Liquid Biopsy and Precision Medicine Updates in GU

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Outline

- Prostate Cancer
- Urothelial Cancer
- RCC

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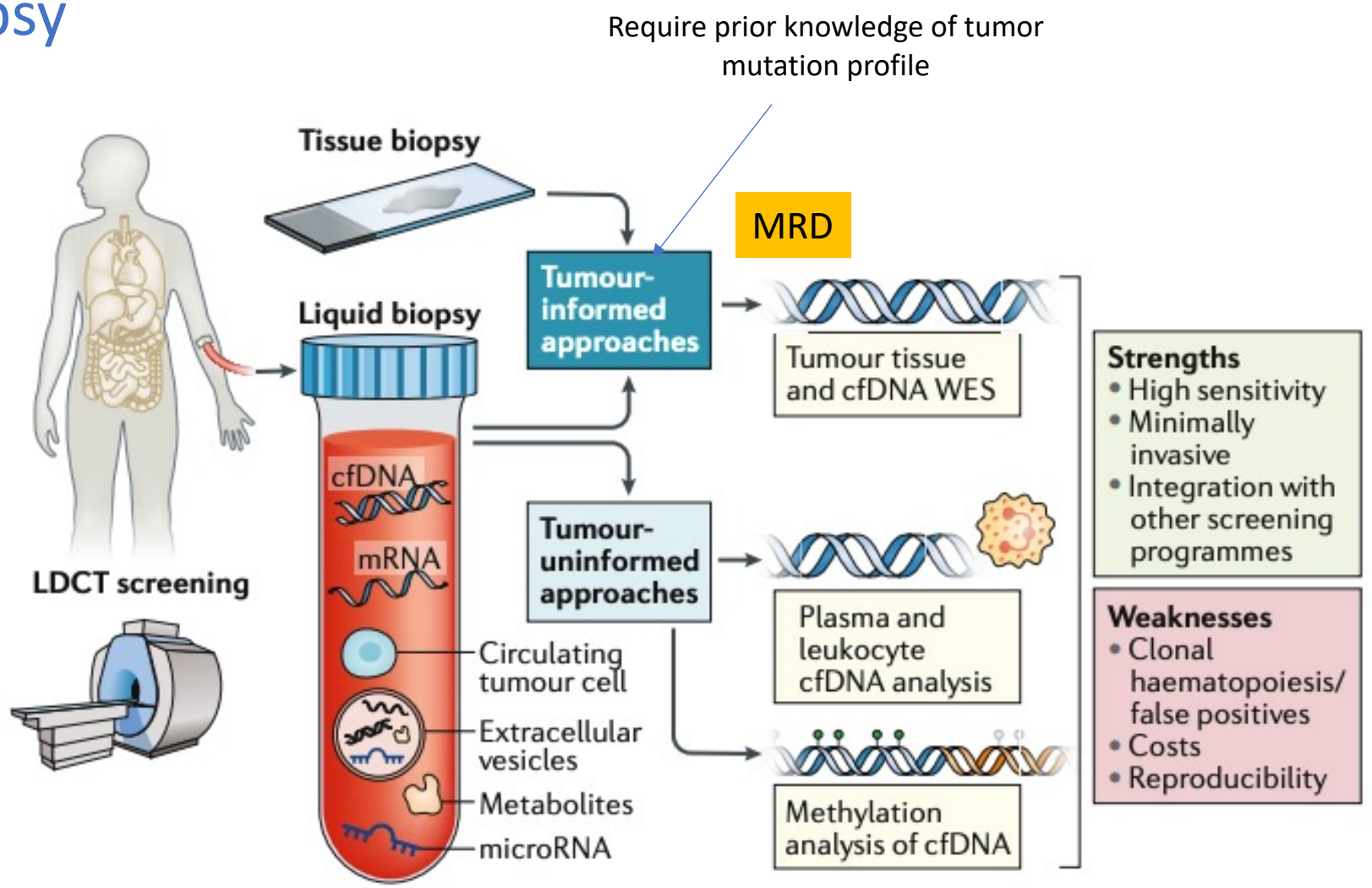
Liquid biopsy



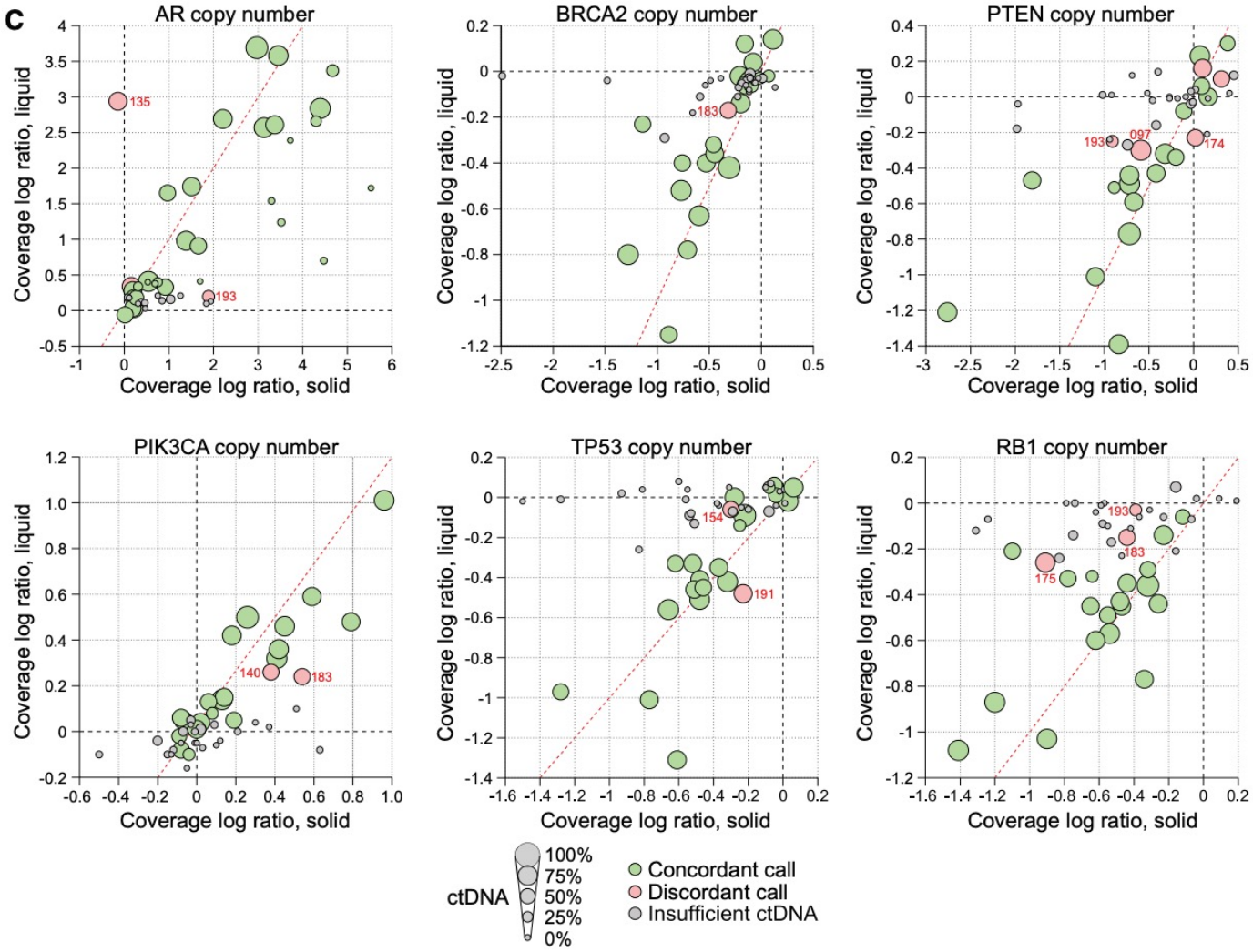
Rolfo et al, Nature Medicine 2020

Concordance tissue and ctDNA

N = 45 matched M1 tissue / ctDNA

- 88.9% concordant

- ctDNA-based assay is (most cases) sufficient to identify the driver DNA alterations present in matched metastatic tissue



Some Questions remain…..

- What is the significance of 0.5% allele fraction?
- What assay to use?

Wyatt et al, JNCI 2017

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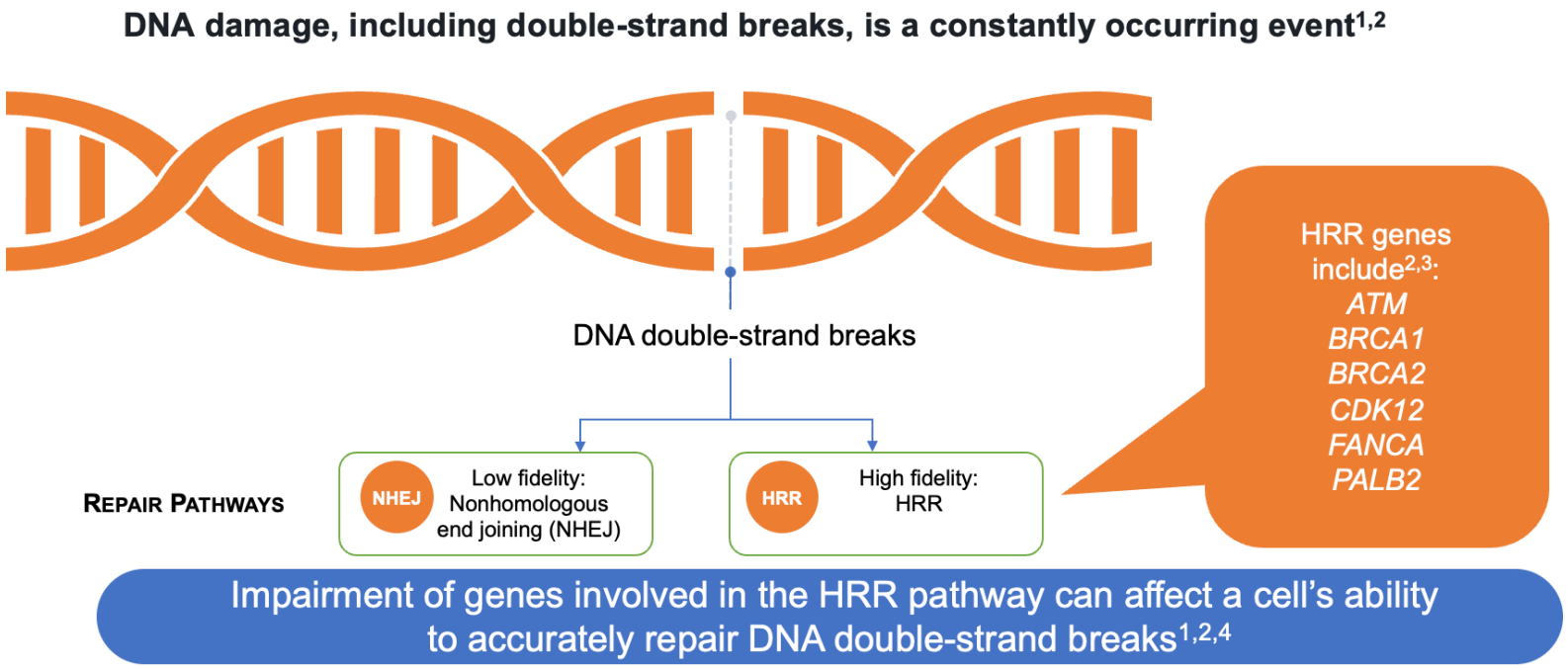
Actionable alterations in advanced prostate cancer

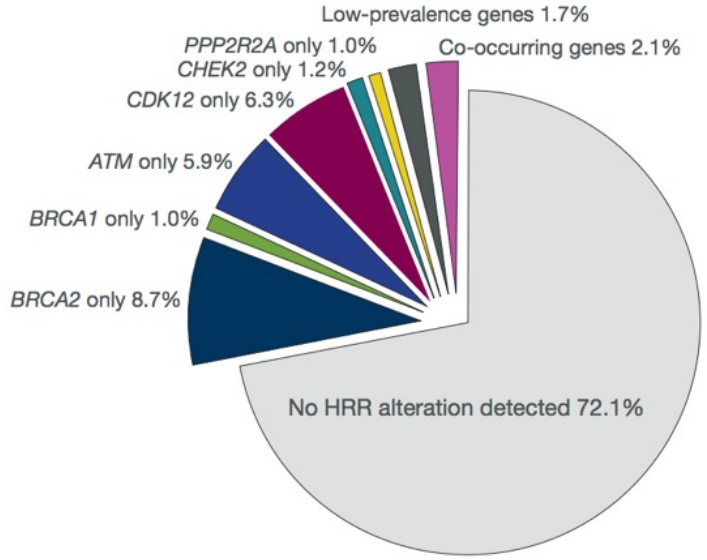
Genomic Mutations	Method of Testing	Treatment	Status of Therapy
AR-V7[59]	Circulating tumor cells	Resistance to androgen axis-targeted therapies	Preliminary testing, not validated
BRCA1/*BRCA2*/*ATM* and other DNA repair mutations[126]	NGS on tissue germline testing on blood/saliva sample	PARP inhibitors	FDA approved, Category 1
MSI-H[29]	NGS on tissue or ctDNA	ICIs such as pembrolizumab	FDA approved
TMB>10 mut/Mb[127]	NGS on tissue or ctDNA	ICIs such as pembrolizumab	FDA approved
PTEN loss[128]	IHC/NGS on tissue or ctDNA	PI3K inhibitors, ipatasertib or mTOR inhibitors	Promising preliminary information
CDK12 mutation[30]	IHC/NGS on tissue or ctDNA	ICIs	Investigational therapy; clinical trials ongoing

Abbreviations: MSI-H, microsatellite index-high; TMB, tumor mutational burden; mut/Mb, mutation/megabase; NGS, next-generation sequencing; ctDNA, circulating tumor DNA; IHC, immunohistochemistry; PARP, poly (ADP-ribose) polymerase; ICIs, immune checkpoint inhibitors.

Jang et al, Onco Targets Ther 2022

HRR Genes Play Important Role in Repairing Double-Strand DNA Damage





N = 778/4,425 (27.9%) patients and the prevalence of HRR gene mutations in genes included in Cohort A was 17.1%. The most common gene mutation was *BRCA2* (8.7%)

TRITON3 Study Design

Key eligibility criteria

- Chemotherapy-naïve mCRPC
- BRCA or *ATM* alteration[a]
- 1 prior second-generation ARPI in any setting[b]

Prior docetaxel or other taxane chemotherapy for castration-sensitive disease was permitted

Randomization 2:1

Stratification:

- ECOG PS 0 vs 1
- Hepatic metastases yes vs no
- *BRCA1* vs *BRCA2* vs *ATM*

Rucaparib (n=270)
600 mg BID

Physician's choice (n=135)[c]

Docetaxel (n=75)

or

Second-generation ARPI (n=60)

Abiraterone acetate or **Enzalutamide**

Patients who progress on physician's choice of treatment may be considered for crossover to rucaparib

Endpoints[d]

Primary:
- rPFS by IRR

Key secondary:
- OS
- ORR by IRR

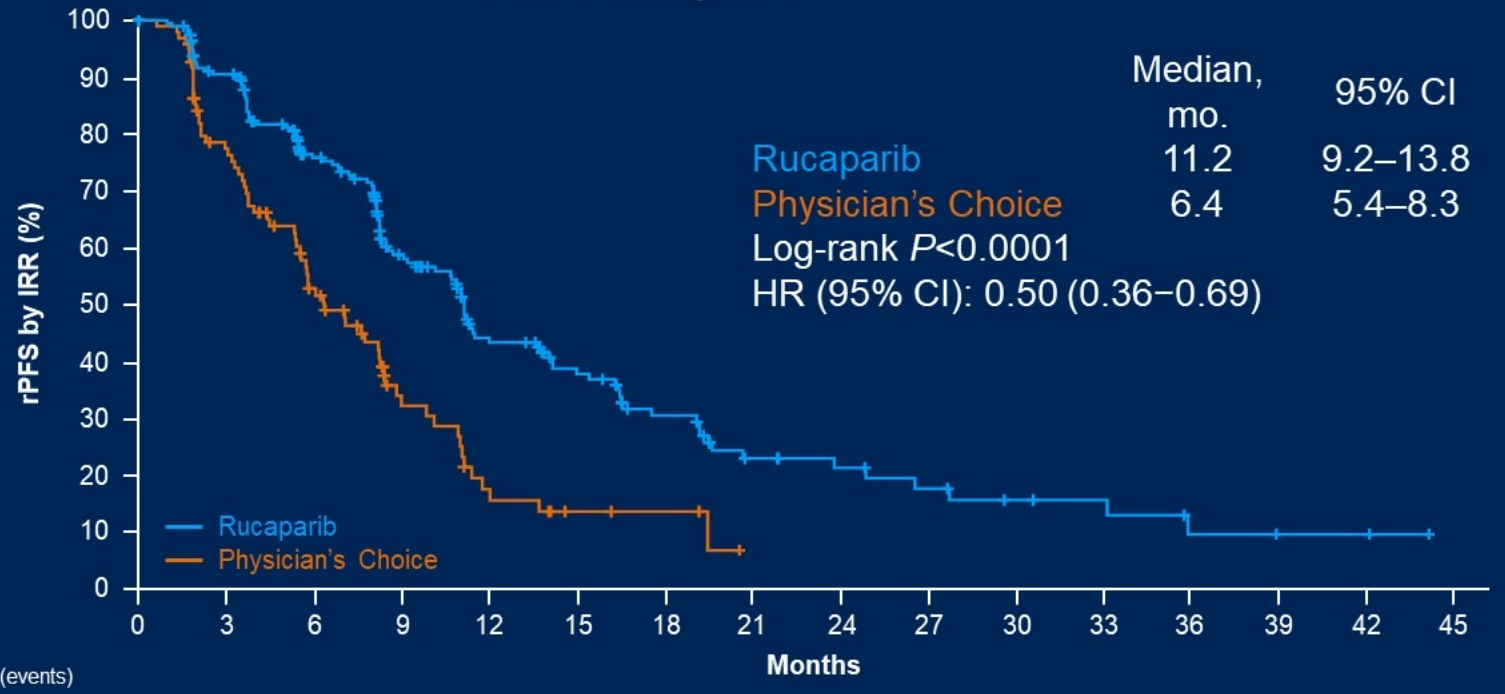
Subgroup analyses:
- OS and rPFS for rucaparib vs docetaxel or second-generation ARPI

Visit cutoff date: 25 August 2022. [a]Determined by Foundation Medicine testing of tissue or plasma. [b]Protocol amendment 19 June 2018: patients' qualifying second-generation ARPI could be in any setting. [c]If chosen, patients received whichever second-generation ARPI had not yet been received. Docetaxel: 75 mg/m^2 Q21D, 10 cycles max; Abiraterone acetate: 1000 mg QD; Enzalutamide: 160 mg QD; [d]Tumor assessments were conducted at baseline and every 8 weeks for 24 weeks, then every 12 weeks, via CT/MRI and technetium-bone scans. [e]84 patients had IRR-confirmed progression, including 3 who were later re-evaluated as having non-progressive disease by IRR. ARPI, androgen receptor pathway inhibitor; BID, twice daily; BRCA, *BRCA1* and *BRCA2*; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostrate cancer; OS, overall survival; Q21D, every 21 days; QD, daily; rPFS, radiographic progression-free survival.

Radiographic PFS

Characteristic	Rucaparib (N=270)	Control (N=135)
Genomic test — no. (%)		
Tissue	79 (29)	39 (29)
Plasma	170 (63)	79 (59)
Other	21 (8)	17 (13)

BRCA subgroup[1]



	Median, mo.	95% CI
Rucaparib	11.2	9.2–13.8
Physician's Choice	6.4	5.4–8.3

Log-rank P<0.0001
HR (95% CI): 0.50 (0.36−0.69)

Patients at risk (events)

Rucaparib	201 (0)	169 (18)	124 (44)	83 (70)	55 (89)	41 (95)	27 (103)	16 (109)	13 (110)	10 (112)	7 (113)	6 (113)	3 (115)	2 (115)	2 (115)	0 (115)
Physician's Choice	101 (0)	69 (21)	42 (42)	19 (55)	9 (64)	4 (66)	3 (66)	0 (67)								

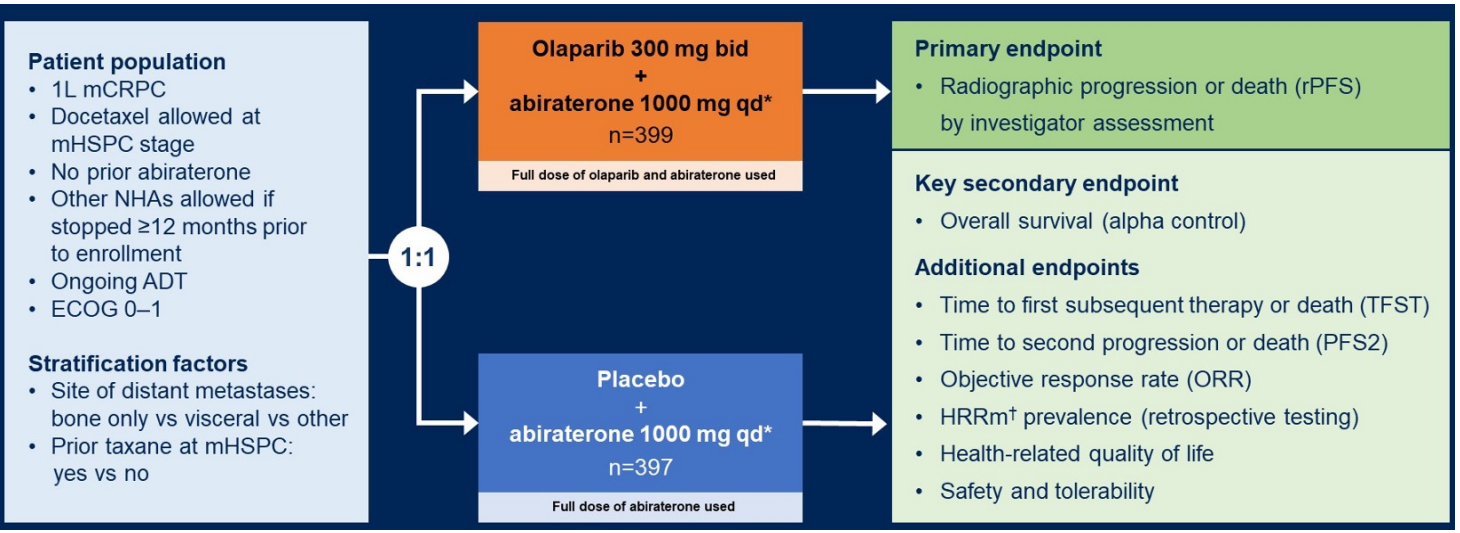
ITT population[1]

	Rucaparib (n=270)	Physician's Choice (n=135)
Median rPFS, mos (95% CI)	10.2 (8.3–11.2)	6.4 (5.6–8.2)
Log-rank P	0.0003	
HR (95% CI)	0.61 (0.47–0.80)	

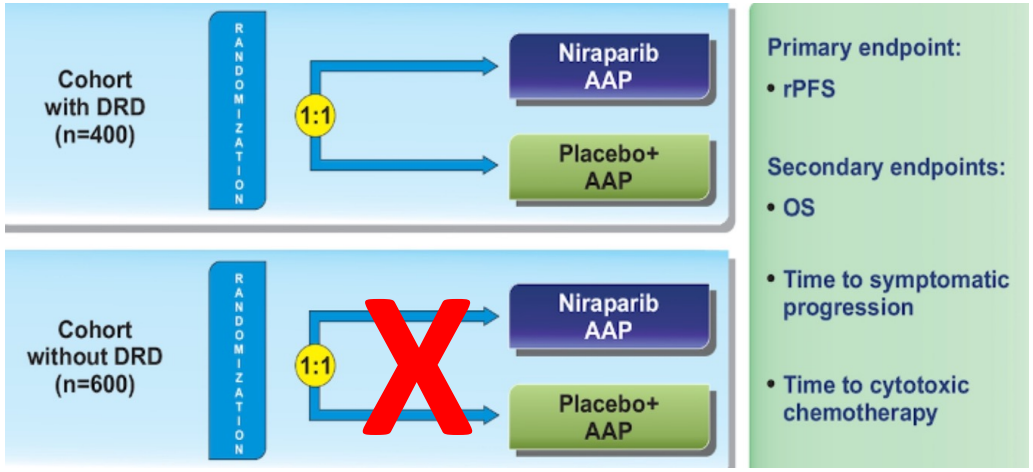
Fizazi et al, NEJM 2023

Visit cutoff date: 25 August 2022. BRCA subgroup data maturity (rucaparib vs physician's choice): 182/302 (60.3%). 1. Bryce et al. Presented at the 2022 PCF Annual Retreat.
BRCA, *BRCA1* and *BRCA2*; HR, hazard ratio; IRR, independent radiology review; ITT, intent to treat; PFS, progression-free survival; rPFS, radiographic progression-free survival.

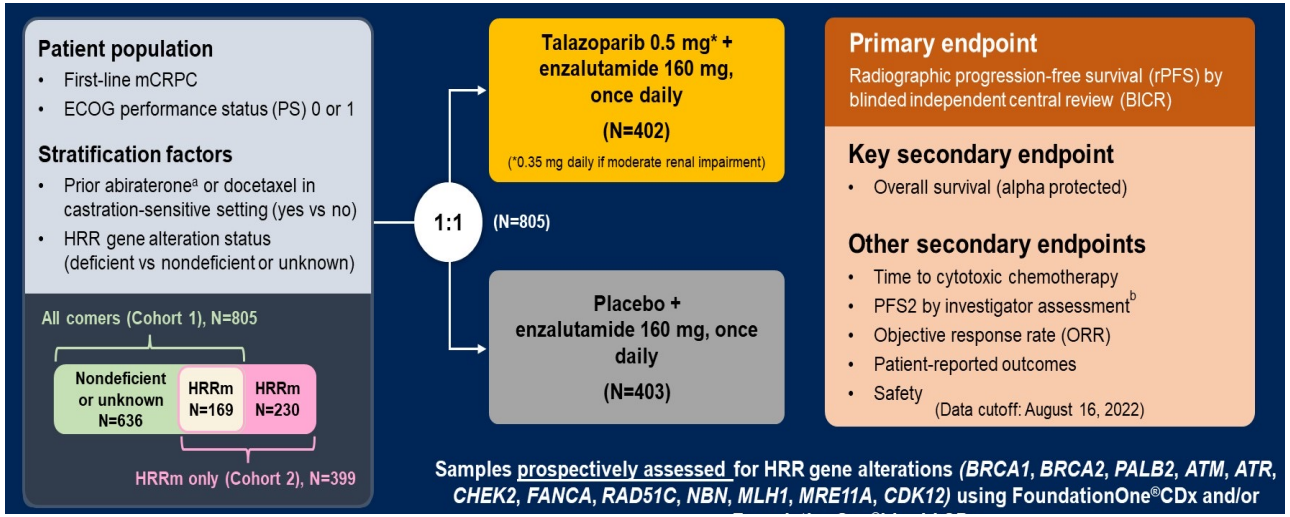
How About PARP Inhibitors in Combination? (Selection tissue / ctDNA)



PROPEL



Magnitude



TALAPRO-2

HRR selection by ctDNA in Ph. 3 Trials PARPi/ARPI

	Abiraterone and Olaparib (n=399)	Abiraterone and Placebo (n=397)
HRRm status§		
Based on ctDNA, n (%)		
HRRm	98 (24.6)	100 (25.2)
Non-HRRm	269 (67.4)	267 (67.3)
HRRm unknown	32 (8.0)	30 (7.6)
Based on tumor tissue test, n (%)		
HRRm	62 (15.5)	56 (14.1)
Non-HRRm	207 (51.9)	210 (52.9)
HRRm unknown	130 (32.6)	131 (33.0)
Based on aggregate, n (%)		
HRRm	111 (27.8)	115 (29.0)
Non-HRRm	279 (69.9)	273 (68.8)
HRRm unknown	9 (2.3)	9 (2.3)

PROPEL

Clarke et al, NEJM Evid 2022

Magnitude

HRR– randomly assigned (tested by both tissue and plasma; n = 247)

HRR– by tissue and plasma (n = 171)
HRR– by plasma only (n = 75)
HRR– by protocol (failed both; n = 1)

TALAPRO-2

Chi et al, JCO 2023

N= 805 pts (100%) tissue
N= 115 (14.5) tissue+plasma

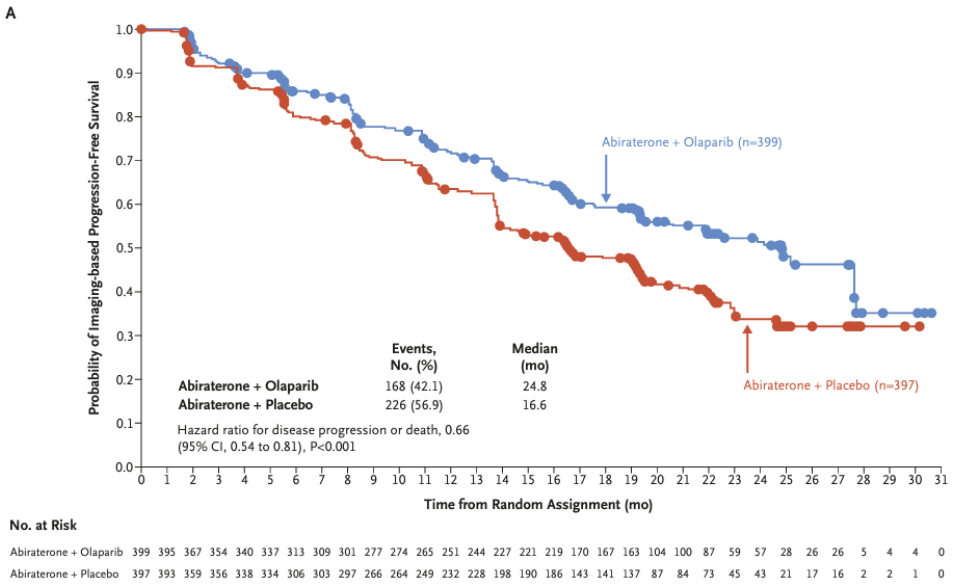
Table 1. Concordance of HRR Deficiency Status Between Prospective ctDNA- and Tumor Tissue-Based Tests (ITT All-Comers Population)

Tumor Tissue-Based Results	Prospective ctDNA Test Results: HRR-Deficient		Non-HRR-Deficient		Unknown*		Total	
HRR-Deficient	**26**	(22.6)	**1**	(0.9)	4	(3.5)	**31**	**(27.0)**
Non-HRR-Deficient	**4**	(3.5)	**64**	(55.7)	8	(7.0)	**76**	**(66.1)**
Unknown	2	(1.7)	3	(2.6)	3	(2.6)	**8**	**(7.0)**
Total	**32**	**(27.8)**	**68**	**(59.1)**	**15**	**(13.0)**	**115**	**(100.0)**

Azad et al, ASCO 2023

PROPEL: Olaparib + abiraterone for mCRPC

All comers



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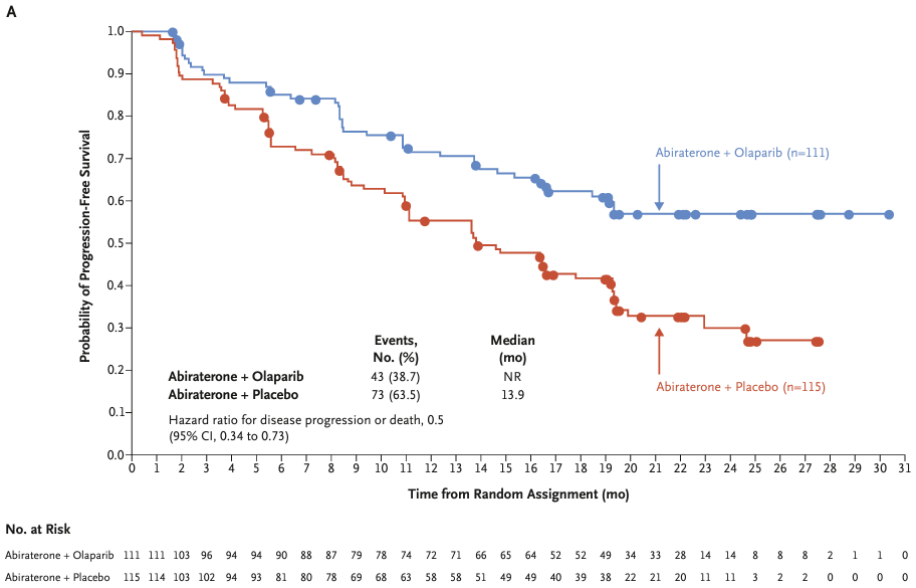
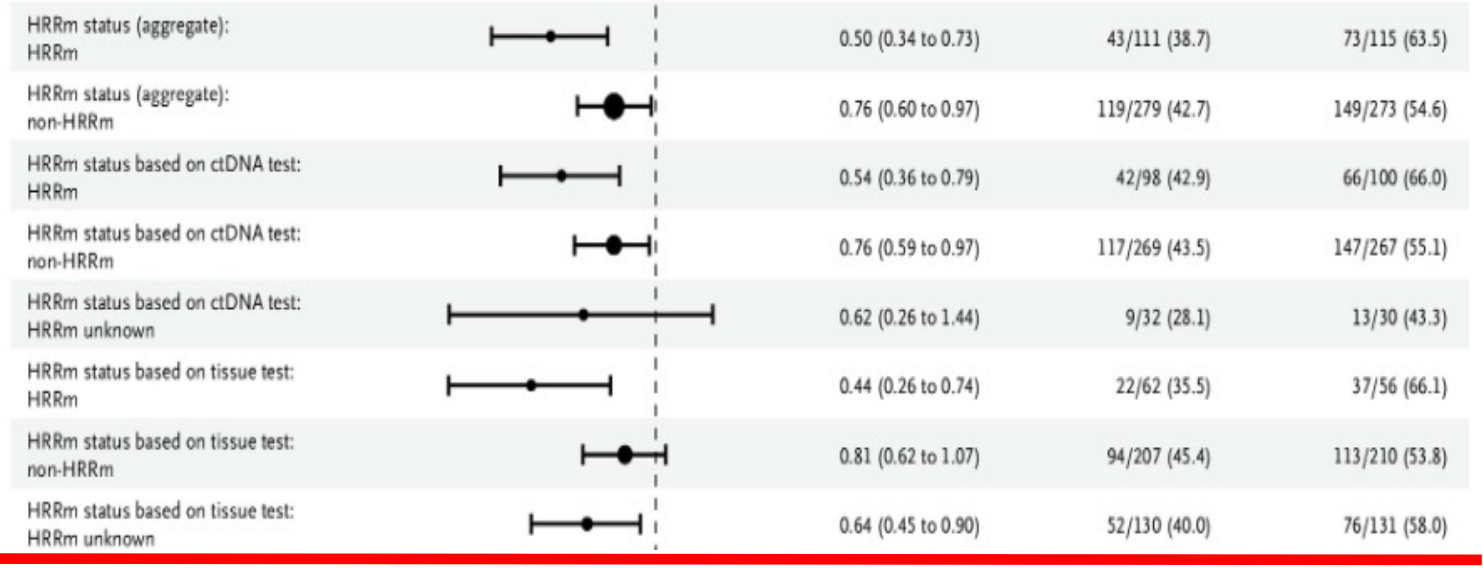
HRR+





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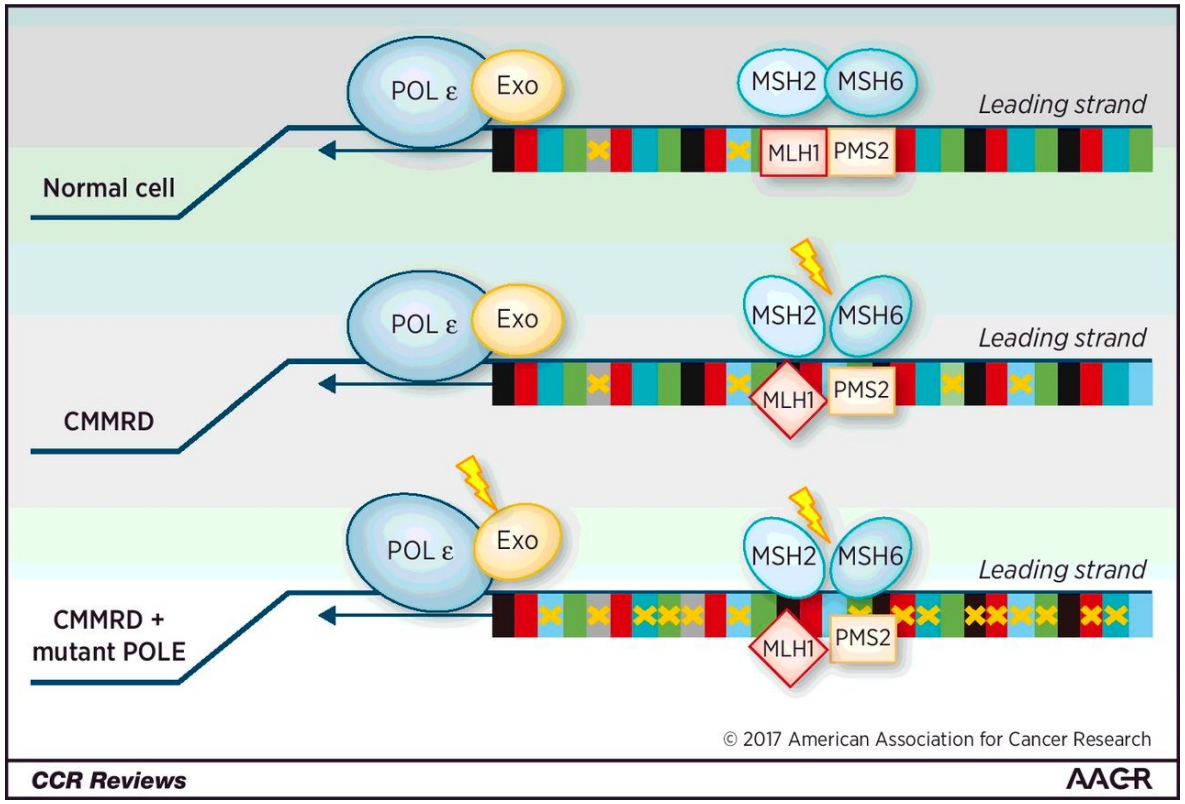
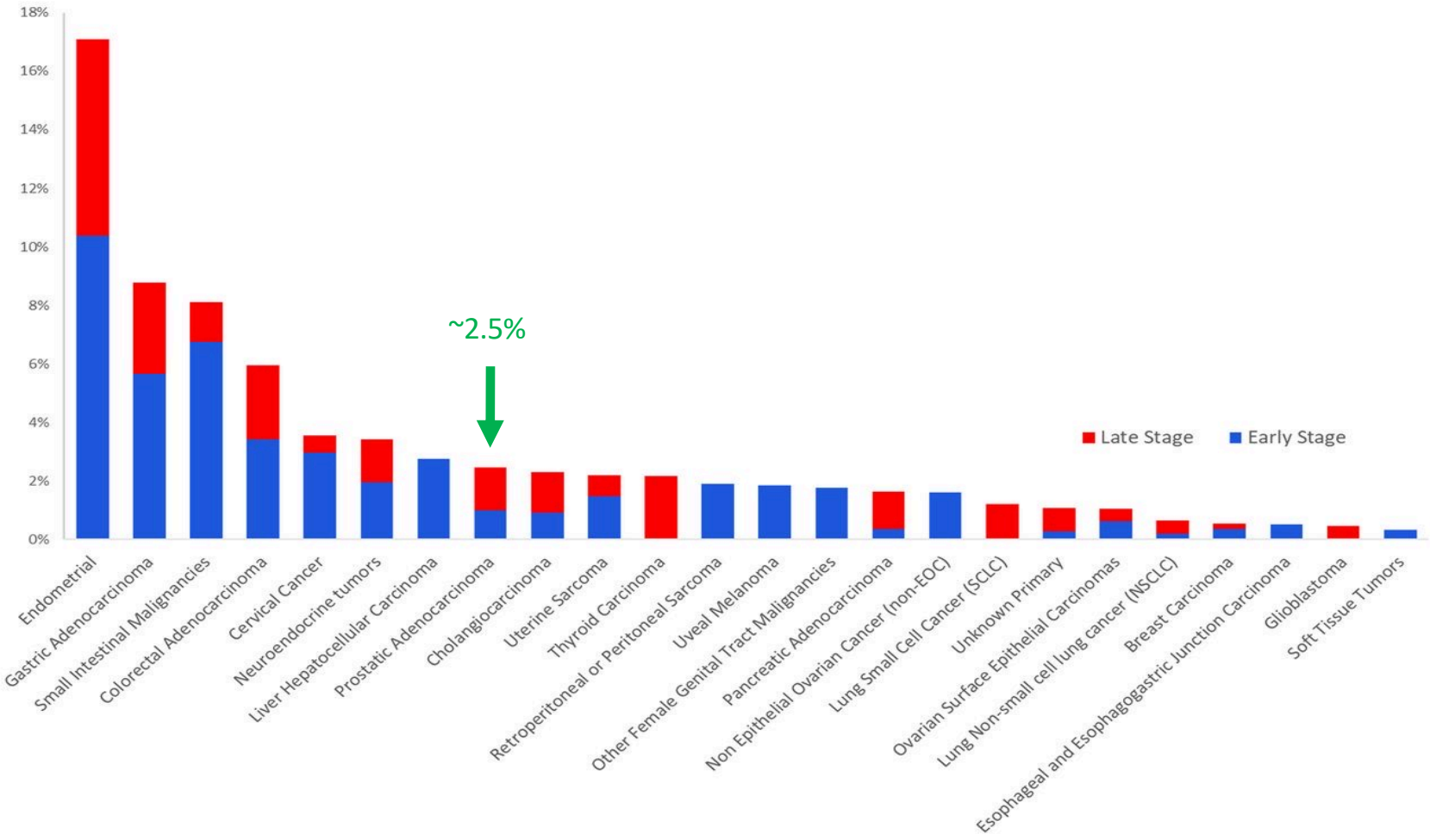
Mismatch Repair Deficiency and Microsatellite instability

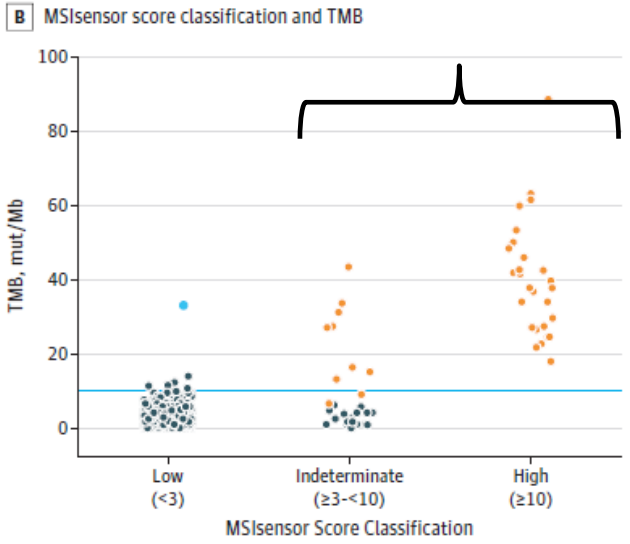


- Mutations in the four MMR genes (*MSH2, MSH6, MLH1*, and *PMS2*) result in known specific types of cancers and predisposition patterns:
- Germline (Lynch Syndrome) Or Somatic
- dMMR have many more mutations than MMR proficient
- IHC reveals loss of the corresponding MMR protein
- Microsatellite instability occurs when the genes that regulate DNA (MMR) don't work correctly

Mismatch Recombination Deficiency Across 12,019 Tumors



32 of 1033 (3.1%) mCRPC samples had *MSI-High* or *MSI-Intermediate* scores



Dung T. Le et al. *Science* 2017

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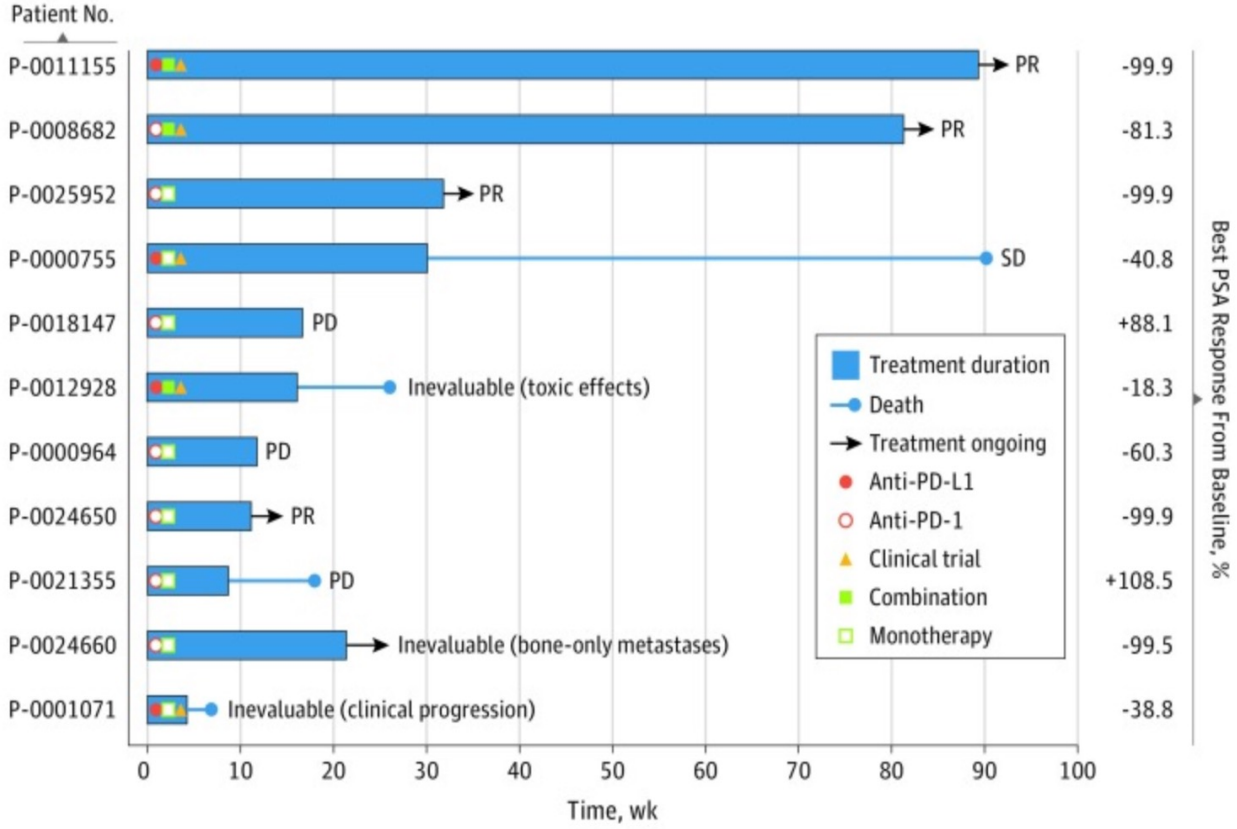
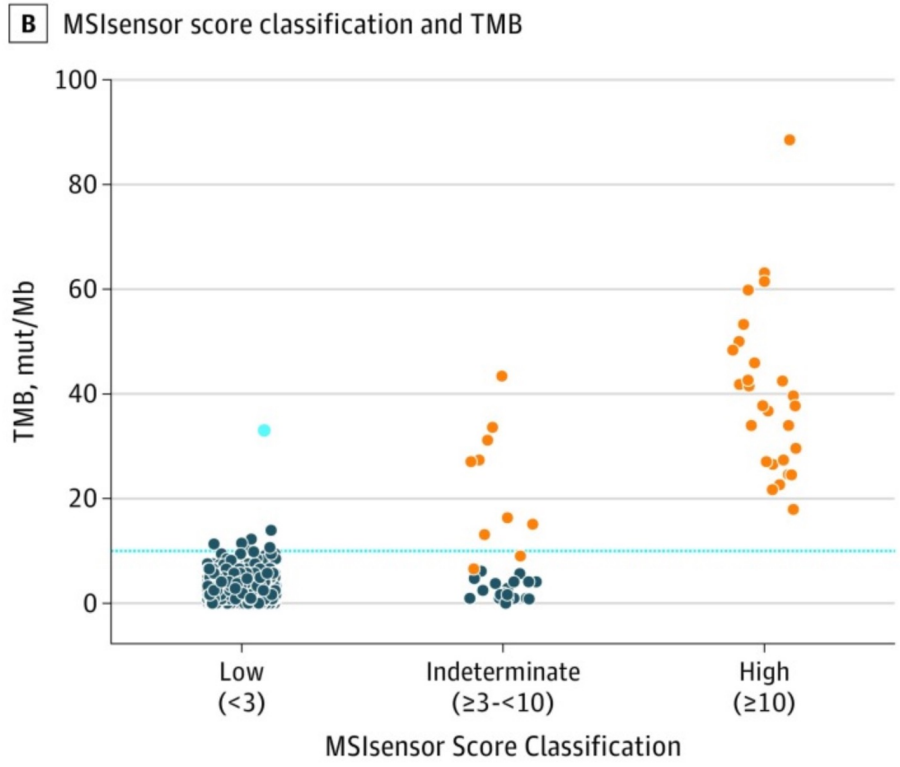
IO in mPCa with MSI-H (tumor tissue MSK platform)

Twenty-three MSI+ score of 1033 patients (2.2%)
N = 11 Pts MSI+ treated with pembrolizumab
ORR = 4/8 (50%) – 4 PR
PSA 50 = 55%



TMB and MSI



TMB – tumor mutational burden; MSI - microsatellite instability

Abida et al, JAMA Onc 2019

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IO in mCRPC with MSI-H detected by circulating tumor DNA (n=15/405)

Characteristic	N = 9 pts
Age, median (range), years	68 (57-88)
Location of metastases, n (%)	
Bones	5 (56)
Soft tissue	1 (11)
Liver	1 (11)
Lymph nodes	3 (33)
Prior lines of therapy for mCRPC, n (%)	
0	1 (11)
1	3 (33)
2	3 (33)
3+	2 (22)
Type of prior oncologic therapies, n (%)	
Abiraterone	6 (67)
Enzalutamide	3 (33)
Ketoconazole	1 (11)
Apalutamide	1 (11)
Docetaxel	2 (22)
Cabazitaxel	1 (11)
Lutetium-177-PSMA-617	1 (11)

ORR = 3/5 (60%) - 1 complete response, 2 partial response (total 5 eligible RECIST pts)
PSA50 = 4/9 (44%)
Estimated median Pembro duration = 9.9 (CI 95%, 1.0-18.8) months

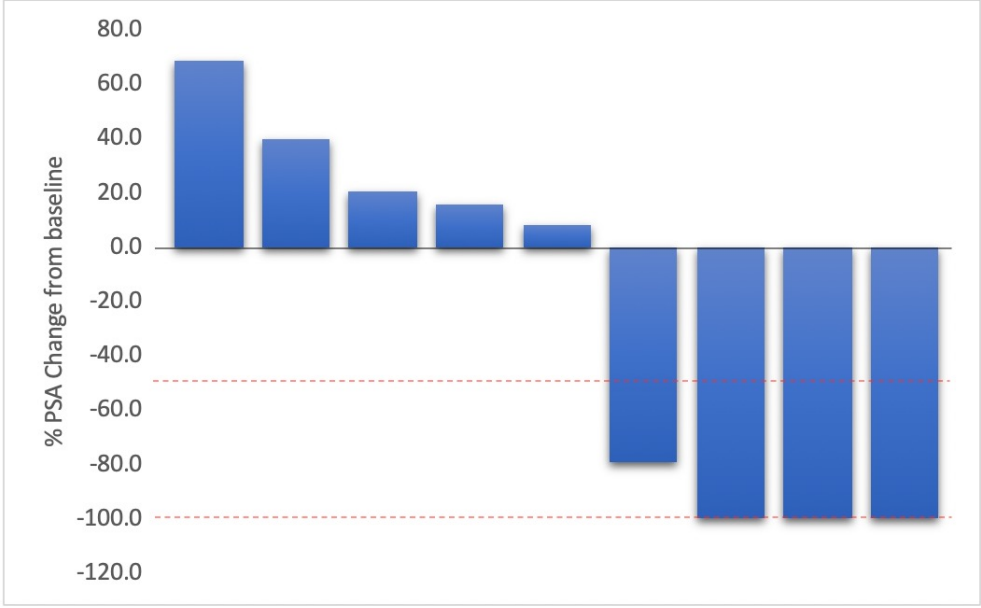
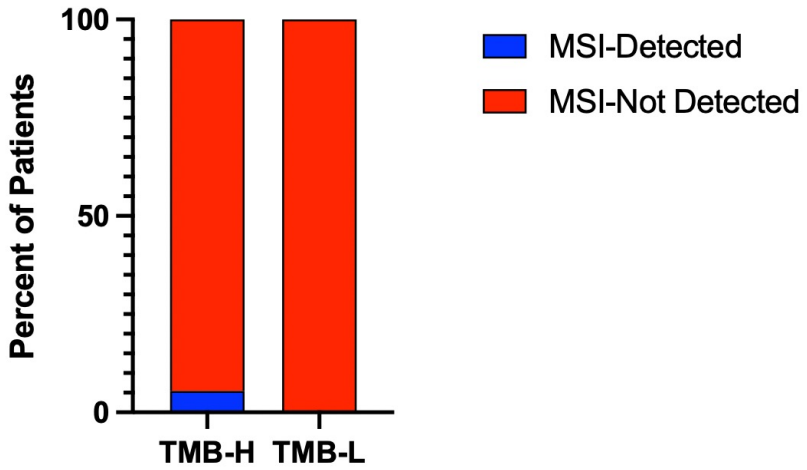


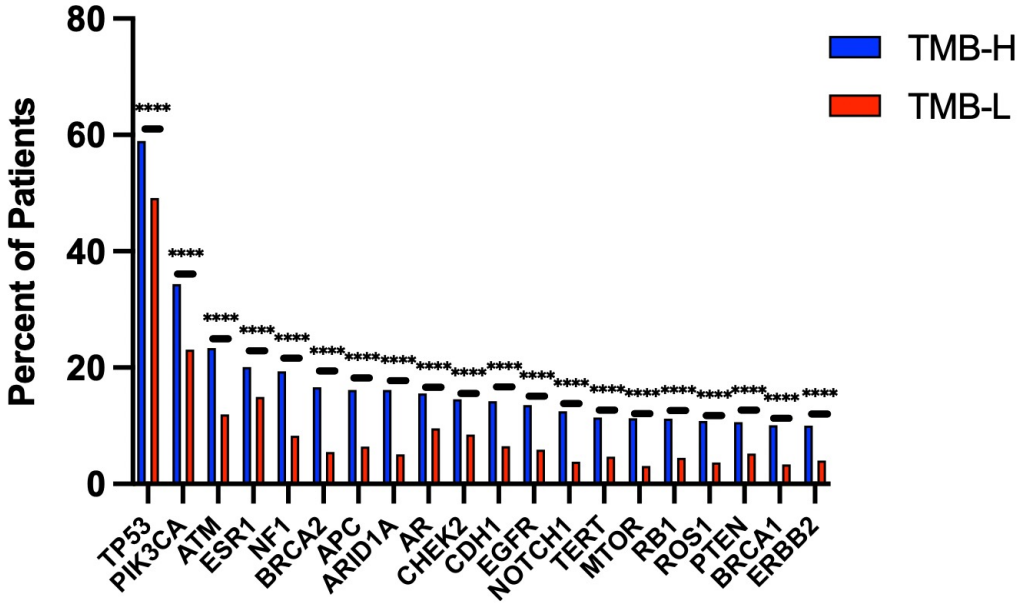
Figure 1 – Best PSA change from baseline in mCRPC patients treated with pembrolizumab (N=9).

How reliable is TMB? It depends….

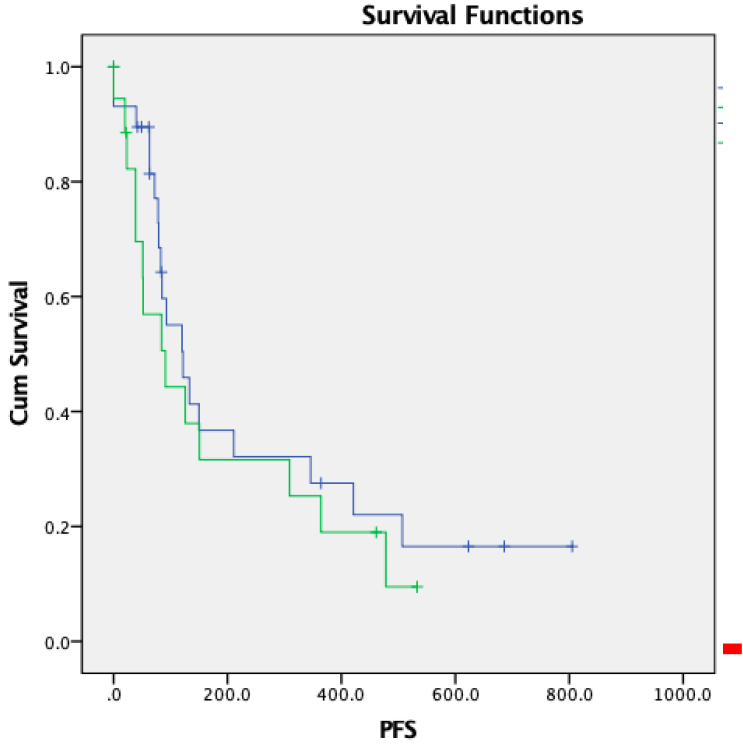
- N = 48 PC + BC treated with IO based on bTMB ≥ 10 Mut/Mb
- bTMB 10 or 16 or 20 Mut/Mb doesn't predict responses to IO
- tTMB correlates with MSI-H and predicts response to IO (Abida et al, JAMA 2019)



Genomic Landscape: TMB cut-off ≥10mut/Mb

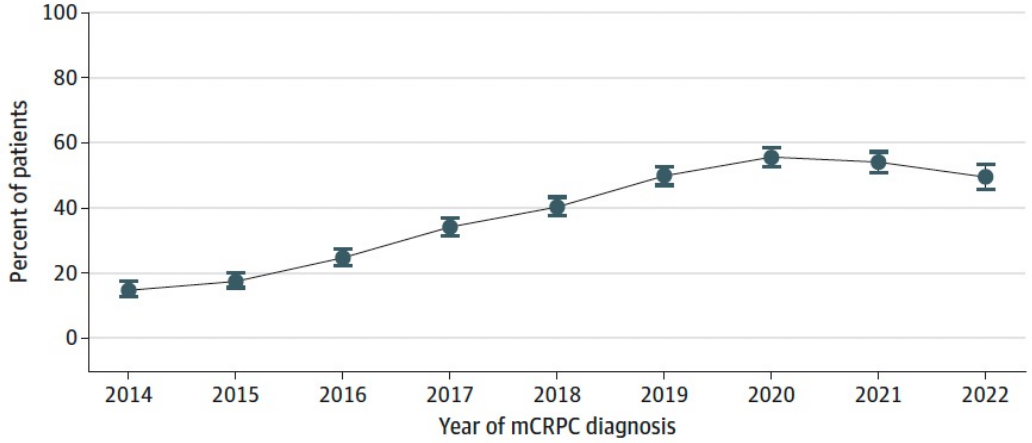


Reagan, Barata et al, Jnpublished Data (PLS DO NOT POST)



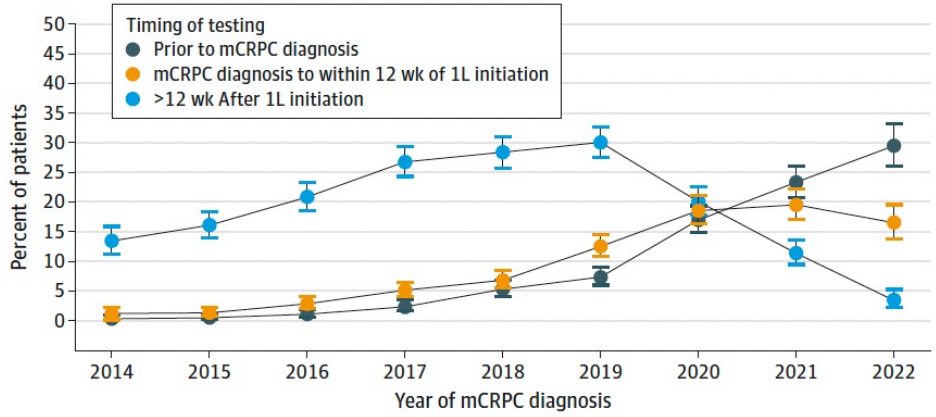
Genetic Testing in Men with mCRPC

A Rates of testing



No. at risk									
Tested	130	185	283	426	454	612	596	525	327
Not tested	752	867	866	822	673	618	477	447	335
All	882	1052	1149	1248	1127	1230	1073	972	662

B Timing of testing



No. at risk									
Tested prior to mCRPC diagnosis	2	4	12	30	59	90	182	226	195
Tested after mCRPC diagnosis to within 12 wk of 1L initiation	10	13	32	63	76	153	199	189	109
Tested >12 wk after 1L initiation	118	168	239	333	319	369	215	110	23
All	882	1052	1149	1248	1127	1230	1073	972	662

Pls do not tweet

Barata et al, JAMA Onc 2024 (*in press*)

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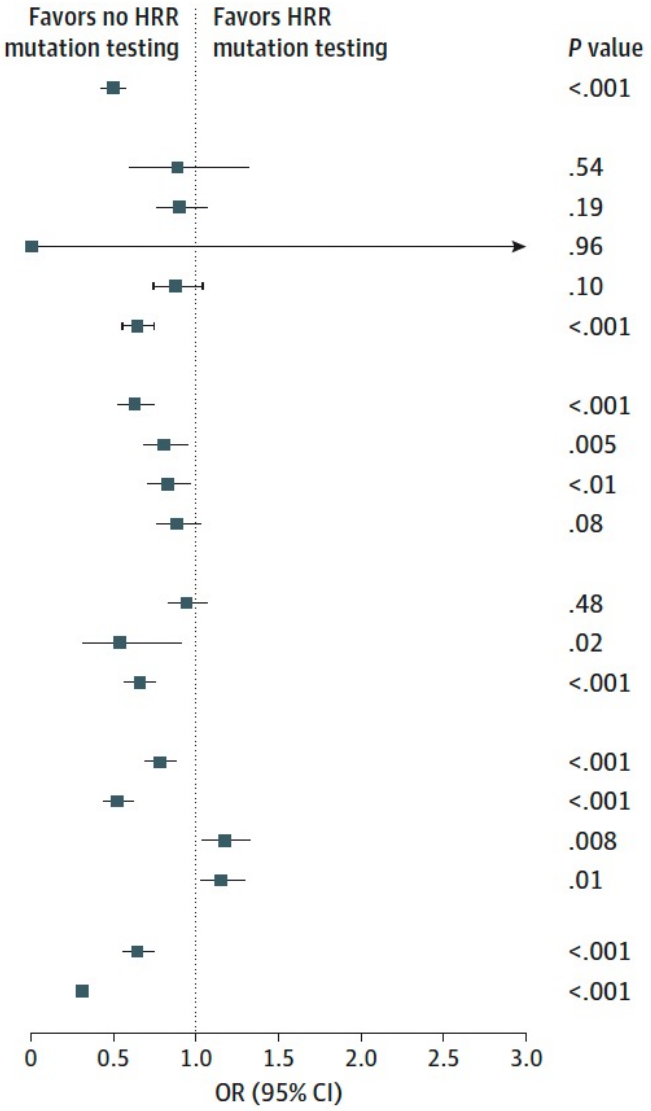
Factors Associated with Genetic Testing in mCRPC

Covariates	OR (95% CI)	P value
Age ≥65 y (vs <65 y)	0.49 (0.43-0.56)	<.001
Race and ethnicity (vs White)		
Asian	0.90 (0.60-1.31)	.54
Black or African American	0.90 (0.76-1.05)	.19
Hispanic or Latino	0.001 (<0.001->999.999)	.96
Unknown	0.87 (0.74-1.03)	.10
Community practice (vs academic)	0.64 (0.56-0.74)	<.001
SES index (vs 5)[a]		
1	0.63 (0.53-0.74)	<.001
2	0.81 (0.69-0.94)	.005
3	0.83 (0.72-0.96)	<.01
4	0.88 (0.77-1.01)	.08
Insurance (vs Medicare)		
Commercial	0.96 (0.86-1.07)	.48
Medicaid	0.54 (0.32-0.90)	.02
No de novo (vs yes)	0.65 (0.57-0.75)	<.001
ECOG PS (vs 0)		
1	0.78 (0.70-0.87)	<.001
≥2	0.52 (0.45-0.61)	<.001
Gleason score >7 (vs ≤7)	1.17 (1.04-1.31)	.008
PSA level less than median (vs median or higher)	1.15 (1.03-1.28)	.01
No prior treatment (vs yes)	0.64 (0.56-0.73)	<.001
mCRPC diagnosis before 2018 (vs 2018 or after)[b]	0.30 (0.28-0.33)	<.001



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Barata et al, JAMA Onc 2024 (*in press*)

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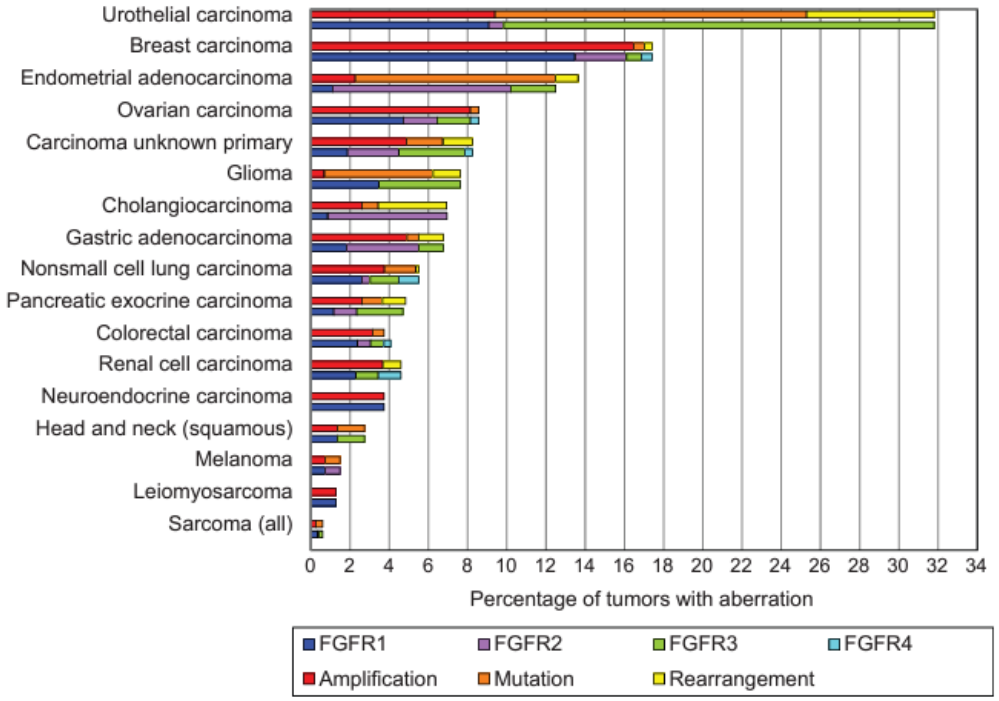
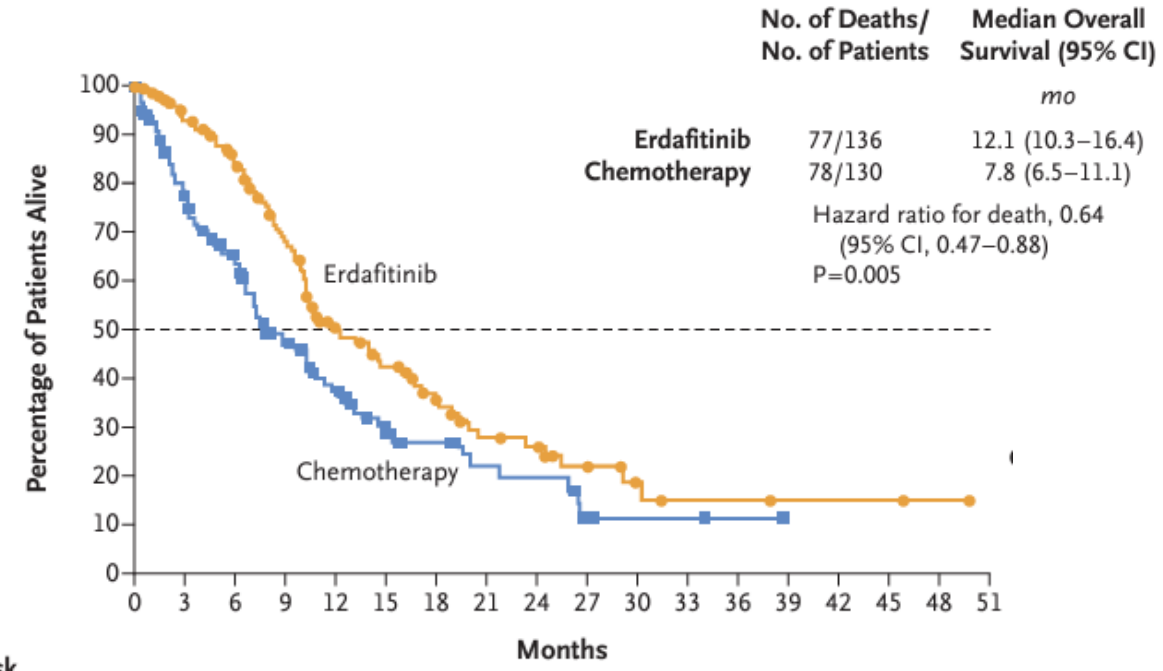
Urothelial Cancer and the Case of FGFR



Helsten et al, CCR 2015

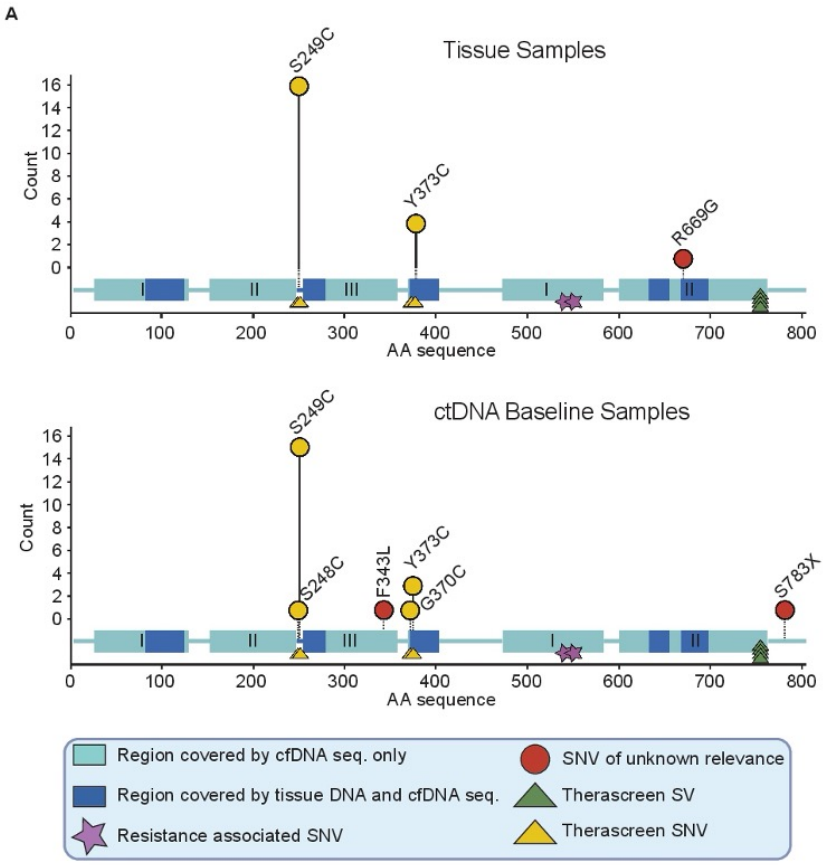
Ph. 3 THOR, Overall Survival



Loriot et al, NEJM 2023

Concordance tissue *vs* liquid biopsy

Spatial localization of FGFR3 alts.



Tissue testing for FGFR alterations

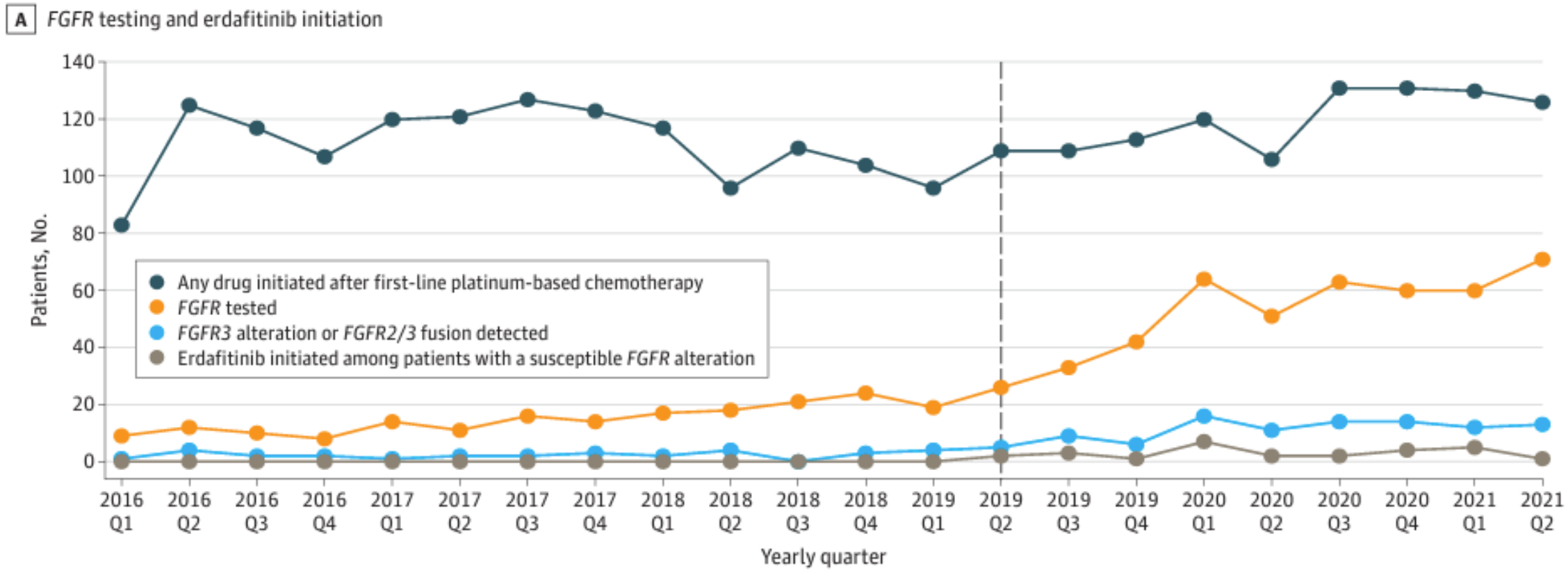
cfDNA testing for FGFR alterations	Negative	Positive	Inconclusive
Negative	34	1	0
Positive	4	16	1
Incon-clusive	12	6	0

	%
Concordance (including inconclusive samples)	89 (67)
Proportion of potentially eligible patients missed by tissue testing	9
Sensitivity (cfDNA testing)	94
Specificity (cfDNA testing)	87
Positive predictive value (cfDNA testing)	76
Negative predictive value (cfDNA testing)	97

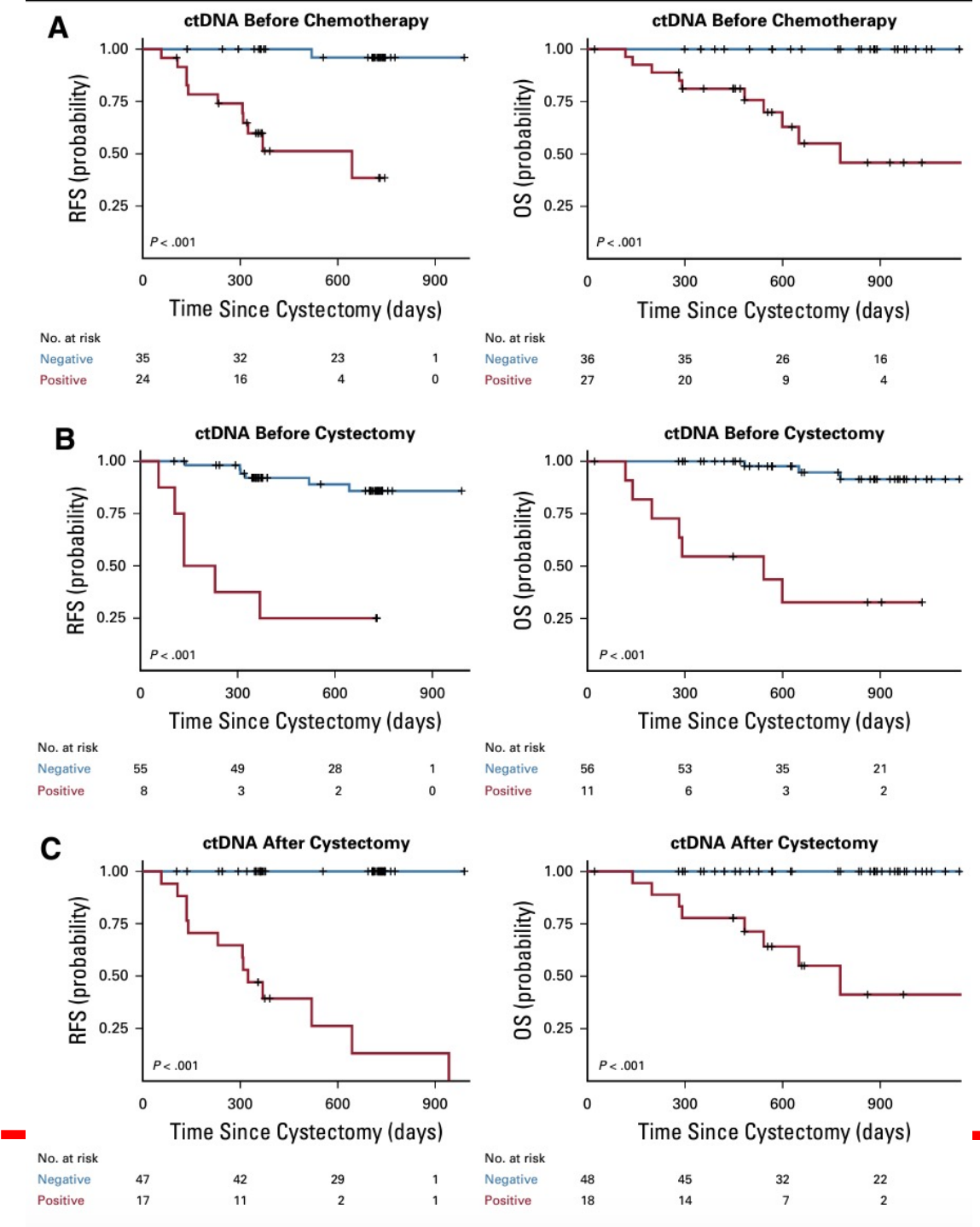
Table 2. Concordance of FGFR testing

Genetic Testing in mUC

Figure 1. Real-world Use of Pan–Fibroblast Growth Factor Receptor (*FGFR*) Testing and Rate of Erdafitinib Uptake



Minimal Residual Disease



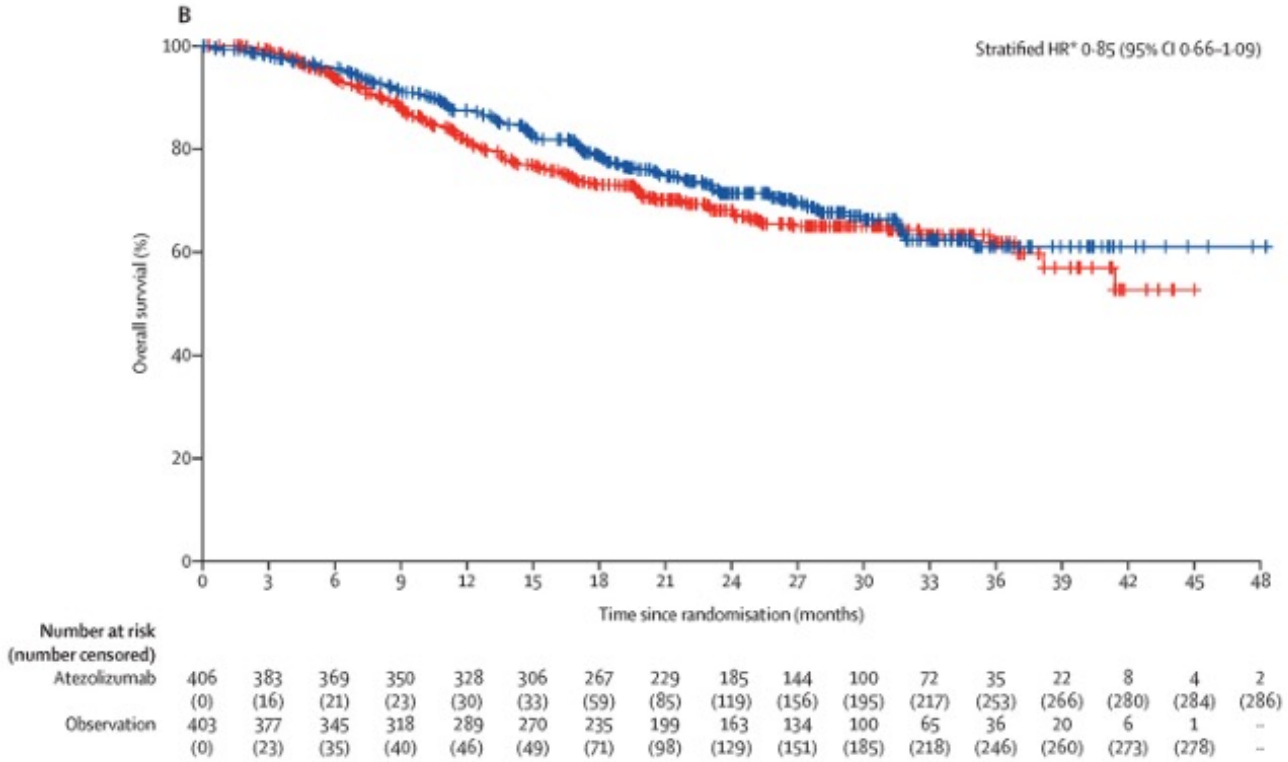
- ctDNA assessment for early risk stratification, therapy monitoring, and early relapse detection in bladder cancer is feasible

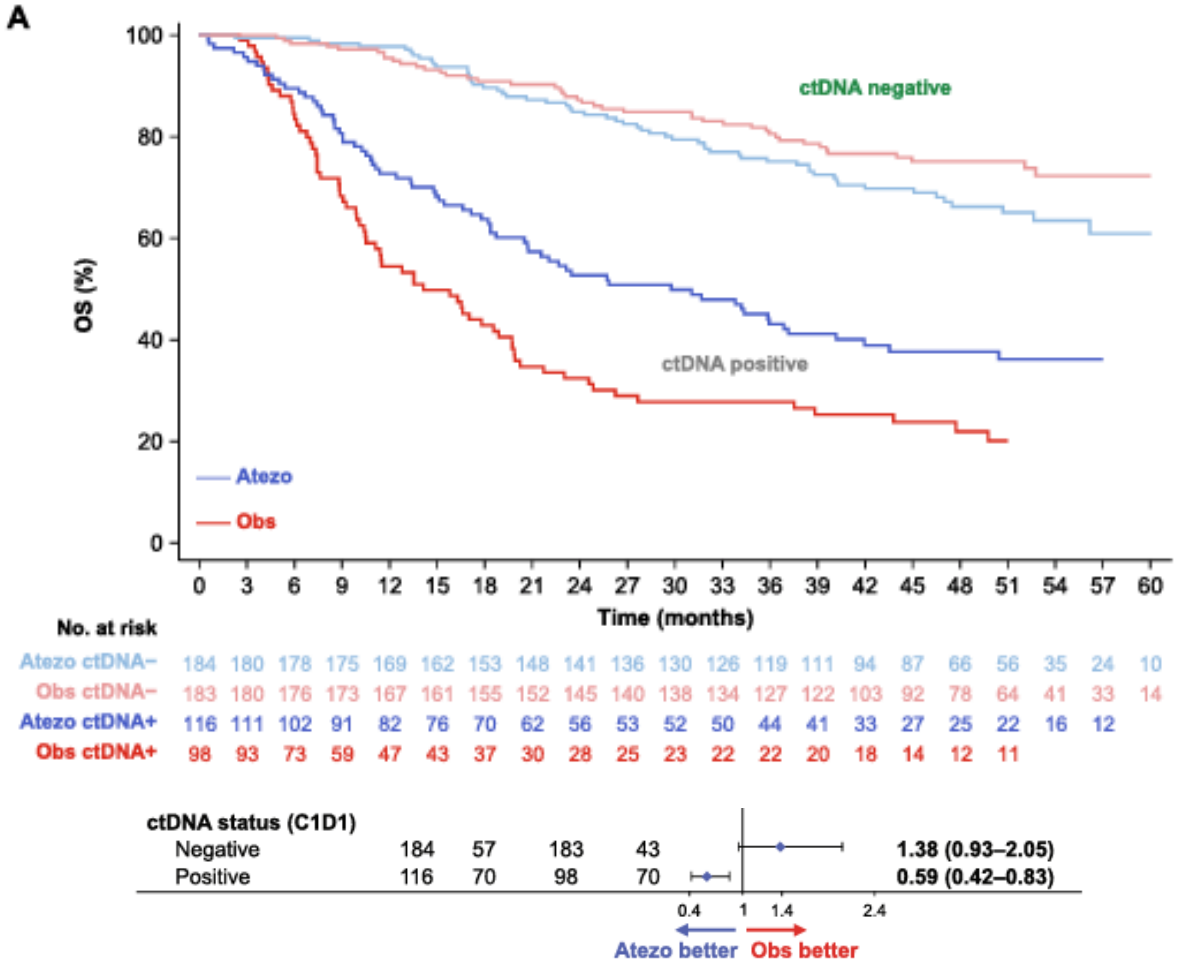
- Presence of ctDNA was highly prognostic at diagnosis before chemotherapy

Christensen E et al, JCO 2019

Pedro C. Barata, MD MSc FACP
@PBarataMD

OS from IMvigor010 Phase 3 Trial – ctDNA for better selection

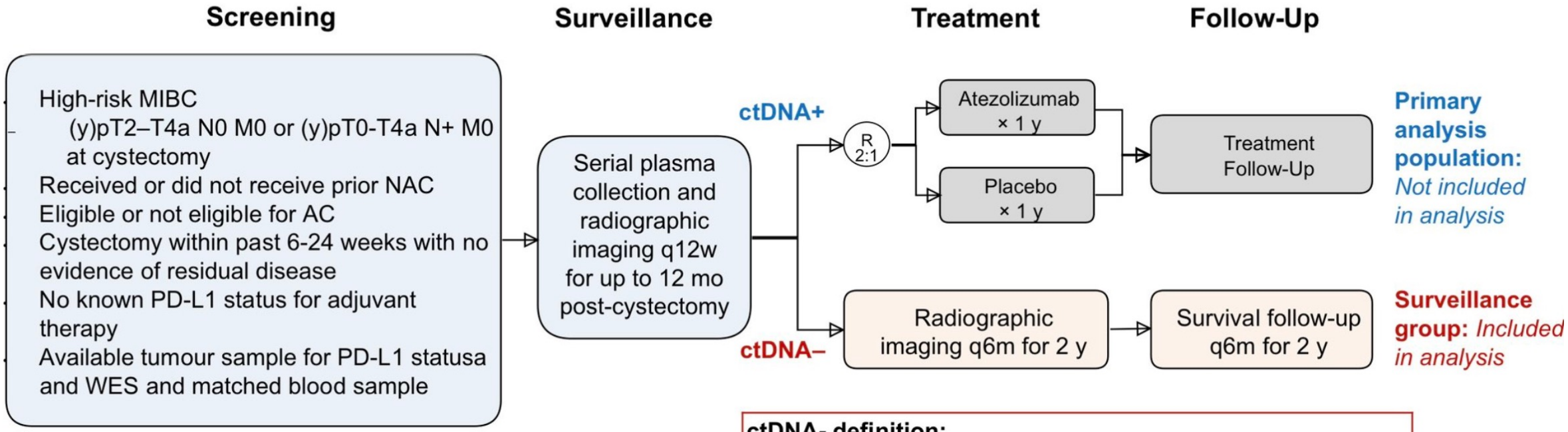




Bellmunt et al, Lancet Oncol 2021

Powles et al, Eur Urol 2023

IMvigor011: surveillance group analysis



Primary endpoint:

- Investigator-assessed DFS

Key secondary endpoint:

- OS

ctDNA- definition:

- Disease-free status at baseline
- ≥1 ctDNA− result and no ctDNA+ result
- ≥1 post-baseline diseases assessment
- Completed ≥12 mo of surveillance post-cystectomy or discontinued surveillance <12 mo with no ctDNA+ result

ClinicalTrials.gov ID, NCT04660344. Stratification factors were nodal status (positive vs negative), tumour stage after cystectomy (≤(y)pT2 vs (y)pT3/(y)pT4), PD-L1 IHC status (IHC score of IC0/1 vs IC2/3 by VENTANA SP142 IHC assay) and time from cystectomy to first ctDNA+ sample (≤20 weeks vs >20 weeks). AC, adjuvant chemotherapy; IHC, immunohistochemistry; NAC, neoadjuvant chemotherapy; OS, overall survival; q6m, every 6 months; q12w, every 12 weeks; WES, whole-exome sequencing. aPD-L1 status was determined by the VENTANA SP142 IHC assay.

University Hospitals Seidman Cancer Center

SCHOOL OF MEDICINE CASE WESTERN RESERVE UNIVERSITY

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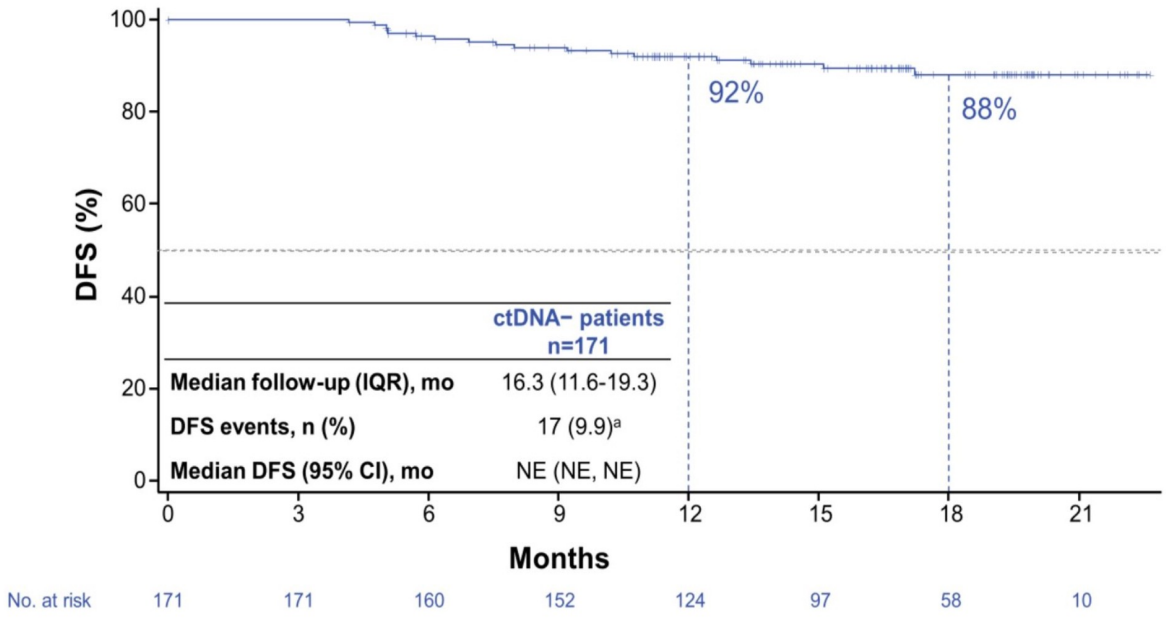
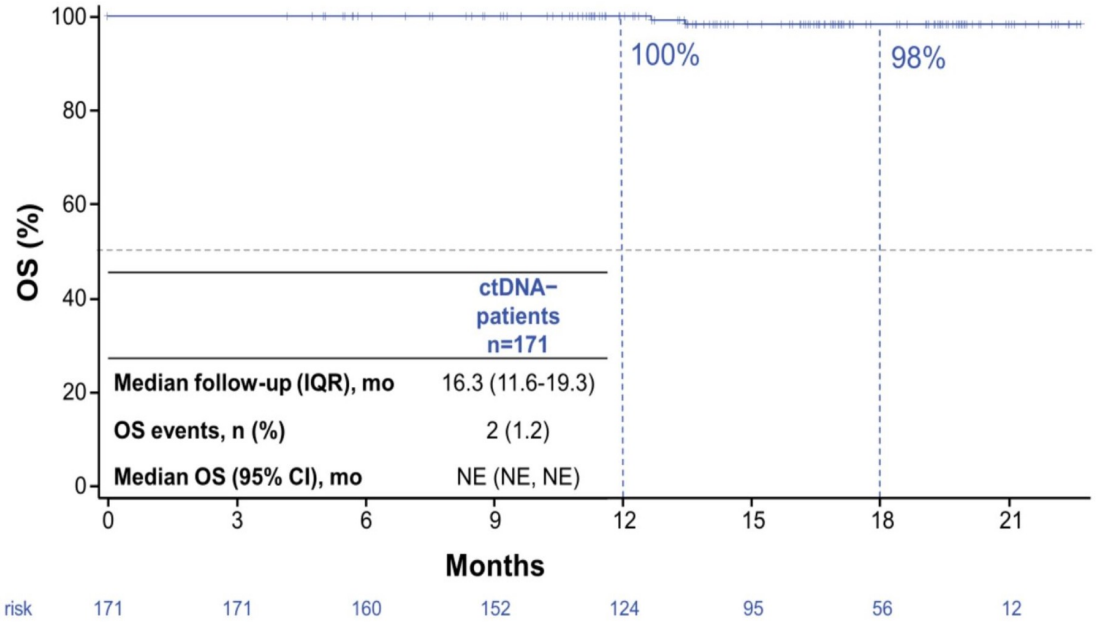
Outcomes ctDNA– (N=171) IMvigor011

DFS in the ctDNA− population

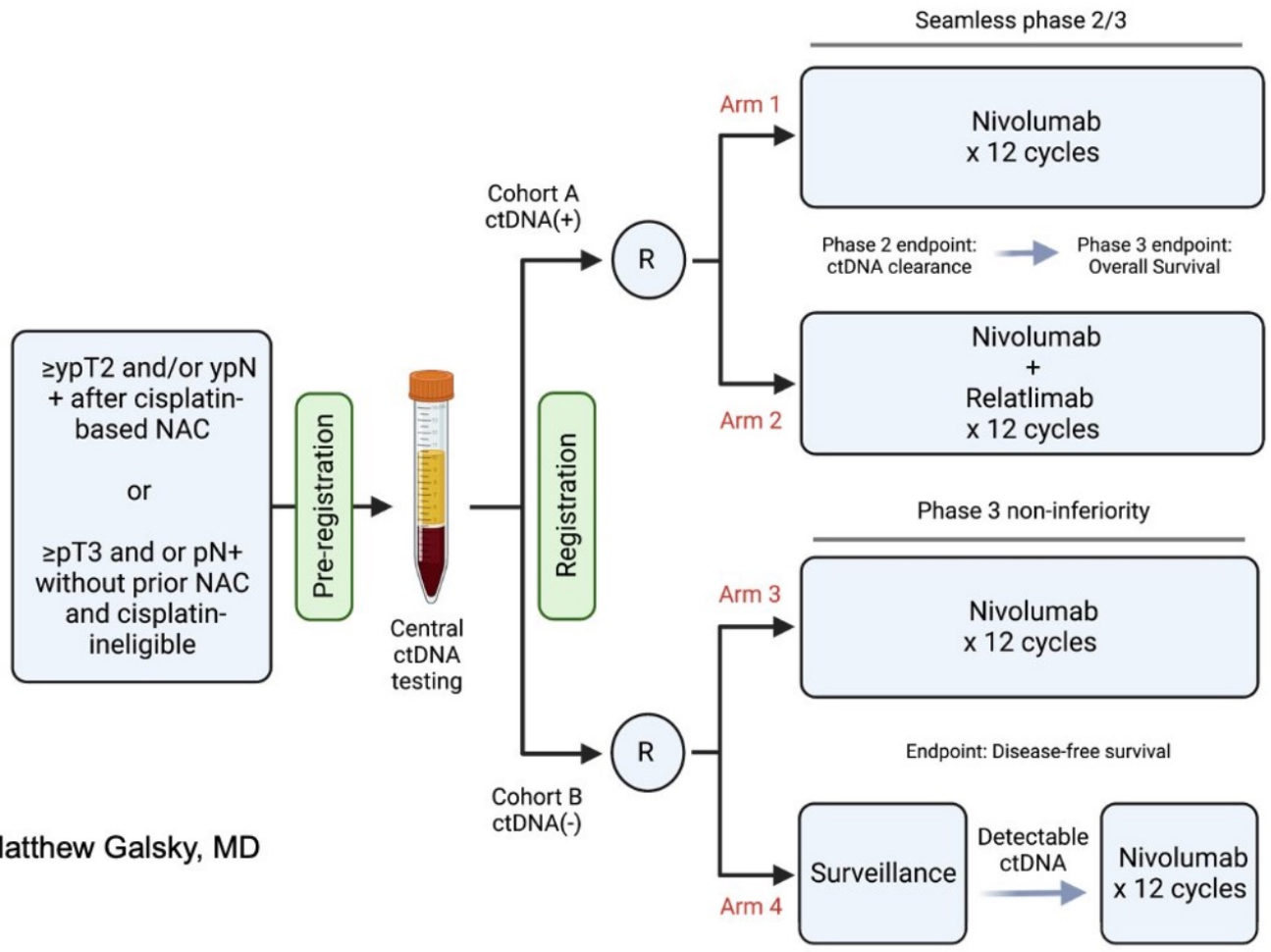


OS in the ctDNA− population



Tom Powles @ EAU24 PARIS, FRANCE 5-8 April 2024

A032103 (MODERN): An integrated Phase 2/3 and Phase 3 Trial of MRD-based Optimization of aDjuvant thErapy in uRothelial caNcer

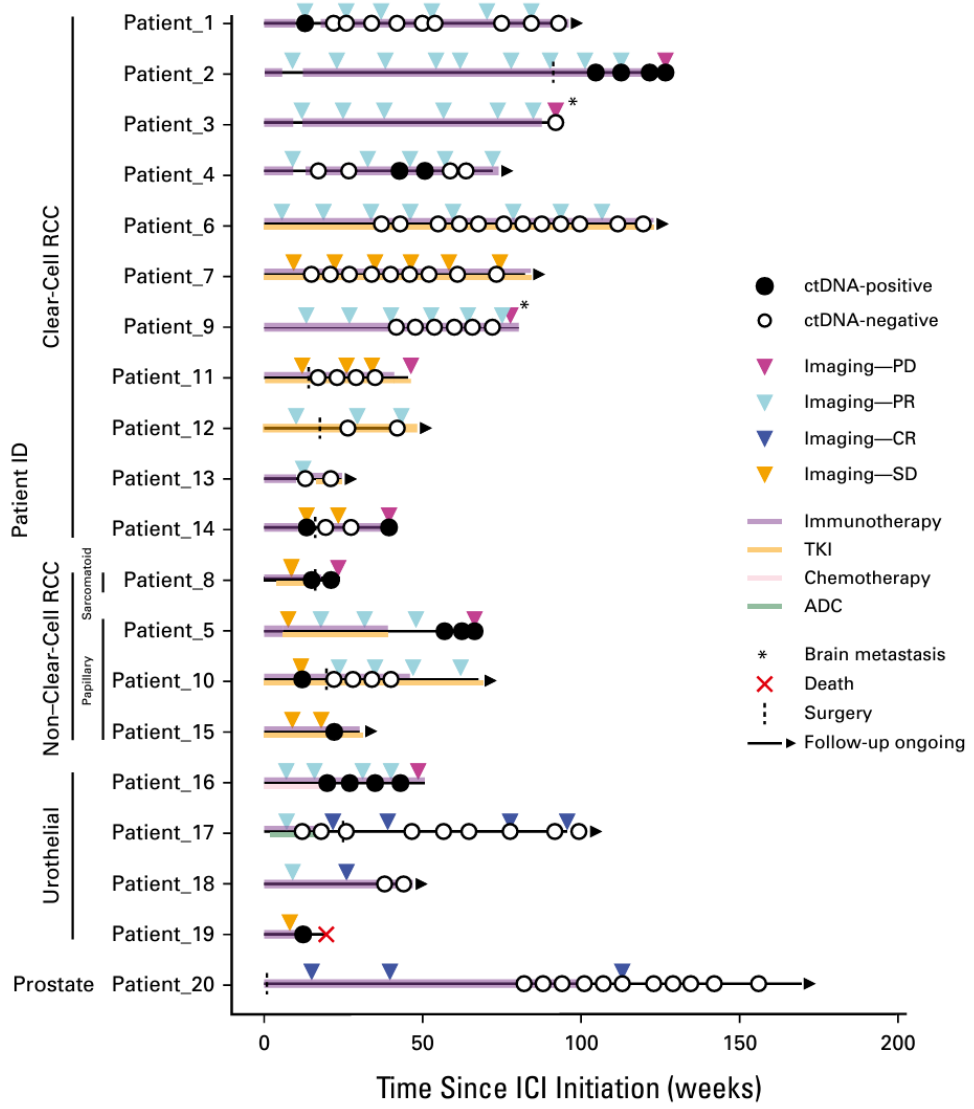


PI: Matthew Galsky, MD

Alliance for Clinical Trials in Oncology

Serial ctDNA changes in M1: pilot study

Characteristic	Total Group (N=20)
Age, years, median (range)	68 (42-85)
Sex, No.	
Male	17
Female	3
ECOG, No.	
0	15
1	5
Cancer type, No.	
Renal cell carcinoma	15
Urothelial cell carcinoma	4
Prostate adenocarcinoma	1
Ethnicity, No.	
Non-Hispanic White	15
Black	4
Hispanic	1
Sites of metastases at ICI initiation, No.	
Lymph nodes	14
Lung	11
Bone	4
Liver	4
Spleen	1
Brain	1[a]

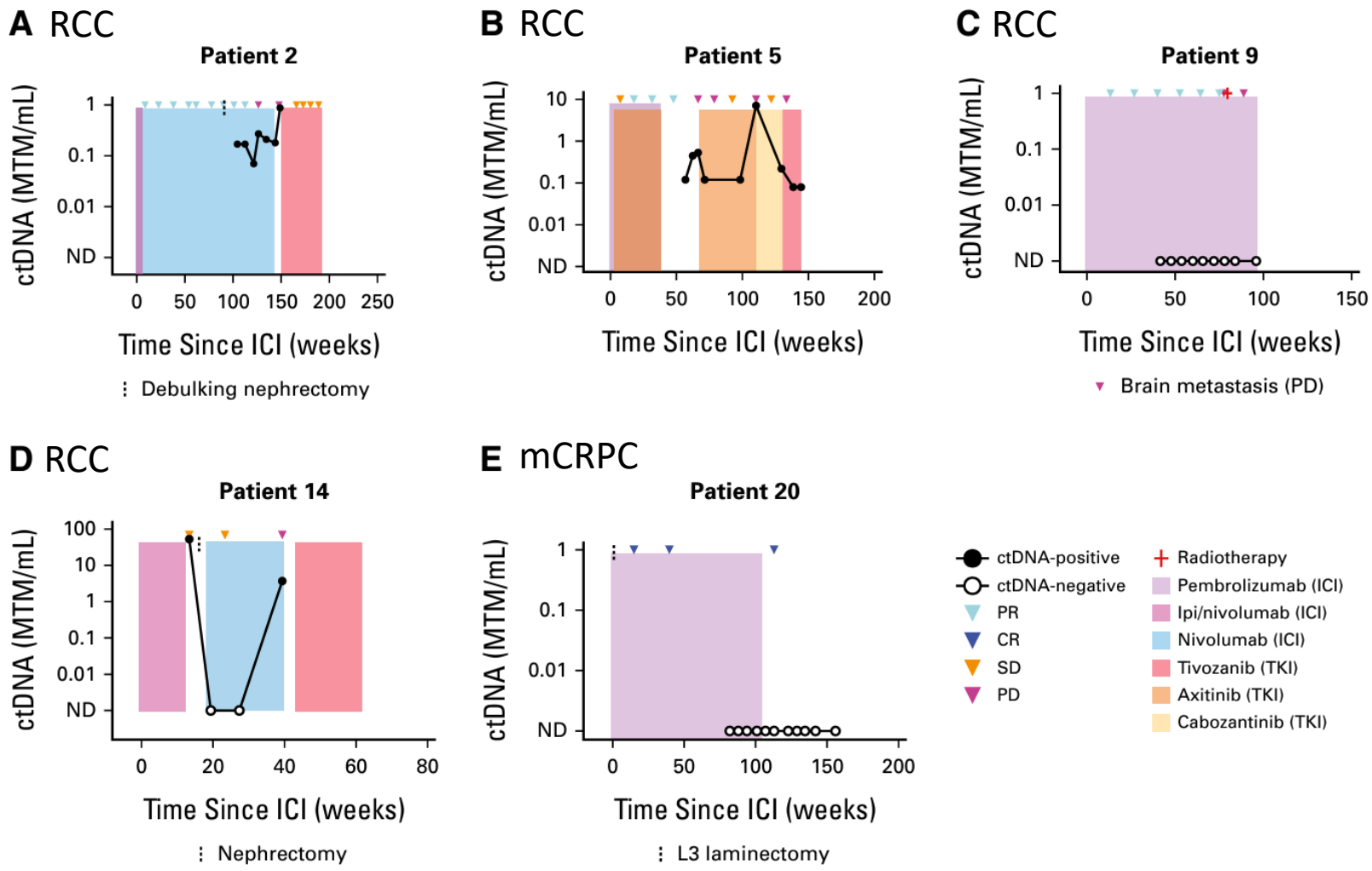


Serial ctDNA changes in M1: pilot study

median Fup = 67.7 weeks

concordance= 83% (15/18)

Discordance - CNS; slow PD



Thank you!

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216-262-1214