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FACE-TO-FACE AND LIVE STREAMING

26-27 JUNIO 2025

Espacio Maldonado, Madrid

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¿HA LLEGADO LA MEDICINA DE PRECISIÓN AL CÁNCER DE PRÓSTATA HORMOSENSIBLE METASTÁSICO?

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Jefe de Sección
Hospital Universitario Vall d'Hebron
Barcelona

Disclosures

- Employee: Vall d'Hebron University Hospital, Teknon Oncology Department
- Consultant and scientific advisory board attendee: Amgen, Astellas, Bayer, BMS, MSD, Johnson & Johnson, Sanofi, Pfizer, Novartis (AAA)
- Speaker bureau: Asofarma, Astellas, Bayer, Johnson & Johnson, Sanofi
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- Institutional Studies Collaborations: AB Science, Aragon Pharmaceuticals, Arog Pharmaceuticals, INC, Astellas Pharma, Astrazeneca AB, Aveo Pharmaceuticals INC, Bayer AG, Blueprint Medicines Corporation, BN Immunotherapeutics INC, Boehringer Ingelheim España, S.A., Bristol-Myers Squibb International Corporation (BMS), Clovis Oncology, INC, Cougar Biotechnology INC, Deciphera Pharmaceuticals LLC, Exelixis INC, F. Hoffmann-La RocheLTD, Genentech INC, Glaxosmithkline, SA, Incyte Corporation, Janssen-Cilag International NV, Karyopharm Therapeutics INC., Laboratoires Leurquin Mediolanum SAS, Lilly, S.A., Medimmune, Millennium Pharmaceuticals, INC., Nanobiotix SA, Novartis Farmacéutica, S.A., Pfizer, S.L.U, Puma Biotechnology, INC, Sanofi-Aventis, S.A., SFJ Pharma LTD. Il, TevaPharma S.L.U.

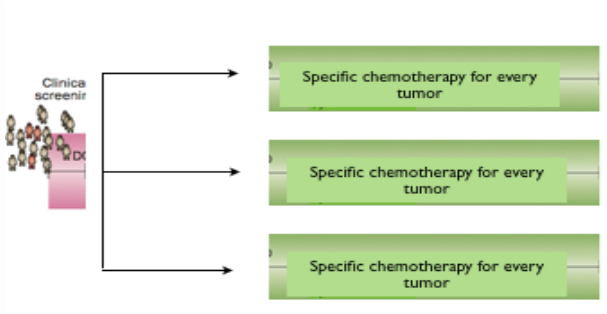
Conceptual evolution of cancer treatment

Nowadays

Clinical Oncology → Pathological Oncology → Molecular Oncology → Personalized Medicine

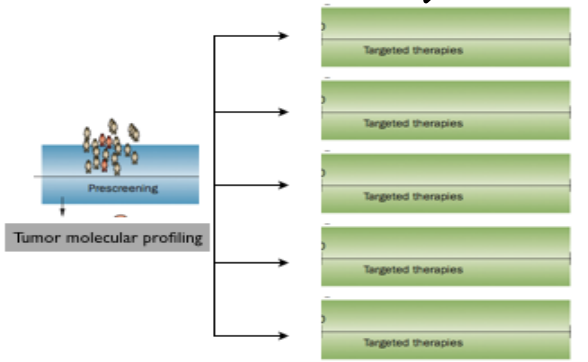
Few therapeutic options combined to treat tumors:

-Surgery
-Radiotherapy
-Few chemotherapies



Increase on therapeutic options allowed specific treatments for different tumor types:

-Combined chemo-radiation
-Specific protocols (NCCN guidelines)



Targeted agents that work in specific molecular alterations:

- Broad knowledge of molecular tumor biology
- Development of molecular analysis and targeted therapies

Disease guided approach → Pathological guided approach → Molecular approach

Conceptual evolution of cancer treatment

Nowadays

Clinical Oncology → Pathological Oncology → Molecular Oncology → **Personalized Medicine**

First "magic bullets":

- BCR/ABL Translocation-imatinib
- HER 2 Amplification –Trastuzumab

Push in Molecular Biology of Cancer


ARTICLE

Signatures of mutational processes in human cancer

A list of authors and their affiliations appears at the end of the paper

Social attention (Nixon declares war on cancer)

Pharma expands the pipeline

NOVARTIS · Roche · Genentech · MERCK · Pfizer · BAYER · gsk GlaxoSmithKline · Takeda · MILLENNIUM THE TAKEDA ONCOLOGY COMPANY · MSD

Changes in the last 15 years

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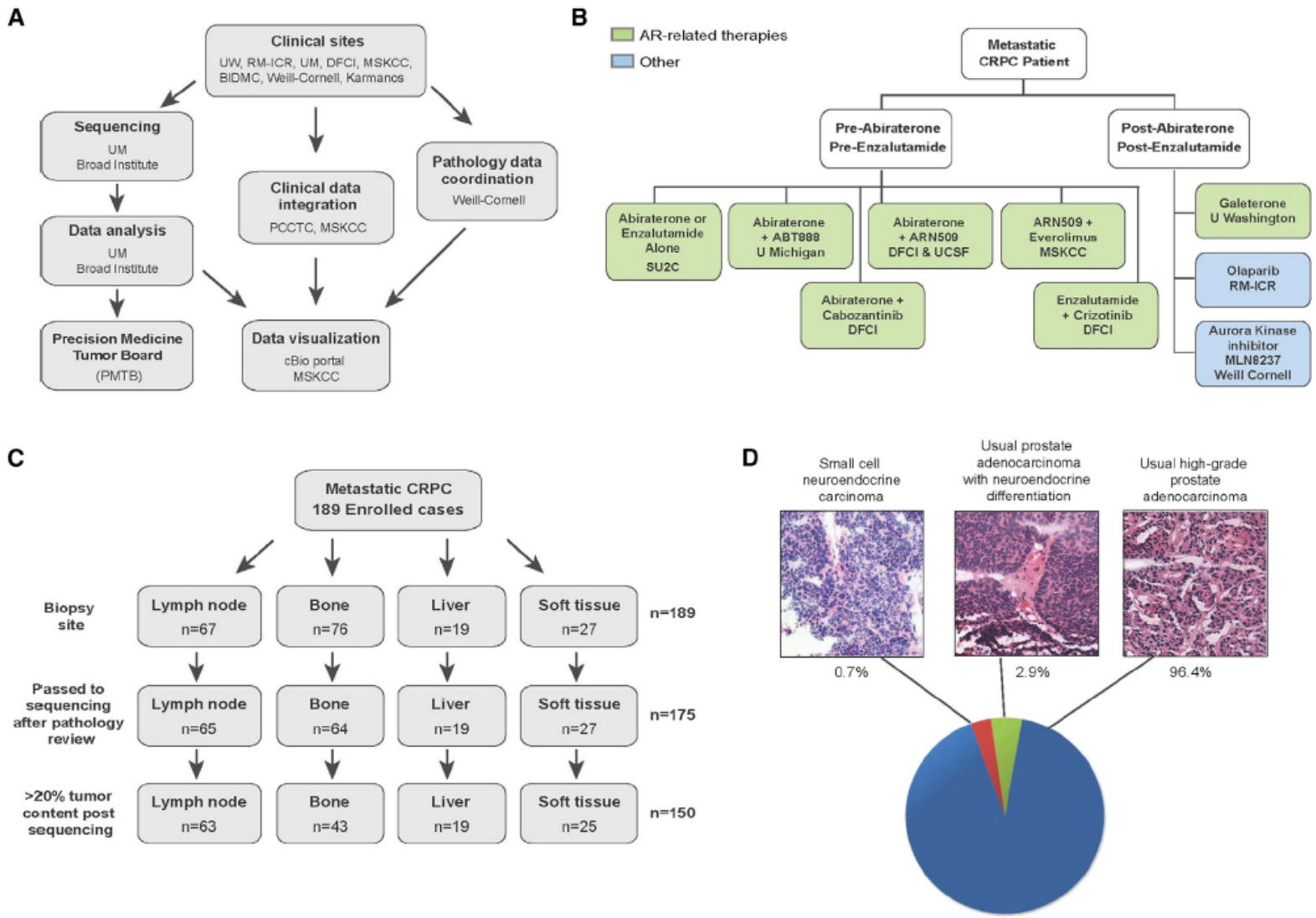
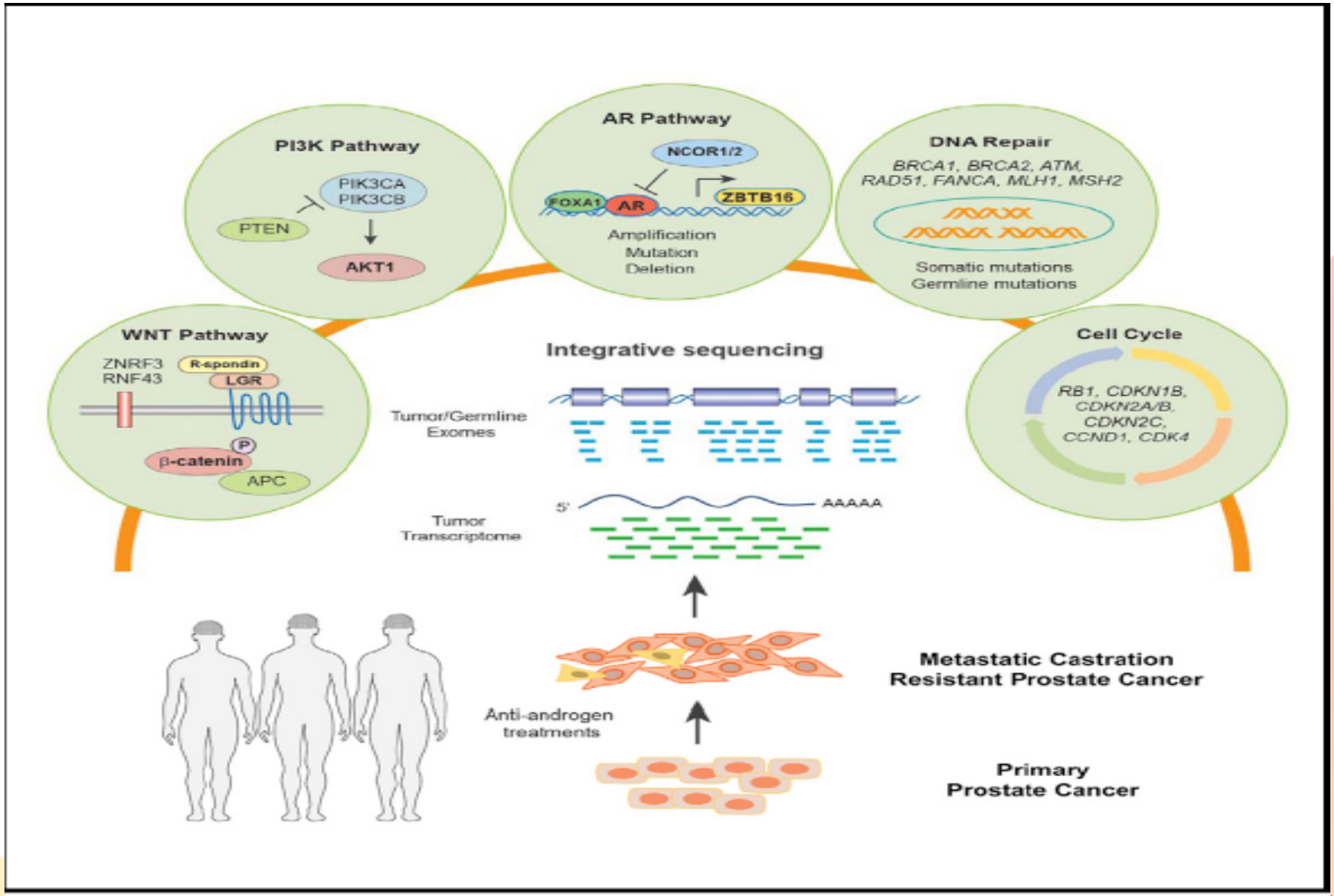


Robinson. Cell 2015;161:1215



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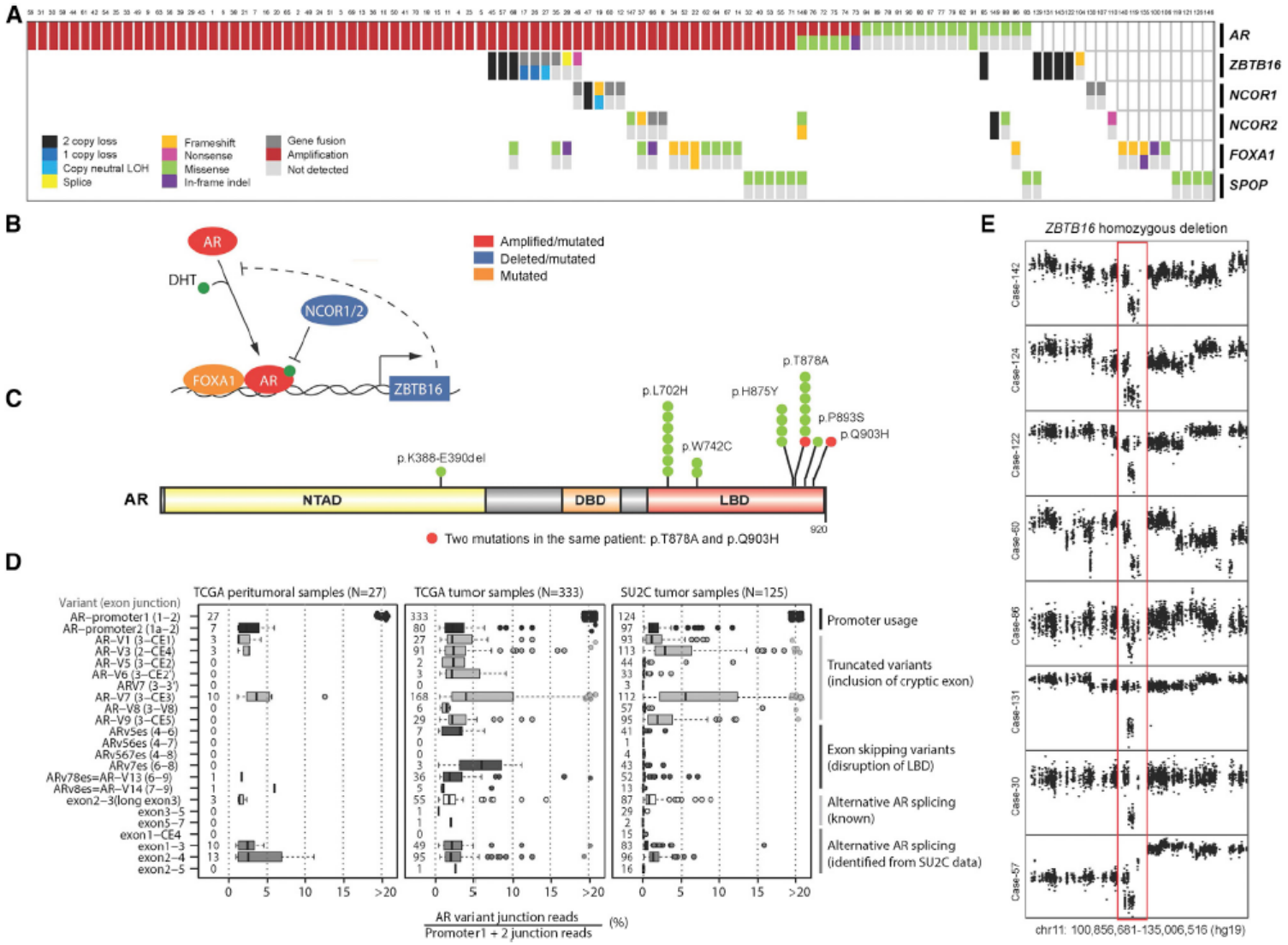
Robinson. Cell 2015;161:1215

Aberrations in AR



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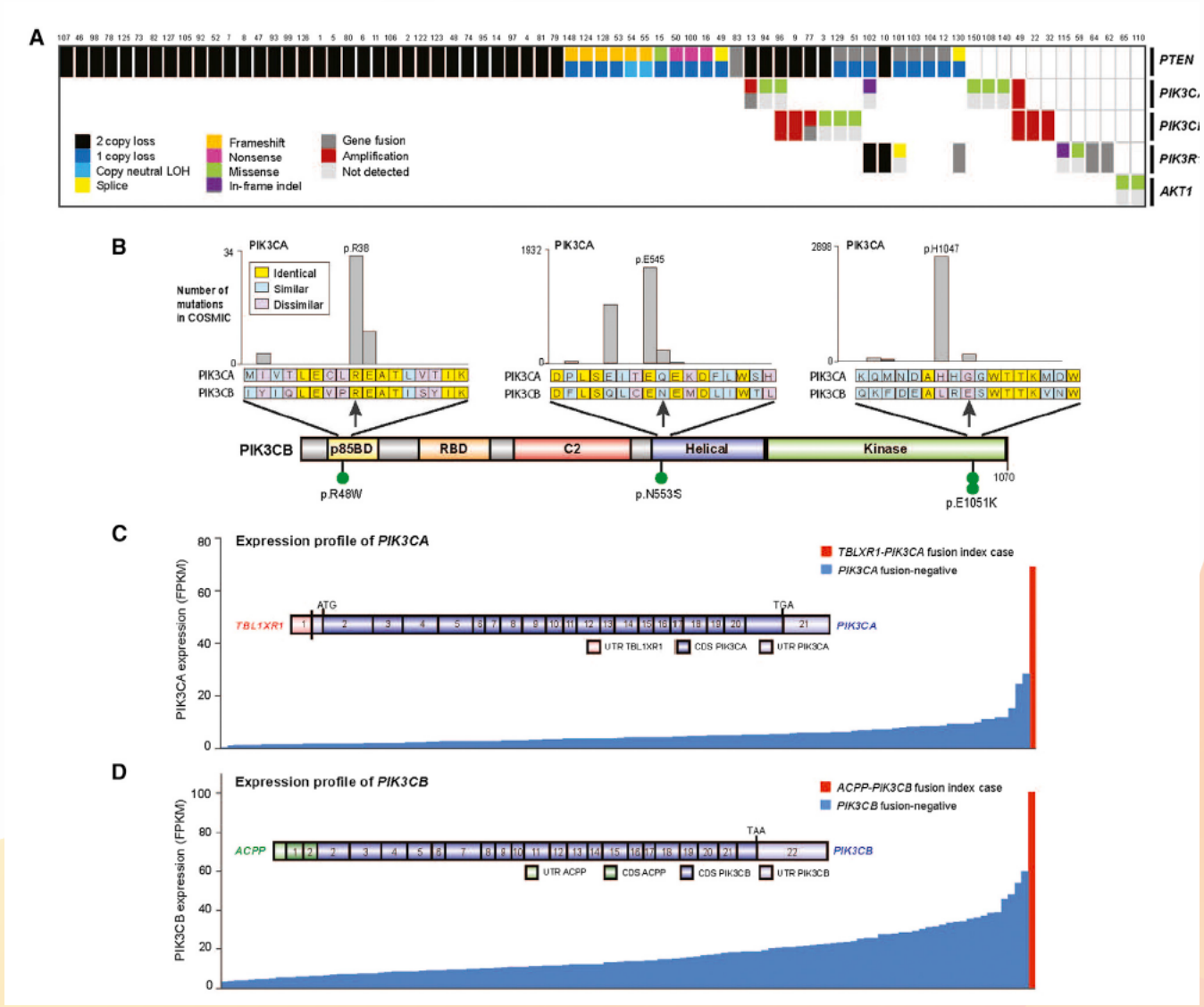
Robinson. Cell 2015;161:1215

Aberrations on Pl3k Pathway



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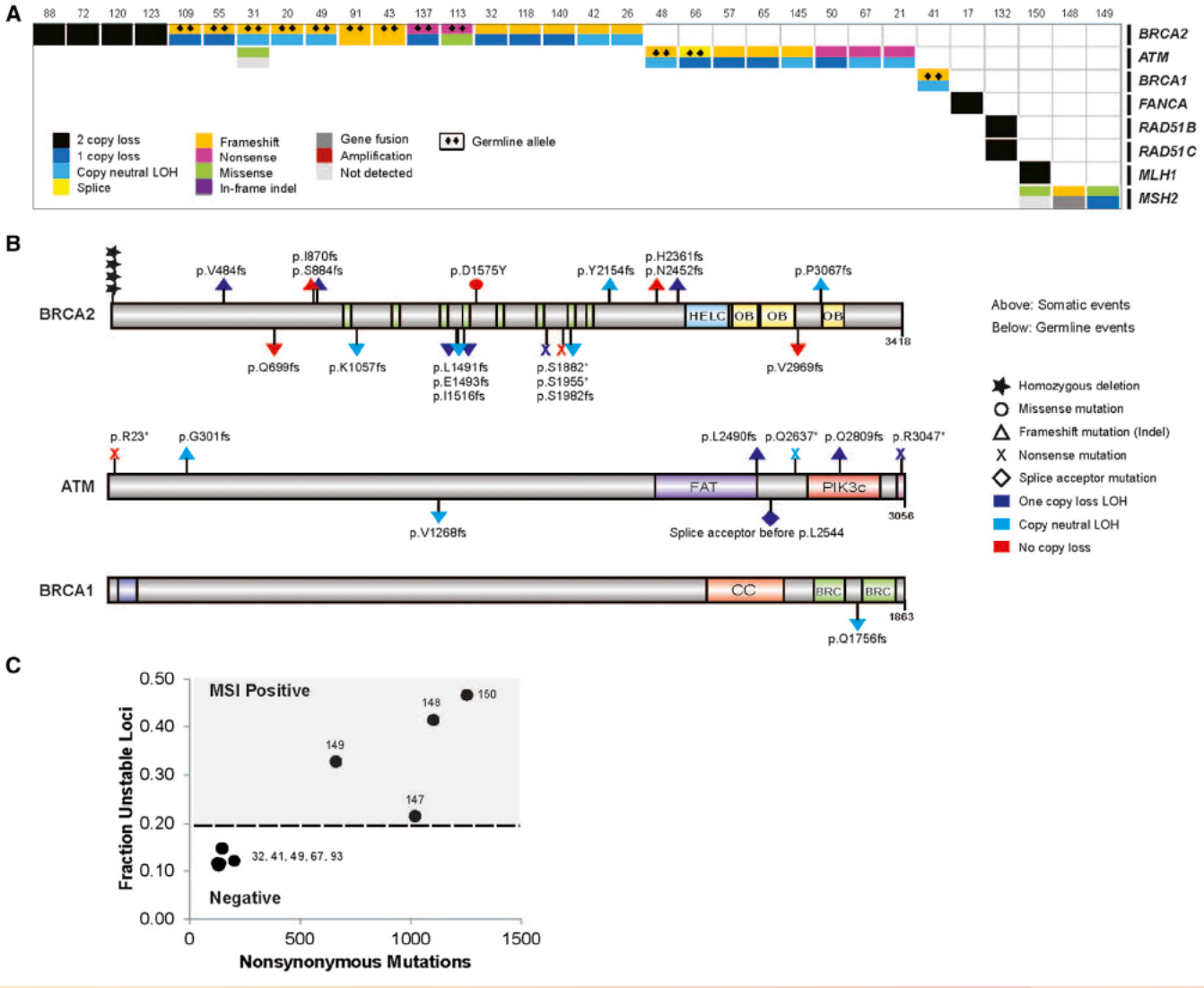
Robinson. Cell 2015;161:1215

Aberrations in DNA repair pathway



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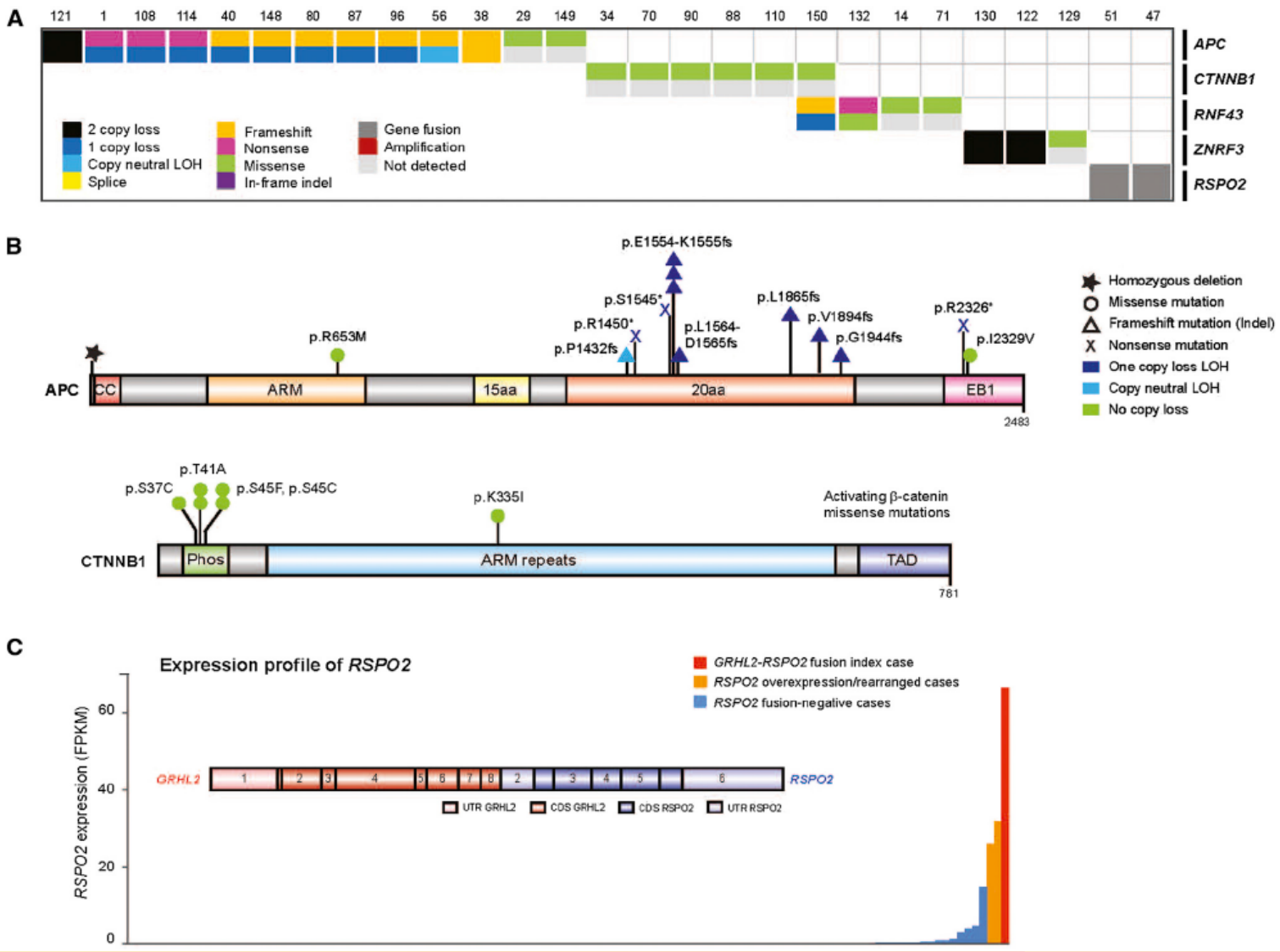
Robinson. Cell 2015;161:1215

Aberrations in Wnt pathway



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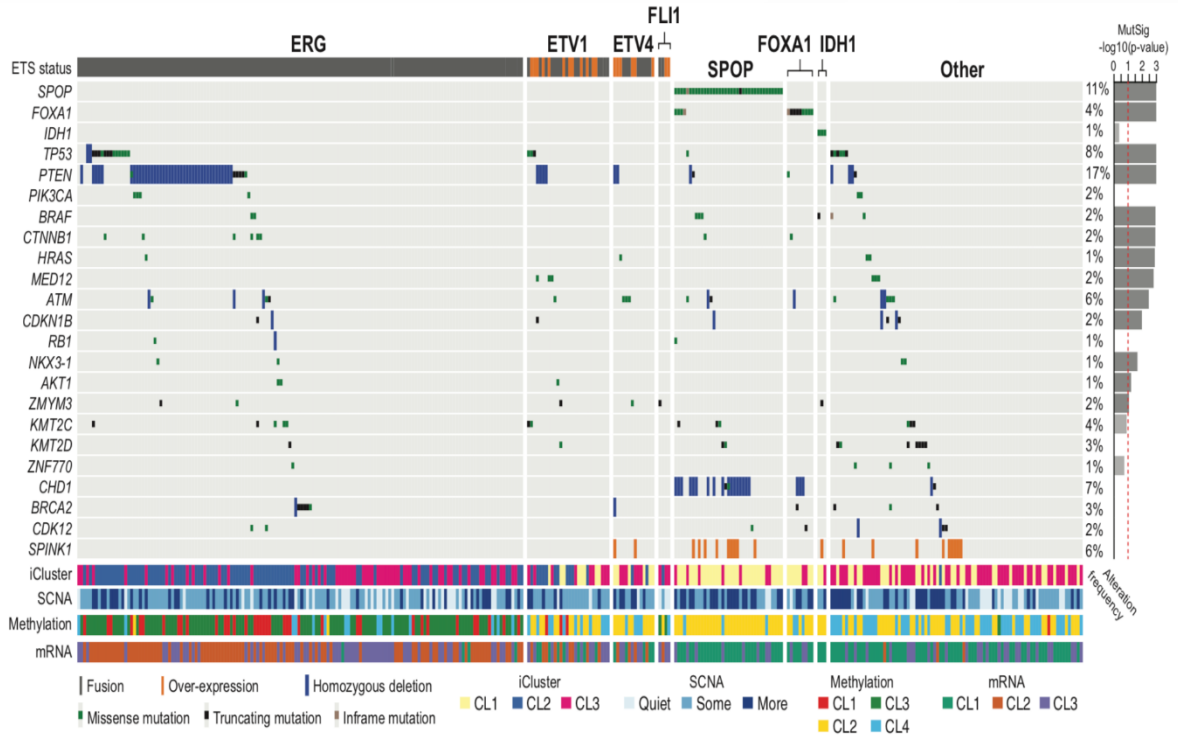
Robinson. Cell 2015;161:1215

The genomic landscape of prostate cancer

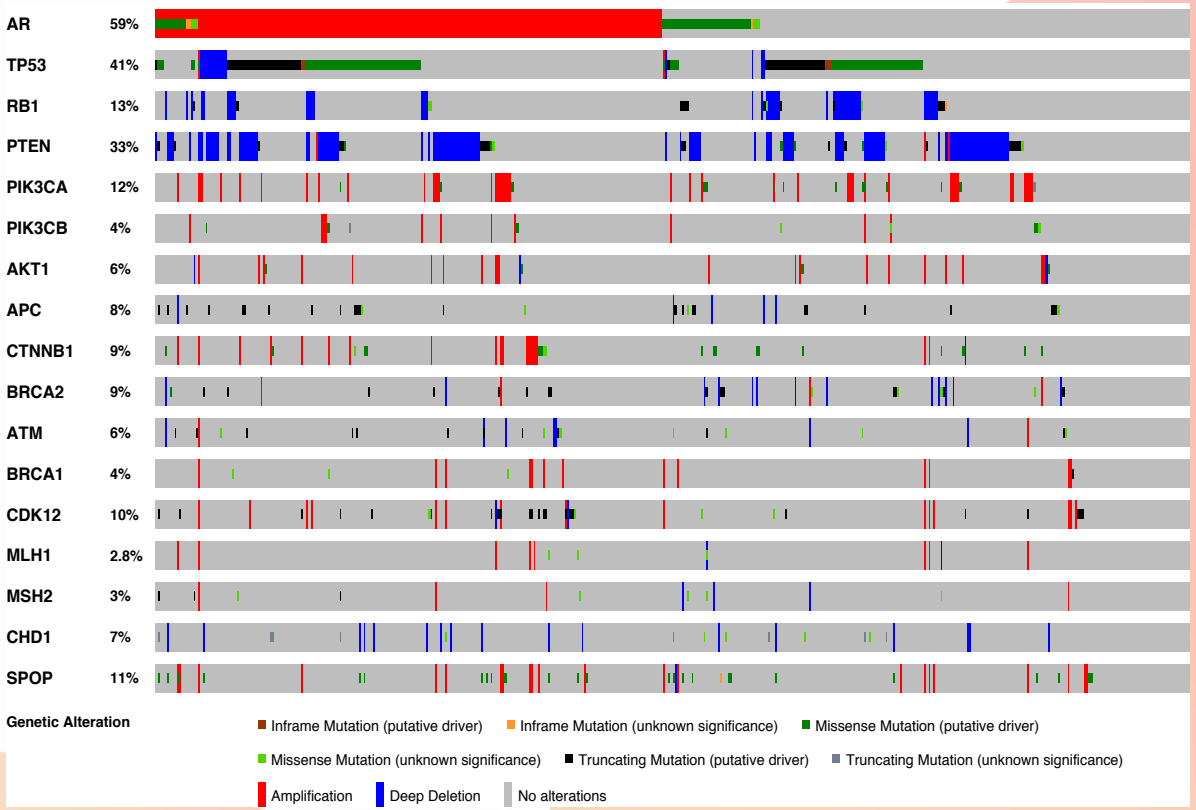
LOCALIZED DISEASE



TCGA. Abehouse et al Cell 2015

333 PRIMARY TUMORS

METASTATIC DISEASE



SU2C-PCF mCRPC Dream Team Study
n=432 (Abida et al, PNAS 2019)
First published at Robinson et al, Cell 2015 (n=150)

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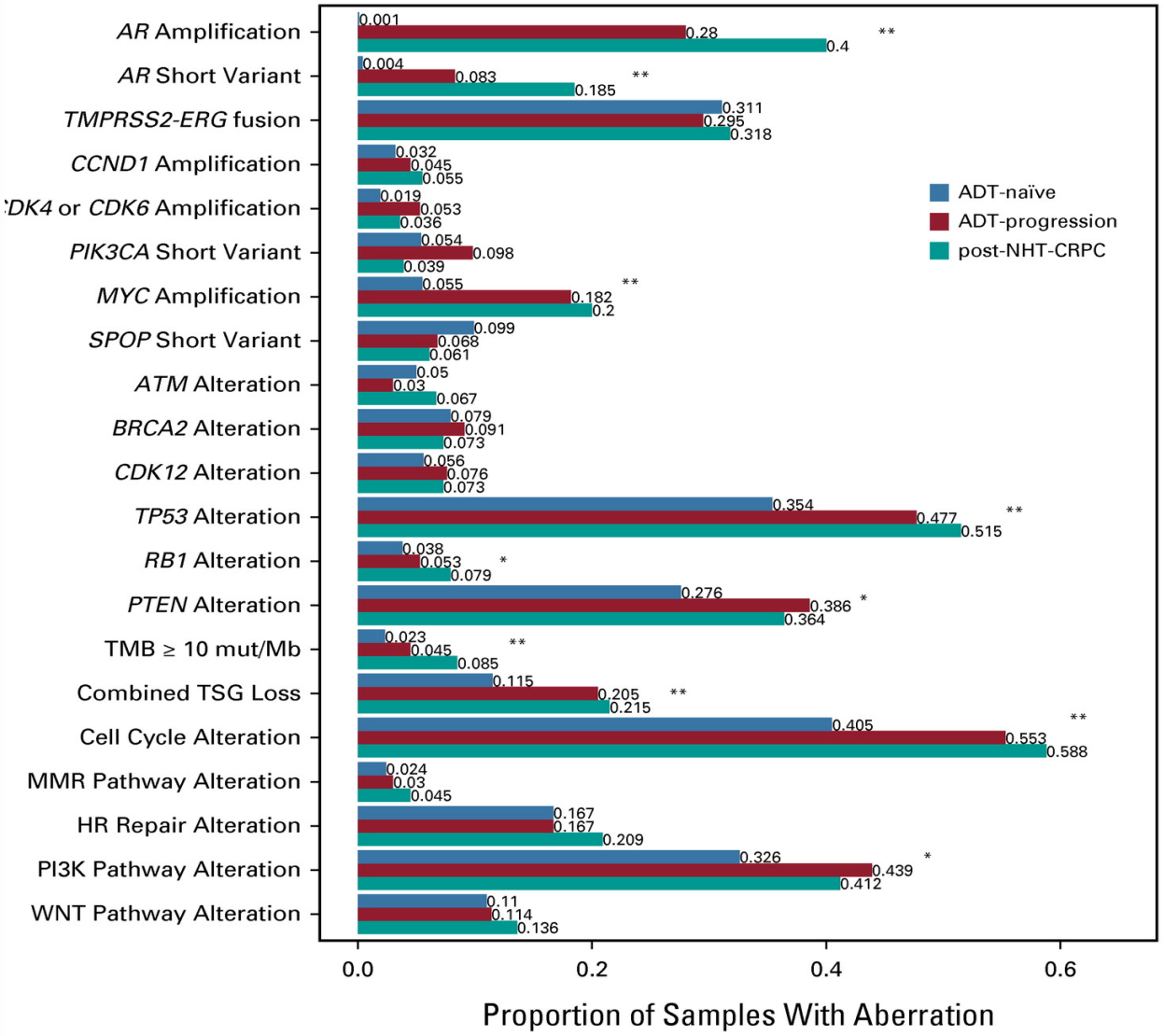
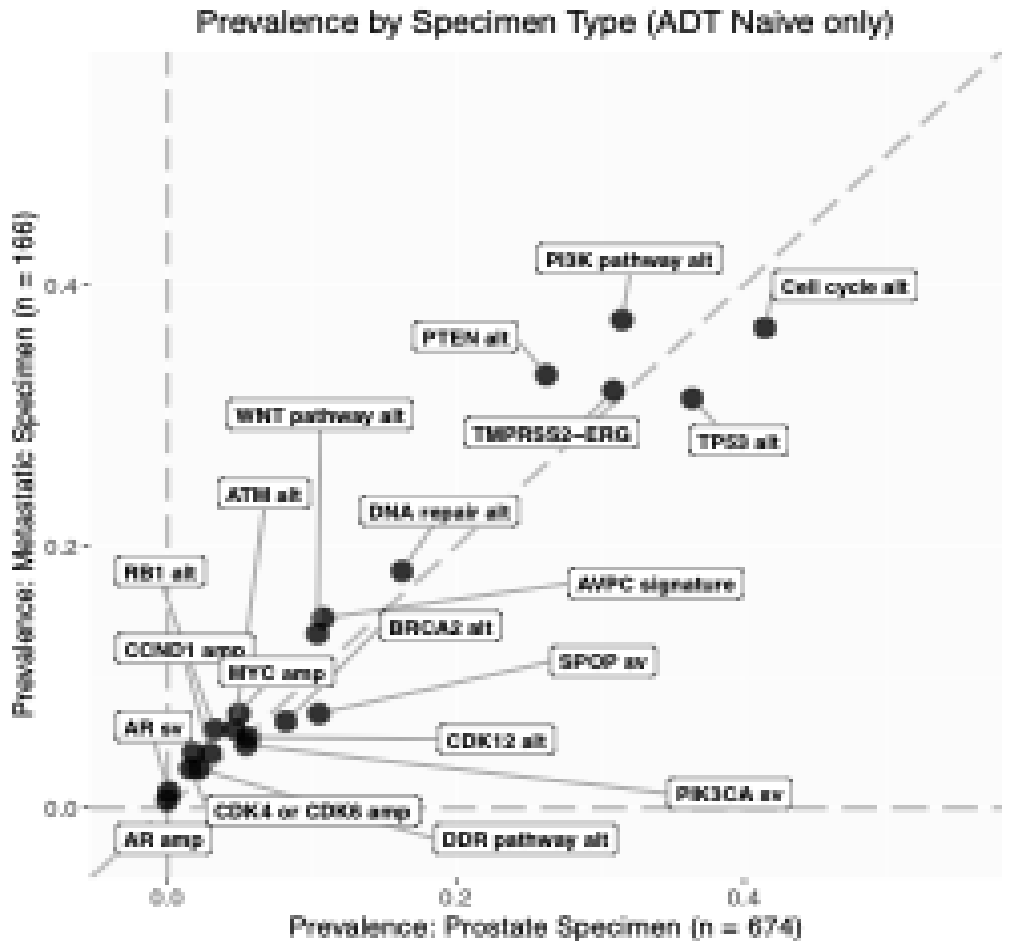
Genomics of HSPC vs CRPC





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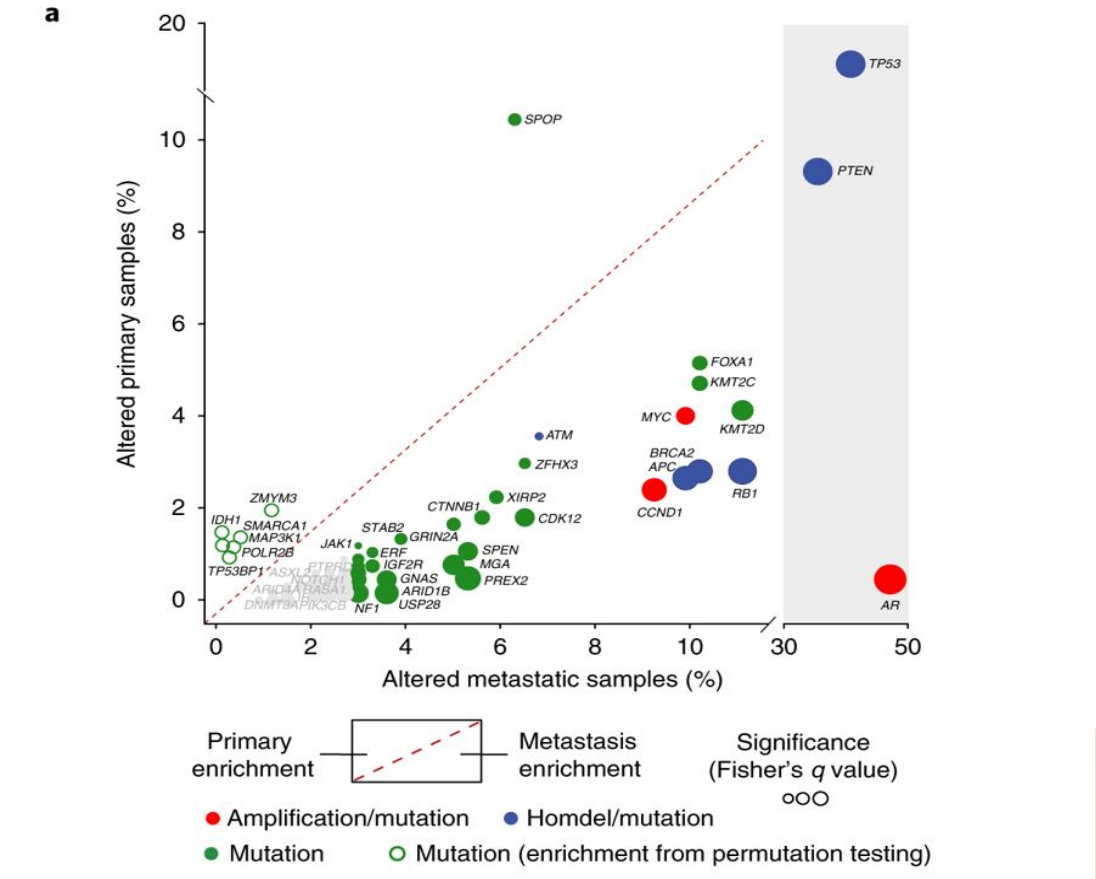
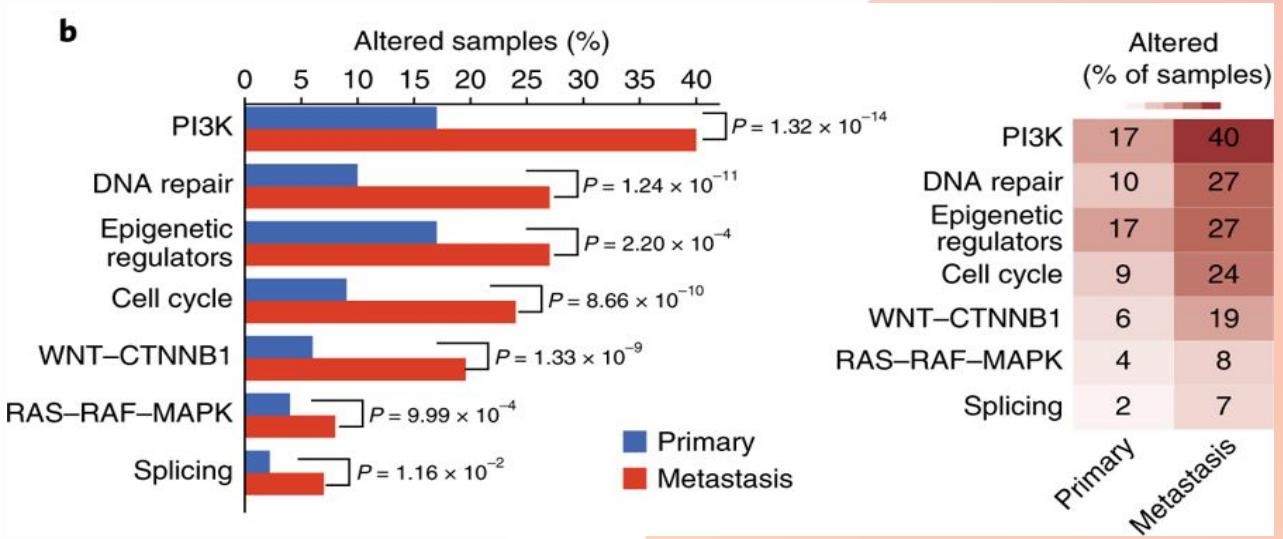
Zurita et al...Mateo, JCO PO 2022

Genomics of locoregional vs lethal prostate cancer





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Armenia et al, for the SU2C-PCF DT Nature Genetics 2018

But…

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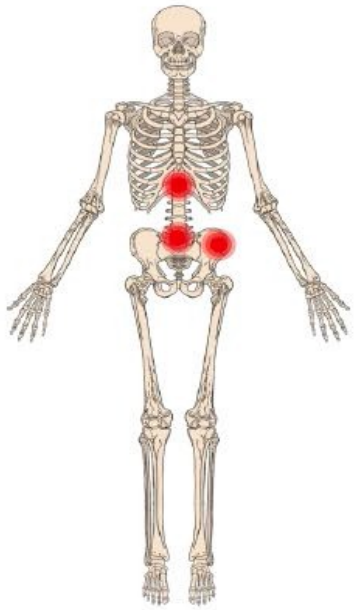
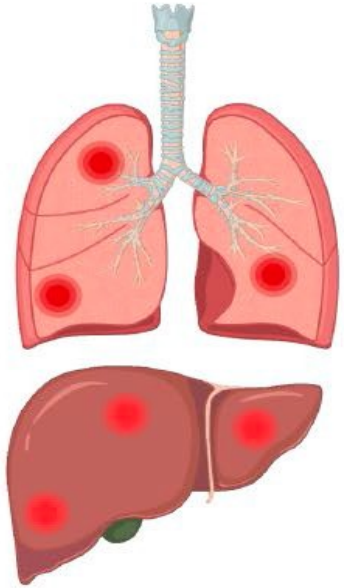
Prognostic classification criterio of High-Risk/Volume M1 HSPC

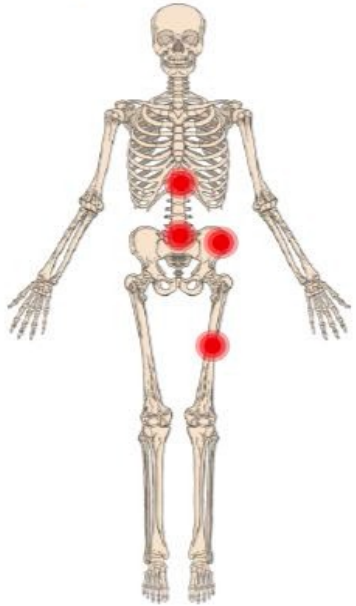
High-risk Disease According to LATITUDE Study (at least 2 of the following criteria)[a]

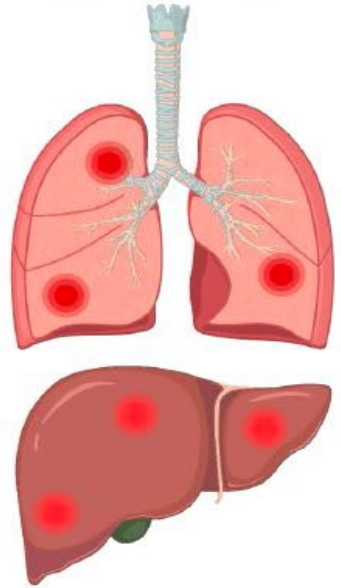




- ≥ 3 bone mets
- Visceral mets
- Gleason score ≥ 8

High-volume Disease According to CHAARTED Study (at least 1 of the following criteria)[b]





- **≥ 4 bone mets** (with ≥ 1 outside the pelvis/column)
- Visceral mets

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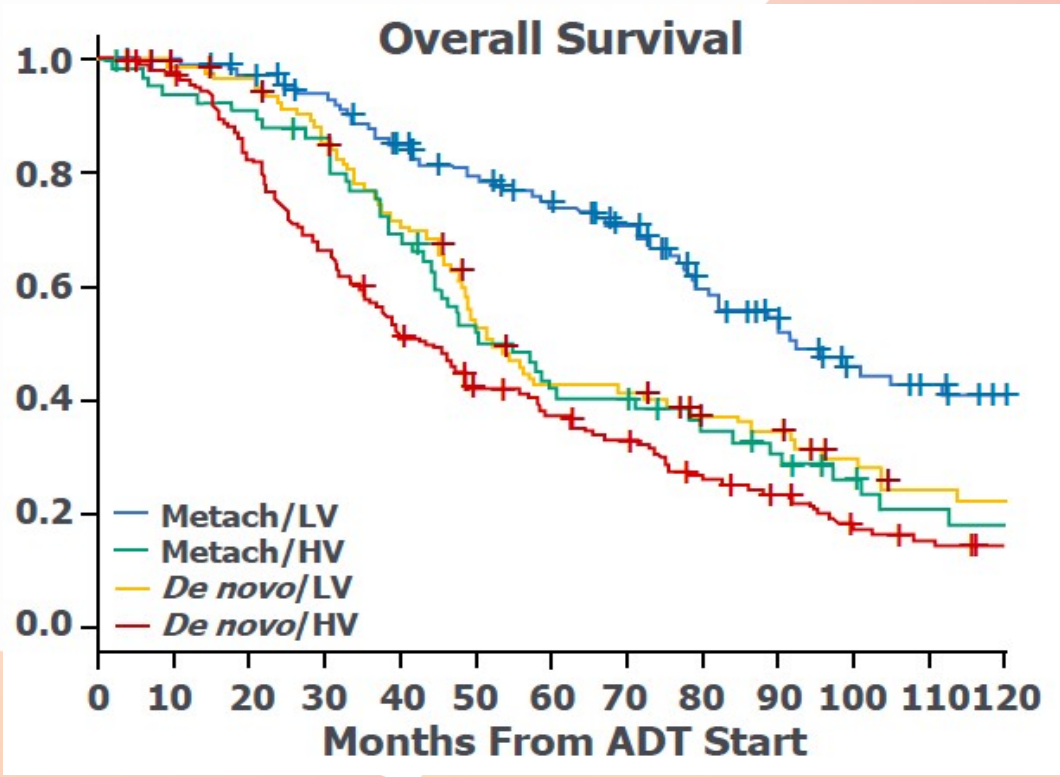
Fizazi K, et al. Lancet Oncol 2019; Sweeney CJ, et al. NEJM 2015

Prognosis according to volume and presentation at diagnosis

High-volumen de Novo metastatic diseases is associated with the poorest prognosis

Groups	N (% events)	mOS, years (95% CI)
Metach/ Low Vol	125 (50)	7.7 (6.7, 10.6)
Metach/ High Vol	67 (75)	4.6 (3.7, 6.7)
De novo/ Low Vol	96 (70)	4.3 (4.0, 6.5)
De novo/ High vol	148 (84)	3.6 (3.1, 4.7)



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Francini E, et al. Prostate 2018

Can genomics help us to select different patient groups for different treatments?

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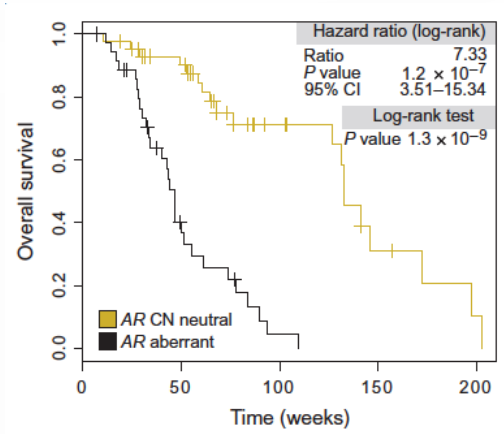
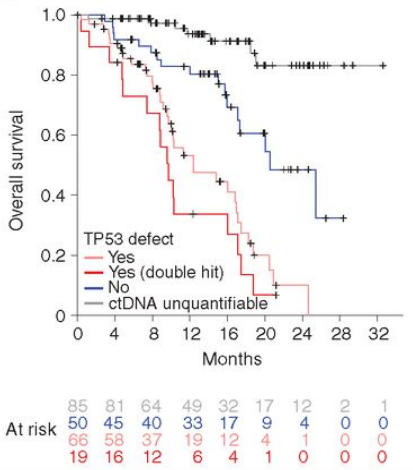
Some gonomic events are prognostic biomarkers

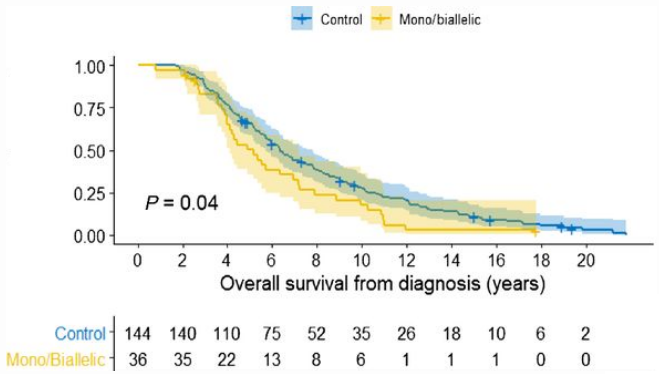
AR aberrations



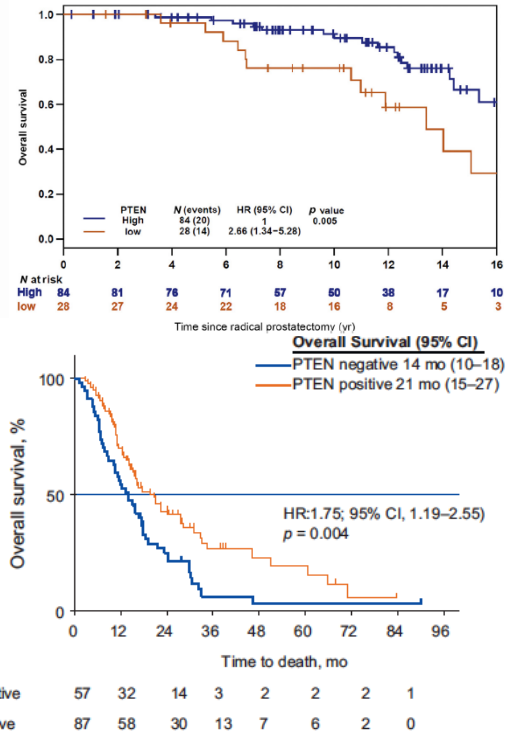
TP53 mutations



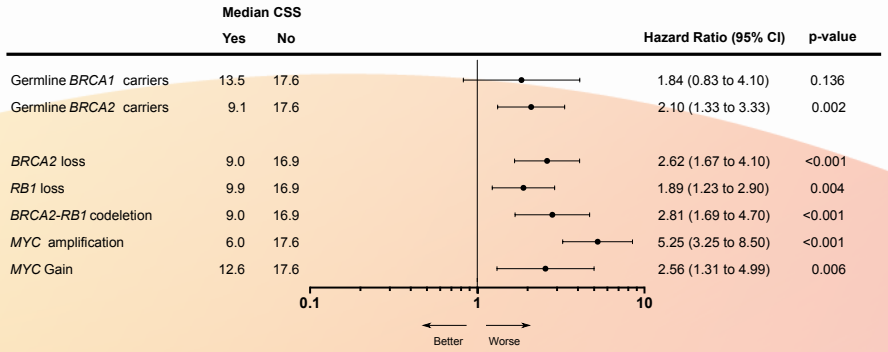
CDK12 mutations



PTEN loss



BRCA2 alterations, *RB1* loss, *MYC* amplification



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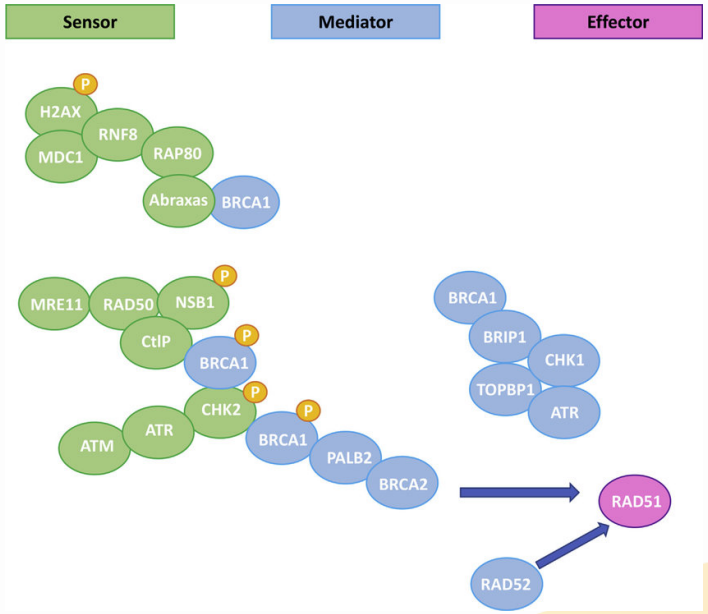
Romanel et al, Sci Trans Med, 2015; Ferraldeschi et al , Eur Urol, 2015; Hamid et al, Eur Urol, 2019; Rescigno et al, Clin Cancer Res, 2021; Lozano et al ESMO 2020

PARPi Monotherapy

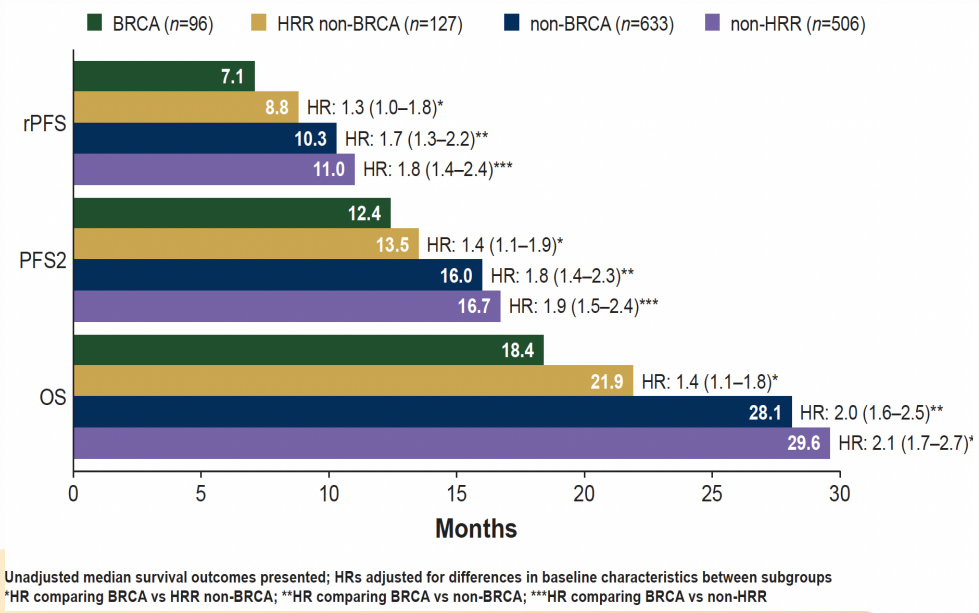
The HRR subgroup is heterogeneous

Different FUNCTIONS



Pellegrino et al, Translational Oncology, 2020

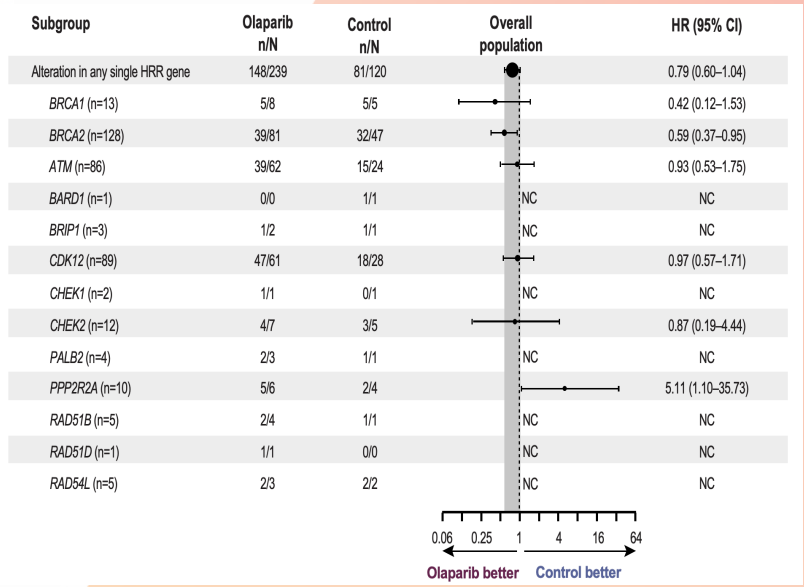
PROGNOSTIC implications



Unadjusted median survival outcomes presented; HRs adjusted for differences in baseline characteristics between subgroups
*HR comparing BRCA vs HRR non-BRCA; **HR comparing BRCA vs non-BRCA; ***HR comparing BRCA vs non-HRR

Olmos et al, Ann Oncol, 2024

SENSITIVITY to PARPi

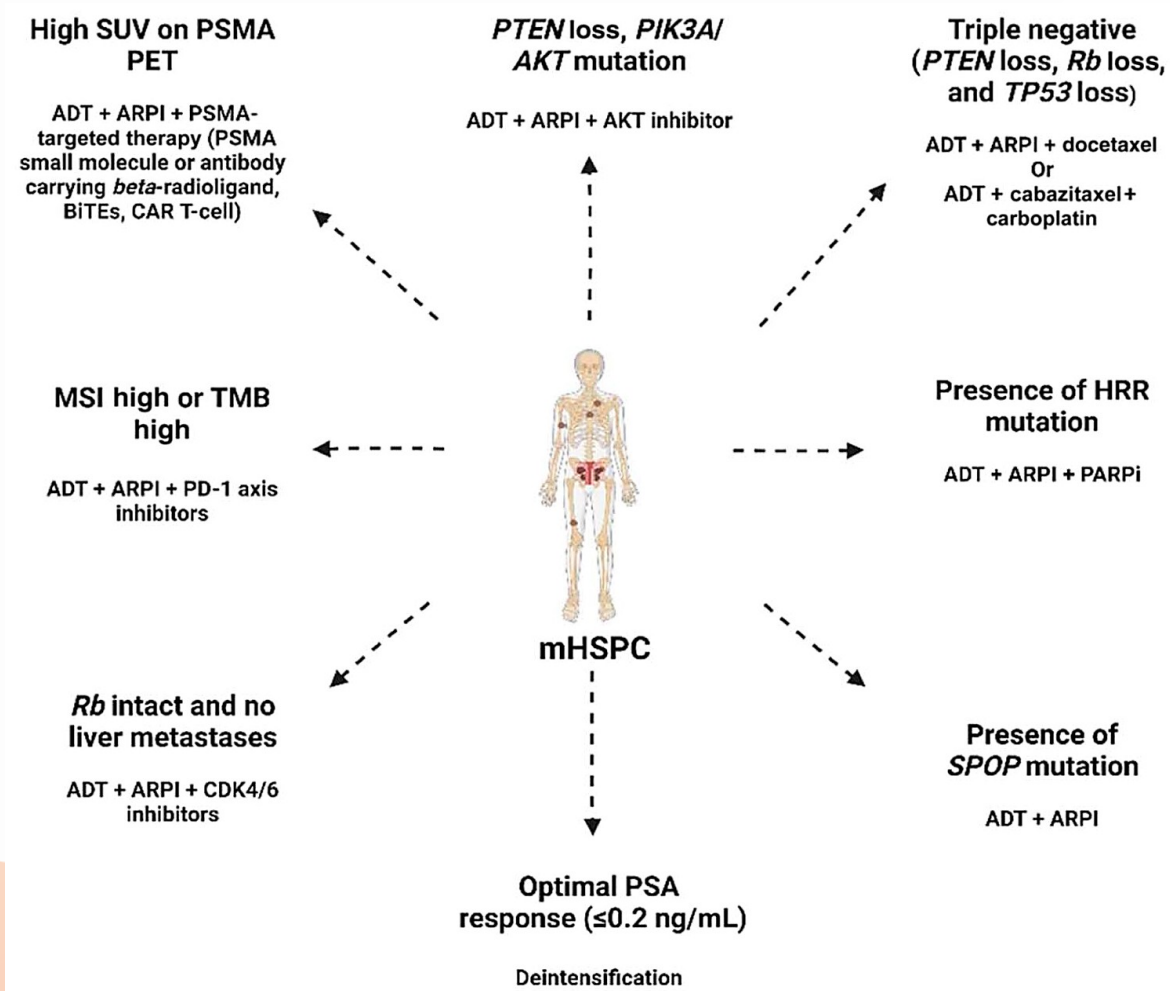


Subgroup	Olaparib n/N	Control n/N	HR (95% CI)
Alteration in any single HRR gene	148/239	81/120	0.79 (0.60–1.04)
BRCA1 (n=13)	5/8	5/5	0.42 (0.12–1.53)
BRCA2 (n=128)	39/81	32/47	0.59 (0.37–0.95)
ATM (n=86)	39/62	15/24	0.93 (0.53–1.75)
BARD1 (n=1)	0/0	1/1	NC
BRIP1 (n=3)	1/2	1/1	NC
CDK12 (n=89)	47/61	18/28	0.97 (0.57–1.71)
CHEK1 (n=2)	1/1	0/1	NC
CHEK2 (n=12)	4/7	3/5	0.87 (0.19–4.44)
PALB2 (n=4)	2/3	1/1	NC
PPP2R2A (n=10)	5/6	2/4	5.11 (1.10–35.73)
RAD51B (n=5)	2/4	1/1	NC
RAD51D (n=1)	1/1	0/0	NC
RAD54L (n=5)	2/3	2/2	NC

Hussain et al, NEJM, 2020

DRIVING THE FUTURE of

PRECISION MEDICINE



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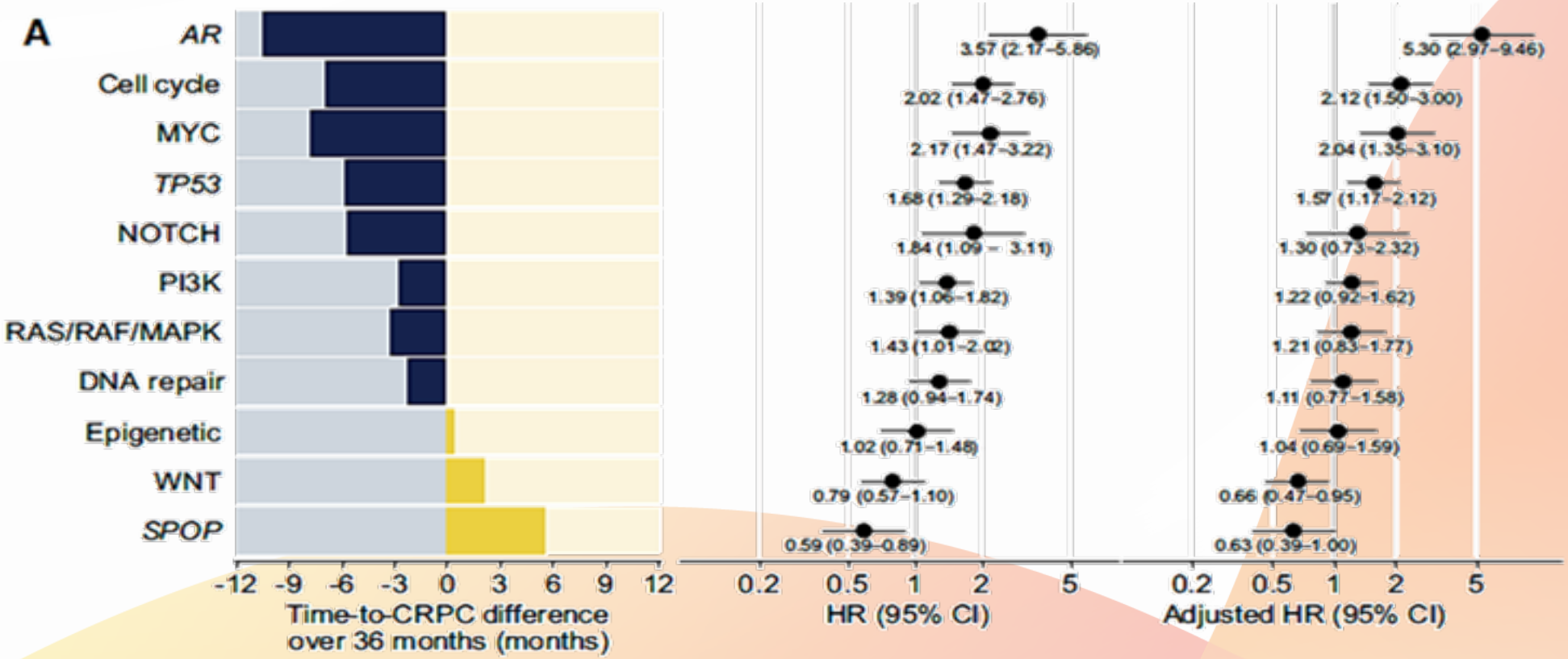
Hamid AA, et al . ASCO educational book 2023

Oncogenic genomic alterarions, clinical phenotypes and outcomes in mHSPC



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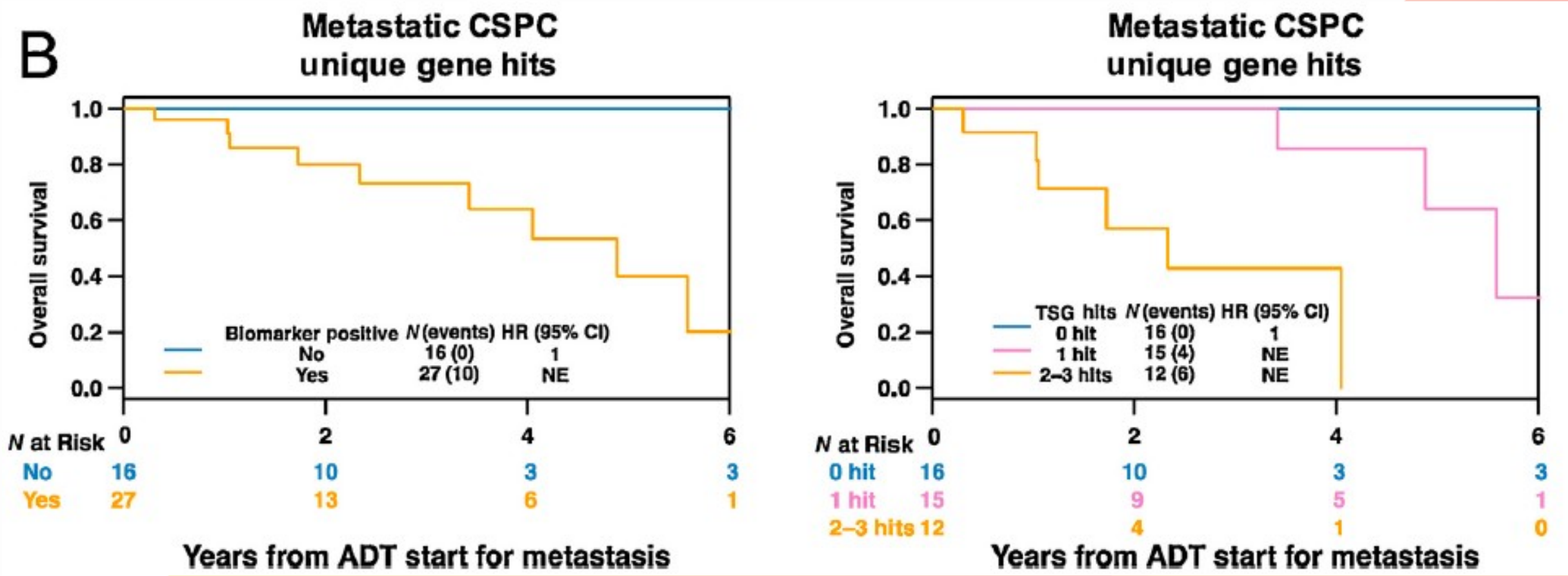
Stopsack KH, et al. Clin Cancer Res 2020

Men with prostate tumours with compound tumour suppressor gene (TP53, PTEN and RB1) mutations have poorer outcomes



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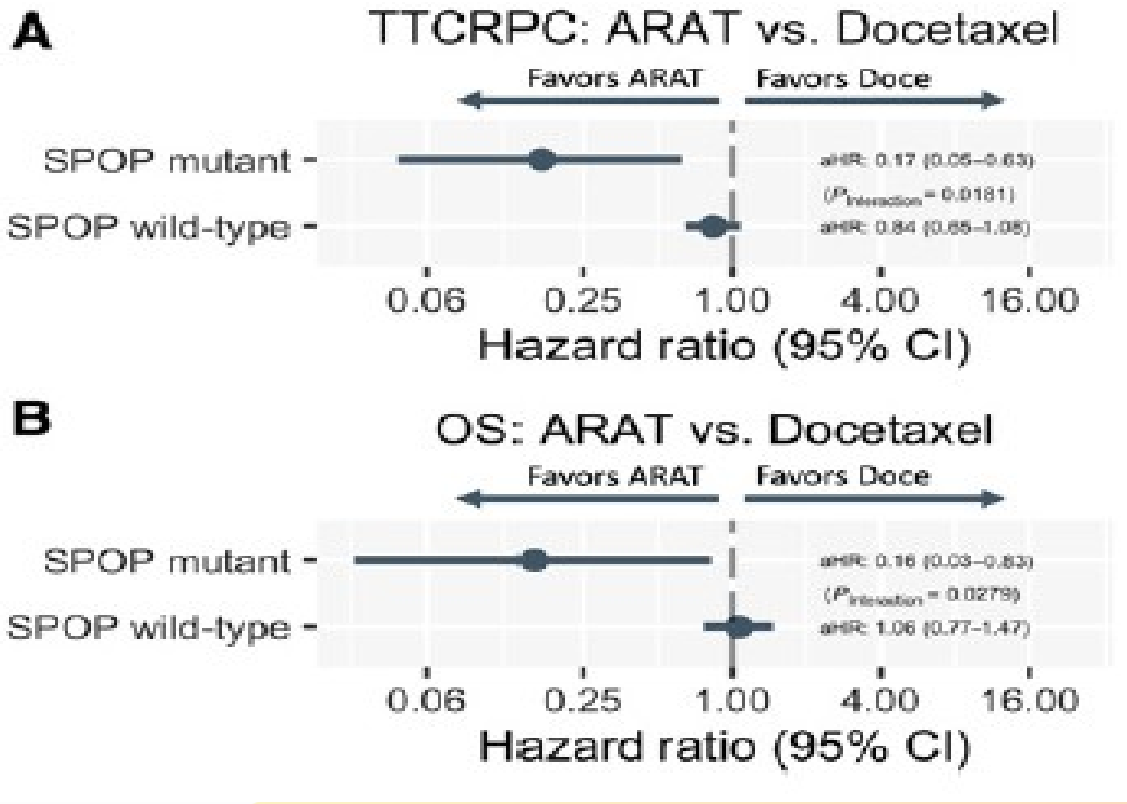
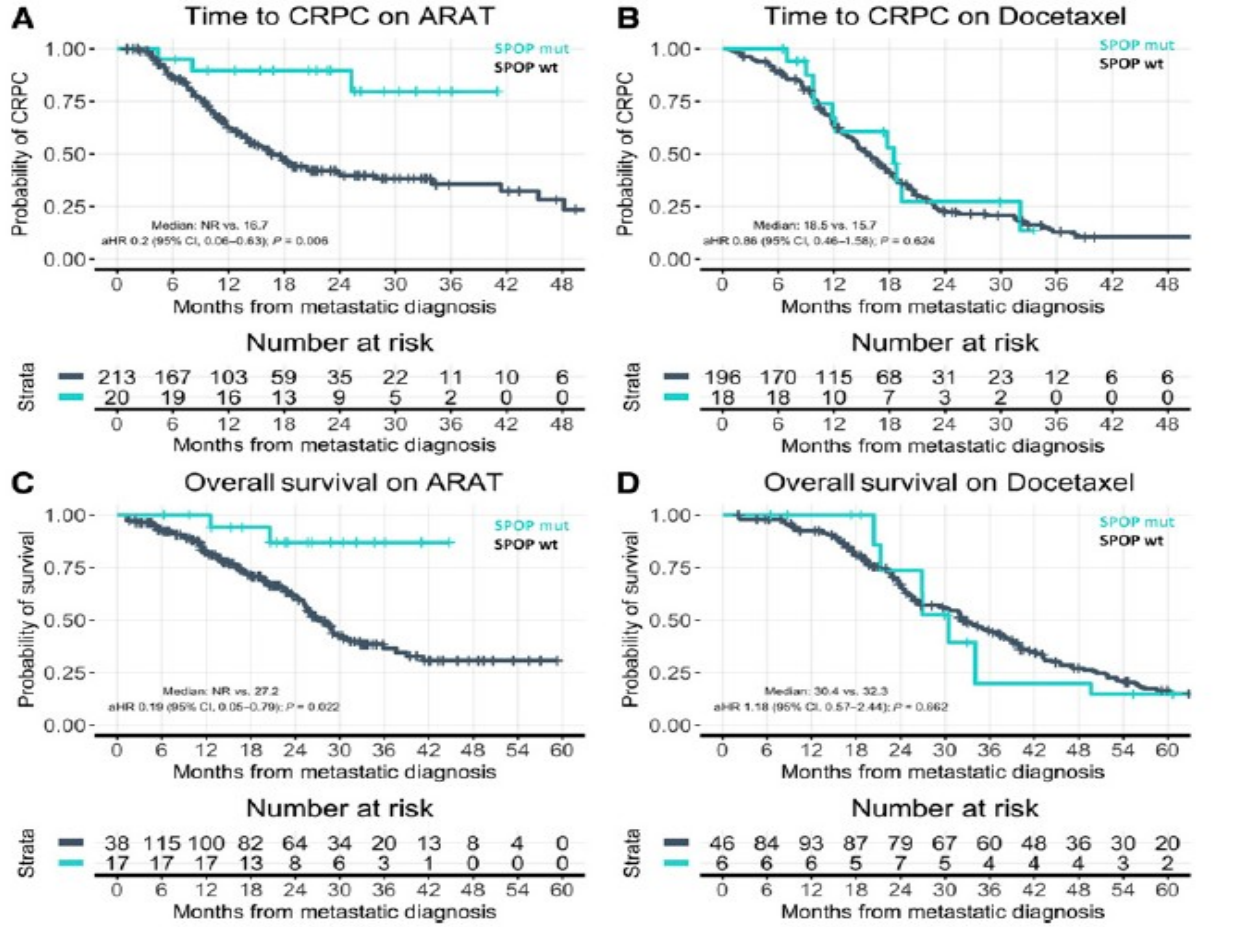
Hamid A, et al. Eur Urol 2019

The association of SPOP mutation with outomes in men with de novo mHSPC





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Swami U, et al. Clin Cancer Res 2022

2025 ASCO ANNUAL MEETING

Transcriptome classification of PTEN inactivation to predict survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for metastatic prostate cancer (PC): an ancillary study of the STAMPEDE trials

Emily Grist*, Peter Dutey-Magni*, Marina A. Parry, Larissa Mendes, Ashwin Sachdeva, James A. Proudfoot, Anis A. Hamid, Mazlina Ismail, Lia DePaula, Oliveira Oluwademilade Dairo, Sharanpreet Lall, Claire L. Amos, Mahesh K.B. Parmar, Elai Davicioni, Tamara L. Lotan, Christopher J. Sweeney, Louise C. Brown, Noel W. Clarke, Nicholas D. James, Gerhardt Attard

Presented by: Dr. Emily Grist

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MERIT AWARD

Eisai Inc. Endowed Merit Award

Supported by Eisai Inc.

ClinicalTrials.gov number, NCT00268476 & Current Controlled Trials number, ISRCTN78818544
Trial conducted by Medical Research Council Trials Unit at University College London, U.K.

105 UK trial sites participated in this study

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STAMPEDE docetaxel and abiraterone phase 3 trials

Metastatic prostate cancer
≥ 1 metastases on bone / CT scan

High-risk localised (adjuvant)
Lymph node positive OR
≥ 2 high risk features:
T3/T4, PSA ≥40ng/ml, Gleason sum 8-10

3909 directly-randomised patients

- ADT versus ADT+ docetaxel+/-zoledronic acid
- ADT versus ADT+ abiraterone

Aim: To link tumour multi-gene expression signatures to 14-year prospective follow-up for overall survival to identify prognostic and predictive biomarkers

95% synchronous M1

STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (MRC-PR08, NCT00268476) www.stampedetrial.org
STRATOSPHERE (STratification for RAtional Treatment-Oncomarker Pairings of STAMPEDE patients starting long-term Hormone treatment) protocol overseen by the STAMPEDE trial management groups and biological research group

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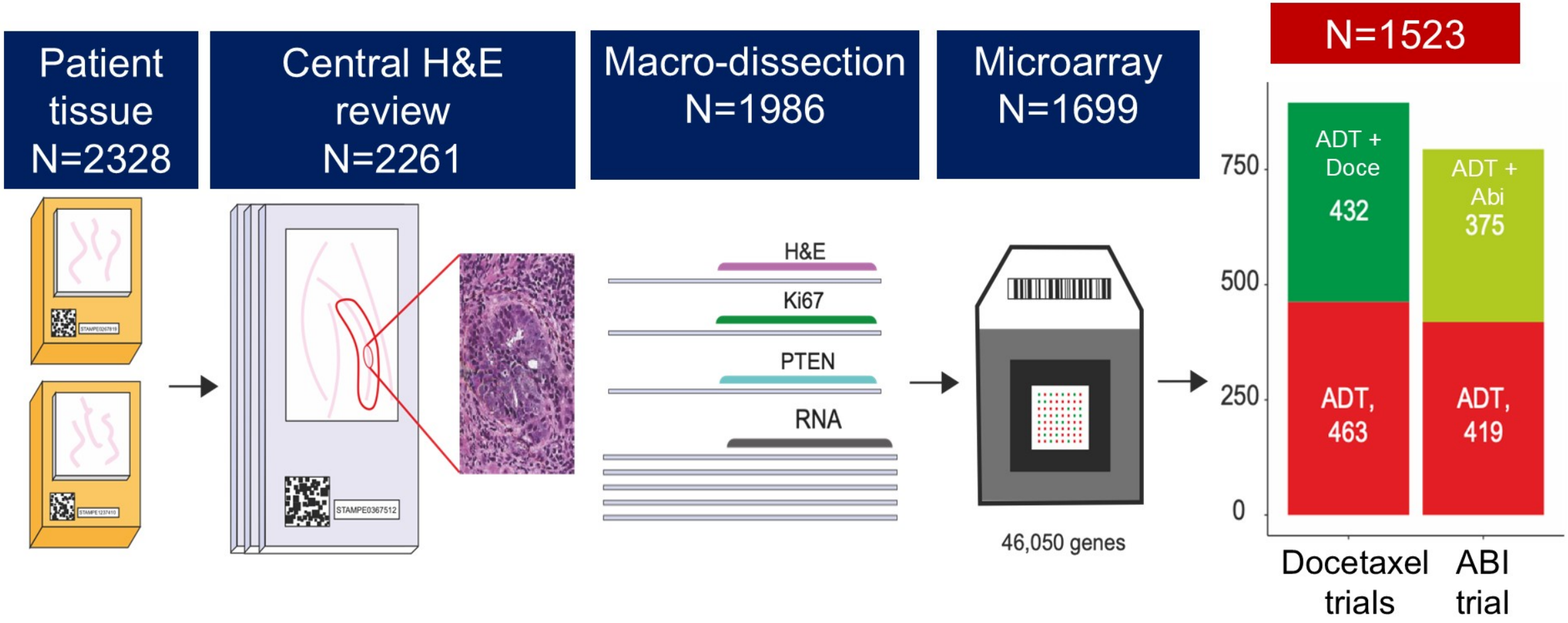
Linking of clinical and multi-omic data



Affymetrix Human Exon 1.0 ST microarray.1.4 million genome-wide features

*166 overlapping controls

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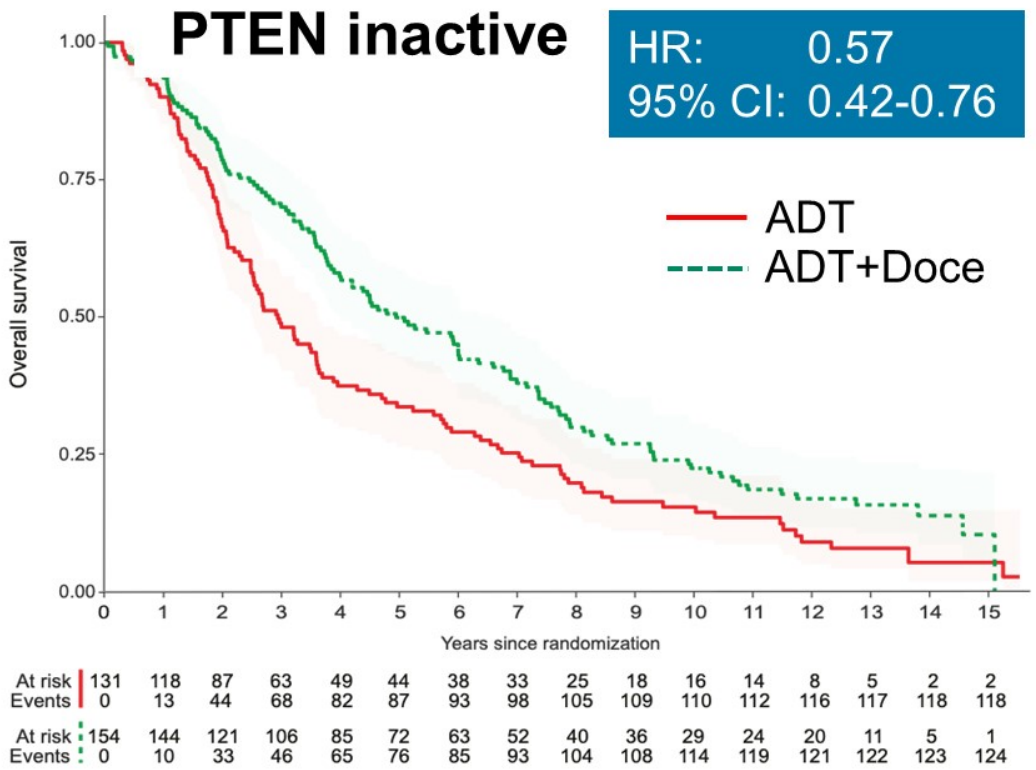
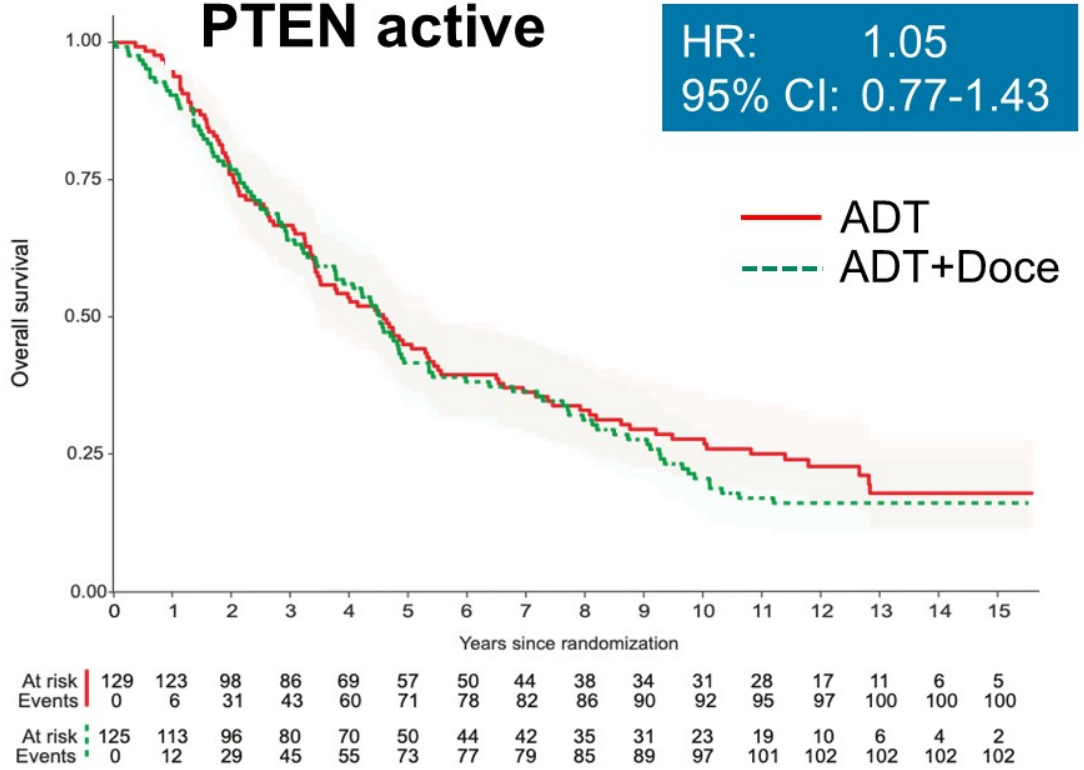
PTEN inactivation predicts docetaxel sensitivity





Tumour PTEN inactivity identifies metastatic patients most likely to benefit from docetaxel
Biomarker-treatment interaction effect p value= 0.002*

Treatment effect uniform in abiraterone comparison trial (adjusted HR):
PTEN inactive HR 0.52, 95% CI 0.36-0.73; PTEN active HR 0.55, 95% CI 0.39-0.77; p=0.784
Direction of treatment effect is the same in CHAARTED biomarker cohort (adjusted HR):
PTEN inactive HR 0.52, 95% CI 0.31-0.87; PTEN active cancers HR 0.62, 95% CI 0.30-1.30

Kaplan-Meier estimates with 95% CI in lighter shade. HR and interaction test from multivariable model adjusted for Gleason score, disease burden, age, pre-ADT PSA, WHO PS, nodal stage, tumour stage, NSAID/aspirin use, and metastatic volume
PTEN score dichotomised around 0.3 based on bimodal distribution

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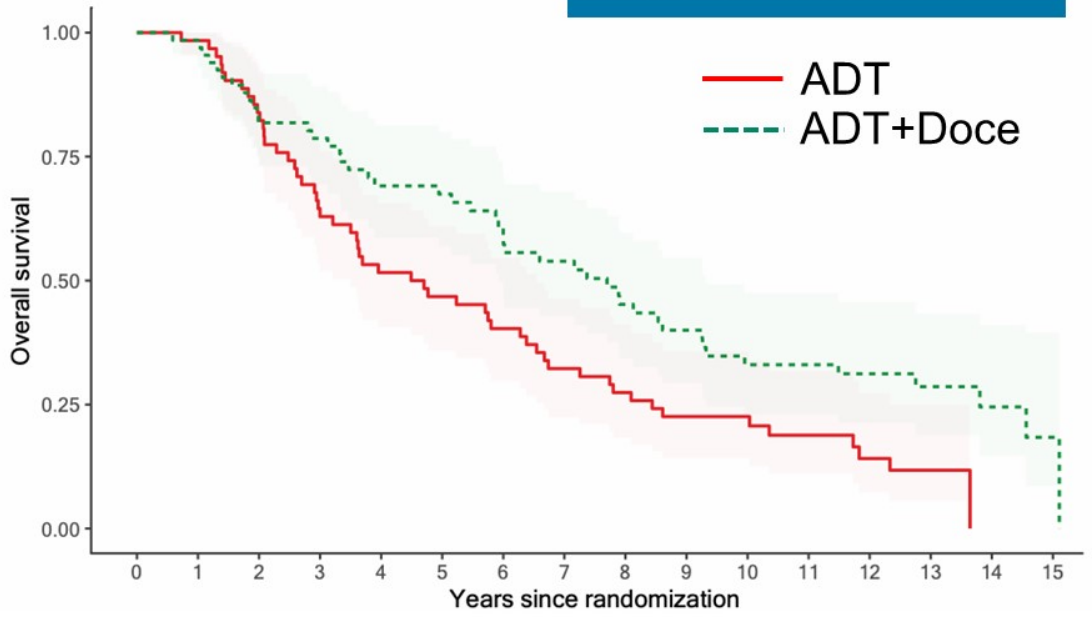
Direction of treatment effect consistent in low volume

PTEN inactive

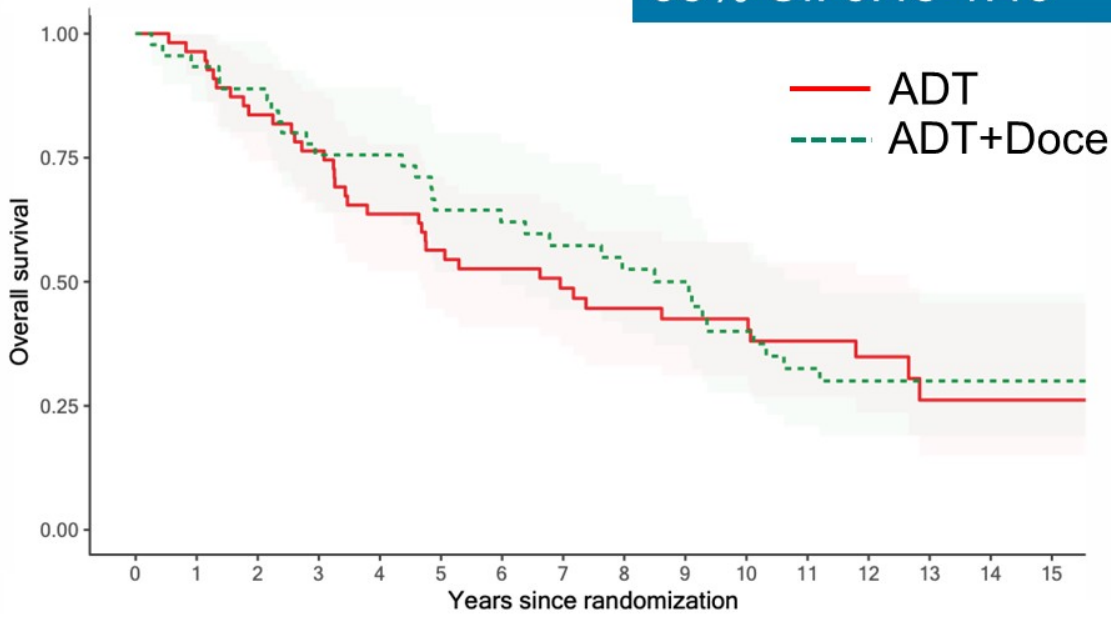
HR: 0.53
95% CI: 0.33-0.86



At risk	62	61	52	39	32	29	25	20	17	13	12	10	6	3	0	0
Events	0	1	10	23	30	33	37	42	45	48	48	50	52	53	54	54
At risk	66	64	54	50	42	40	35	31	26	23	19	19	17	8	5	1
Events	0	2	12	14	20	21	26	29	34	37	41	41	42	43	44	45

PTEN active

HR: 0.82
95% CI: 0.48-1.40



At risk	55	53	46	42	35	30	28	24	21	20	19	17	10	6	3	2
Events	0	2	9	13	20	24	26	28	30	31	31	33	34	36	36	36
At risk	45	42	40	34	34	28	26	24	21	20	16	13	6	4	2	2
Events	0	3	5	11	11	16	17	19	21	22	26	29	30	30	30	30

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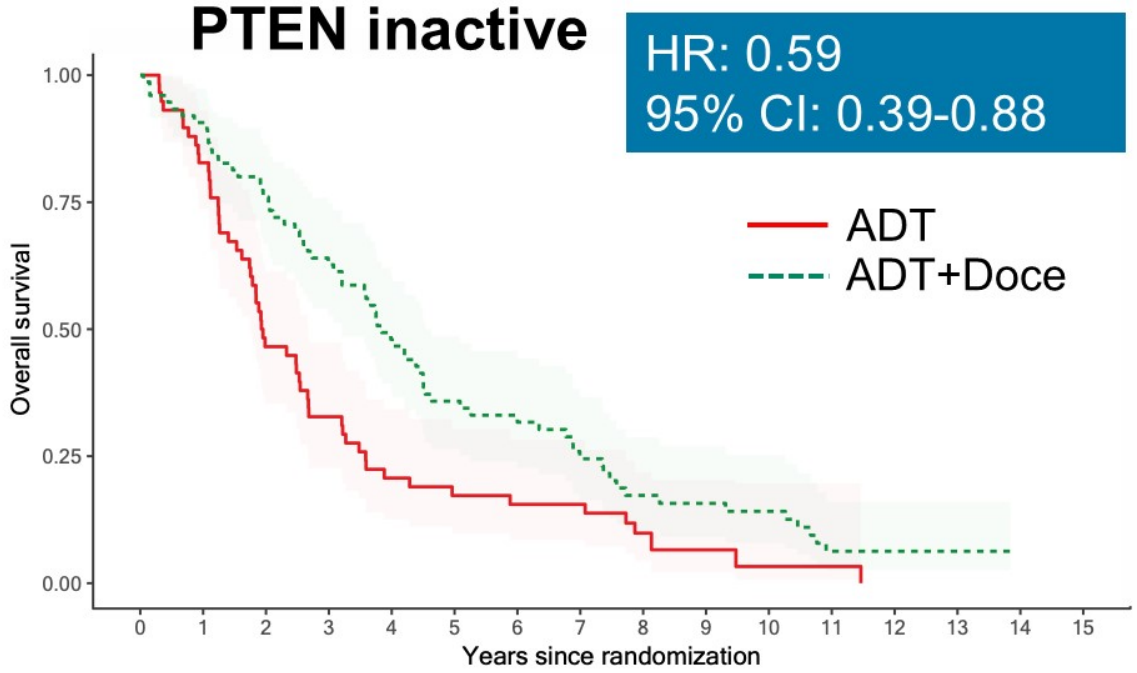
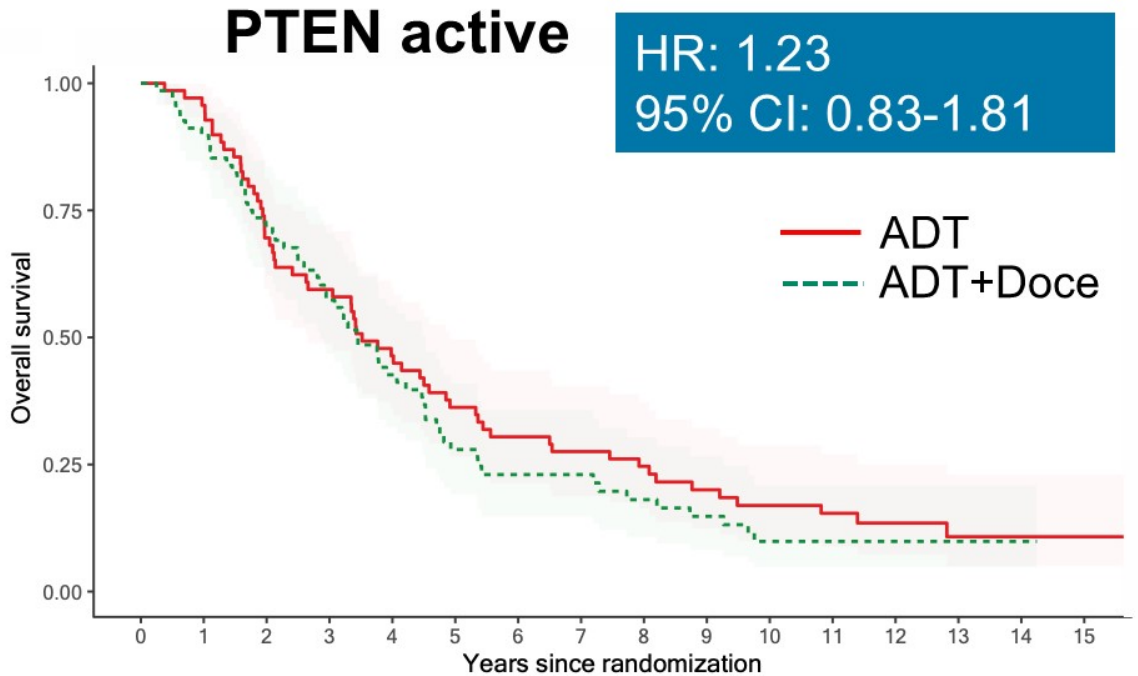
Direction of treatment effect consistent in high volume



At risk	58	48	27	19	12	10	9	9	5	2	1	1	0	0	0	0
Events	0	10	31	39	46	48	49	49	52	53	54	54	55	55	55	55
At risk	75	68	57	47	36	26	23	17	11	10	9	4	3	3	0	0
Events	0	7	18	28	39	48	51	56	61	62	63	68	68	68	68	68



At risk	69	66	48	41	32	25	21	19	16	13	11	10	6	4	2	2
Events	0	3	21	28	37	44	48	50	52	55	57	58	59	60	60	60
At risk	68	61	49	39	29	18	14	14	11	9	6	6	4	2	2	0
Events	0	7	19	29	39	49	52	52	55	57	60	60	60	60	60	60

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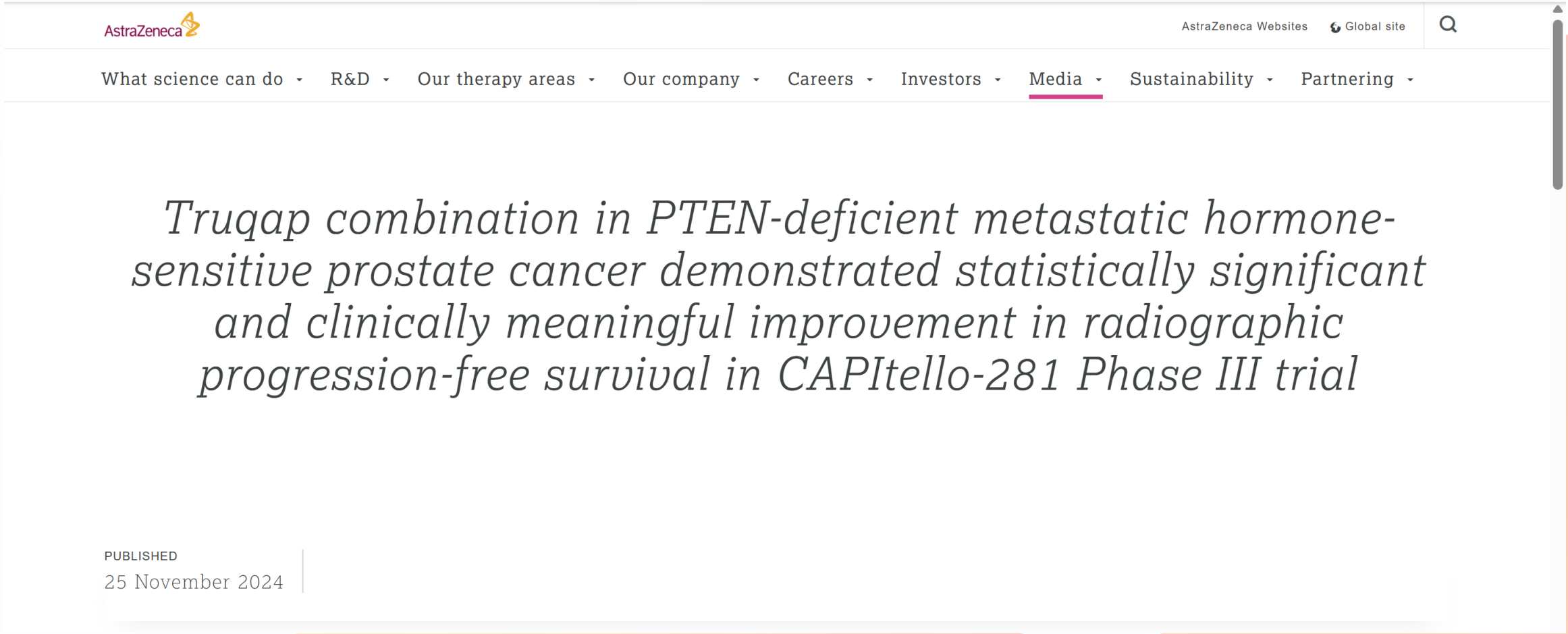
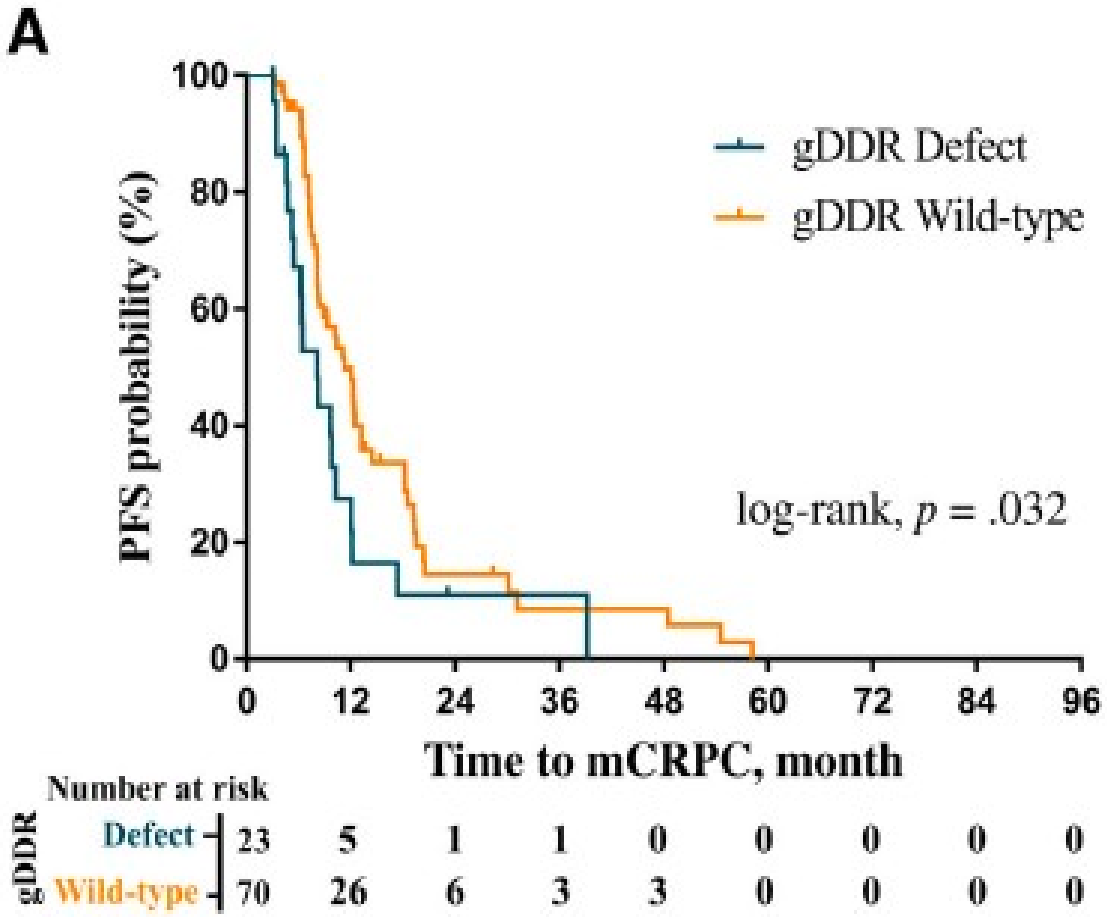
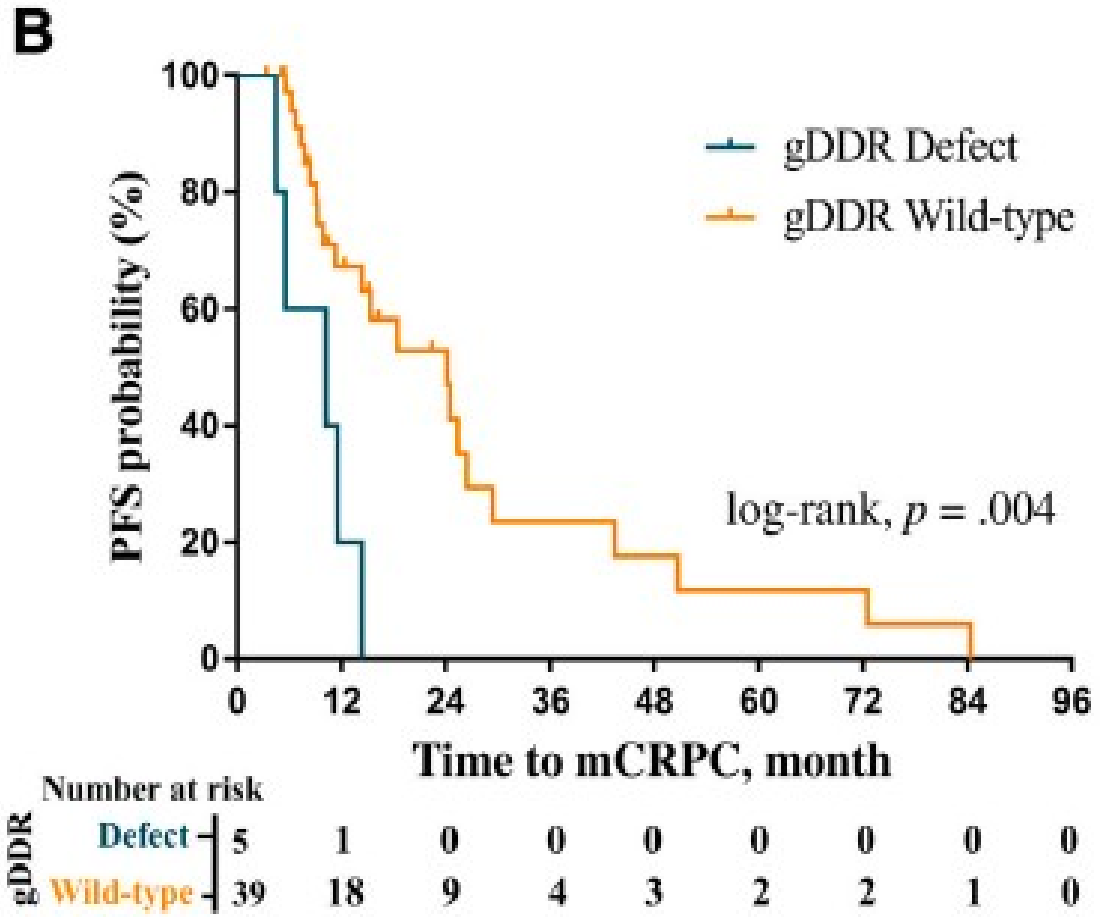

AstraZeneca
AstraZeneca Websites
Global site
What science can do
R&D
Our therapy areas
Our company
Careers
Investors
Media
Sustainability
Partnering
Truqap combination in PTEN-deficient metastatic hormone-sensitive prostate cancer demonstrated statistically significant and clinically meaningful improvement in radiographic progression-free survival in CAPItello-281 Phase III trial
PUBLISHED
25 November 2024

Prognostic value of Germline DNA repair gene mutations in de novo metastatic and castration-sensitive prostate cancer





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Fizazi et al. N Engl J Med 2023; 388:719-732 DOI: 10.1056/NEJMoa2214676

Study design and population

Key Inclusion Criteria.

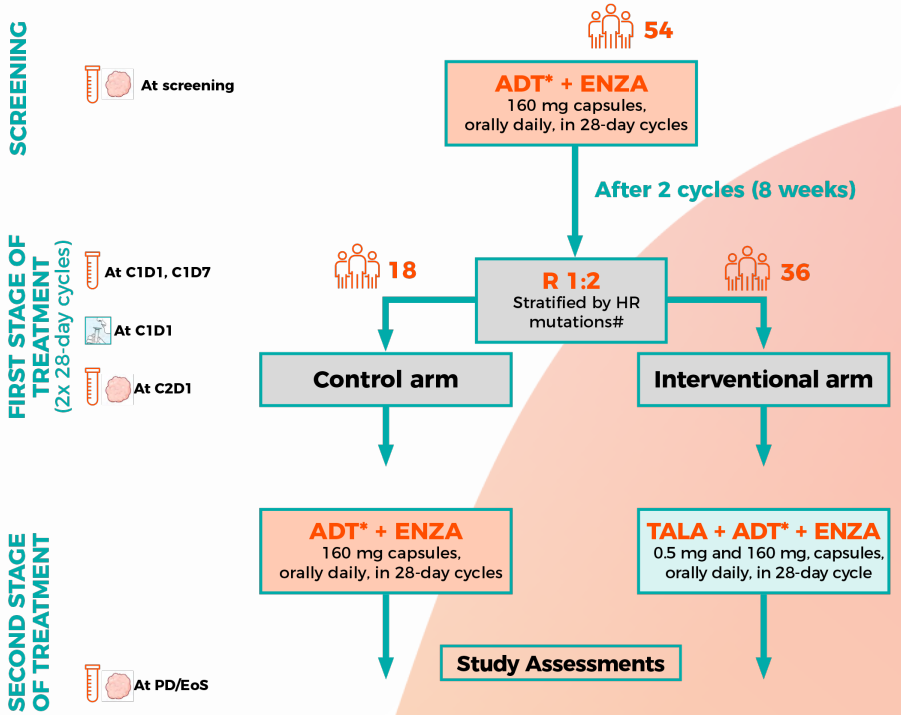
- Male ≥18 years.
- Histologically confirmed adenocarcinoma of the prostate without predominance of small-cell or neuroendocrine features (ASCO/CAP guidelines).
- High-volume metastatic disease documented on bone scan or CT/MRI scan.
- Life expectancy ≥ 12 months.
- Prior (neo)adjuvant ADT-based regimen is allowed if PD occurred while on non-castrate testosterone levels > 12 months after discontinuation.
- No prior treatment with enzalutamide, apalu-tamide, darolutamide or abiraterone acetate.
- PSA ≥ 4 ng/mL at diagnosis or before starting ADT therapy.
- No prior systemic therapy for metastatic prostate cancer.

PRIMARY ENDPOINT

· PSA-complete response (PSA-CR) (PSA<0.2 ng/mL) after 12 months of therapy in pts with mHNPC in the androgen deprivation therapy (ADT) + enzalutamide (ENZA) + talazoparib (TALA) arm.
H0: 20%; H1 ≥40%.

SECONDARY ENPOINTS

- PSA-CR rate at any time point and at month 7 and 12.
- PSA progression-free survival (PSA-PFS)
- Radiologic PFS (rPFS) as per RECIST v.1.1/PCWG3
- Overall survival (OS)
- Safety and tolerability (CTCAE v.5.0).



- Tumor imaging was performed at screening, every 8 weeks for the first 6 months and every 12 weeks thereafter.
- Serum prostate-specific antigen (PSA) was assessed at screening, C1D1, and every 4 weeks during first 13 cycles, and every 8 weeks thereafter
- Whole-body diffusion-weighted magnetic resonance imaging (MRI) was performed in a subset of pts at baseline and during treatment to explore biomarkers of response and resistance in bone metastases.

* Pts to continue treatment with ADT throughout the study (except for surgical orchiectomy).
#Randomization will be stratified based on HR gene alterations detected in the baseline biopsy (presence versus absence/unknown).

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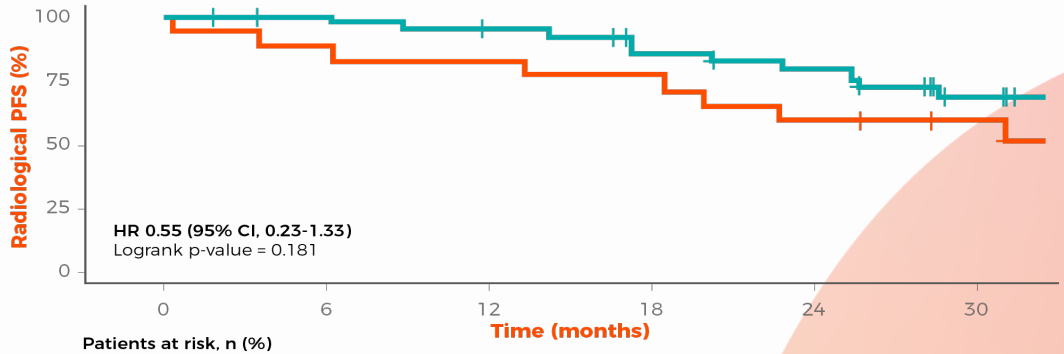
Primary endpoint

C13D1 PSA-CR in ENZA+TALA arm was 73% (95% CI, 55.9%-86.2%, p<0.001),

C13D1 PSA-CR in ENZA arm was 64.7%

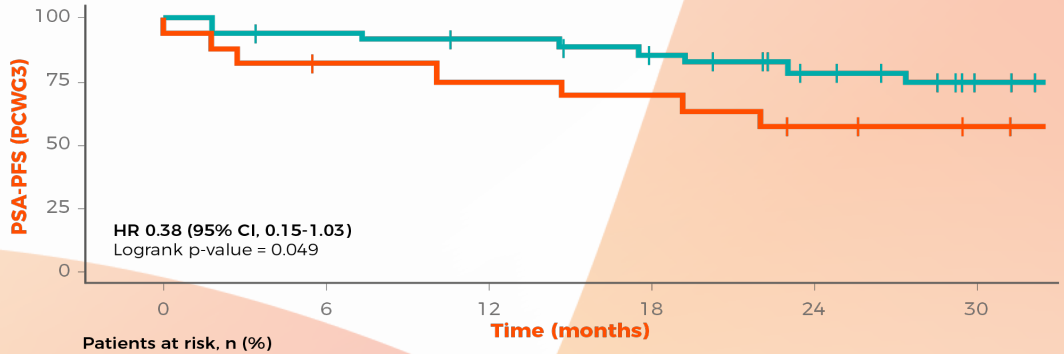
Key secondary endpoints

Figure 2. Radiologic PFS according to RECIST v.1.1.



Patients at risk, n (%)						
Control	17 (100)	15 (88)	14 (82)	13 (76)	10 (59)	8 (47)
Interventional	37 (100)	35 (95)	32 (86)	27 (73)	24 (65)	16 (43)

Figure 3. PSA-PFS according to PCWG3 criteria.



Patients at risk, n (%)						
Control	17 (100)	13 (76)	12 (71)	11 (65)	8 (47)	6 (35)
Interventional	37 (100)	34 (92)	32 (86)	28 (76)	22 (59)	15 (41)

2025 ASCO ANNUAL MEETING

Phase 3 AMPLITUDE trial: Niraparib and abiraterone acetate plus prednisone for metastatic castration-sensitive prostate cancer patients with alterations in homologous recombination repair genes

Gerhardt Attard[1], Neeraj Agarwal[2], Julie N Graff[3,4], Shahneen Sandhu[5], Eleni Efstathiou[6], Mustafa Özgüroğlu[7], Andrea J Pereira de Santana Gomes[8], Karina Vianna[9], Hong Luo[10], Heather H Cheng[11,12], Won Kim[13], Carly R Varela[14], Daneen Schaeffer[14], Shiva Dibaj[15], Susan Li[14], Fei Shen[14], Suneel D Mundle[16], David Olmos[17], Kim N Chi[18], Dana E Rathkopf[19], on behalf of the AMPLITUDE investigators

[1]Cancer Institute, University College London, London, UK; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [3]Oregon Health & Science University and Knight Cancer Institute, Portland, OR, USA; [4]Veterans Affairs Portland Health Care System, Portland, OR, USA; [5]Peter MacCallum Cancer Centre, Melbourne, Australia; [6]Houston Methodist Cancer Center, Houston, TX, USA; [7]Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Istanbul, Türkiye; [8]Liga Norte Riograndense Contra o Cancer, Natal, Brazil; [9]Centro Integrado de Oncologia de Curitiba, Curitiba, Brazil; [10]Chongqing University Cancer Hospital, Chongqing, China; [11]University of Washington, Seattle, WA, USA; [12]Fred Hutchinson Cancer Center, Seattle, WA, USA; [13]Johnson & Johnson, Los Angeles, CA, USA; [14]Johnson & Johnson, Spring House, PA, USA; [15]Johnson & Johnson, San Diego, CA, USA; [16]Johnson & Johnson, Raritan, NJ, USA; [17]i+12 Biomedical Research Institute, Hospital Universitario 12 de Octubre, Madrid, Spain; [18]BC Cancer – Vancouver Center, University of British Columbia, Vancouver, BC, Canada; [19]Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY, USA

1

AMPLITUDE: Randomized, Double-Blind, Placebo-Controlled Trial in HRRm mCSPC

First and final rPFS analysis and first interim analysis of time to symptomatic progression and overall survival. Median follow-up: 30.8 months

Key inclusion criteria:
- mCSPC[a]
- Alteration in ≥1 HRR eligible gene: *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *PALB2*, *RAD51B*, *RAD54L*[b]
- ECOG PS 0-2

Key exclusion criteria:
- Any prior
  - PARPi
  - ARPI other than AAP

Prior allowed treatments in mCSPC:
- ADT ≤6 months
- Docetaxel ≤6 cycles[c]
- AAP ≤45 days
- Palliative RT

Randomized 1:1 (N=696)

- **Nira** (200 mg QD) + **AAP** (1000 mg QD + 5 mg QD) + **ADT** (n=348)
- **PBO** + **AAP** (1000 mg QD + 5 mg QD) + **ADT** (n=348)

Stratification factors:
- *BRCA2* vs *CDK12* vs all other alterations
- Prior docetaxel (yes vs no)
- Disease volume (high vs low)

Primary end point
- rPFS by investigator review

Key secondary end points
- Time to symptomatic progression
- OS
- Safety

Clinical data cutoff: January 7, 2025

[a]Patients with lymph node–only disease are not eligible. [b]HRR gene panel was fixed prior to trial initiation based on MAGNITUDE trial and external data from the published literature. [c]Last dose ≤3 months prior to randomization.
ECOG PS, Eastern Cooperative Oncology Group performance status; Nira, niraparib; OS, overall survival; PBO, placebo; RT, radiotherapy; QD, once daily.

4

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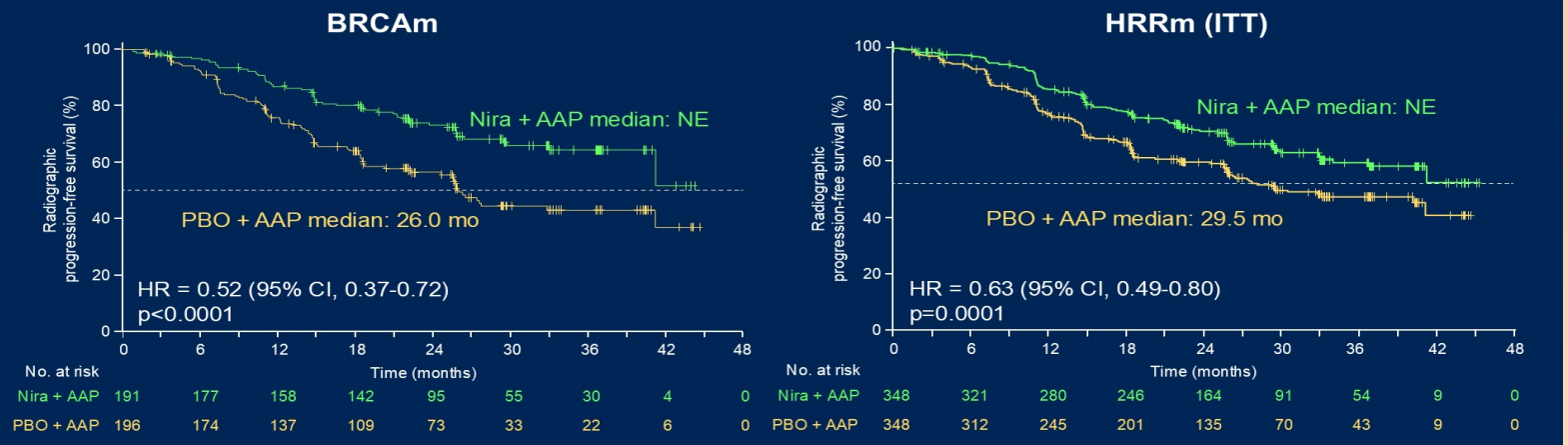
Primary End Point: Radiographic Progression-Free Survival



AMPLITUDE met the primary end point: Nira + AAP significantly reduced the risk of radiographic progression[a] or death by 48% in BRCAm group and by 37% in HRRm population

9

[a]rPFS by investigator review; rPFS improvement by blinded independent central review was as large: HR = 0.51 (95% CI, 0.37-0.72) for BRCAm group and 0.61 (95% CI, 0.47-0.79) for HRRm group.
NE, not estimable.

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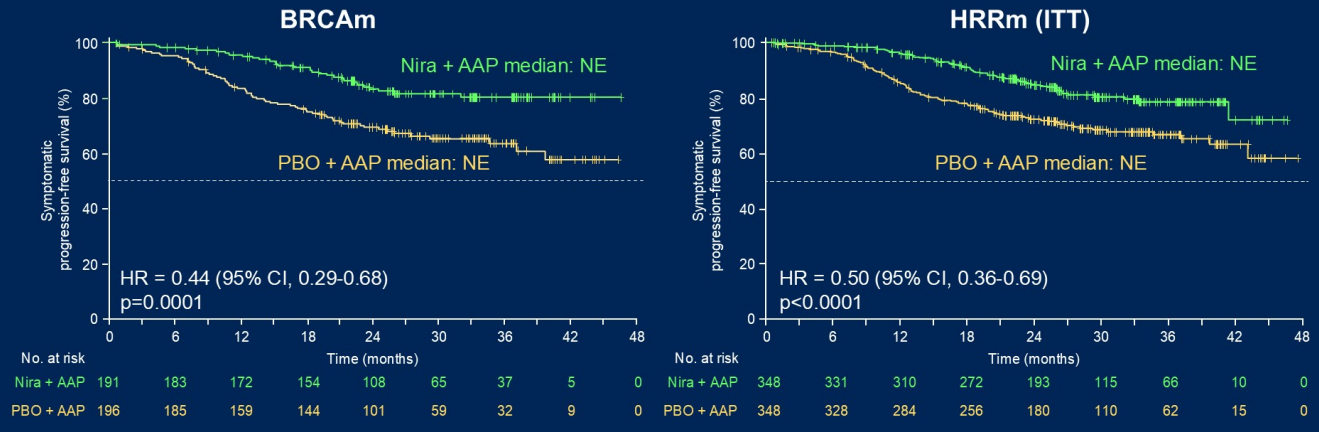
Secondary End Point: Time to Symptomatic Progression



Nira + AAP significantly reduced the risk of symptomatic progression by 56% in BRCAm group and by 50% in HRRm population

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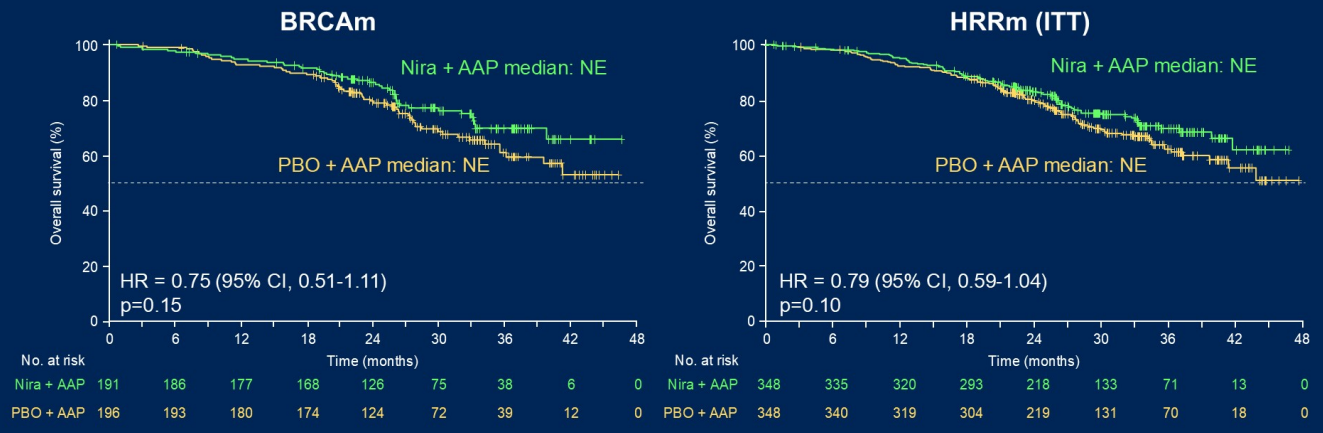
Secondary End Point: Overall Survival (First Interim Analysis)



This first interim analysis (≈50% of total needed events) estimates show Nira + AAP reduced risk of death by 25% in BRCAm group and by 21% in HRRm population

[a]The first interim analysis for OS was conducted when 193 patients had died (of a target of 389, an information fraction of 50%), 85 of 348 (24%) in the Nira + AAP arm and 108 of 348 (31%) in the PBO + AAP arm.

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There are several mHSPC Trials implementing molecular biomarkers that either recruiting already or being planned

- *BRCA2*/DRD: **AMPLITUDE** (NCT037486641), **TALAPRO-3** (NCT04821622), and **STAMPEDE** (NCT00268476)
- *PTEN* loss: **CAPItello-281** (NCT04493853)
- PSMA positive: **PSMAddition** (NCT04720157)
- Cell cycle: **CYCLONE 3** testing abiraterone + prednisone +/- LY2835219 (NCT05288166)

Can we improve the results with a better selection?

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How to perform all these studies?

Primary Tumor

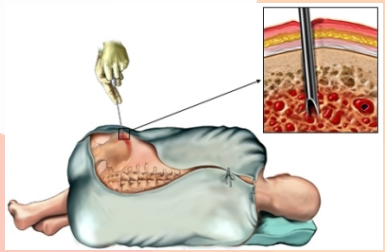
Liquid Biopsy

— CTCs

— cfDNA

— Exosomes

CT Guided Bone Marrow Biopsy



Different diagnostics strategies can be considered to assess for HRR alterations

	Advantages	Disadvantages
Tumour tissue testing	**Gold standard** (High clinical sensitivity) **Fresh or archival** tumour samples can be used (but older samples can have lower success rates) Can detect both **germline and somatic** mutations	**High failure rate**, especially for older samples Tissues for sampling may be in locations that are not safe or amenable to biopsy Single-site biopsies do not capture intra-individual heterogeneity (across metastases in an individual or changes over time or with disease progression)
Plasma ctDNA testing	**Non-invasive**, safer, serial analysis Can detect both **germline and somatic** mutations Useful where no tissue is available or when re-biopsy is undesirable Capture relative **contribution of metastases** in different anatomical sites	Low levels of tumour fraction can lead to false negative results CHIP may lead to false positives Blood collection must be timed in order to evaluate progressive disease Relative sensitivity at a prospective cohort level is unknown (clinical validation in PC still limited)
Germline testing (Blood or saliva)	Assess **familial risk** **Easy to obtain** samples from blood, saliva or buccal swabs	Misses alterations of somatic origin (≃ 50% of HR alterations)

Wyatt 2016; Pellegrino 2019; Moreno 2019; Merker 2019; Hennigan 2019; Hussain 2020; Gilson 2020; Mateo 2020

BRCA 1/2 and other DDR alterations are likely early events

High concordance in DDR mutational status between primary prostate and metastatic tissue/ctDNA

	HHR gene alteration prevalence %
All patients	27.9
All primary tumors	27
Archived primary	27
Newly collected primary	26.5
All metastatic tumors	32.3
Archived metastatic	33.9
Newly collected metastatic	29.7

BRCA1/2: 99% Overall concordance

Table 1. Patients with BRCA mutation in primary tumor

Pt #	BRCAm primary	Interval	BRCAm cfDNA 1
1	Detected	3.13 months	Not Detected
2	Detected	0.93 months	Detected
3	Detected	0.2 months	Detected
4	Detected	97.93 months	Not Detected
5	Detected	40.77 months	Detected

Table 2. Patients with no BRCA mutation in primary tumor

Matched CGP	Median (range)	New BRCA1	New BRCA2
Primary test to 1st cfDNA (n=191)	23.6 months (0.1 - 232)	None	None
Primary test to 2nd cfDNA (n=27)	58.9 months (7.23 - 211)	None	None
Primary test to 3rd cfDNA (n=2)	65.5 months (21.9 - 109)	None	None

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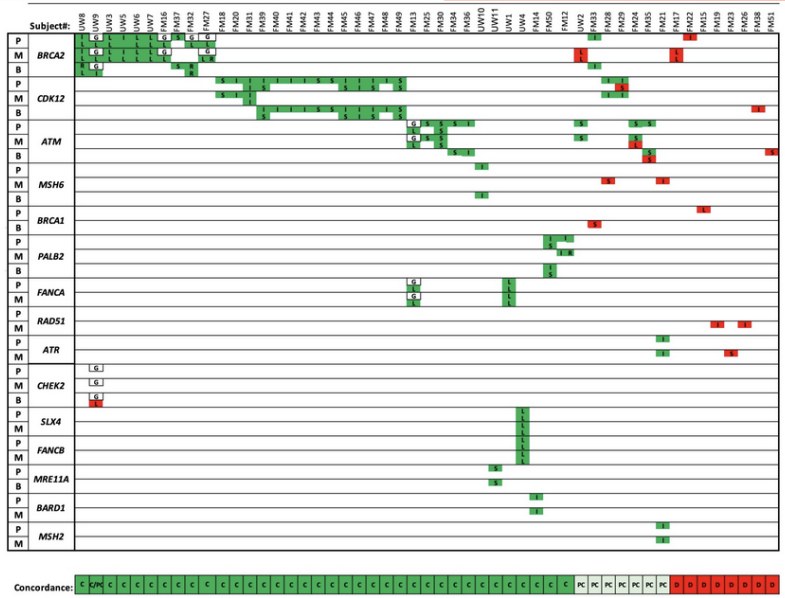

BRCA and other DDR: 84% concordance

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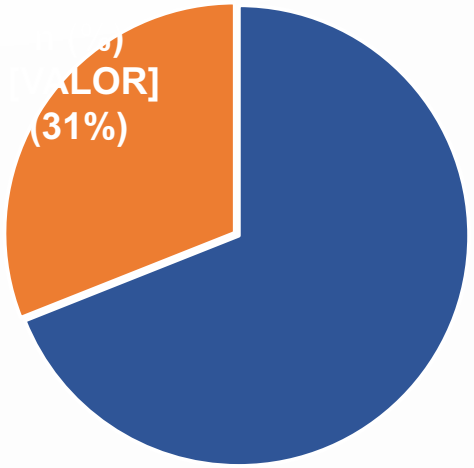
Presented By Dr McFarland at 2021 ASCO GU; Schweizer at al JAMA Oncol, 2021

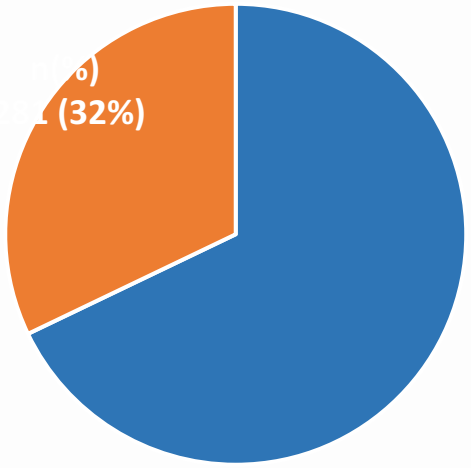
TISSUE is the ISSUE

PROfound[1]
N = 4047 samples



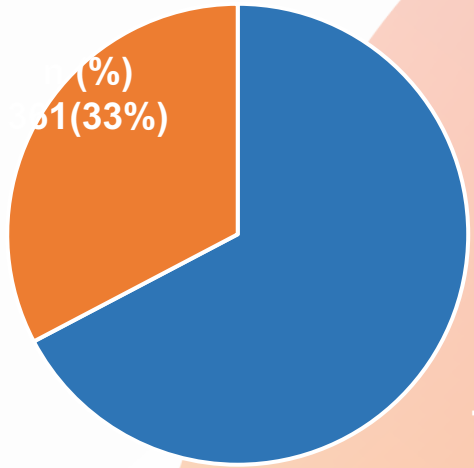
Successful
Failed

TRITON2[2*]
N = 875 samples



Successful
Failed

IPATential150[3]
N = 1104 samples



Evaluable
Not evaluable

Sample selection and optimisation of tissue collection is critical, since 30–50% of prostate cancer samples fail NGS[1–3]

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de Bono J, et al. Ann. Oncol. 2019 (ESMO 2019, #5118); 2. Green F, et al. AACR 2019; (#727); 3. de Bono JS, et al. Journal of Clinical Oncology. 2021;39 (suppl_6):13-13.

Different diagnostic strategies can be considered to assess for HR alterationss

	Advantages	Disadvantages
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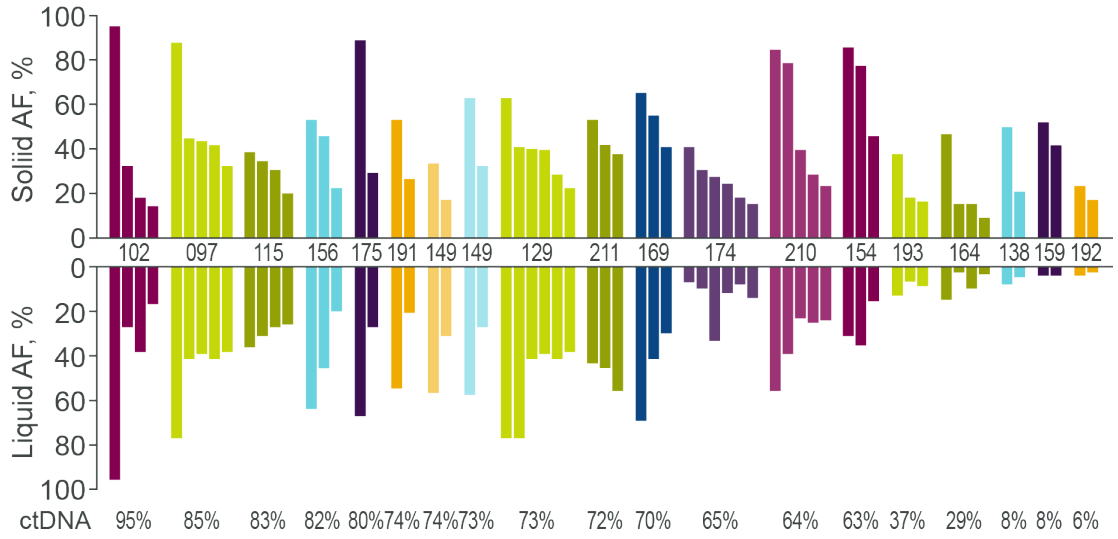
Wyatt 2016; Pellegrino 2019; Moreno 2019; Merker 2019; Hennigan 2019; Hussain 2020; Gilson 2020; Mateo 2020

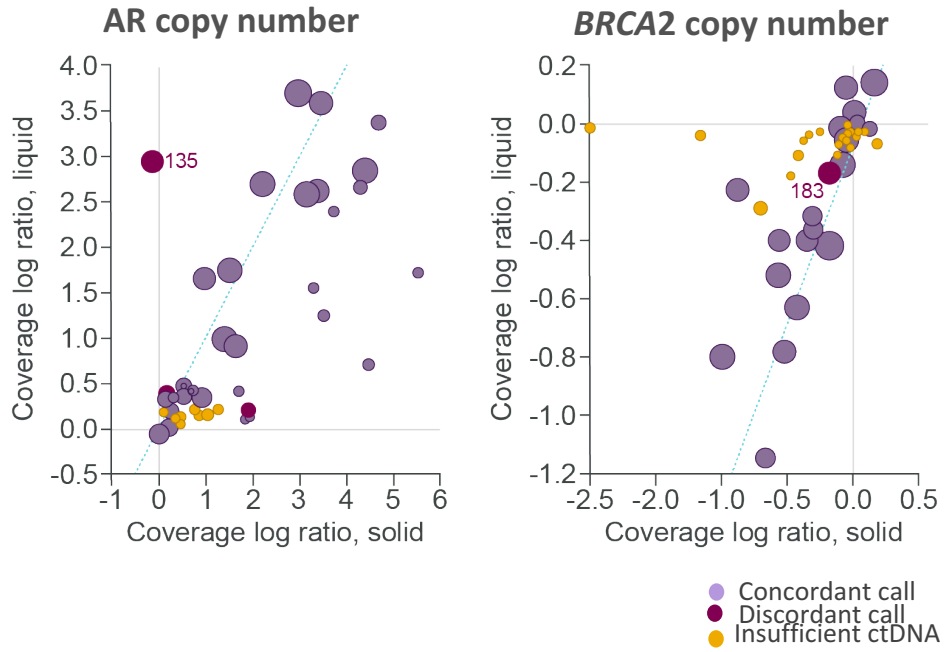
Assessment of genomic alterations of tumor in ctDNA

Concordance between biopsies and ctDNA is high

Similar mutation profiles



Similar gene copy numbers



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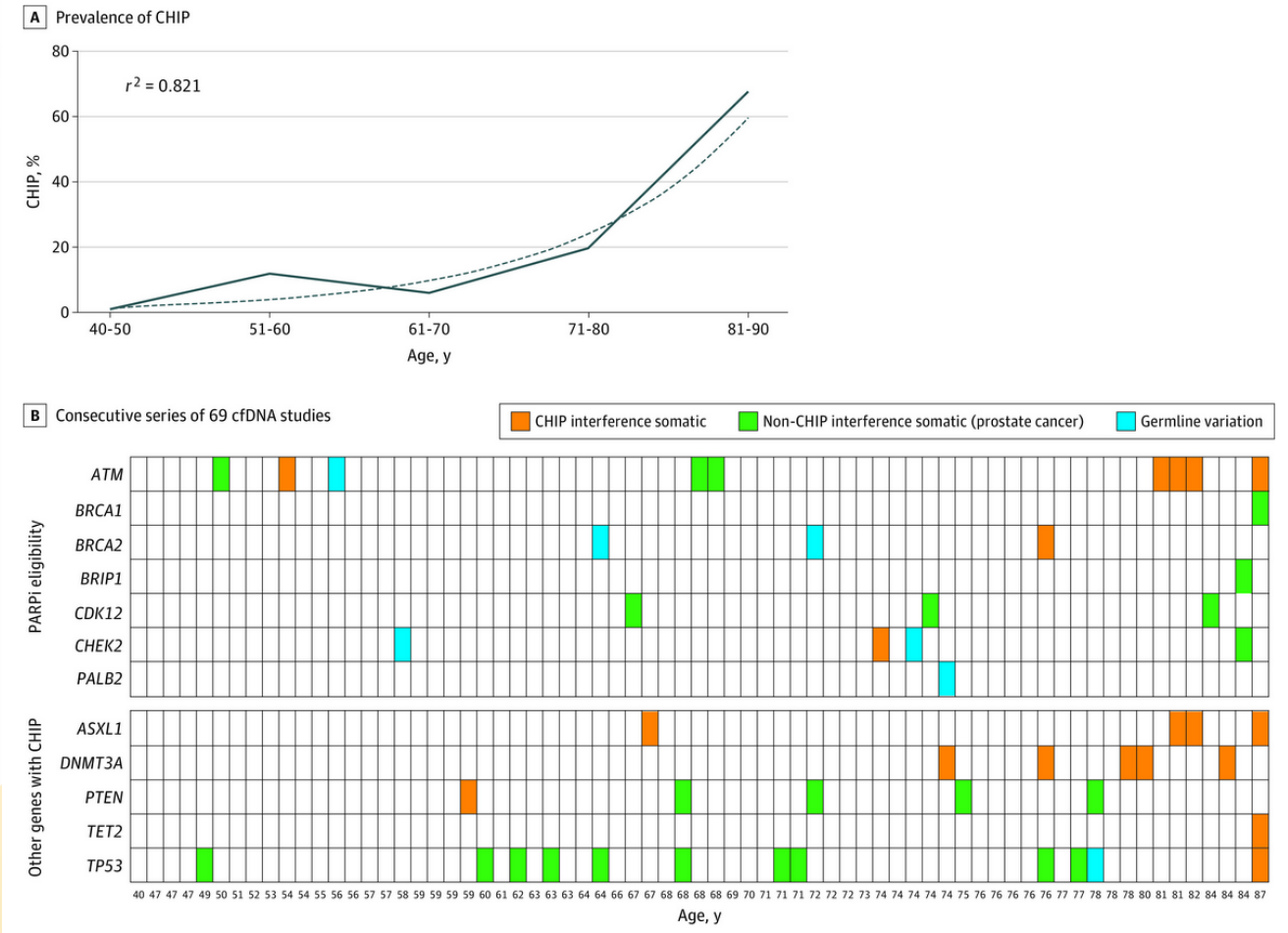
Wyatt et al, JNCI, 2017

Clonal hematopoiesis of indeterminat potencial may lead to false positives



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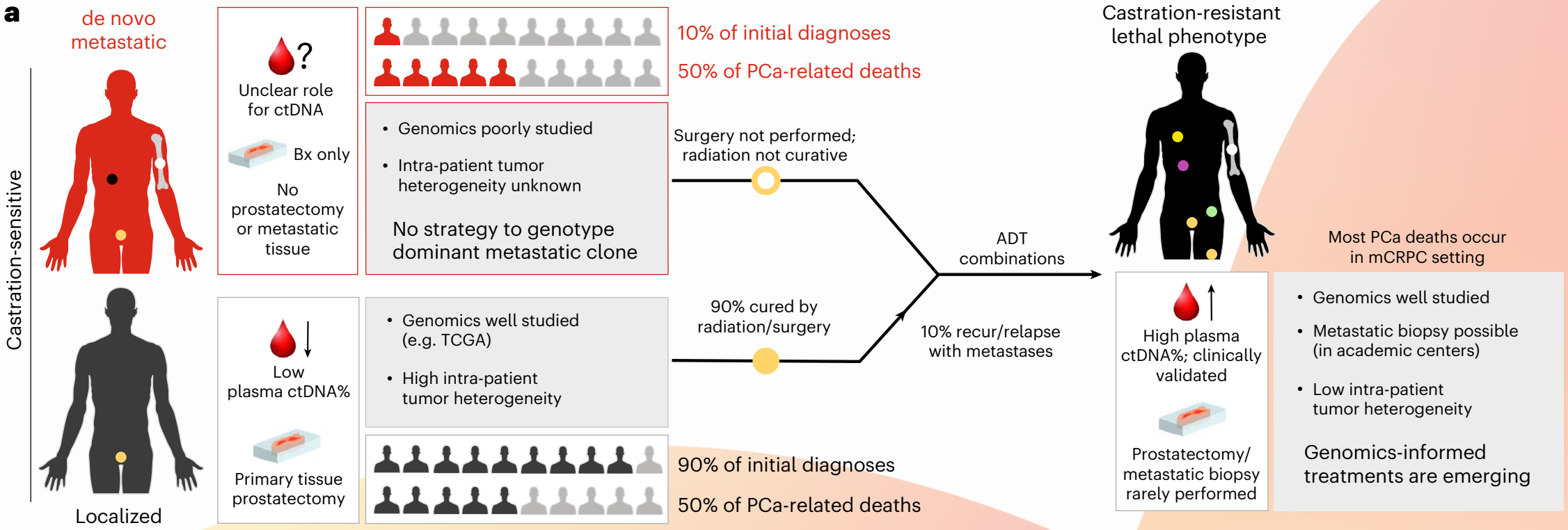
Jensen et al, JAMA Oncol, 2021

The biological and clinical challenge of the novo mCSPC



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Warner EW... & AW Wyatt. Nat Cancer 2023

Why should we think about the de-escalation?

Living Longer

- But with more side-effects
- No significant improvement in HRQoL
- A substantial increase in cost

A tale of Efficacy vs. value for the Patients and the health care system

The content of this slide, reflects a personal opinion.

Why should we think about de-escalation?

IT'S ALL ABOUT THE VALUE

For patients

- To live better and longer, avoid burdensome further treatment, and improve quality of life.

For payers

- Is it acceptable cost-wise? Can we afford it?
- Incremental cost-effectiveness ratio (ICER)

The content of this slide, reflects a personal opinion.

Conclusiones

- A mi juicio todavía es pronto para afirmar que hemos entrado en la época de la implementación de la medicina de precisión en la enfermedad hormonosensible metastásica.
- Si bien es cierto que los resultados presentados este año nos permiten decidir / intuir el mejor de los tratamientos para nuestros enfermos.
- La intensificación terapéutica ha permitido mejorar los resultados globales de nuestros enfermos, sin embargo, ahora tenemos un problema que es seleccionar aquellos que nos podemos permitir desescalarlos.

¡Gracias!

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