



IX SIMPOSIO · SYMPOSIUM | 2024 BIOPSIA LÍQUIDA · LIQUID BIOPSY

EL CAMINO A LA ONCOLOGÍA DE PRECISIÓN · THE WAY TO PRECISION MEDICINE

25, 26 Y 27 DE ENERO · JANUARY 25th, 26th and 27th

Multi-modal liquid biopsy to inform metastatic prostate cancer evolution

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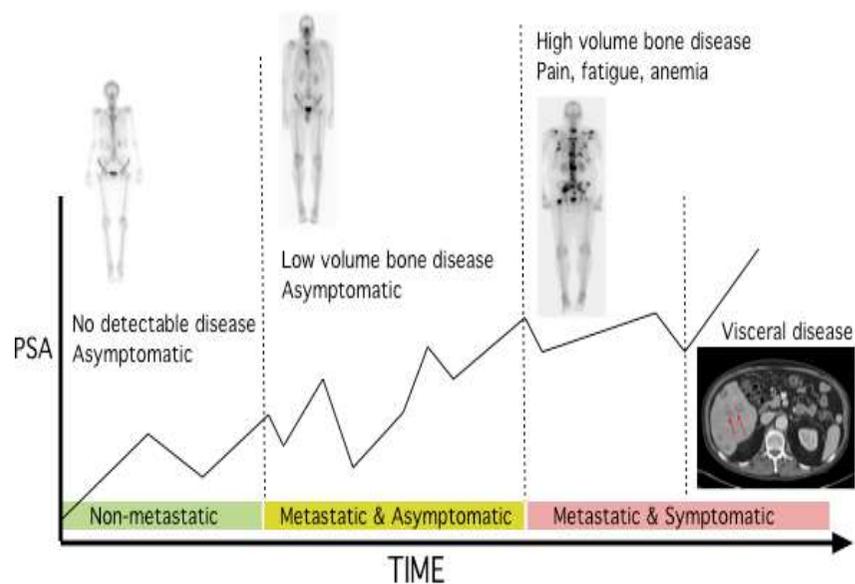
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Disclosures

- I have served in advisory boards for AstraZeneca, Roche, Amgen, MSD, Janssen and Pfizer Oncology.
- I have received research grants from AstraZeneca and Pfizer
- I have participated in symposiums sponsored by AstraZeneca, Astellas, Guardant, Janssen, Pfizer, Sanofi

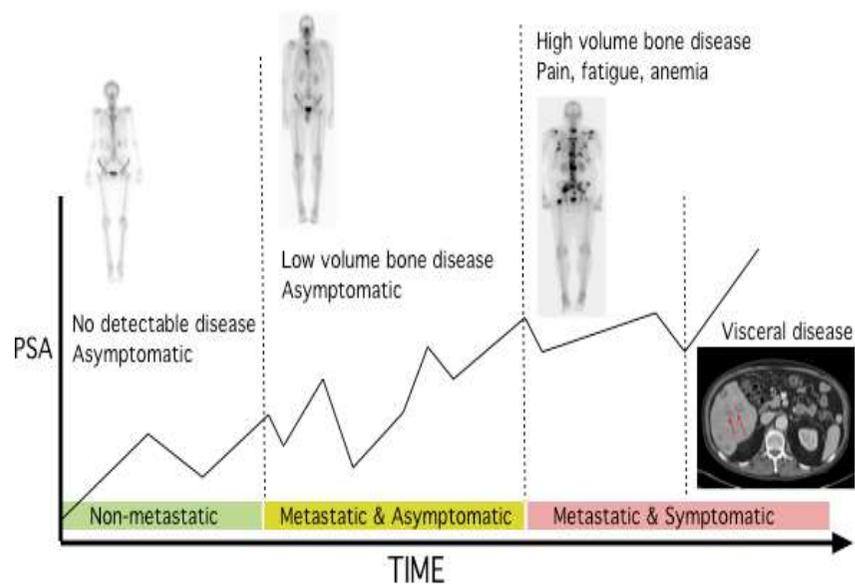


Lorente, Mateo, Perez-Lopez et al. Lancet Oncol 2015

- AR signaling is the major driver of prostate cancer progression
- Targeting AR is the mainstay of treatment
- Drug resistance:
 - Ligand independent AR activation
 - Activation of alternative transcriptional programs

Genomic instability - structural rearrangements from DSB

- High density of copy-number losses and gains
- High burden of fusions, translocations, indels
- Low burden of point mutations



Lorente, Mateo, Perez-Lopez et al. Lancet Oncol 2015

Met Prostate Cancer usually spreads to the bone, and many times only to the bones – no measurable disease

Intermediate endpoints:

- RECIST Response Rate
- PSA 50% declines
- PFS endpoints based on “new lesions on bone scans” (2+2)

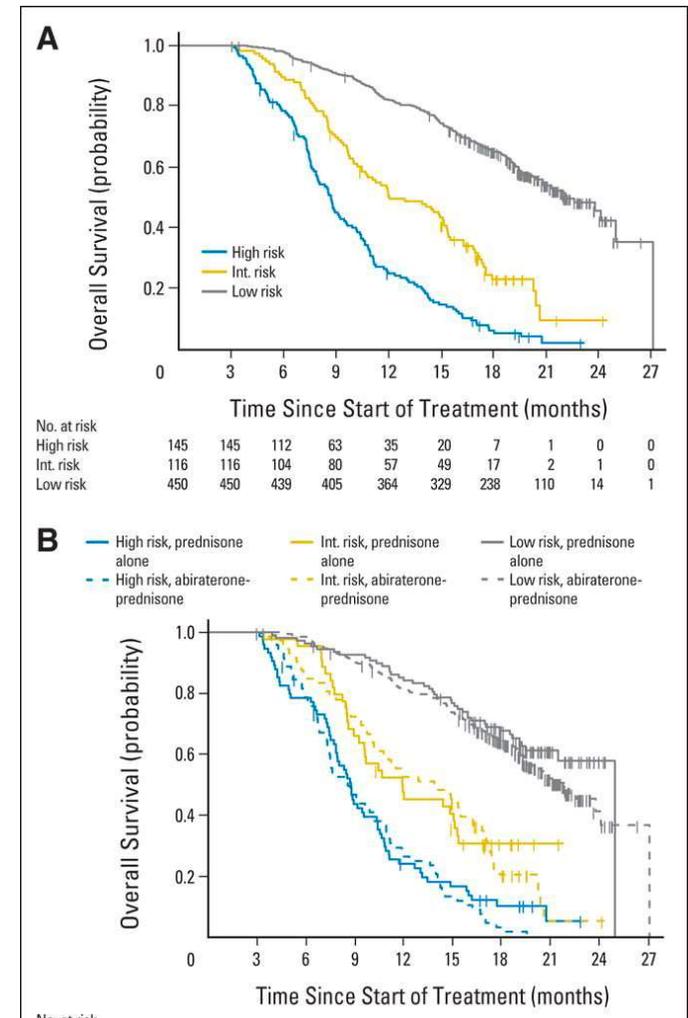
Challenge 1

- Difficult to know if a drug is working
- Difficult to know when to change therapy

Marker Combination*	Weighted C-Index†	SE	P‡
CTC	0.82	0.02	
CTC absolute change§	0.73	0.03	
CTC relative change§¶	0.73	0.03	
CTC plus LDH	0.80	0.02	
LDH	0.78	0.02	.075
PSA ₅₀ §	0.73	0.03	.008
PSA ₃₀ §	0.71	0.02	.002
HGB	0.71	0.03	.002
ALK	0.72	0.03	.026
ALB	0.71	0.03	< .001

Surrogate Category	AA Plus Prednisone (n = 484)		Prednisone Alone (n = 227)		All Patients (n = 711)		Survival Probability			
	No.	%	No.	%	No.	%	1 Year		2 Years	
							%	95% CI	%	95% CI
High risk (CTCs ≥ 5 cells/7.5 mL; LDH > 250 U/L)	71	15	74	33	145	20	0.25	0.19 to 0.33	0.02	0.00 to 0.11
Intermediate risk (CTCs ≥ 5 cells/7.5 mL; LDH ≤ 250 U/L)	72	15	44	19	116	16	0.51	0.42 to 0.61	0.10	0.03 to 0.29
Low risk (CTC < 5 cells/7.5 mL)	341	70	109	48	450	63	0.82	0.79 to 0.86	0.46	0.39 to 0.54

NOTE. Prentice²⁵ criterion two is satisfied by AA Plus Prednisone and Prednisone Alone columns, which show higher frequency of the favorable (low risk) category in patients treated with AA plus prednisone (ie, that surrogate measure reflected treatment effect of AA plus prednisone).
Abbreviations: AA, abiraterone acetate; CTC, circulating tumor cell; LDH, lactate dehydrogenase.

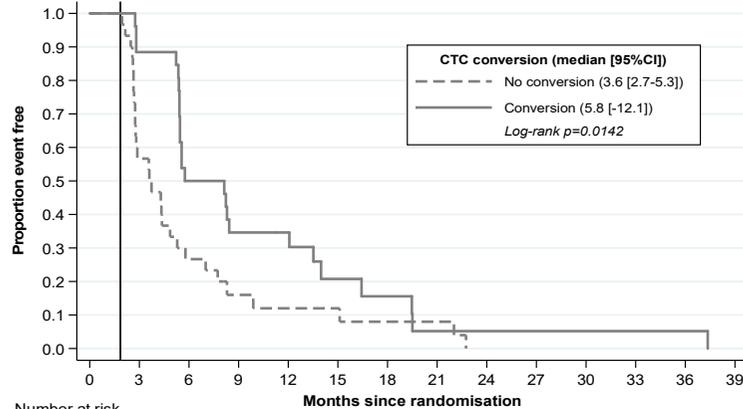


- COU-AA-301, a randomized, double-blind phase III trial of abiraterone acetate plus prednisone versus prednisone alone in patients with metastatic CRPC previously treated with docetaxel.
- CTC, PSA, LDH and other biomarkers were measured at baseline and 4, 8, and 12 weeks

Scher et al, J Clin Onc 2015

TOPARP: an adaptive phase II trial of olaparib in mCRPC

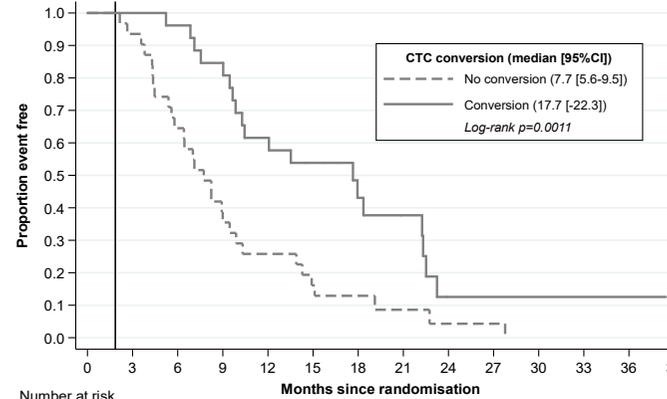
rPFS by CTC conversion at 8 weeks



Number at risk (number censored)

No conversion	30	(0)	17	(0)	8	(1)	4	(1)	3	(1)	3	(1)	2	(1)	2	(1)	0	(1)	0	(1)	0	(1)	0	(1)	0	(1)	0	(1)
Conversion	26	(0)	23	(0)	13	(0)	9	(1)	8	(2)	4	(2)	3	(2)	1	(2)	1	(2)	1	(2)	1	(2)	1	(2)	1	(2)	1	(2)

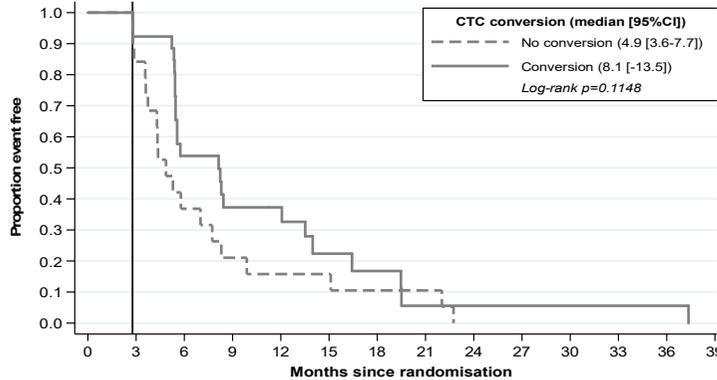
OS by CTC conversion at 8 weeks



Number at risk (number censored)

No conversion	31	(0)	29	(0)	20	(0)	11	(0)	8	(0)	5	(1)	3	(1)	2	(1)	1	(1)	1	(1)	0	(1)	0	(1)	0	(1)	0	(1)
Conversion	26	(0)	26	(0)	25	(0)	22	(0)	16	(2)	12	(4)	8	(5)	6	(6)	1	(6)	1	(6)	1	(6)	1	(6)	1	(6)	1	(6)

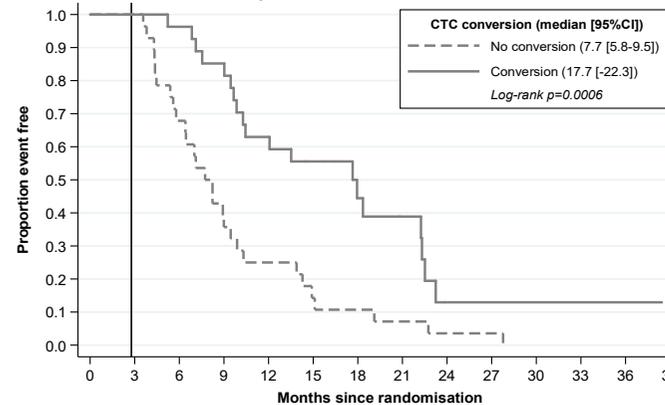
rPFS by CTC conversion at 12 weeks



N.at risk (N.events)

No CTC conv.	19	(3)	16	(9)	7	(3)	4	(1)	3	(0)	3	(1)	2	(0)	2	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
CTC conv.	26	(2)	24	(10)	14	(4)	9	(0)	8	(3)	4	(1)	3	(2)	1	(0)	1	(0)	1	(0)	1	(0)	1	(0)	1	(0)	1	(1)

OS by CTC conversion at 12 weeks



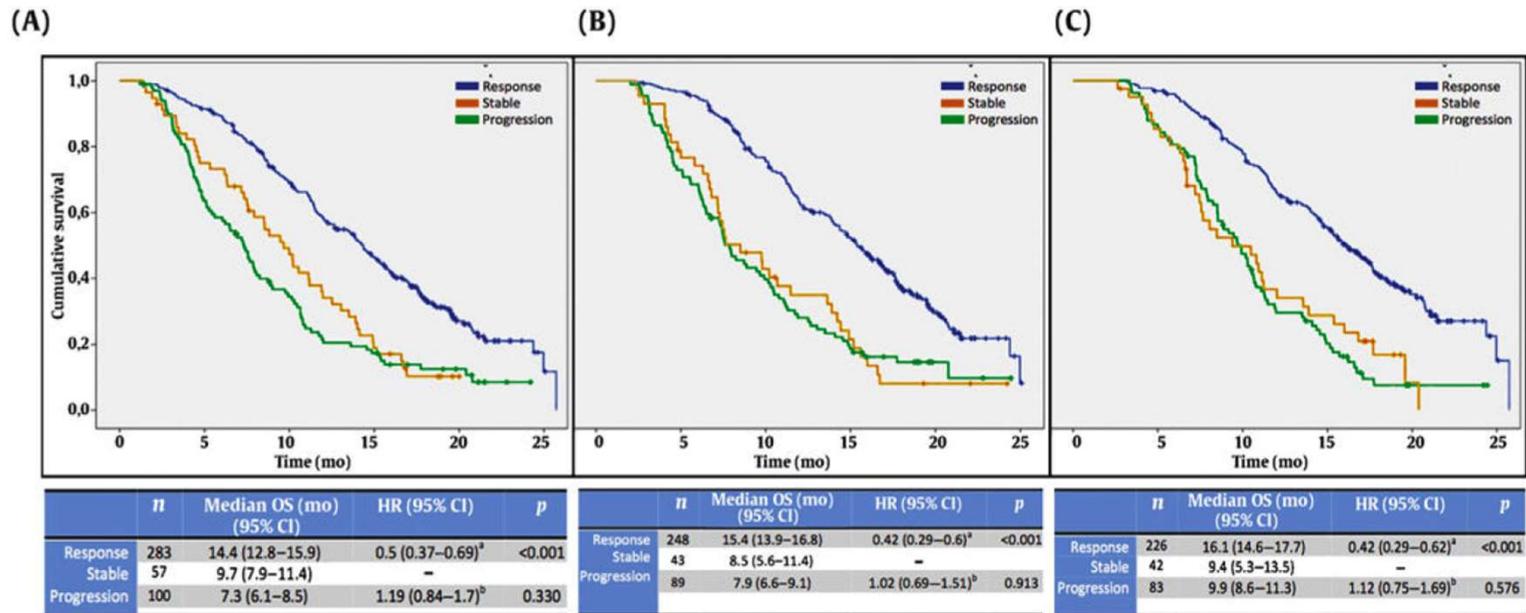
N.at risk (N.events)

No CTC conv.	28	(0)	28	(9)	19	(10)	3	(7)	3	(4)	1	(3)	1	(2)	1	(1)	0	(1)	0	(1)	0	(0)	0	(0)	0	(0)	0	(0)
CTC conv.	27	(0)	27	(1)	26	(3)	23	(6)	17	(2)	13	(2)	8	(1)	6	(4)	1	(0)	1	(0)	1	(0)	1	(0)	1	(0)	1	(0)

Mateo et al, N Eng J Med 2015
 Mateo et al, Lancet Onc 2020
 Carreira et al, Cancer Discovery 2021

CTC kinetics value in the “CTC high” population

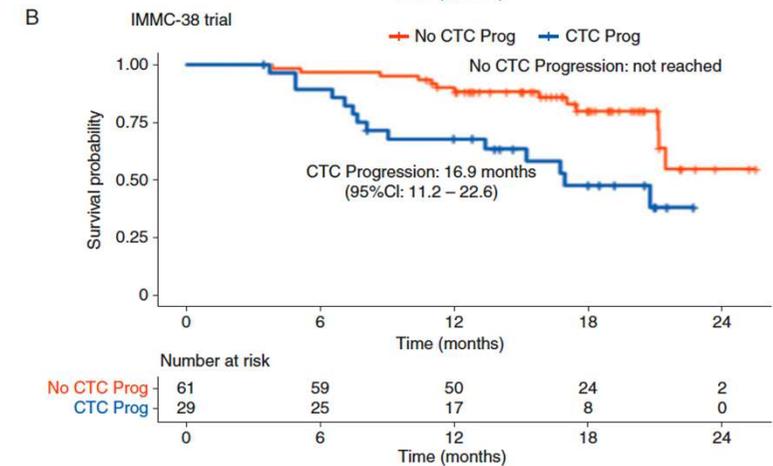
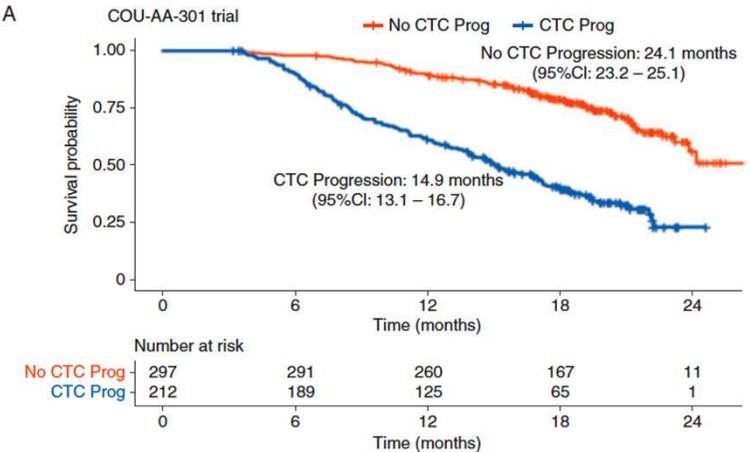
- Outcome analysis for patients with “HIGH” (≥ 5 /7.5ml) CTC count at baseline
- Setting: COU-301 trial (abiraterone+prednisone vs placebo+prednisone)
- CTC measured at baseline, +4 weeks, +8 weeks, +12 weeks



- “No decrease” means bad prognosis (stable or increasing CTC count vs 30% decrease)
- Consider therapy switch if no 30% decrease is achieved by week 12

CTC kinetics value in the “CTC low” population

- Outcome analysis for patients with “low” (<5 /7.5ml) CTC count at baseline
- Setting: IMMC-38 trial (chemotherapy), COU-301 trial (abiraterone) ^A
- CTC measured at baseline, +4 weeks, +8 weeks, +12 weeks
- Increases (any increase) in CTC after 4, 8, 12 weeks of treatment was defined as “CTC progression”
- “CTC progression” associates with worst outcome on chemotherapy, abiraterone and also in the placebo arms.
- “CTC progression” could be an early indicator for recommending therapy switch.



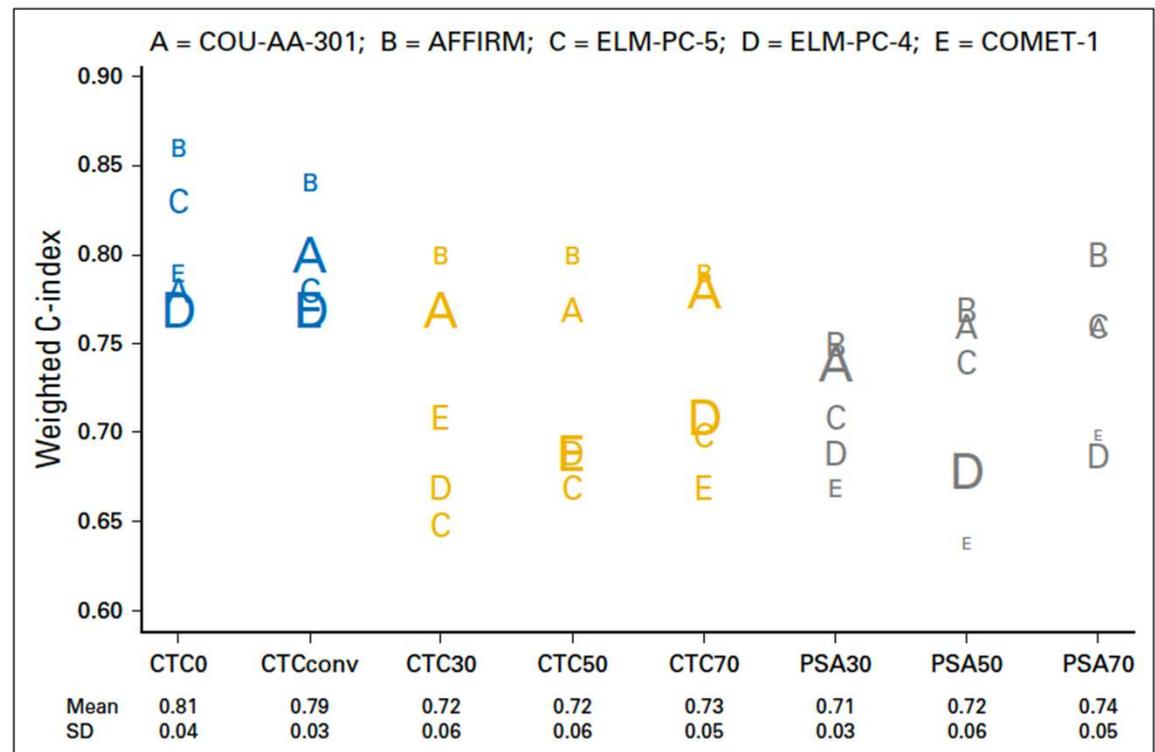
Lorente, Olmos, Mateo et al. Ann Onc 2018

Evaluating multiple CTC endpoints

- Associations between CTC counts (baseline vs week 12) and patient outcome (vs PSA change at week 12) in a meta-analysis of 5 phase III clinical trials (total 6081 patients)

- CTC=0 at week 12
- CTC conversion from high to low
- 30% CTC count decrease
- 50% CTC count decrease
- 70% CTC count decrease

- 30% PSA decrease
- 50% PSA decrease (current definition of “response”)
- 70% PSA decrease

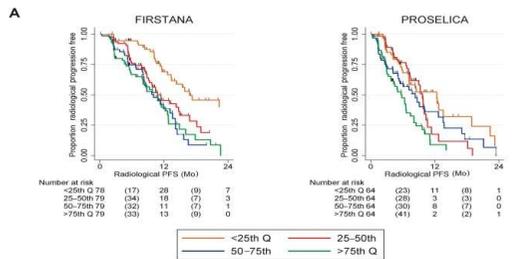


Heller, McCormak, Kheoh et al, J Clin Onc 2018

cfDNA and ctDNA prognostic and response biomk

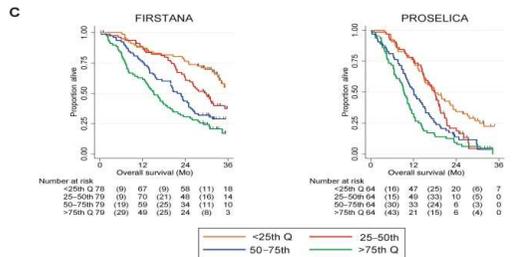
Taxanes

Mehra et al, Eur Urol 2018



B Radiological progression-free survival

Study	HR (95% CI)	Number of patients
FIRSTANA	1.82 (1.13-2.95)	264
PROSELICA	1.26 (0.72-2.20)	209
Overall ($\tau^2 = 0.0\%$, $p = 0.323$)	1.96 (1.08-2.24)	473

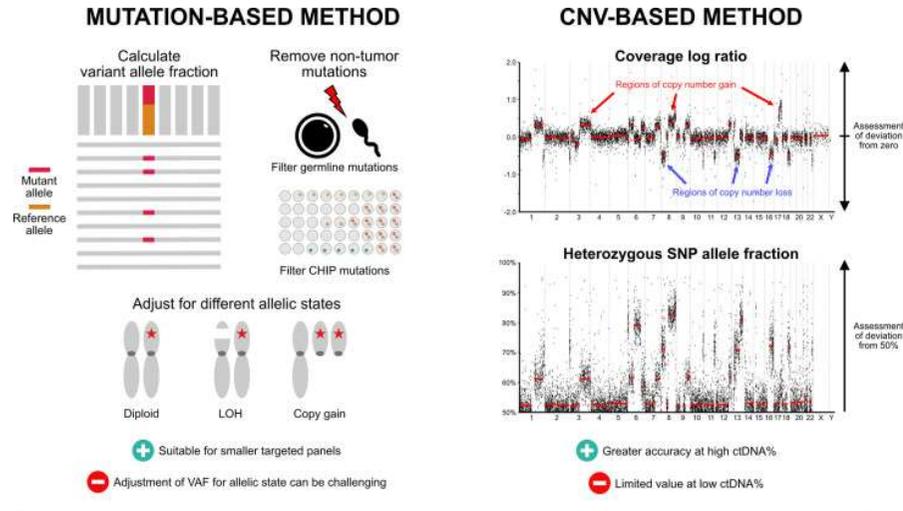
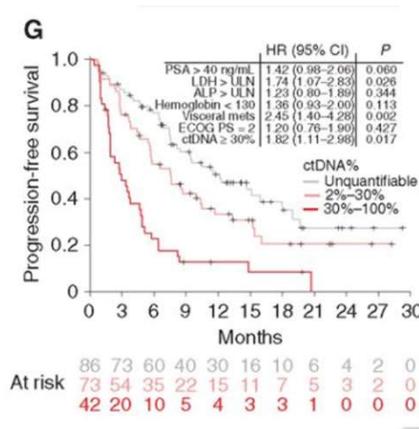


D Overall survival

Study	HR (95% CI)	Number of patients
FIRSTANA	1.80 (1.16-2.79)	264
PROSELICA	1.36 (0.91-2.05)	209
Overall ($\tau^2 = 0.0\%$, $p = 0.360$)	1.55 (1.15-2.09)	473

Abi/Enza

Annala et al, Cancer Discov 2018



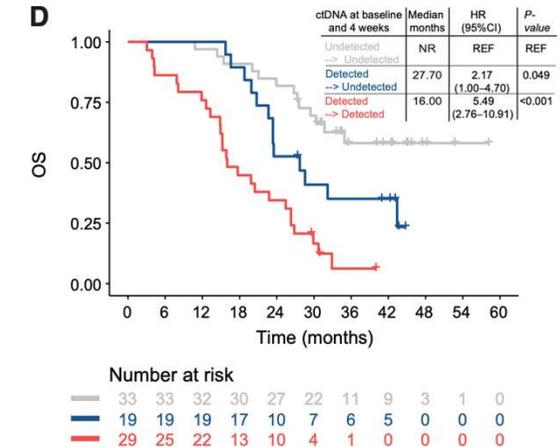
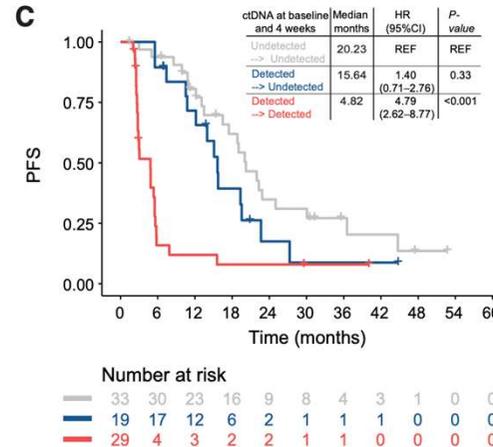
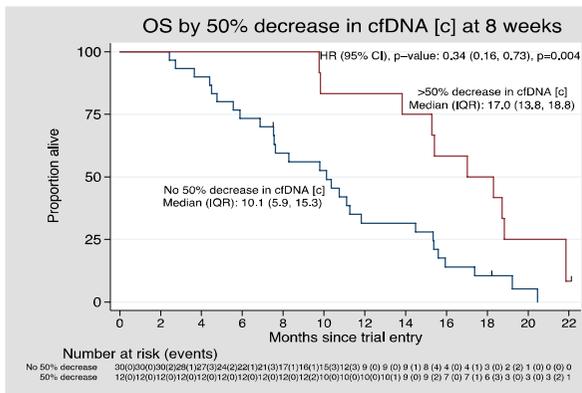
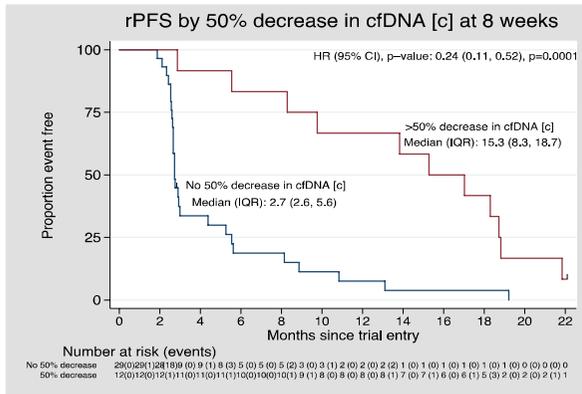
Accuracy of ctDNA% estimate scales with greater depth and breadth of sequencing

Kwan et al (review), 2022

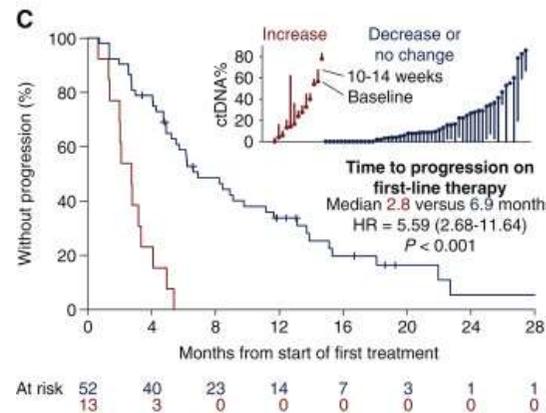
cfDNA and ctDNA prognostic and response biomk

PARP inhibitors

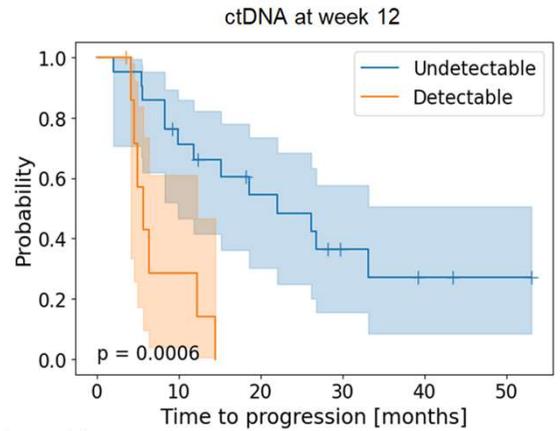
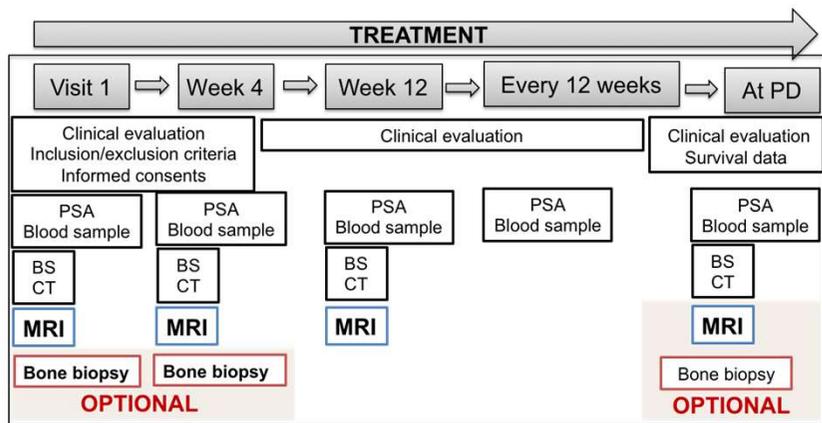
Goodall*, Mateo* et al, Cancer Discov 2017



Tolmeijer et al, Clin Can Res 2023



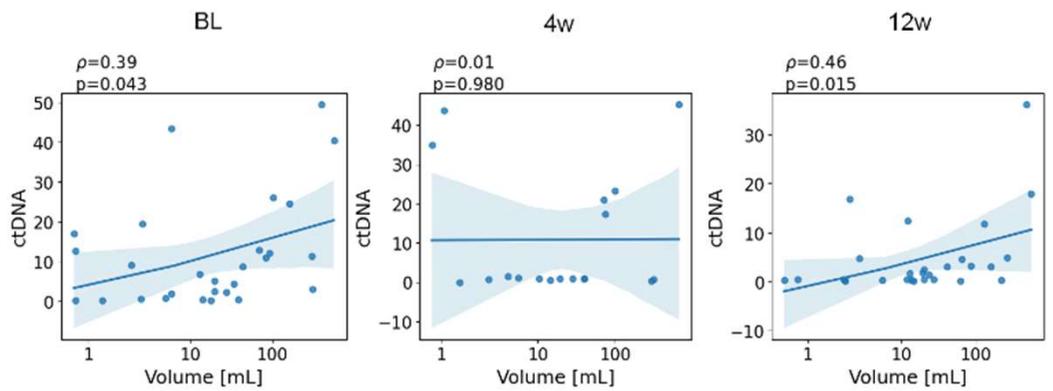
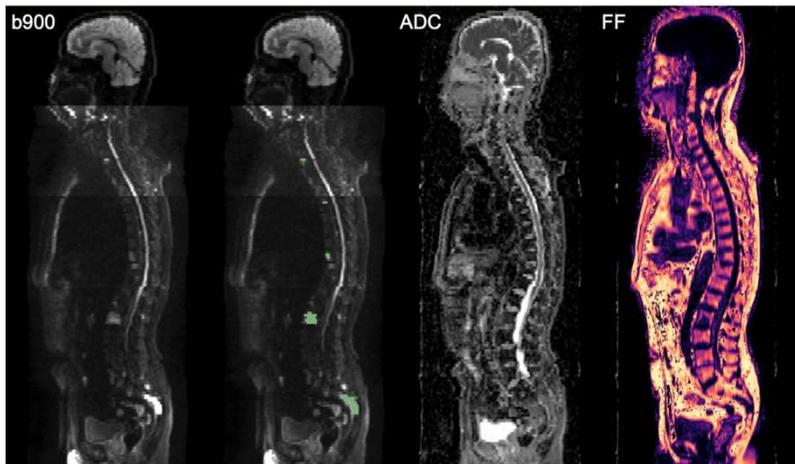
Annala et al, Ann Onc 2021



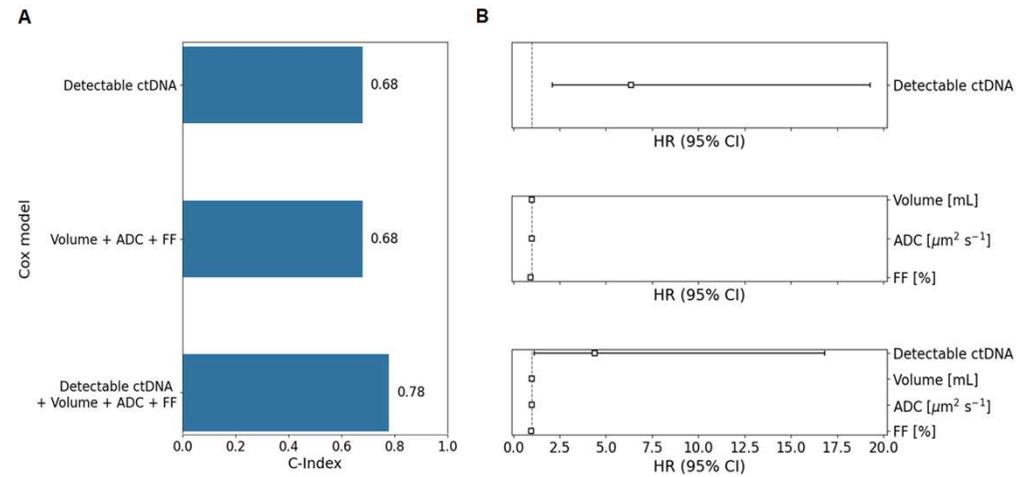
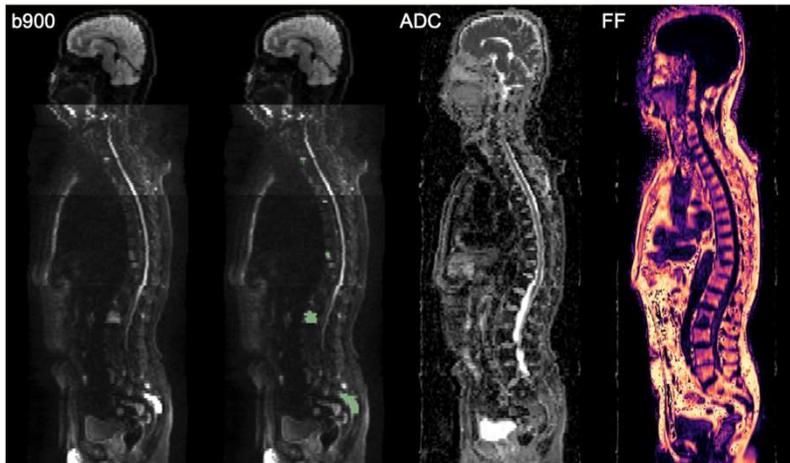
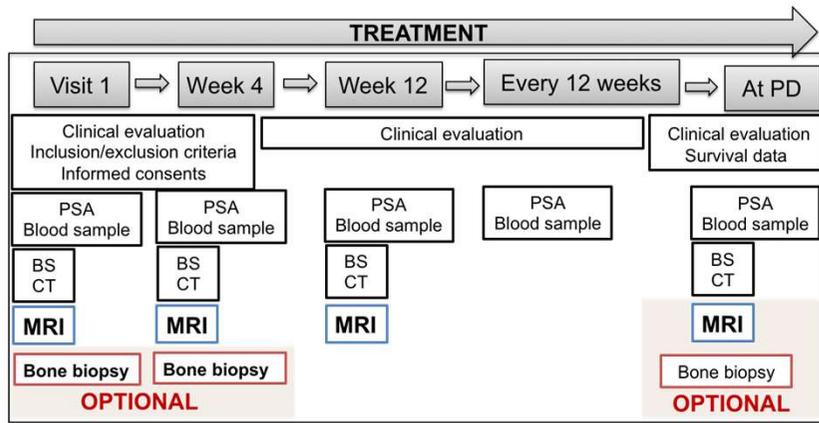
	0	10	20	30	40	50
Undetectable	21	14	9	4	2	1
Censored	0	1	3	5	6	7
Events	0	6	9	12	13	13
Detectable	8	2	0	0	0	0
Censored	0	1	1	1	1	1
Events	0	5	7	7	7	7



Prostate Cancer Foundation
Curing Together.



Garcia, Macarro, Zacchi et al, under review

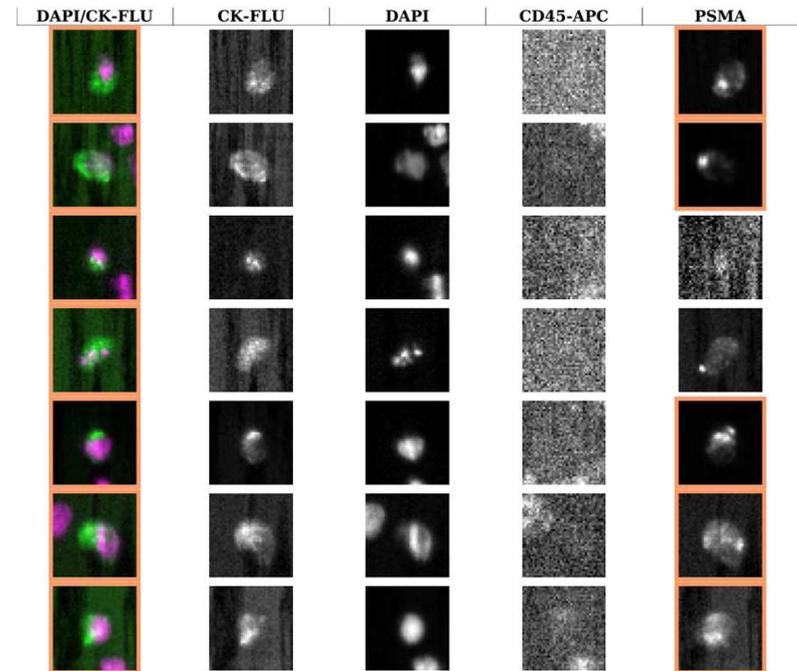
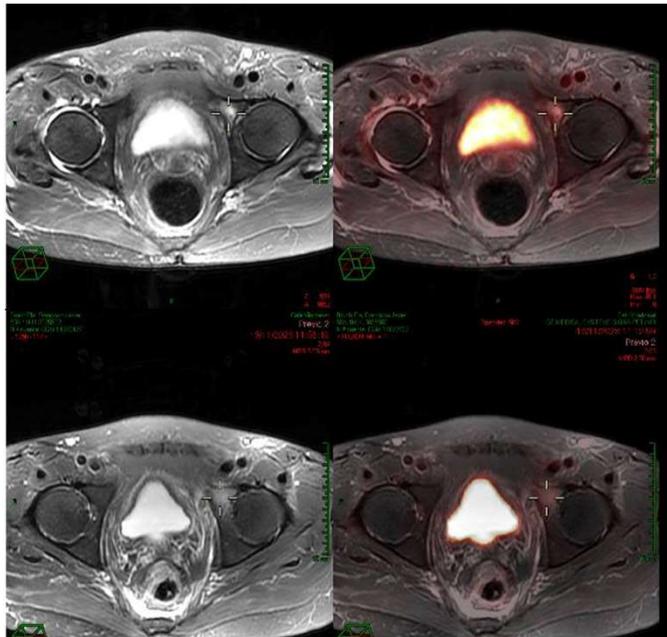


MARION

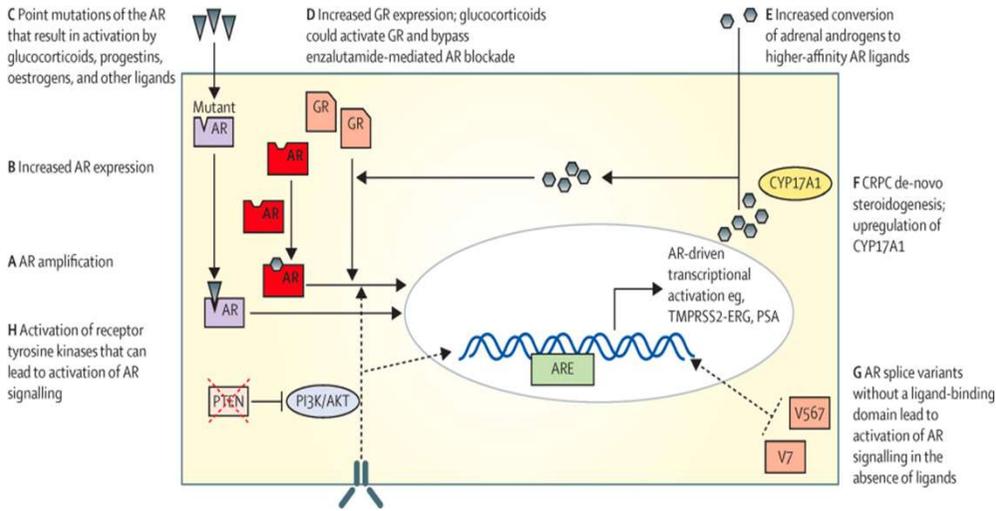
Multimodal Biomarkers For PRecise Management of Metastatic PrOstate caNcer



- Dual whole-body MRI and ^{18}F -PSMA-PET
- Circulating tumor cells (CTC) (total counts and PSMA-positive) in collaboration with IDIS
- Cell-free tumor DNA (ctDNA).



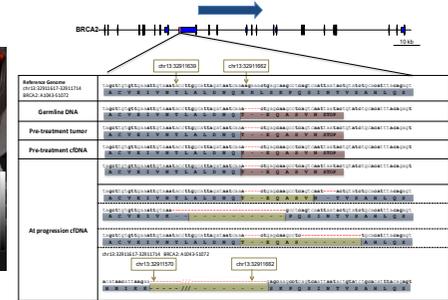
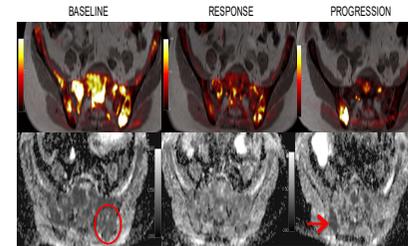
AR signaling is the primary driver of prostate cancer progression



Attard et al *The Lancet* 2016 (review)

Challenge 2

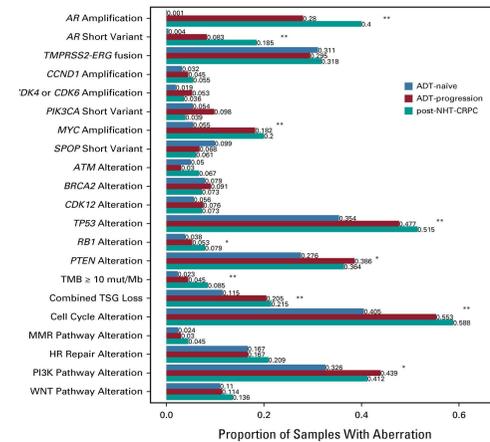
- Limited genomic evolution upon therapy resistance
- Transcriptomic and epigenomic modulation as MoR



Goodall*, Mateo* et al, *Cancer Discovery* 2017

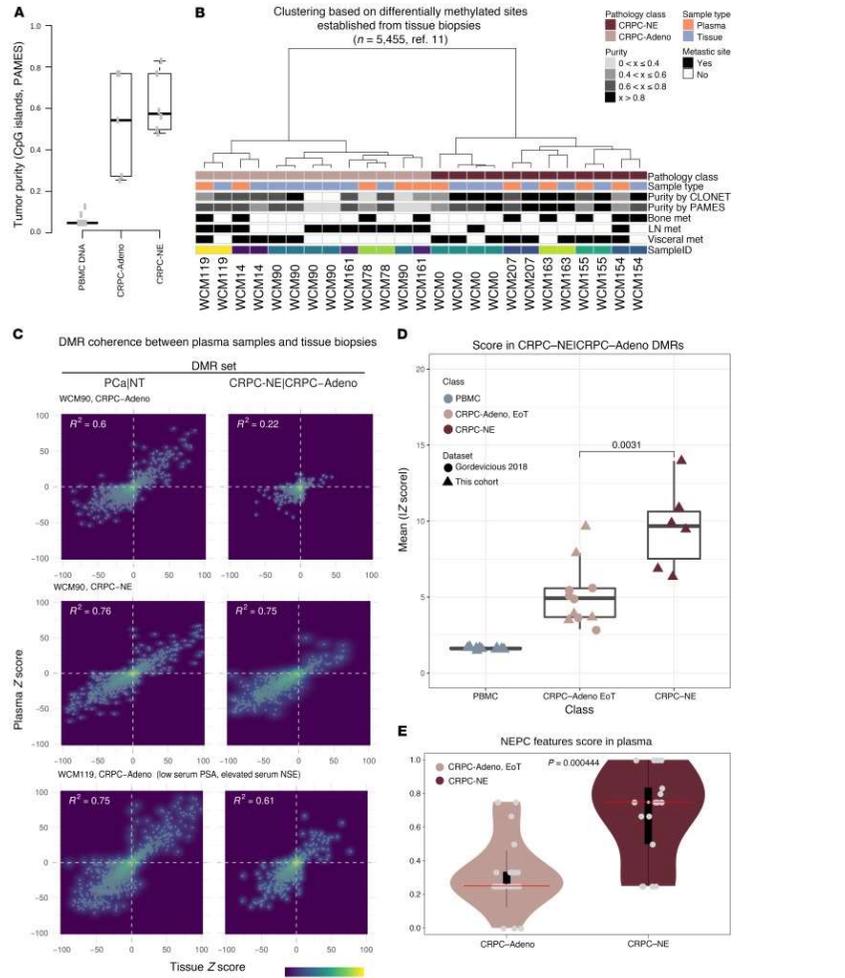
exceptions

- PARPi resistance mutations
- AR mutations (incomplete info)
- TP53/RB1 loss (? New? Subclonal?)

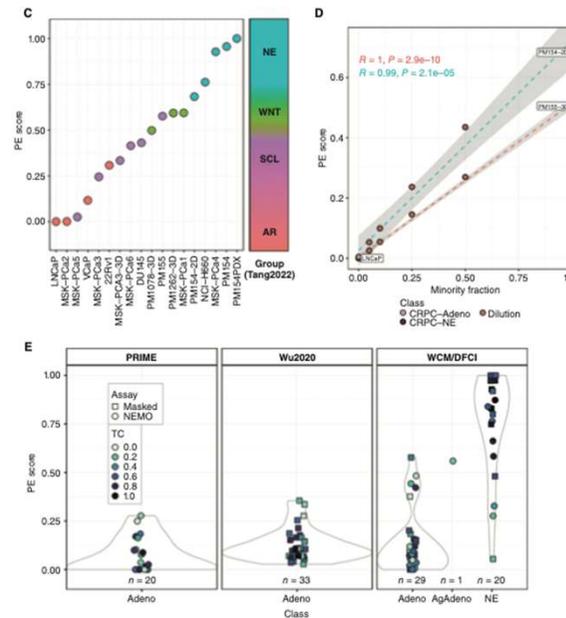
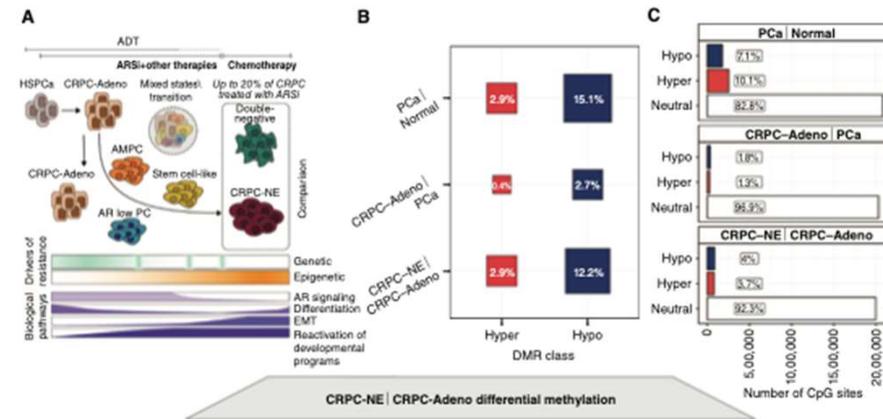


Zurita et al...Mateo, *JCO* PO 2022

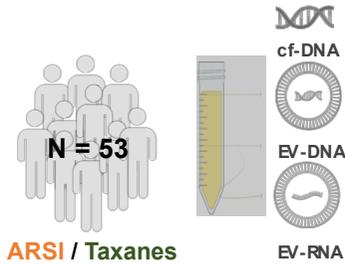
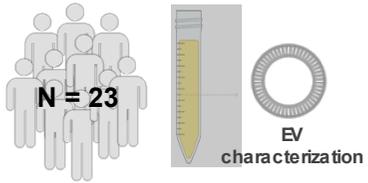
Methylation of ctDNA during mPC de-differentiation



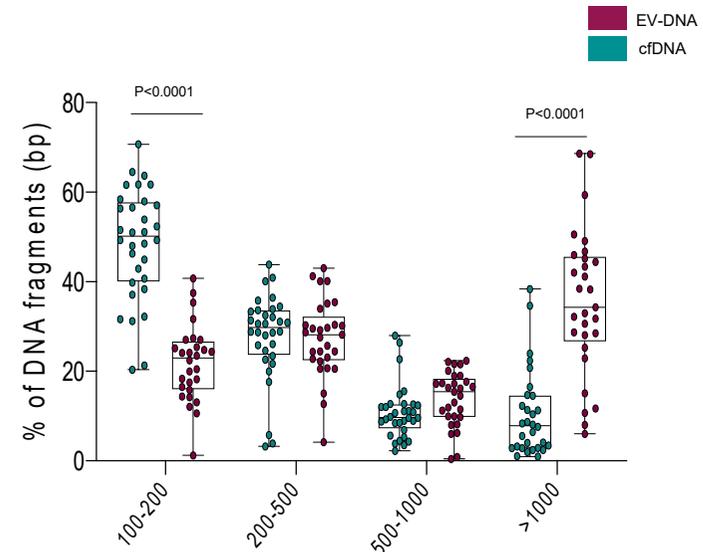
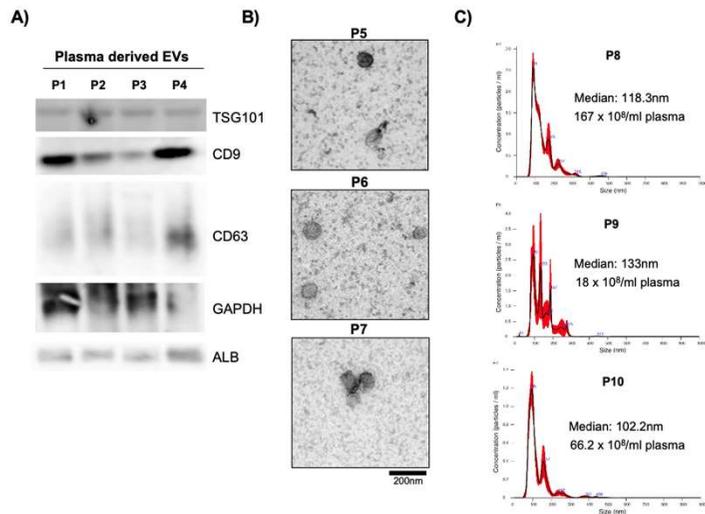
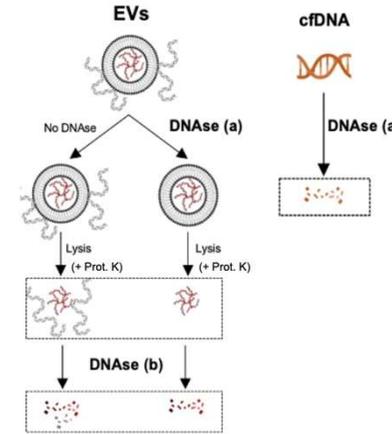
Beltran et al, J Clin Inv 2020



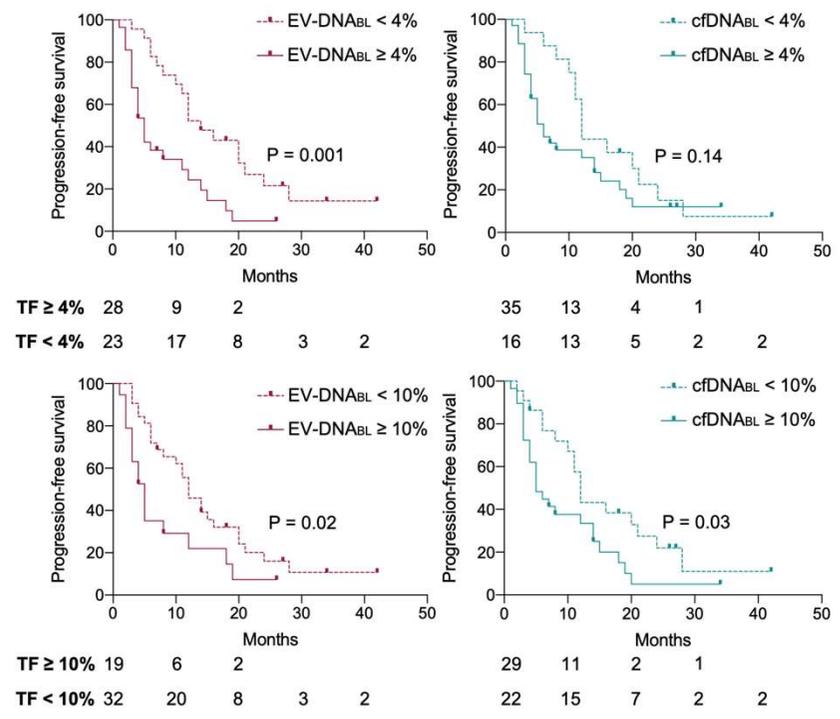
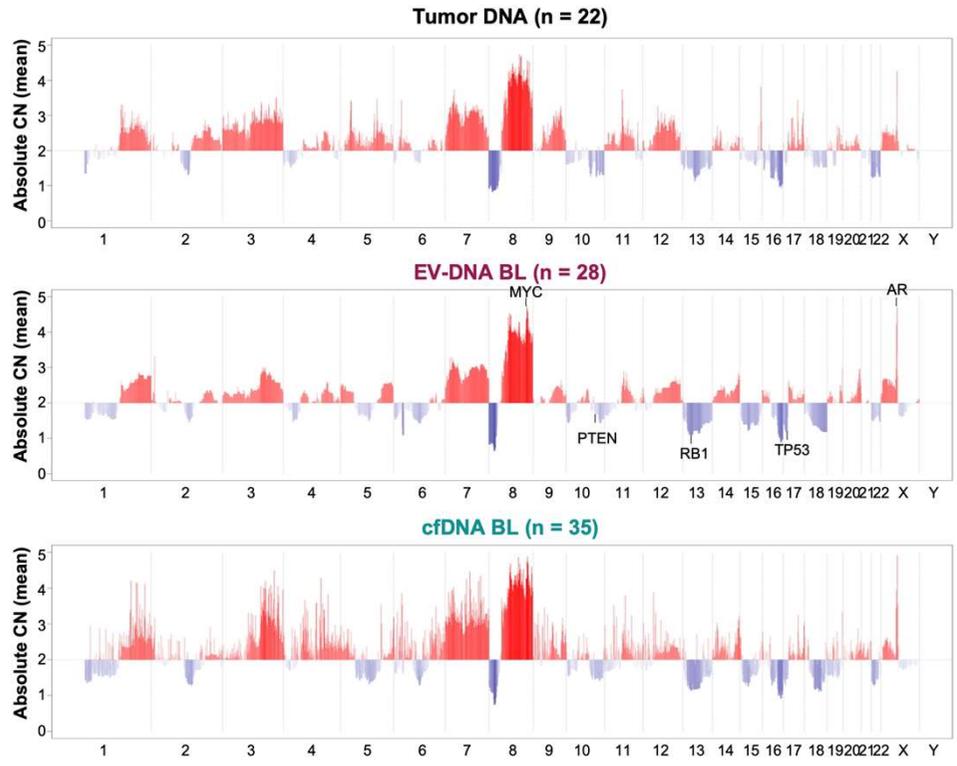
Francescini et al,
Cancer Discovery 2024



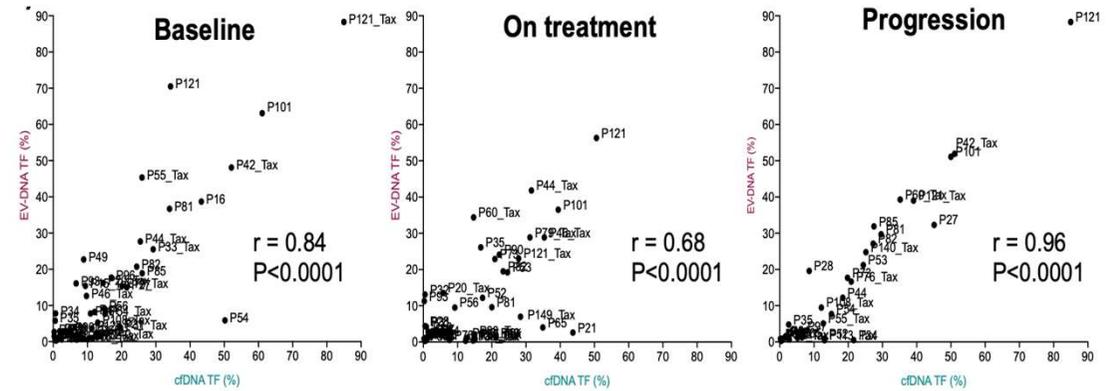
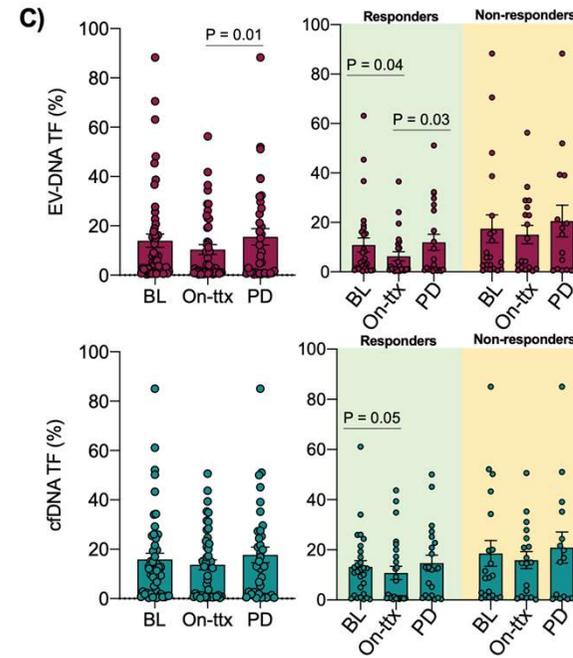
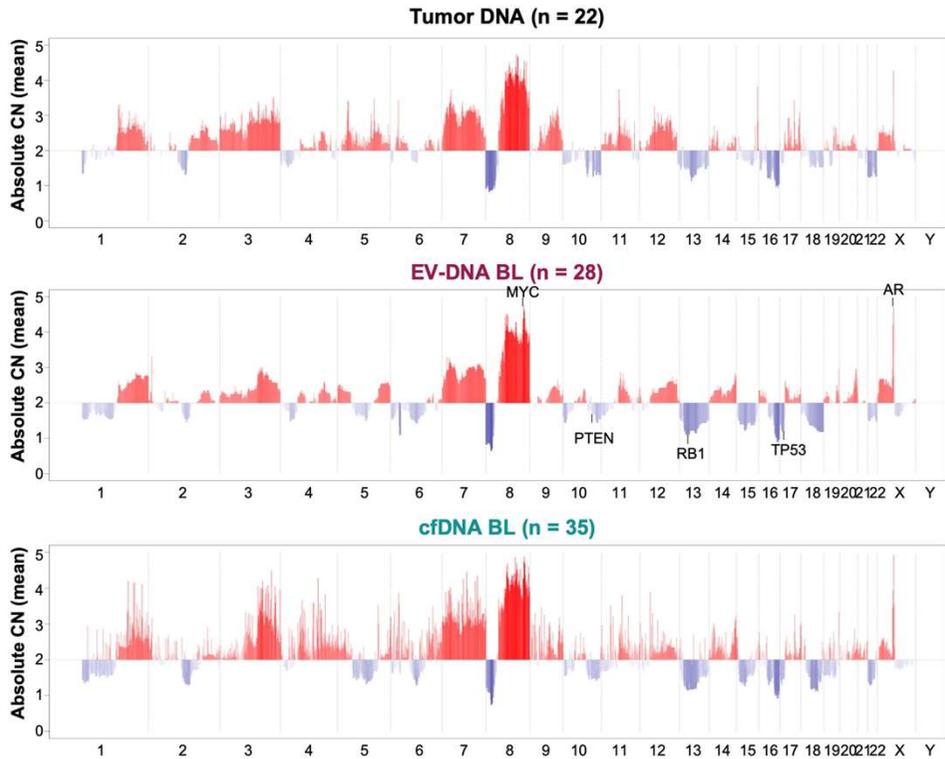
23 samples EVs	132 samples EV-DNA + 132 samples cfDNA	
WB	92 samples on ARSI	40 samples on Taxanes
TEM	35 Pts on ARSI	18 Pts on Taxanes
NTA	<ul style="list-style-type: none"> BL 35 On-ttx 32 PD 25 	<ul style="list-style-type: none"> BL 16 On-ttx 14 PD 10
Protection assays		
Iodixanol gradient		



UNPUBLISHED – DO NOT POST Casanova-Salas et al, under review



UNPUBLISHED – DO NOT POST Casanova-Salas et al, under review



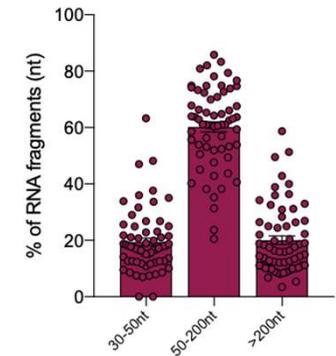
UNPUBLISHED – DO NOT POST Casanova-Salas et al, under review



23 samples EVs	132 samples EV-DNA + 132 samples cfDNA	
WB	92 samples on ARSI	40 samples on Taxanes
TEM	35 Pts on ARSI	18 Pts on Taxanes
NTA	<ul style="list-style-type: none"> BL 35 On-ttx 32 PD 25 	<ul style="list-style-type: none"> BL 16 On-ttx 14 PD 10
Protection assays	82 samples EV-RNA	
Iodixanol gradient	38 samples on ARSI	33 samples on Tax. 11 Healthy vol.
	15 Pts on ARSI	13 Pts on Taxanes
	<ul style="list-style-type: none"> BL 14 On-ttx 14 PD 10 	<ul style="list-style-type: none"> BL 13 On-ttx 10 PD 10

RNA isolation from:

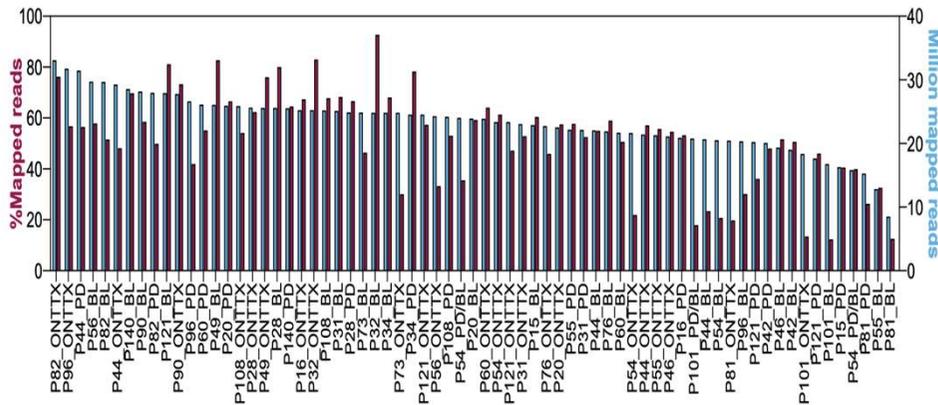
- mCRPC patient plasma (EVs)
- mCRPC patient PBMC
- Healthy volunteer's plasma (EVs)



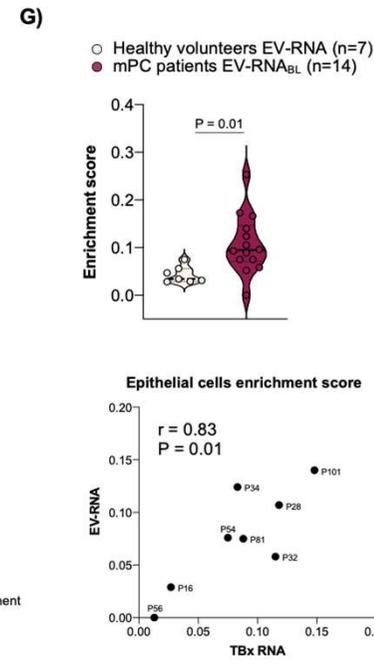
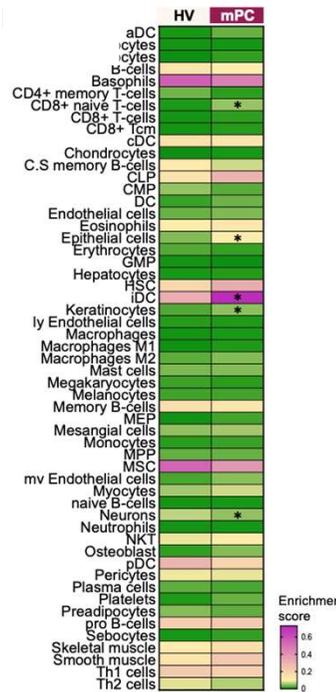
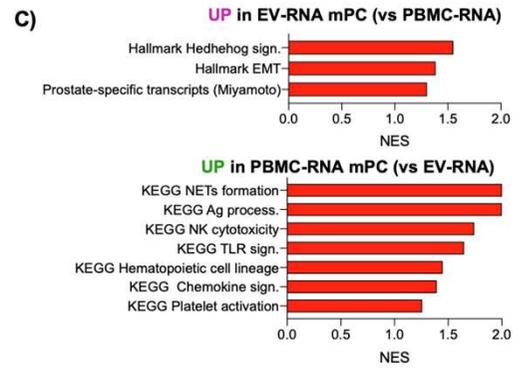
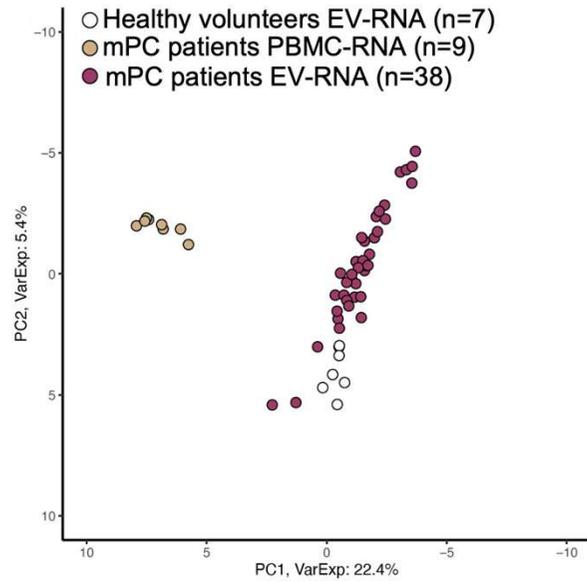
RNA conversion to cDNA (REXCUE protocol)

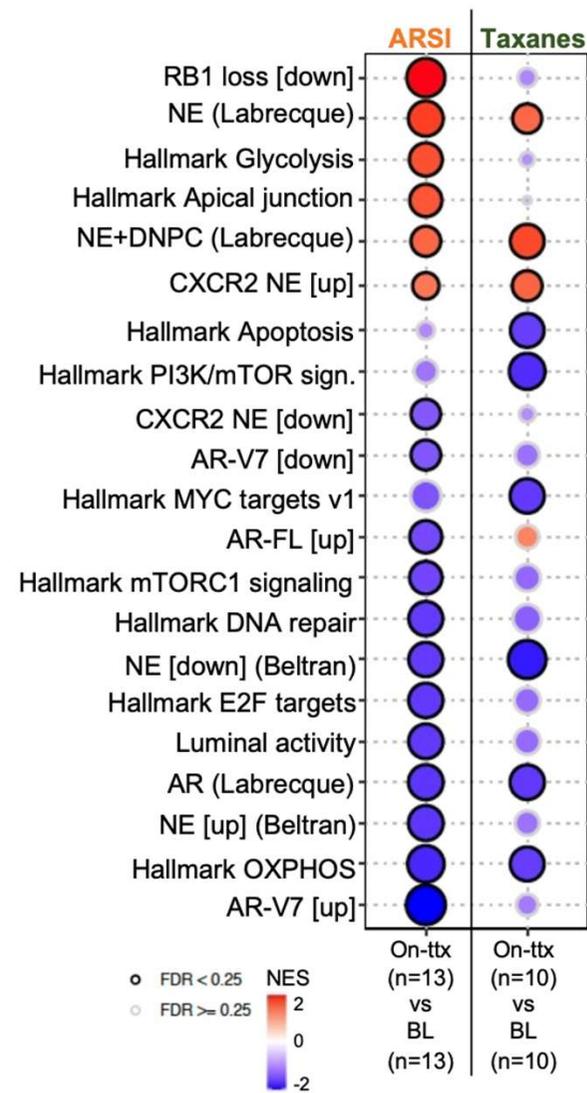
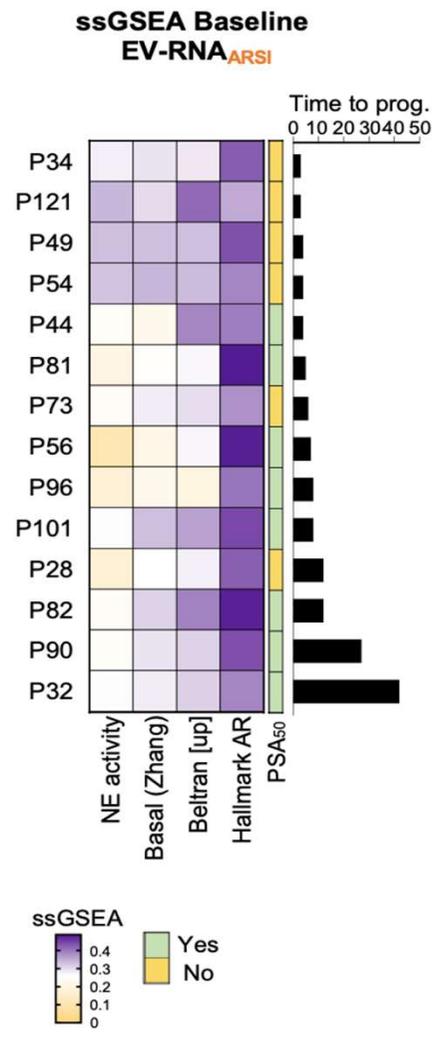
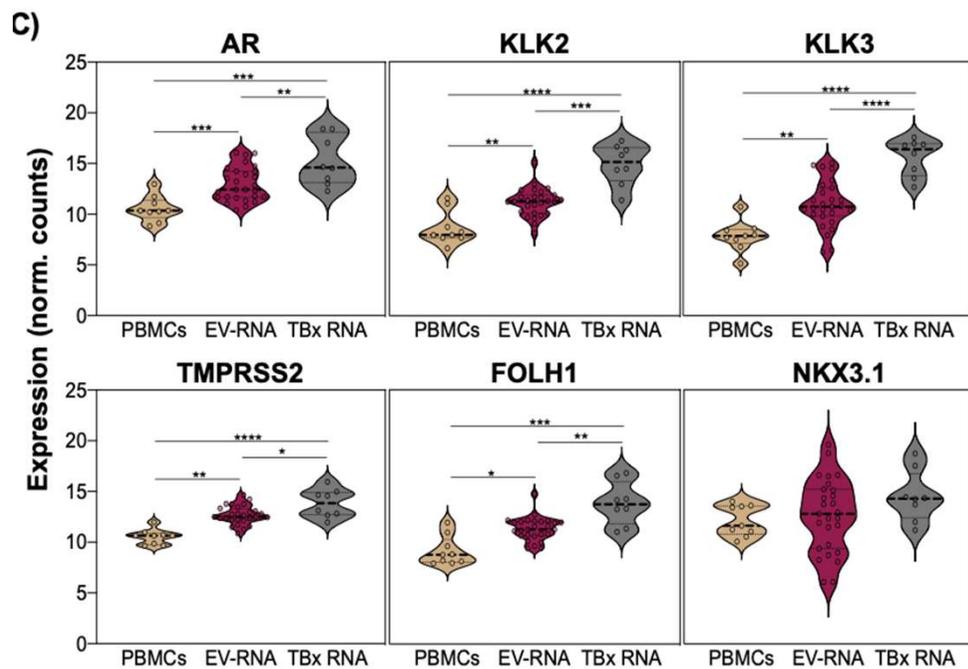
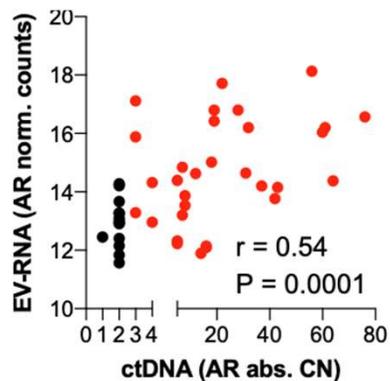
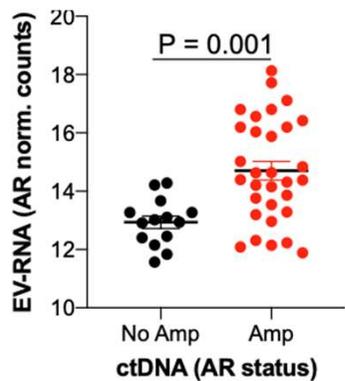
Library preparation

Sequencing (50-80M)



UNPUBLISHED – DO NOT POST Casanova-Salas et al, under review





Take home messages

- Genomic stratification has entered mPC care with PARPi (and more to come) – straight-forward application of ctDNA NGS, but there is more
- Need for validated prognostic and response biomarker for:
 - Individual patient therapy switch decisions
 - Fast readout intermediate endpoints for phase I/II trials
- CTC counts have been clinically qualified, but implementation is lacking (logistics, costs,...)
- ctDNA kinetics have great potential to guide treatment decisions – prospective trials are needed
- Combining multiple –omics biomarker
- Study of tumor evolution in mPC needs to go beyond ctDNA NGS
 - CTC comprehensive profiling (DNA, RNA, protein)
 - ctDNA methylation to study MoR and tumor evolution
 - Potential of circulating EV for transcriptomics (work ongoing)



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