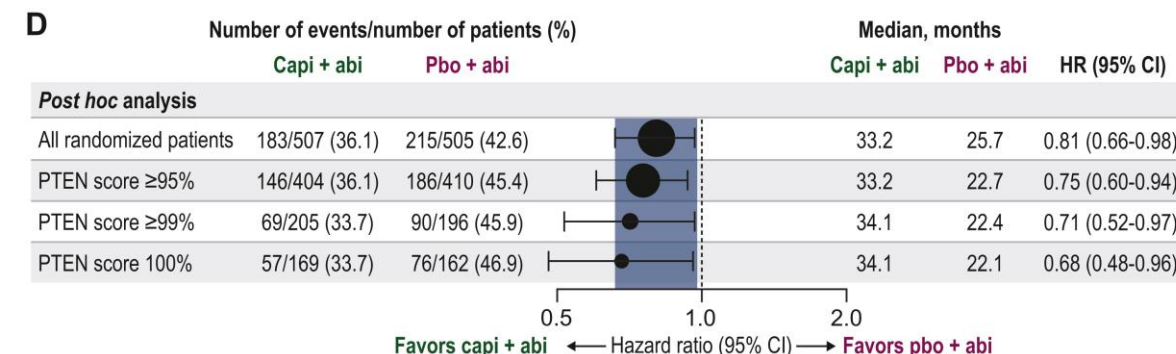
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Number of patients at risk (100% PTEN deficiency)

Capi + abi 169	152	142	105	90	76	68	51	34	25	16	15	7	2	1	0
Pbo + abi 162	151	137	104	79	64	59	45	30	21	12	10	7	3	1	0



Prognostic genomic alterations

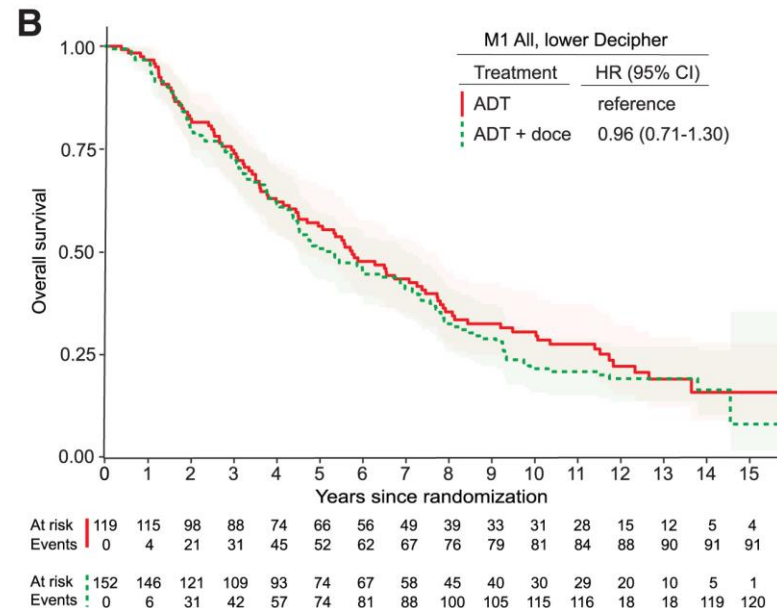
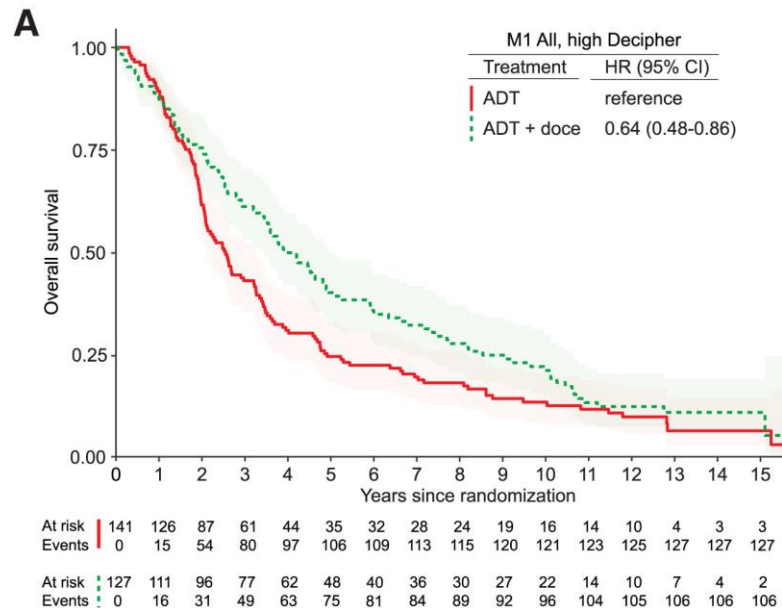
Other insights from NGS panels

Good prognosis	Bad Prognosis	Predicting poor responses
<i>SPOP</i>	<i>RB1</i>	<i>AR Amp/Rearrangements (ARPI)</i>
<i>FOXA1</i> mutations	<i>TP53</i>	<i>CCND1 Amp (Taxanes)</i>
<i>CHD1</i> loss	<i>PTEN</i>	
	HRR genes	
	Cell cycle / proliferation (<i>MYC</i> , <i>AURKA</i> , <i>MYCN</i>)	



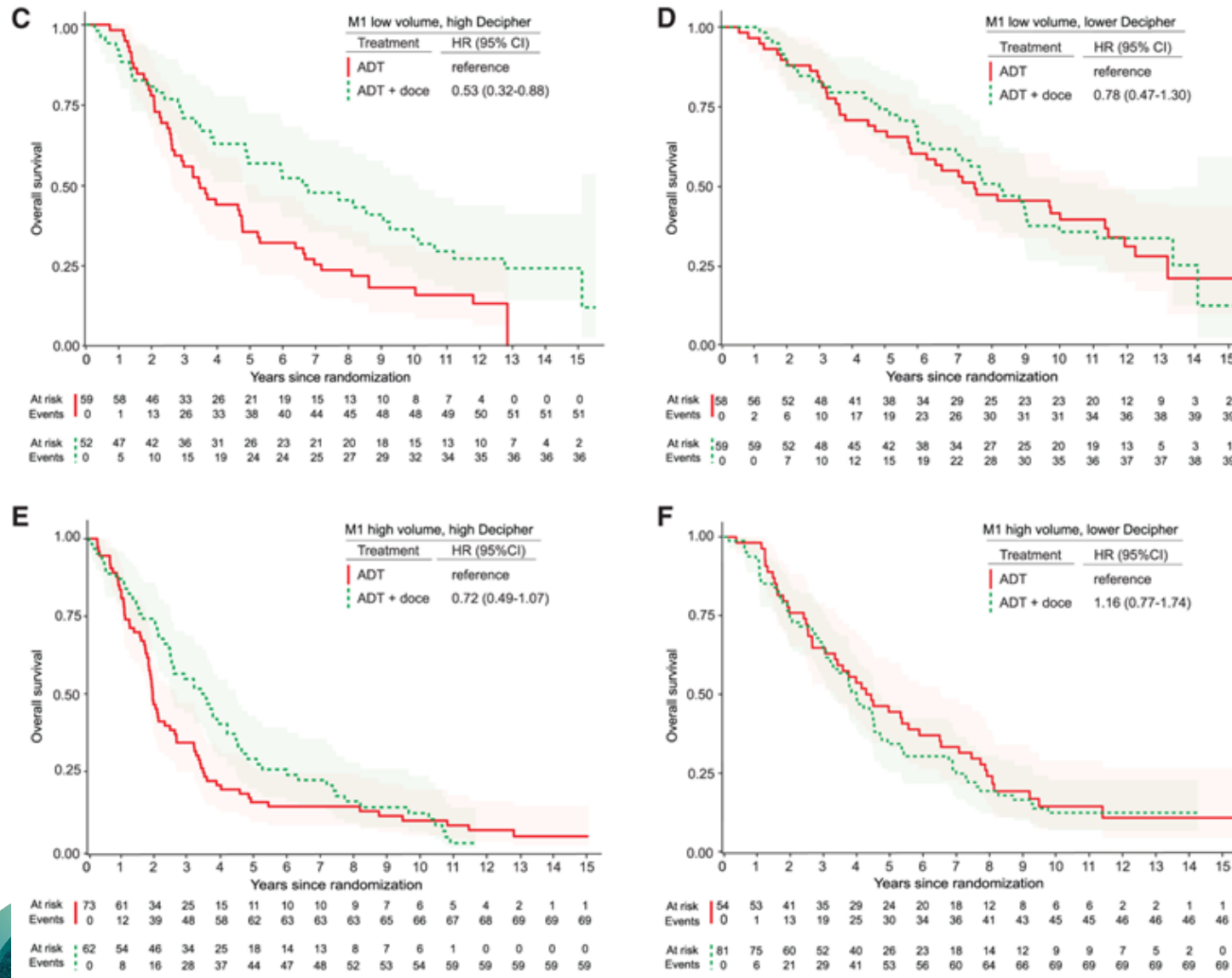
Future Perspectives: Gene expression assays

mHSPC – Decipher predicts benefit from Docetaxel



Future Perspectives: Gene expression assays

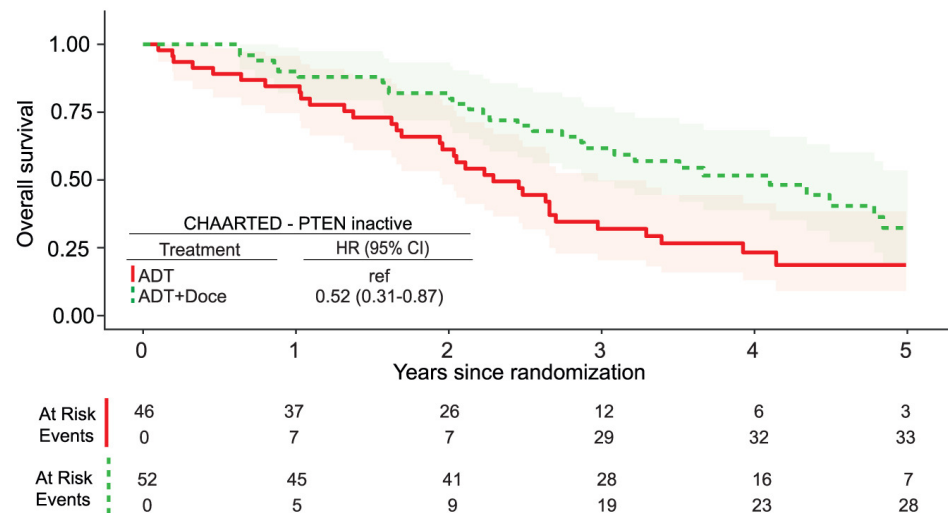
Subgroup analyses suggest
Decipher score could better
predict benefit from Docetaxel
compared to metastatic burden



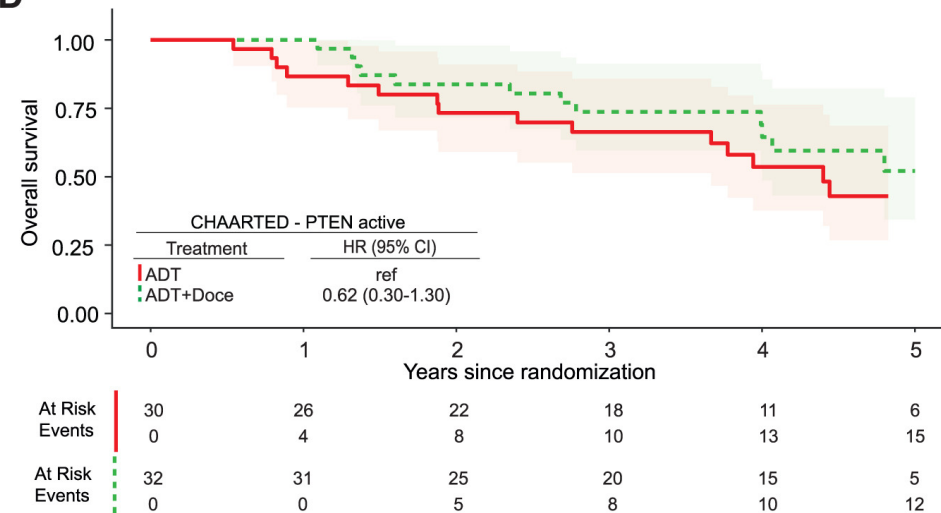
Future Perspectives: Gene expression assays

mHSPC – PTEN Loss Signature predicts benefit from Docetaxel

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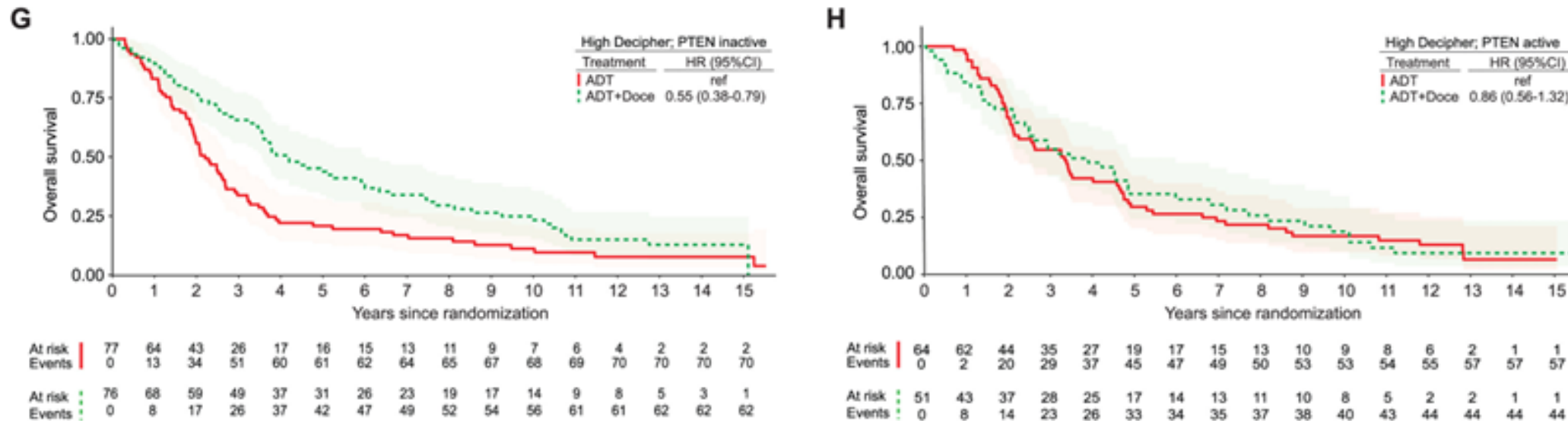


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Future Perspectives: Gene expression assays

mHSPC – Combination of PTEN Loss Signature and Decipher



ADT+Docetaxel is not SOC combination for mHSPC anymore, as triplet therapies are now gold standard.

Difficult to prospectively validate these findings.

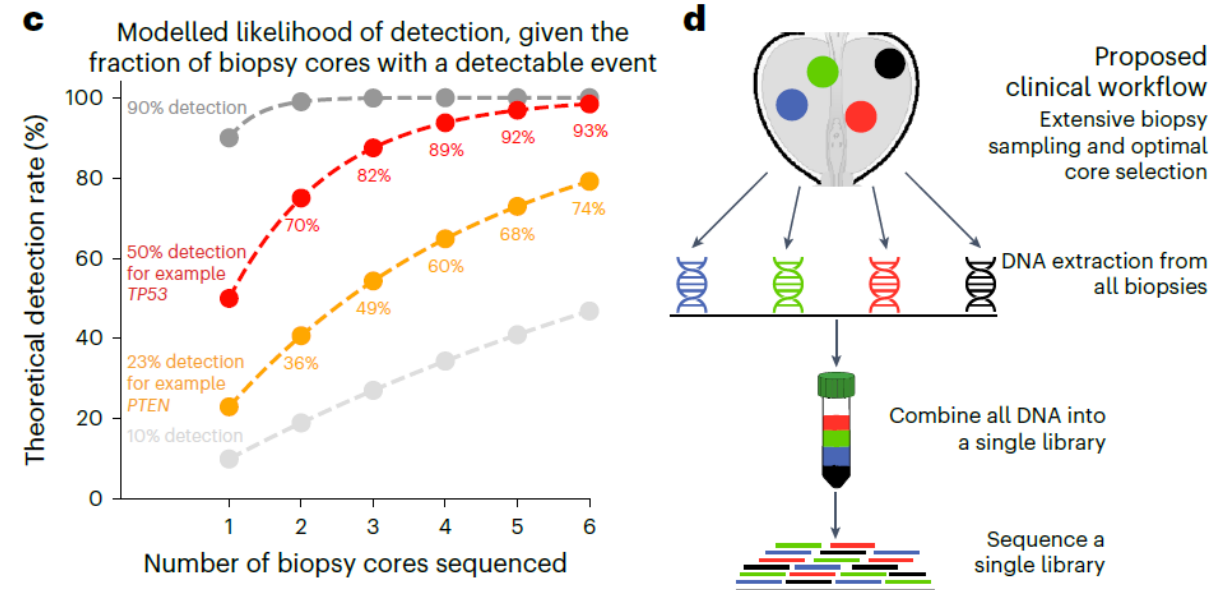
Tissue to be used for molecular analyses

Archival is an obvious, easy choice

- Most archival tissue samples come from diagnostic prostate biopsies (or prostatectomy for some metachronous patients).
- **Question:** how well do molecular analyses conducted on a single archival core from the prostate recapitulate the genomic landscape of the disease?
 - Metachronous patient: the archival samples may be very old
 - De-novo metastatic: disease will be very heterogeneous

Pragmatic approach (for patients with easily accessibly metastatic sites – no bones):

- For the novo high volume metastatic disease: biopsy and NGS of a metastatic site.
- For metachronous disease: re-perform biopsy if archival tissue is very old (>5 years), or the patient received significant systemic treatment for multiple years.



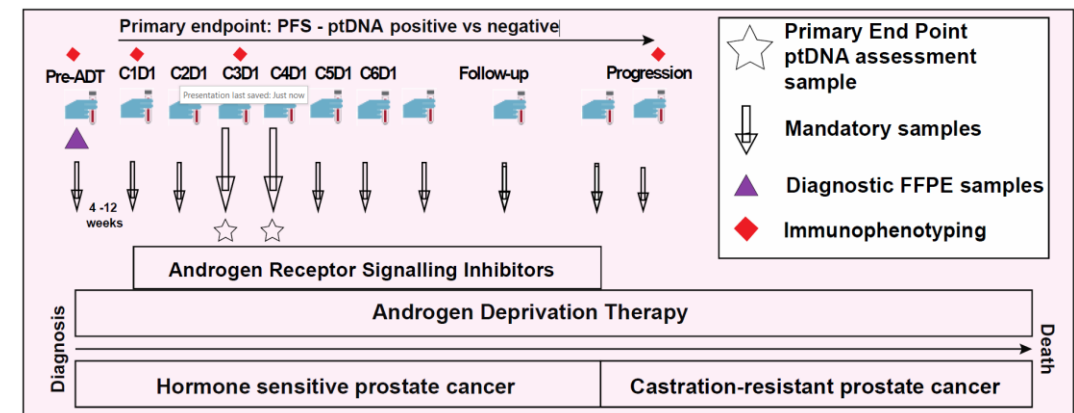
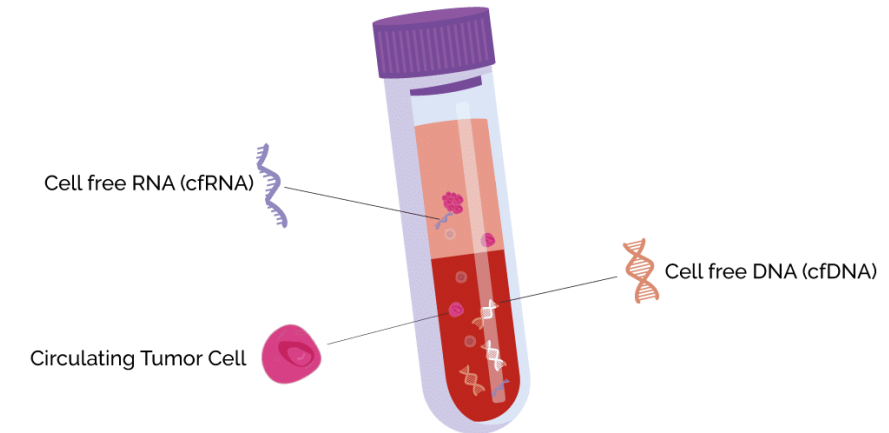
Liquid biopsy

Achieving the dream: longitudinal monitoring of the genomic landscape

Pro	Cons
Minimally invasive	Sensitivity due to ctDNA concentration (Best results with high burden of disease, while disease is progressing)
Better recapitulates heterogeneity	ccfDNA concentration is influenced by other factors
Repeatable	

Value of ctDNA:

- Quantitative (ctDNA negative vs positive)
- Qualitative (Tracking alterations)



Watch the space! PARADIGM trial
To be presented at IPCS2026

Thank you for your attention

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