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PROSTATE CANCER: MOLECULAR BIOLOGY AND INFLUENCE ON CLINICAL TRIALS DESIGN IN THE ERA OF PRECISION MEDICINE

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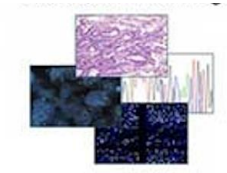
MOLECULAR PROFILING OF PROSTATE CANCER

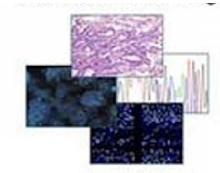
LOCALISED PC



Tumoural tissue
Blood specimen

To stratify by risk, detect early recurrence
+/- consider adjuvant treatment

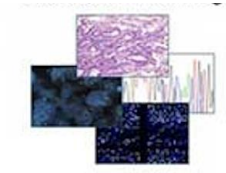
METASTASTIC PC



Tumoural tissue
Blood specimen

To look for actionable targets

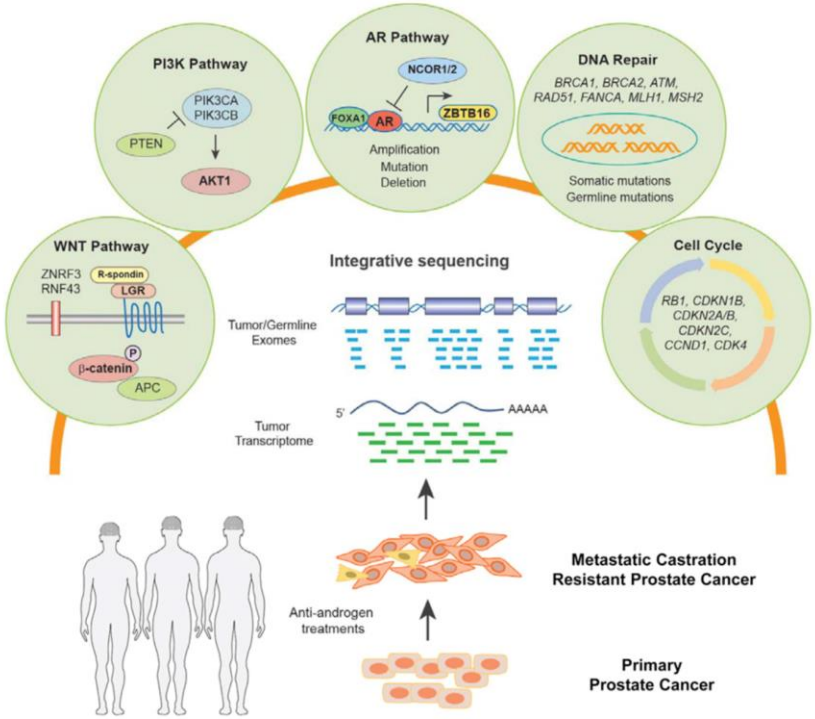
REFRACTORY PC



Tumoural tissue
Blood specimen

To identify treatment sensitivity/resistance

MOLECULAR PROFILING OF PROSTATE CANCER



mCRPC has revealed recurrent alterations in key pathways (in comparison to localised PC)

90% of mCRPC harbour clinically actionable molecular

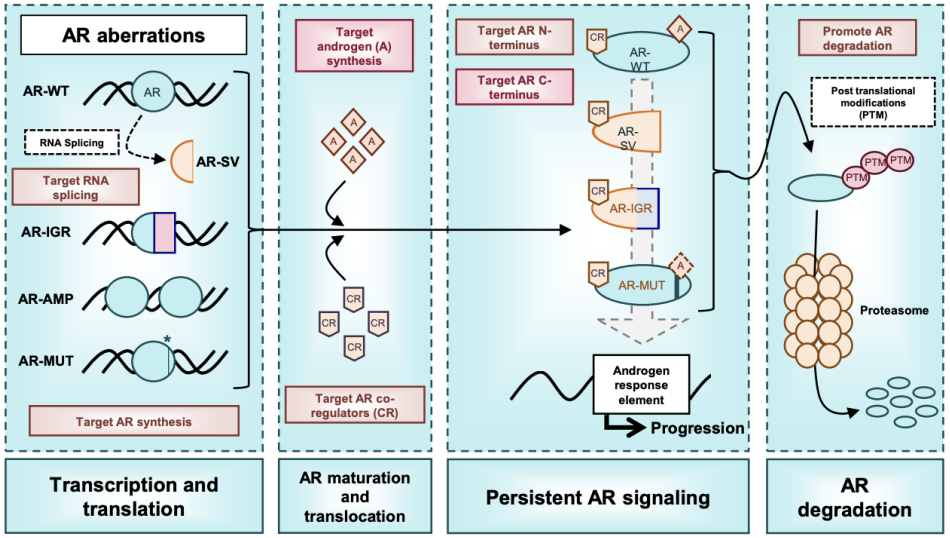
Frequency of pathway alterations in mCRPC:

- AR pathway: 60-70%
- PI3K pathway: 40-60%
- DNA repair: 25%
- Cell cycle: 25%
- WNT pathway: 20%

AR PATHWAY

AR signaling is the major driver of CRPC

- AR mutations
- AR amplification
- AR rearrangements
- AR splice variants
- AR driven transcripts
- Androgen synthesis (extra-gonadal and intratumoural)



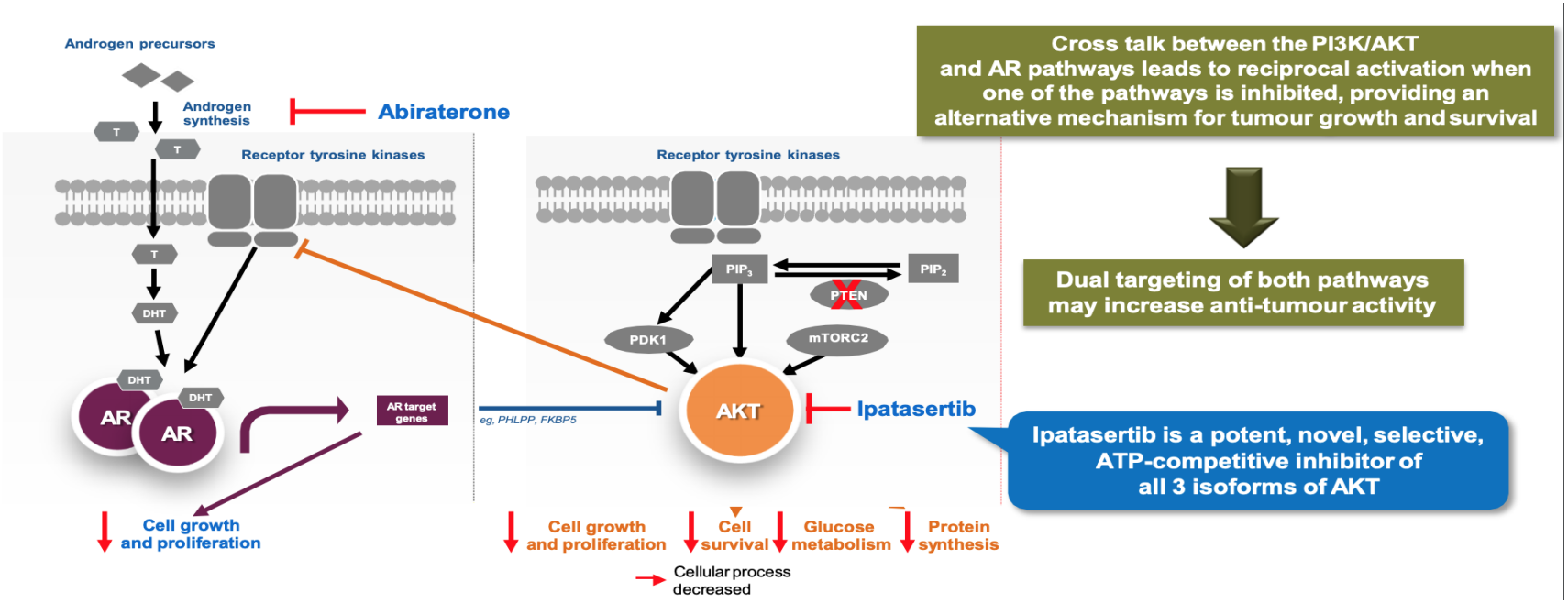
Acquisition of **AR alterations** (amplification and mutation) is a hallmark of resistant PC and **is associated with persistent AR signaling independent of androgen ->** Potent inhibition of the androgen signaling axis with abiraterone and enzalutamide

AR splice variants, most notably **AR-V7 (around 20%)**, emerges in therapy-resistant disease and is associated with inferior outcomes in patients treated with abiraterone/enzalutamide but is not established how best to use this as a predictive biomarker in the clinic.

Studies are needed with novel agents against continued AR signaling and to further understand the prognostic and predictive role of AR variants with respect to therapy resistance

Antonarakis ES, *et al.* N Engl J Med 2014; 371:1028-1038; De Laere B. J Clin Oncol 2019; Armstrong AJ. J Clin Oncol 2020; Annala M, *et al.* Cancer Discov 2018.

PI3K/AKT PATHWAY: RATIONALE OF DUAL PATHWAY INHIBITION



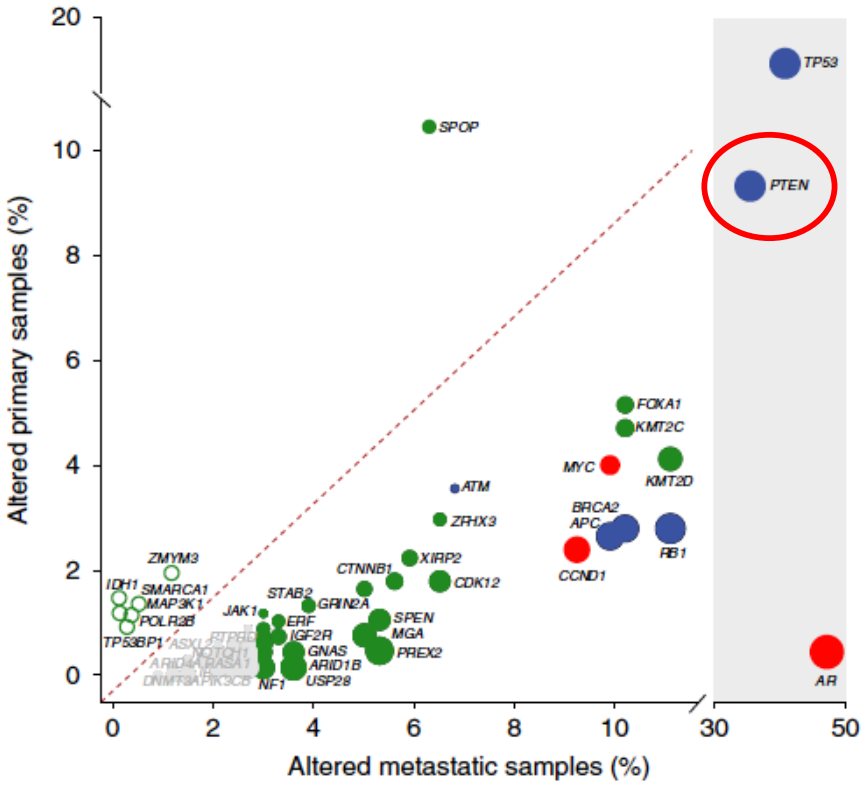
Lin J, *et al.* Clin Cancer Res 2013; 2. Carver BS, *et al.* Cancer Cell 2011; 3. Bitting RL, Armstrong AJ. Endocr Relat Cancer 2013;4. Hodgson MC, *et al.* Cancer Res 2011; 5. Mulholland DJ, *et al.* Cancer Cell 2011; 6. Jamaspishvili T, *et al.* Nat Rev Urol 2018.

de Bono J. IPATential150. ESMO 2020. With permission from Prof J. de Bono.

PI3K PATHWAY

PTEN loss (most commonly by homozygous deletion or mutation) leads to loss of **negative regulation of PI3K/Akt** signaling and resultant increase in cellular proliferation and tumour growth

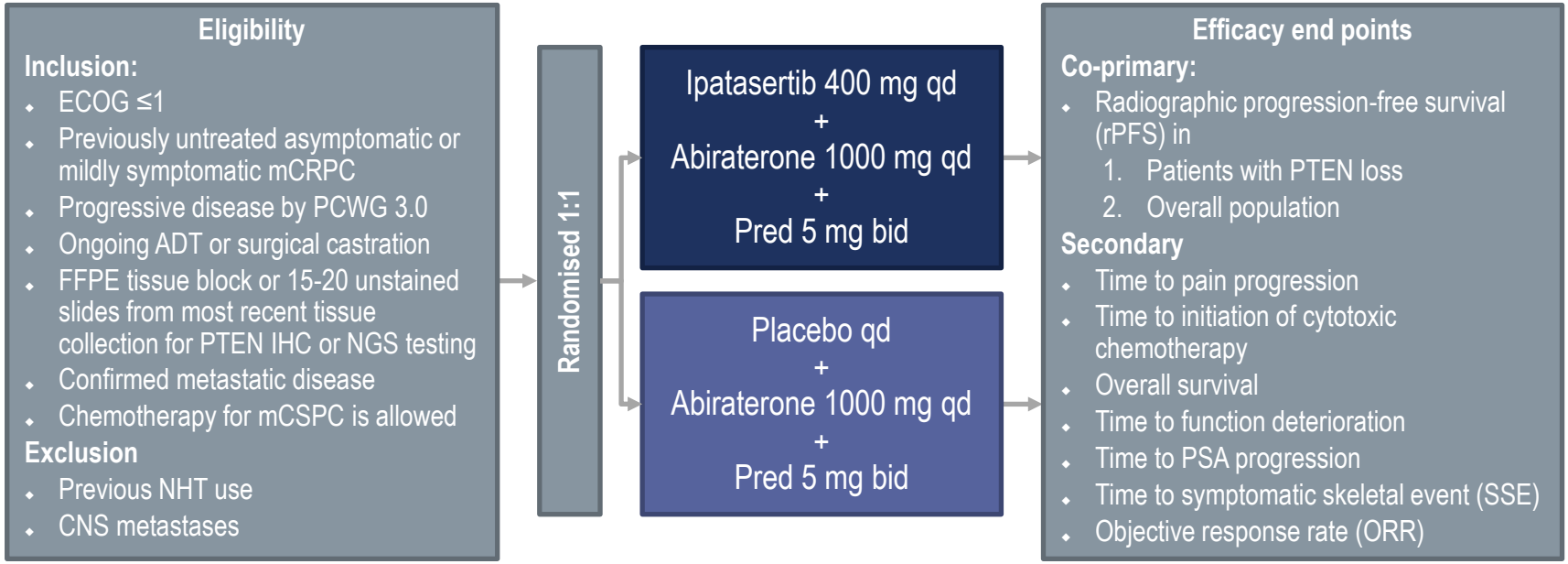
PTEN loss associates with **poor prognosis and relative endocrine resistance** and is enriched in metastatic and castration resistant disease relative to primary tumours). PI3K pathway alterations are present in up to 40% of metastatic prostate cancers



Robinson D, *et al.* Cell 2015; Ferraldeschi R, *et al.* Eur Urol 2014; Carver BS, *et al.* Cancer Cell 2011.

PI3K PATHWAY

The Phase 3 study (IPATential150) met its coprimary endpoint of rPFS in mCRPC patients with PTEN loss tumours.
OS is not available yet

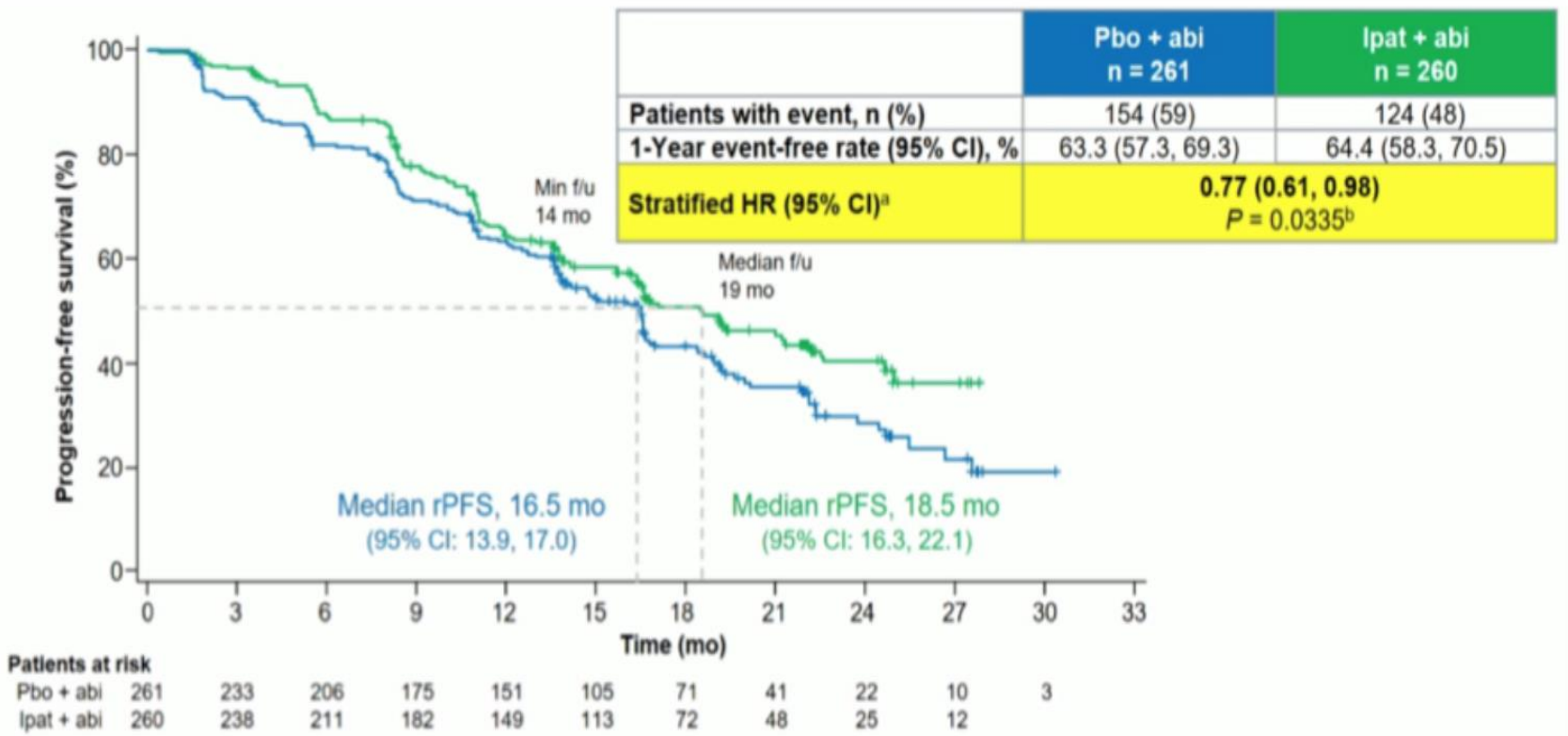


1101 patients randomised
Stratification: prior taxane therapy in hormone-sensitive setting; PTEN status by IHC; and geographic region

A Phase 3 trial is planned in **mHSPC setting** evaluating capivasertib and abiraterone versus abiraterone for patients with de novo mHSPC (NCT04493853)

Other **AKT inhibitors combinations** including chemotherapy or immunotherapy are under investigation

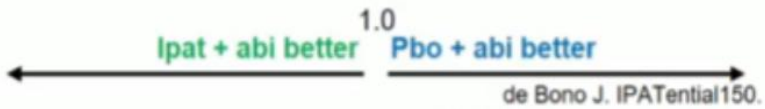
www.clinicaltrials.gov: IPATential150 (NCT03072238)



Data cut-off, 16 Mar 2020; median follow-up 19 months.
a. Stratified for prior taxane-based therapy and PSA-only progression factor; b. Statistically significant at α = 0.05 level.

de Bono J, IPATential150. ESMO 2020. https://bit.ly/31s8gje. With permission from Prof J. de Bono.

Characteristic		Patients, n	Pbo + abi Median, mo	Ipat + abi Median, mo	HR (95% CI)
All patients (PTEN loss)		521	16.5	18.5	0.78 (0.61, 0.99)
ECOG PS	0	397	16.6	19.2	0.76 (0.58, 1.01)
	1	123	13.6	16.6	0.89 (0.56, 1.42)
Age, y	< 65	145	18.4	17.1	0.84 (0.54, 1.31)
	65 to < 75	229	16.6	18.6	0.84 (0.58, 1.21)
	≥ 75	147	13.7	21.0	0.67 (0.43, 1.04)
Lactate dehydrogenase level	≤ ULN	376	16.7	21.3	0.77 (0.57, 1.03)
	> ULN	141	10.9	13.4	0.83 (0.55, 1.25)
Prior taxane-based therapy	Yes	94	18.4	15.6	1.00 (0.58, 1.74)
	No	427	16.5	19.1	0.74 (0.57, 0.96)
Progression factor	PSA only	249	16.6	24.6	0.77 (0.54, 1.11)
	Other	272	14.2	16.5	0.77 (0.56, 1.06)
Liver or lung metastases	Yes	74	8.4	11.9	0.66 (0.37, 1.18)
	No	447	16.6	19.1	0.80 (0.62, 1.04)



de Bono J. IPATential150.

ULN, upper limit of normal

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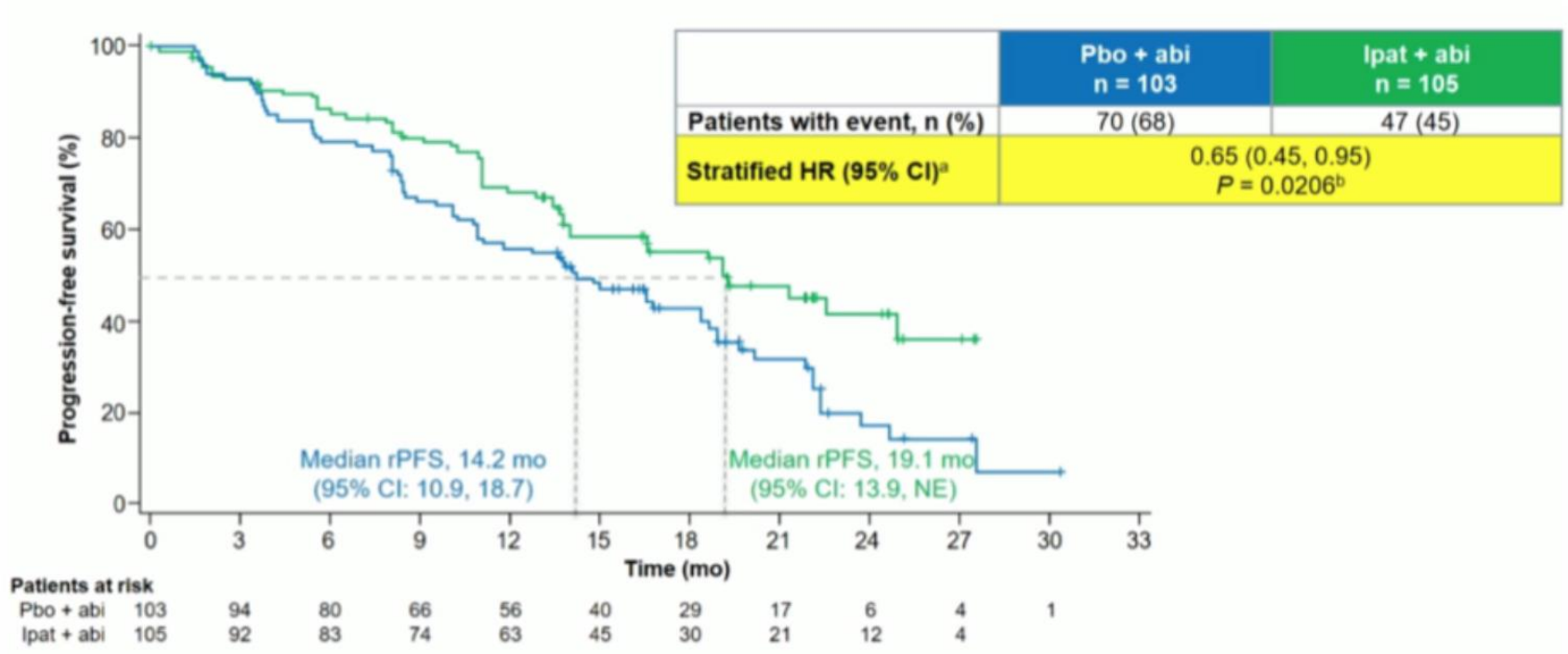


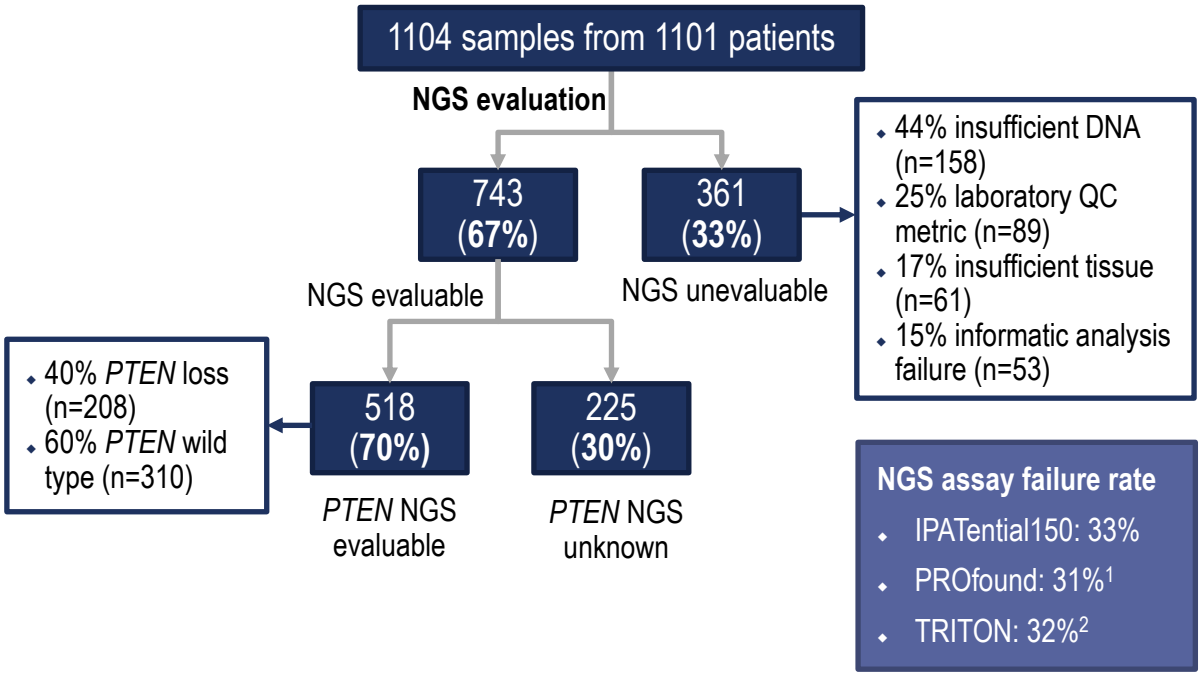
	Pbo + abi n = 103	Ipat + abi n = 105
Patients with event, n (%)	70 (68)	47 (45)
Stratified HR (95% CI)[a]	0.65 (0.45, 0.95) *P* = 0.0206[b]	

Data cut-off, 16 Mar 2020; median follow-up 19 months.
a. Stratified for prior taxane-based therapy and PSA-only progression factor; b. Descriptive.

de Bono J, IPATential150. ESMO 2020. https://bit.ly/31s8gje. With permission from Prof J. de Bono.

DEFINITIONS OF *PTEN* LOSS BY NEXT-GENERATION SEQUENCING (NGS)

PTEN status	Sequence classification	
Loss	*PTEN*-inactivating alterations	Homozygous deletion (CN=0)
		Heterozygous deletion (CN=1)
		DN mutations
		Bi-allelic inactivation[a]
Unknown	*PTEN*-inactivating status unknown	
Wild type	No *PTEN*-inactivating mutations	

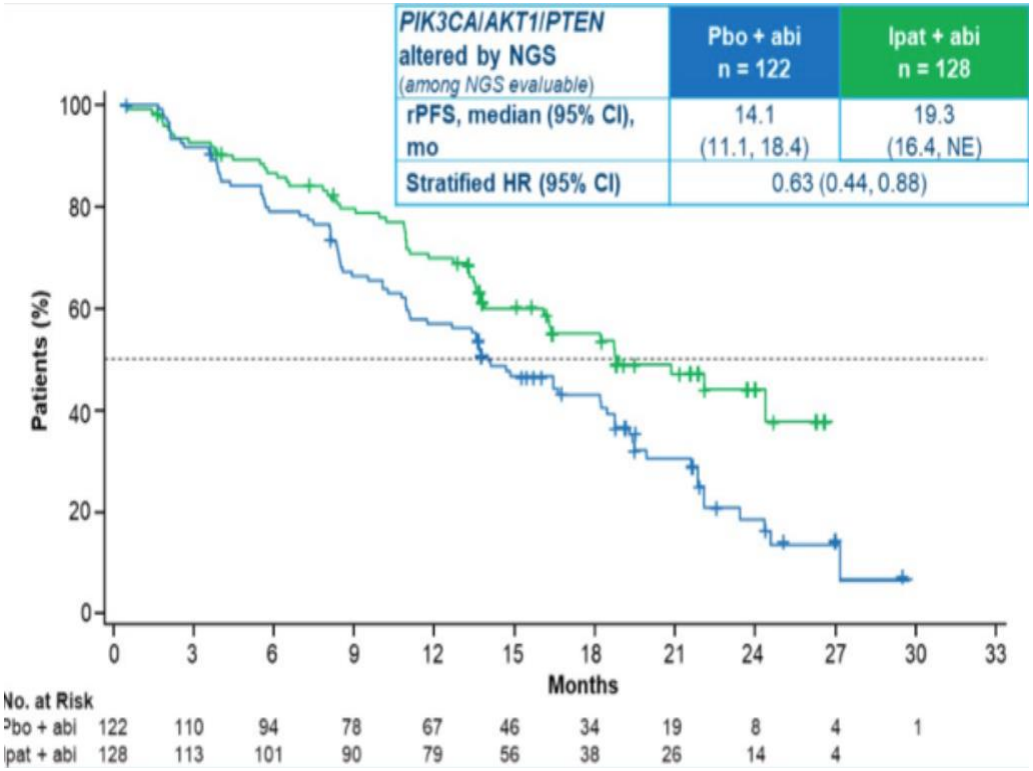


PTEN loss was predefined as ≥50% of tumour cells with no specific cytoplasmic IHC staining

Exploratory analysis evaluated different IHC staining cut-offs

Tumour genomic alterations were profiled with NGS using Foundation Medicine FoundationOne CDx NGS assay (Shi, ASGO-GU 2020; n=743 evaluable by NGS, of which n=518 were *PTEN* evaluable)

de Bono J. IPATential150. ASCO-GU 2021. With permission from Prof J. de Bono.



PIK3CA/AKT1/PTEN non-altered (among NGS evaluable)	Pbo + abi n = 257	Ipat + abi n = 236
rPFS, median (95% CI), mo	16.6 (13.9, 19.3)	17.7 (14.8, 22.3)
Stratified HR (95% CI)	0.93 (0.72, 1.18)	

PIK3CA/AKT1/PTEN altered + non-altered (among NGS evaluable)	Pbo + abi n = 379	Ipat + abi n = 364
rPFS, median (95% CI), mo	16.5 (13.8, 18.4)	19.1 (16.4, 22.6)
Stratified HR (95% CI)	0.80 (0.66, 0.98)	

rPFS for *PTEN*-loss (14.2 months on PBO + ABI vs 19.1 months on IPAT + ABI; HR 0.65) /wt (16.6 months on PBO + ABI vs 20.9 months on IPAT + ABI; HR 0.85) population

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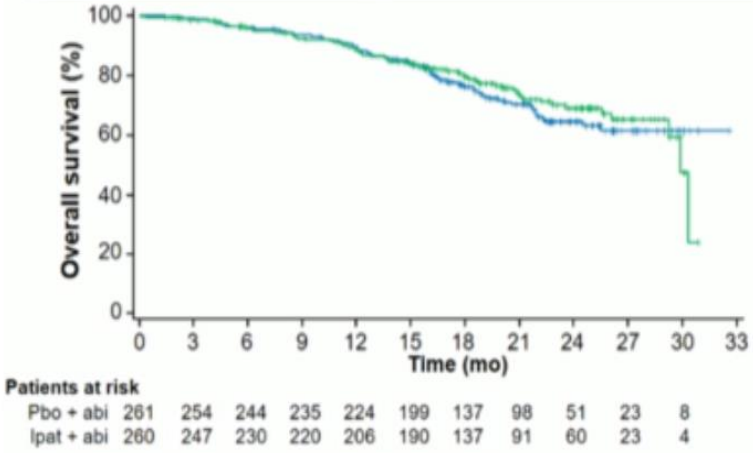
PTEN loss by IHC

	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	75 (29)	65 (25)
Stratified HR (95% CI)[a]	0.91 (0.65, 1.27)	

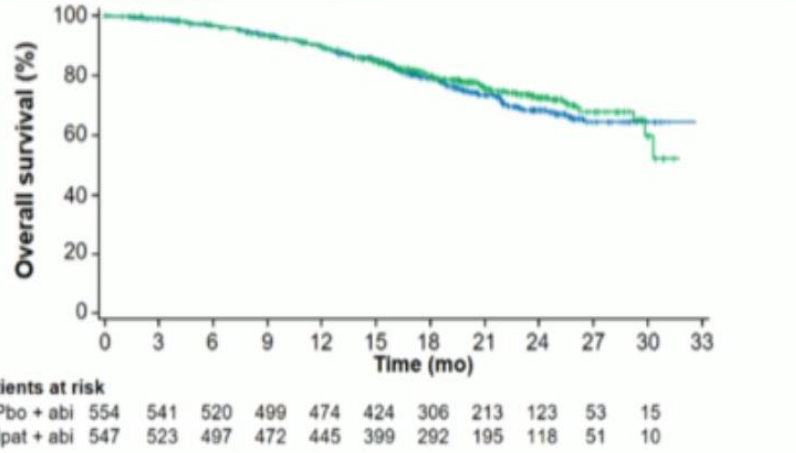


Patients at risk

Pbo + abi	261	254	244	235	224	199	137	98	51	23	8
Ipat + abi	260	247	230	220	206	190	137	91	60	23	4

ITT

	Pbo + abi n = 554	Ipat + abi n = 547
Patients with event, n (%)	143 (26)	124 (23)
Stratified HR (95% CI)[b]	0.93 (0.73, 1.18)	



Patients at risk

Pbo + abi	554	541	520	499	474	424	306	213	123	53	15
Ipat + abi	547	523	497	472	445	399	292	195	118	51	10

Data cutoff, 16 Mar 2020; median follow-up, 19 months.

[a] Stratified for prior taxane-based therapy and PSA-only progression factor.

[b] Stratified for prior taxane-based therapy, PSA-only progression factor and tumour PTEN loss status by IHC.

de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje 19

To date, overall survival data remains immature, and conclusions cannot be drawn

de Bono J, IPATential150. ESMO 2020. https://bit.ly/31s8gje. With permission from Prof J. de Bono.

SAFETY

Diarrhoea and skin rash were the predominant severe toxicities among those receiving ipatasertib, abiraterone acetate, and prednisone

Exposure	PBO + ABI (n=546)	IPAT + ABI (n=551)
Treatment duration, median (range), mo		
IPAT/PBO	14.0 (0-32)	11.1 (0-31)
ABI	14.0 (0-32)	14.2 (0-31)

Safety summary, n (%)	PBO + ABI (n=546)	IPAT + ABI (n=551)
All grades AEs	519 (95.1)	548 (99.5)
Grade 3-4 AEs	213 (39.0)	386 (70.1)
Grade 5 AEs	20 (3.7)	24 (4.4)
Serious AEs	124 (22.7)	218 (39.6)
AEs leading to discontinuation of PBO/IPAT	**28 (5.1)**	**116 (21.1)**
AEs leading to dose reduction of PBO/IPAT	**34 (6.2)**	**220 (39.9)**
AEs leading to dose interruption of PBO/IPAT	125 (22.9)	319 (57.9)
AEs leading to discontinuation of ABI	22 (4.0)	47 (8.5)

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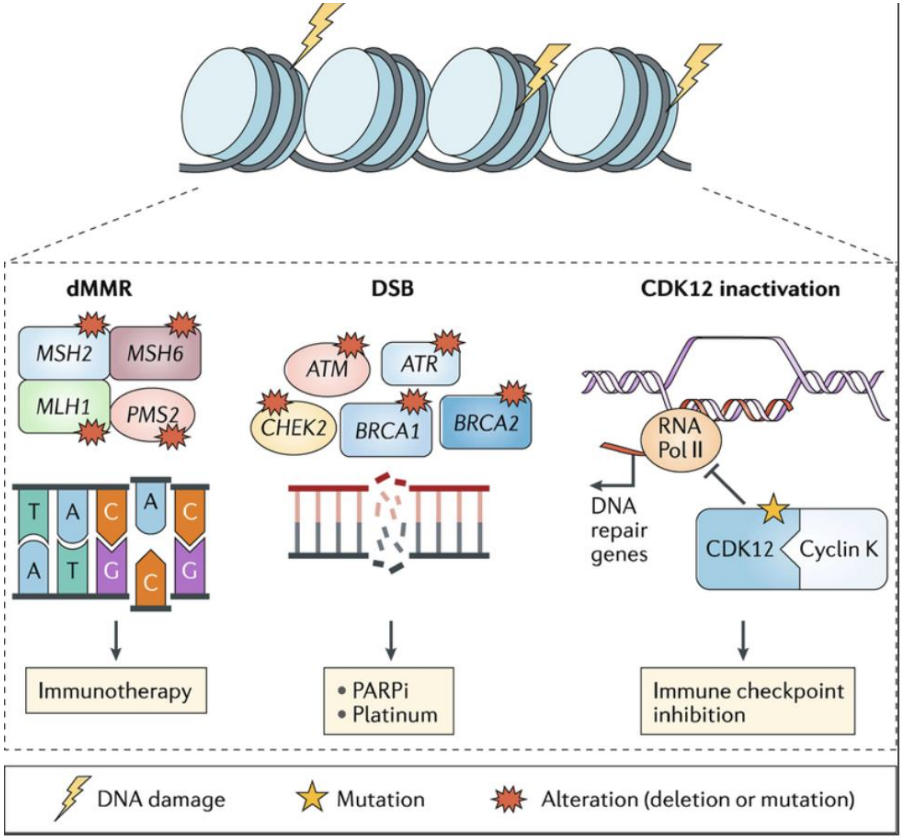
DNA REPAIR



DSB (double-strand break)

- **23%** of mCRPC (11-33%)
- Most common defect: BRCA2 (13%). Germline mutations in BRCA1/2: 8% of mCRPC
- Treatment with PARP inhibitors and platinum-based chemotherapy

dMMR

- **3–5%** of PC patients → associated with hypermutation and increased neoantigen burden
- May benefit from immunotherapy

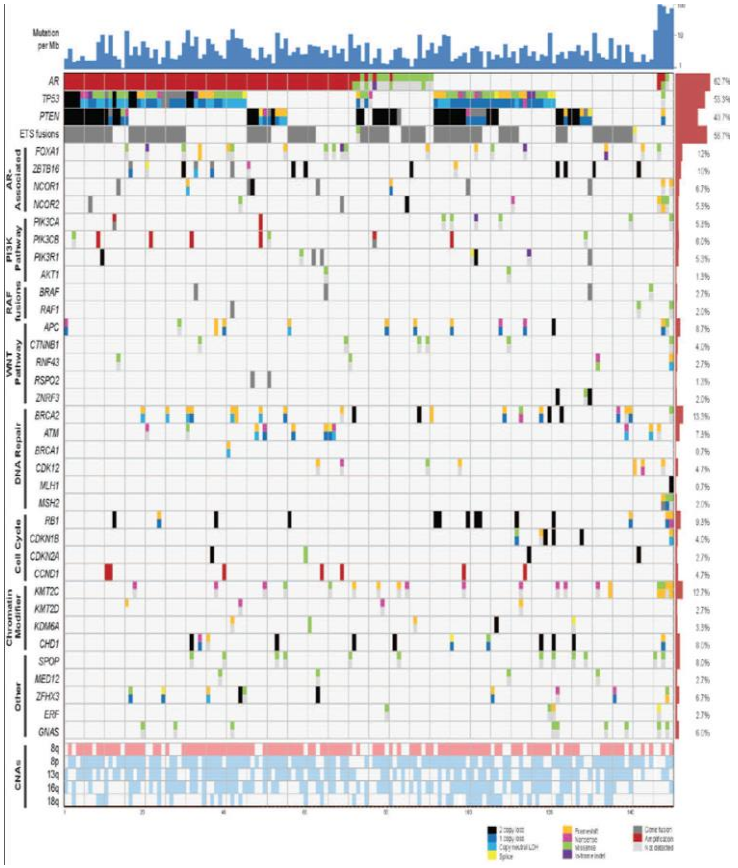
CDK12 loss

- **7%** of mCRPC patients - > associated with increased neoantigen burden
- May benefit from immunotherapy

GENOMIC LANDSCAPE OF PROSTATE CANCER

23% of mCRPCs harbour DNA reparation alterations

Frequency of DNA repair alterations increase in disease progression



More aggressive cancer (vs non-carriers)

BRCA2: younger onset, higher T stage, higher Gleason, more node involvement

BRCA1 or 2 or ATM: 4-fold higher risk lethal Pca, shorter survival

BRCA1: higher recurrence, shorter Pca specific survival

Reprinted from Cell 161, Robinson D, *et al.* Integrative Clinical Genomics of Advanced Prostate Cancer, 1215-1228, Copyright 2015, with permission from Elsevier.

DNA REPAIR

Studies of PARP inhibitors in monotherapy for mCRPC

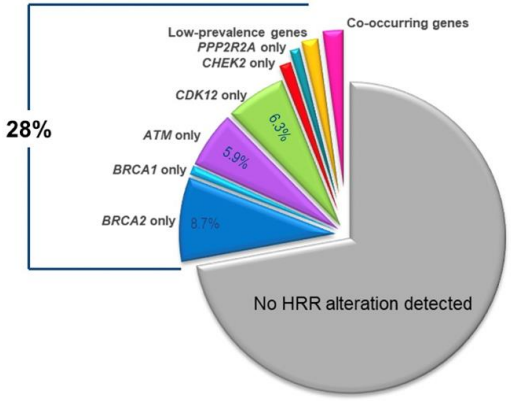
	PROFOUND	TRITON 2	TALAPRO 1	GALAHAD
Drug	Olaparib 300 mg bid	Rucaparib 600 mg bid	Talazoparib 1 mg qd	Niraparib 300 mg qd
Study design	Phase 3	Phase 2	Phase 2	Phase 2
Population	mCRPC Progression to ARSi	mCRPC Progression to ARSi and taxane	mCRPC Progression to ARSi and taxane	mCRPC Progression to ARSi and taxane
Primary objective	rPFS in patients with alterations in ATM, BRCA1, BRCA2	ORR and PSA response (≥50% decline) in patients with DDR alterations	ORR in patients with DDR alterations	ORR in patients with Bi-allelic BRCA1/2 alterations
Specimen tested	Tumour tissue Central	Plasma or tumour tissue Central/local	Tumour tissue Central/local	Plasma Central
Test used	FoundationOne®	FoundationOne® FoundationACT® Local	FoundationOne®	Resolution-HRD®
Genes screened	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*	*ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*	*ATM, BRCA1, BRCA2, BRIP1, CHEK2, FANCA, HDAC2, PALB2*
Genomic alteration required		Mono- Bi- allelic DDR alterations		Bi-allelic DDR alterations

De Bono J, *et al.* N Engl J Med 2020; Abida W, *et al.* Clin Cancer Res 2020; De Bono J, *et al.* J Clin Oncol 2020; Smith C, *et al.* Annals Oncology 2019

DNA REPAIR

The role of individual DDR gene alterations and response to PARP inhibition remains an area of much debate and active research

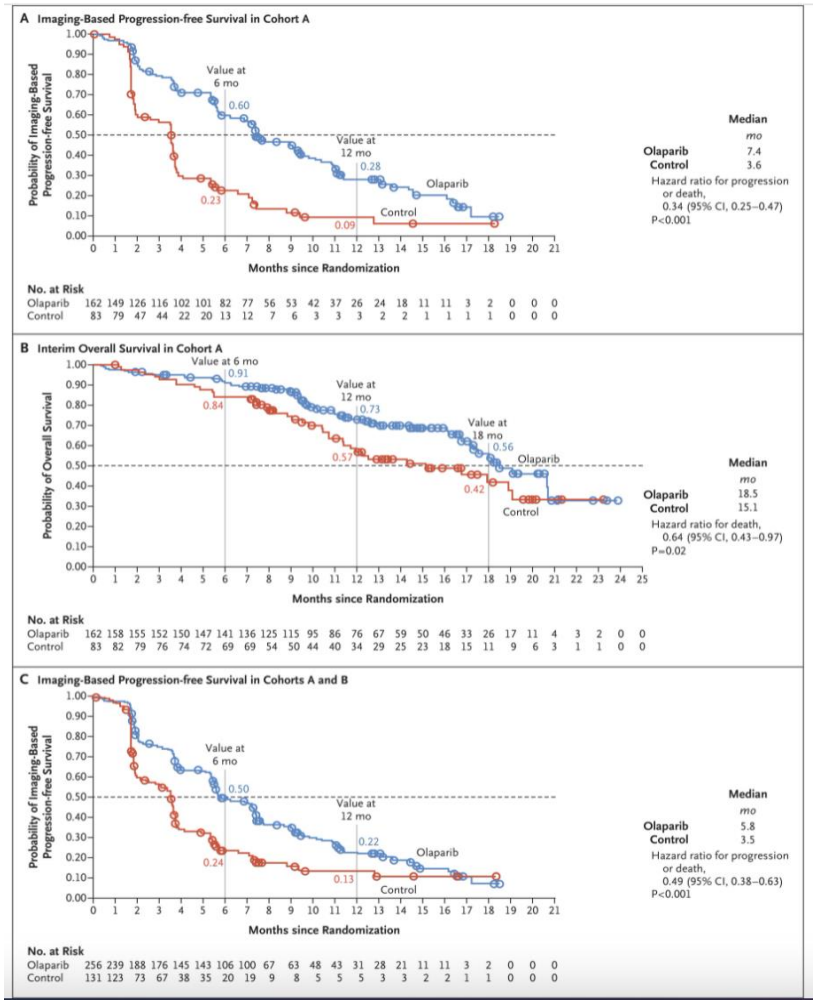
Results from TOPARP-B (Mateo, Lancet Oncol 2019), TRITON2 (Abida, Clin Cancer Res 2020) and PROFOUND (De Bono, NEJM 2020), suggest that benefit from PARP inhibition may be limited in non-BRCA mutated mCRPC



ATM	*RAD51B*
BRCA1	*RAD51C*
BRCA2	*RAD51D*
BARD1	*FANCL*
BRIP1	*PALB2*
CDK12	*PPP2R2A*
CHEK1	*RAD54L*
CHEK2	

Alterations in DDR genes in PROFOUND trial

Olaparib was associated with longer PFS than either enzalutamide or abiraterone in mCRPC patients who had DDR gene alterations

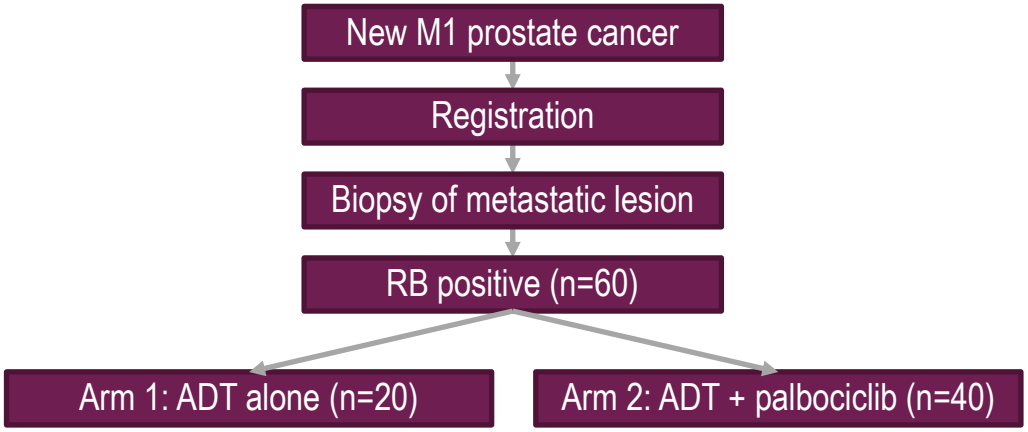


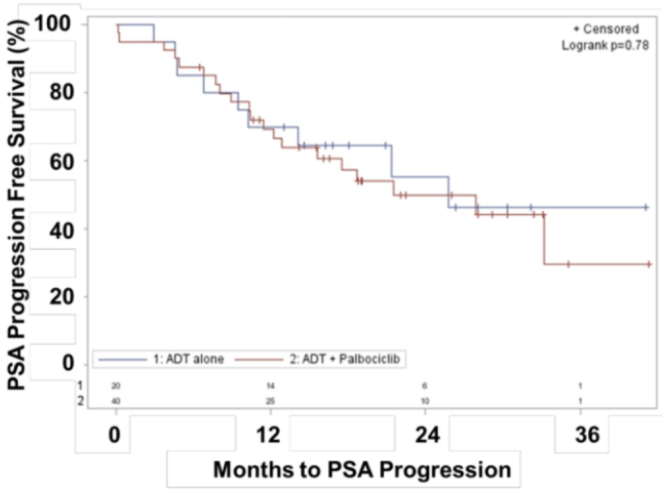
From N Engl J Med, de Bono J, *et al.* Olaparib for Metastatic Castration-Resistant Prostate Cancer, 382, 2091-2102

CELL CYCLE

Biomarker stratified randomised Phase 2 trial of the addition of palbociclib to ADT in mHSPC

No difference in PSA or clinical response was observed after 28 weeks of therapy





Further studies with CDK4/6 inhibitors monotherapy and combination are ongoing

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Palmbos PL, *et al.* ASCO 2020. With permission from Dr PL Palmbos.

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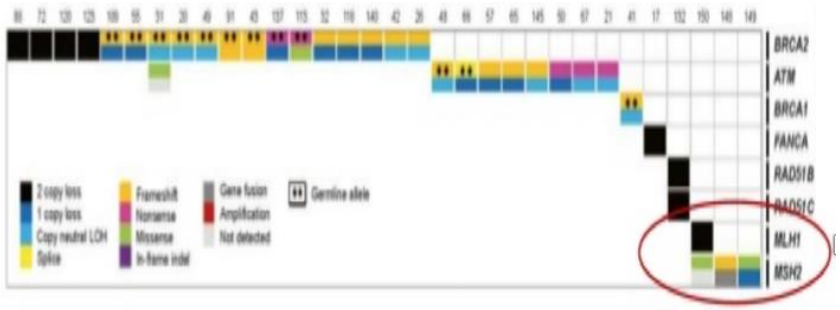
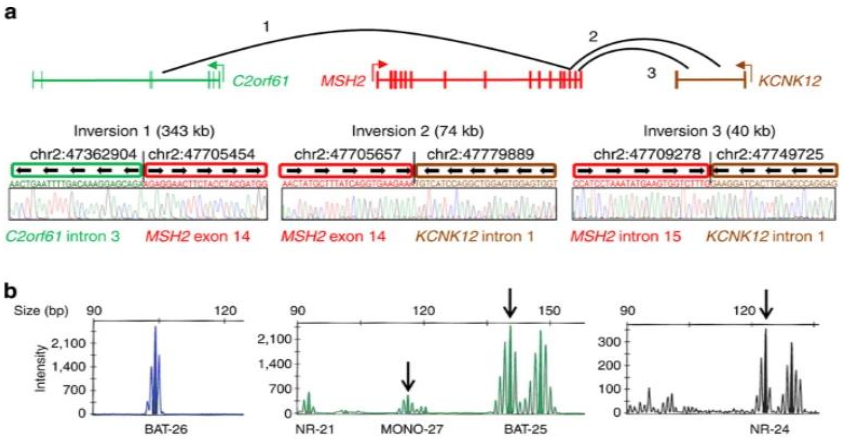
MMR MUTATIONS IN MCRPC

3/150 (2%) had MMR mutations

4/150 (2.7%) were MSI-high

Patient cases with DNA repair defects



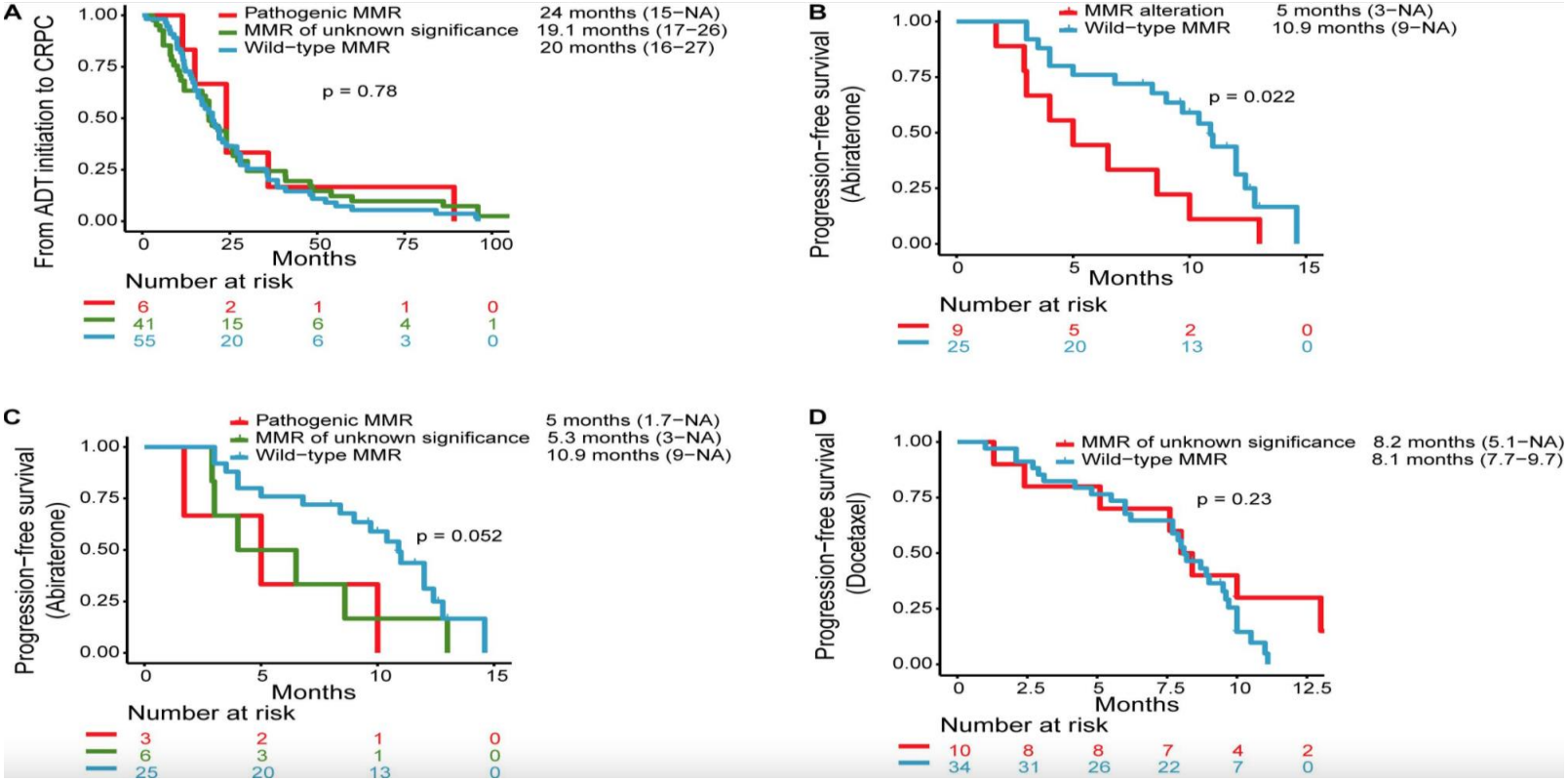


Germline MMR mutations: 1%

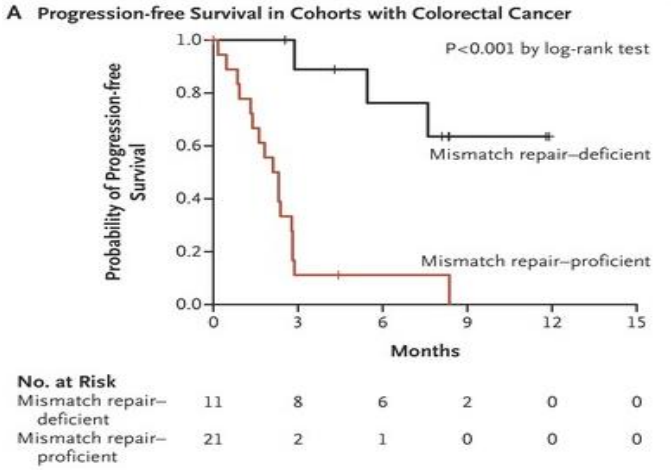
Somatic MMR mutations: 5% (range: 3–8%)

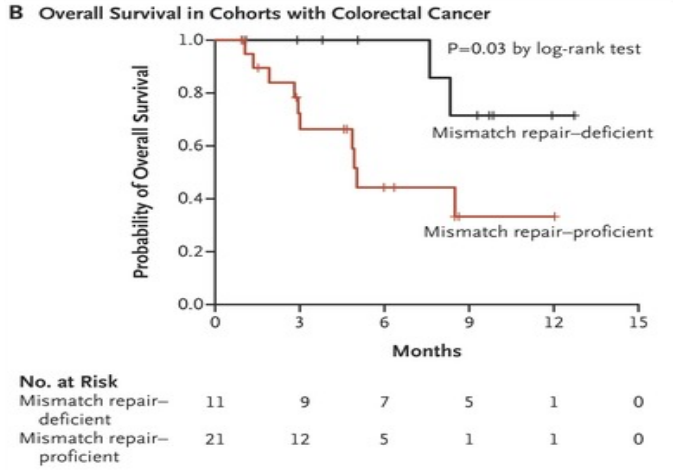
CLINICAL OUTCOMES OF THE DMMR GENOTYPE MCRPCS

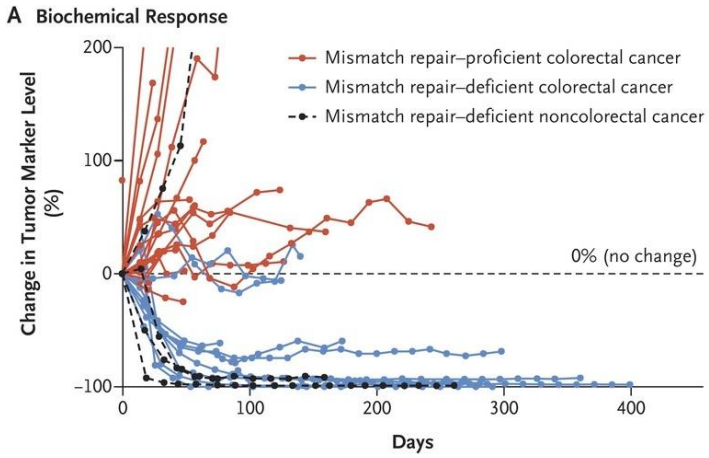
In response to novel hormone therapies and taxane chemotherapy (50 patients)

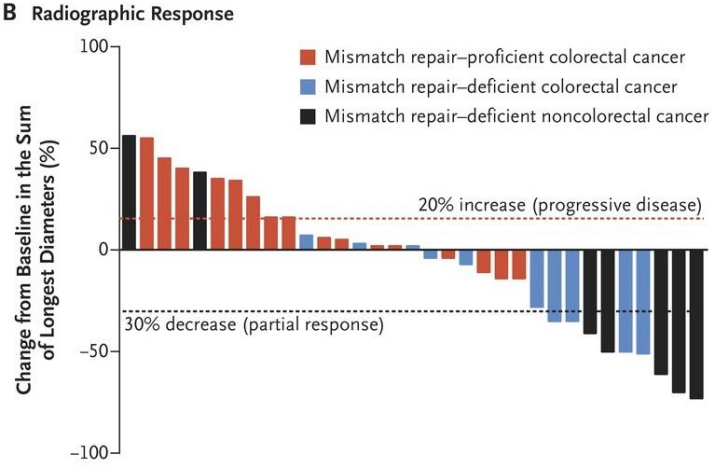


PD-1 INHIBITION IN MMR-DEFICIENT CANCERS







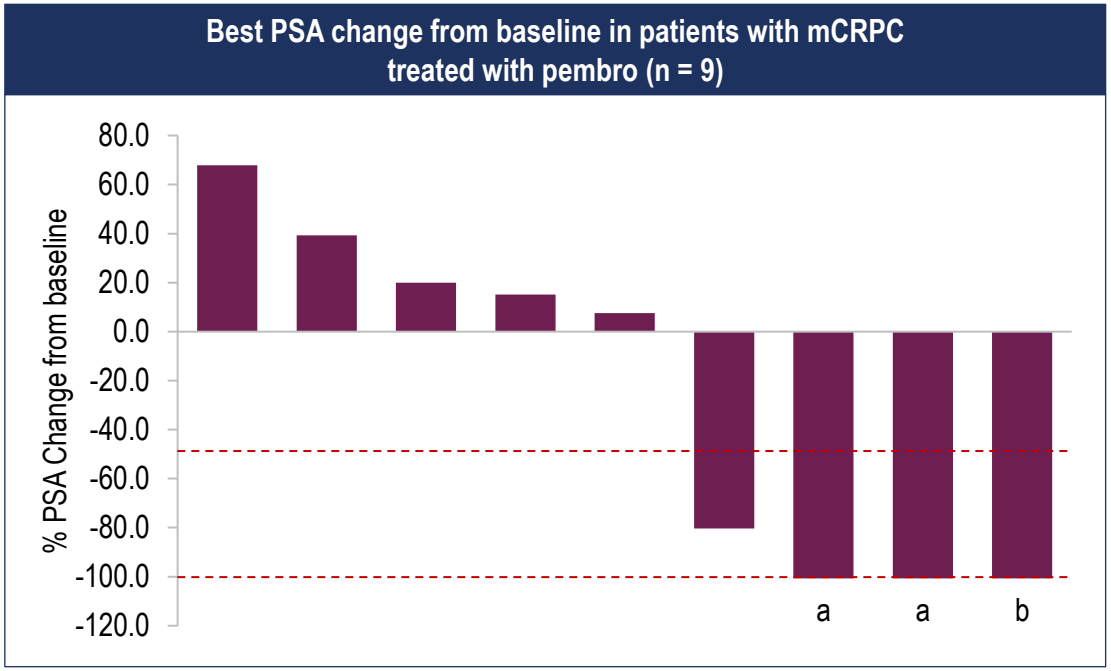


Le DT, *et al.* ASCO 2016 Abstract 103;
From N Engl J Med, Le DT, *et al.* PD-1 Blockade in Tumors with Mismatch-Repair Deficiency, 372(26), 2509-20

CLINICAL ACTIVITY OF PEMBROLIZUMAB

In mCRPC with MSI-H detected by circulating tumour DNA

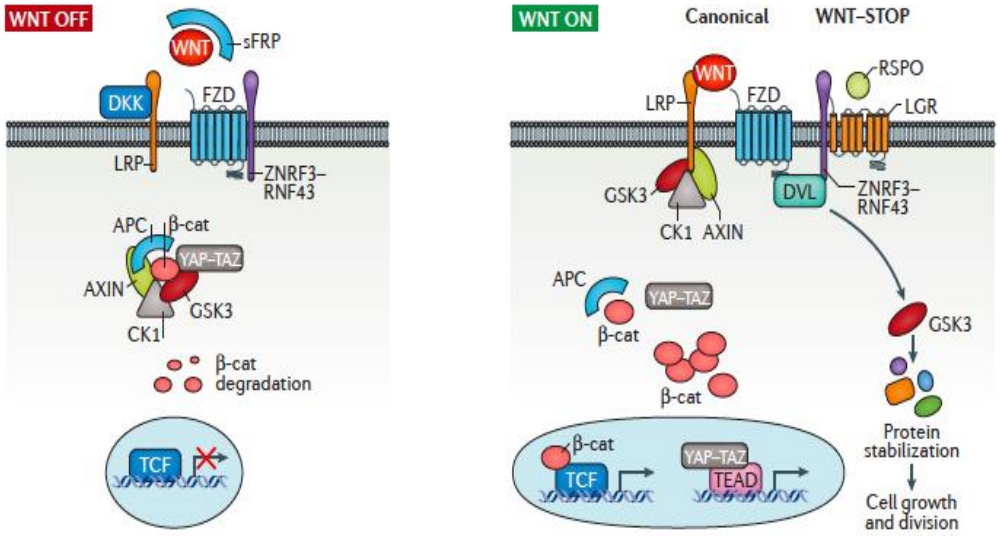
- Retrospective analysis of patients with mCRPC and MSI-H tumour detected
- The use of liquid biopsy to identify mCRPC patients with MSI-H is feasible in clinical practice and may overcome some of the obstacles associated with prostate cancer tumour tissue testing
- The robust activity of pembro in selected patients supports the generalised testing for MSI-H



a. Partial response; b Complete response.
MSI-H, microsatellite instability high; pembro, pembrolizumab.
Barata P, *et al.* J Immunother Cancer 2020;8:e001065. Reproduced under the terms of the Creative Commons Attribution, Attribution 4.0 International licence (CC BY 4.0; available at: https://creativecommons.org/licenses/by/4.0/; accessed Jul 2021).

WNT/BETA-CATENIN PATHWAY

Genetic changes in APC and CTNNB1 (that activate canonical β-catenin-dependent WNT signalling) are observed in up to 22% of castration-resistant prostate cancers (CRPC)

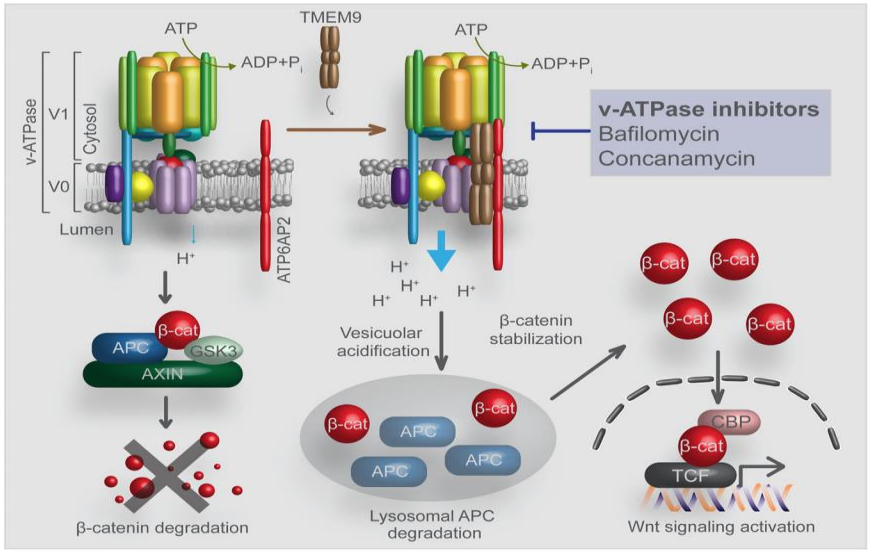


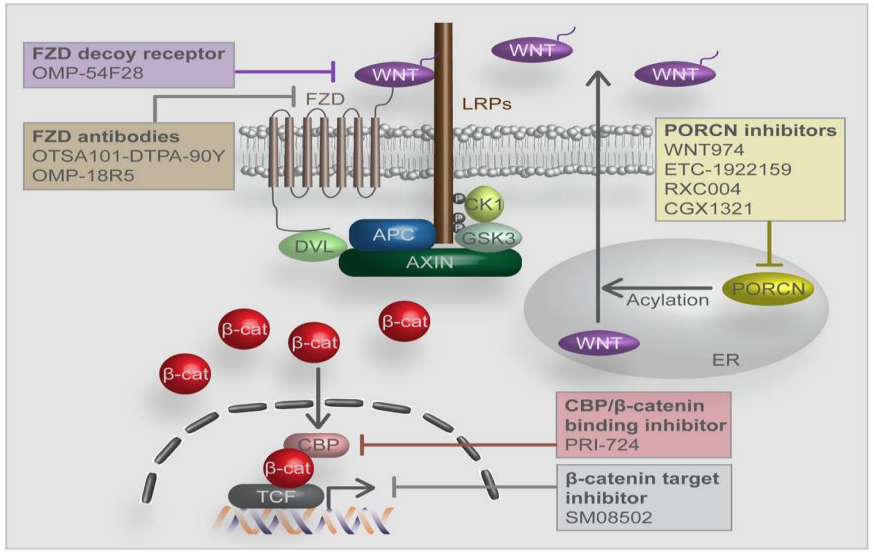
Prostate cancer stroma secrete WNT proteins that activate WNT signalling in tumour cells and promote therapy resistance and disease progression

Cons: Blockade of Wnt signaling impairs tissue homeostasis and regeneration → looking for Wnt signaling regulators whose expression is specific to cancer cells

WNT/BETA-CATENIN PATHWAY

Inhibition of Wnt/β-catenin signaling activity by targeting the TMEM9-v-ATPase axis





Agents that target WNT signalling are in early-stage clinical trials for some cancers, including prostate cancer

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Murillo-Garzón V. Nat Rev Urol, 2017; Jung YS, Park JI. Wnt signaling in cancer: therapeutic targeting of Wnt signaling beyond β-catenin and the destruction complex. Exp Mol Med 52, 183–191 (2020). Reproduced under the terms of the Creative Commons Attribution, Attribution 4.0 International licence (CC BY 4.0; available at: https://creativecommons.org/licenses/by/4.0/; accessed Jul 2021).

ESMO

OVERVIEW OF PREDICTIVE BIOMARKERS IN PROSTATE CANCER

Predictive biomarker:

- Measurement associated with response or lack of benefit to a specific therapy
- Benefit for some patients and only if therapies available
- Validated assay required to measure consistently and reliably

Possibly response to **checkpoint inhibitors**

- MSI and high TMB
- CDK12 loss

Possibly response to **PARPi or platinum chemotherapy**

- DNA deficiency – primarily *BRCA1/BRCA2*; also, non-*BRCA* such as *CDK12*, *PALB2*

Possibly response to **AKTi / PI3Ki**

- *PTEN* loss

Lack of response to **next generation AR-targeted therapy**

- AR splice variants (eg. AR-V7) [controversial]
- Loss of TP53 and RB1

Differential benefit from upfront **docetaxel** or **AR-targeted therapy** for mHSPC

- Luminal-basal transcriptional subtype (Hamid, *et al*, GU ASCO 2020; Feng, *et al*, ASCO 2020)

CHALLENGES IN IMPLEMENTING MOLECULAR TEST

Tumour heterogeneity (a single biopsy may not capture the overall molecular landscape)

- Mutational profiles differ within tumours and between disease sites due to heterogeneity and the clonality of alterations during tumour evolution
- Evolution results in differing mutation profiles over time

Actionable alterations of oncogenic pathways are **not always predictive of target agents response**

Cancer evolution and resistance in response to treatments

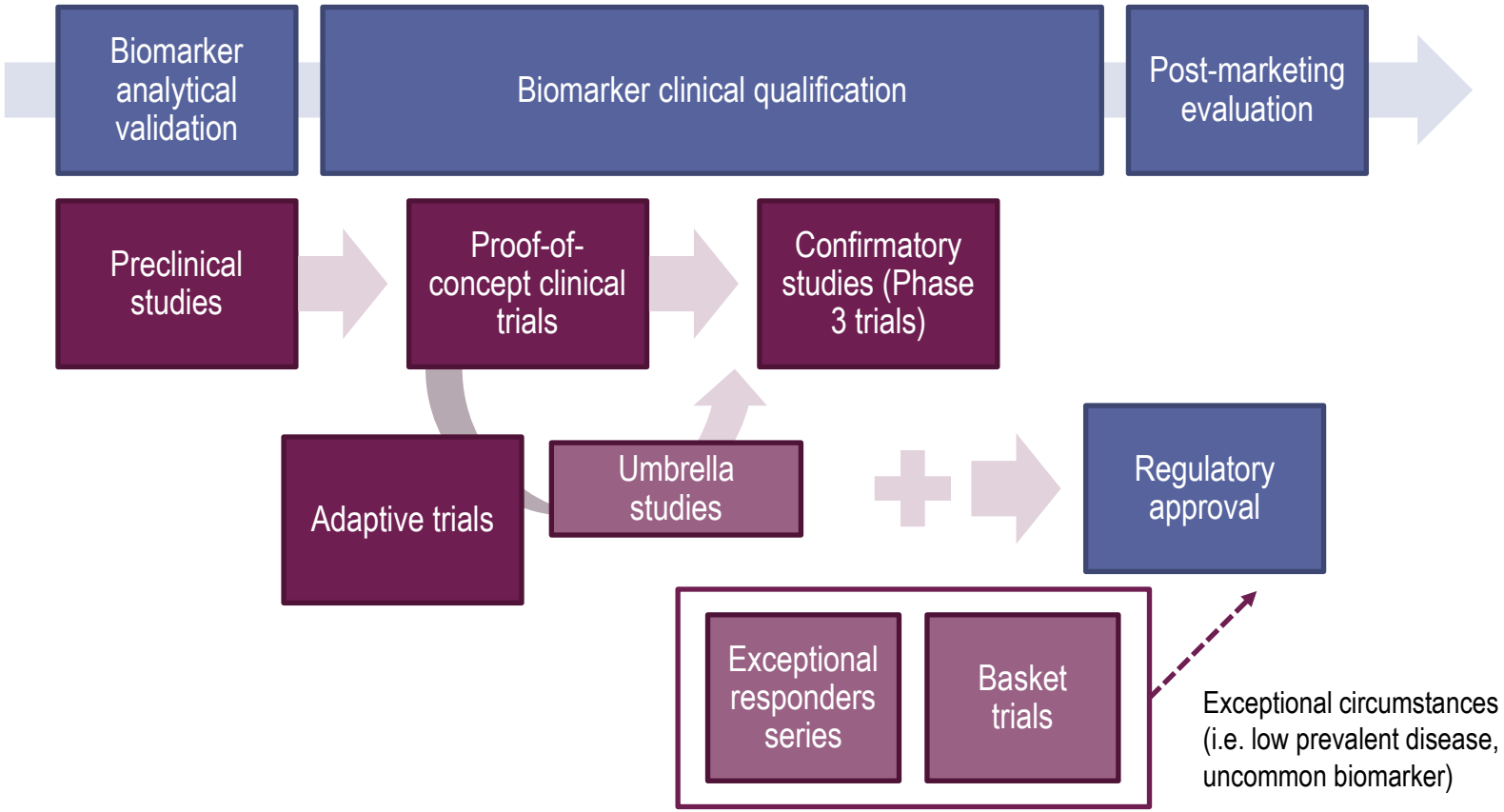
Pathway cross-talk

Evolving treatment paradigms

Increasing **complexity of detectable genomic changes in cancer**

- Interpretation of variants required pooled knowledge and collaboration with multiple disciplines to predict effect in relation to cancer biology and targeted therapies

STRATEGIES IN THE CLINICAL TRIAL DEVELOPMENT

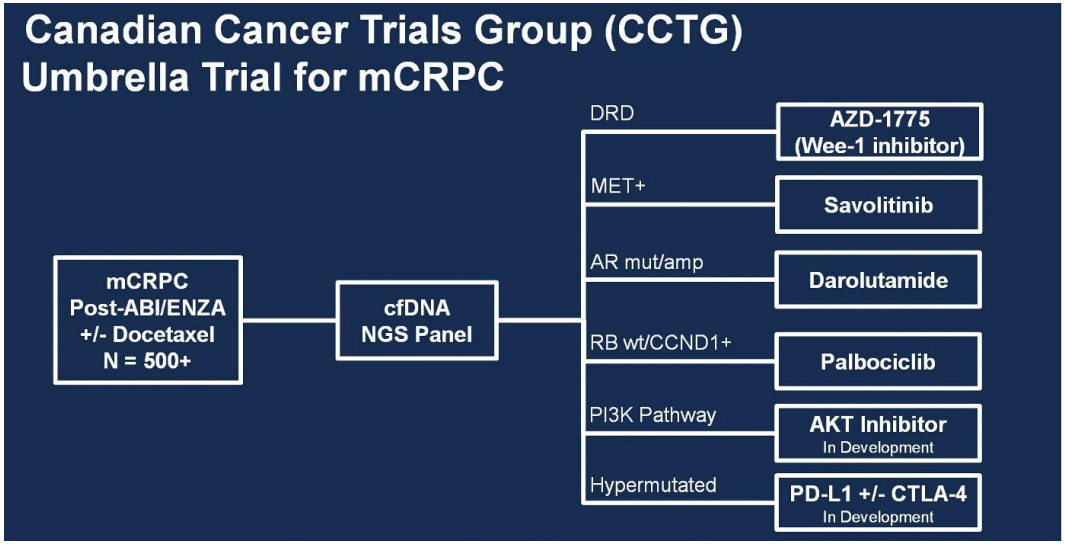


Mateo J & De Bono J. ASCO Educational Book 2016. With permission from Prof J. de Bono.

STRATEGIES IN THE CLINICAL TRIAL DEVELOPMENT

1) Develop biomarker-driven trials for advancing precision medicine in prostate cancer

- Precision cancer trial model: the goal being to increase the probability of benefit in distinct patient subsets and reducing the probability of non-benefit in those predicted to derive little benefit from these strategies

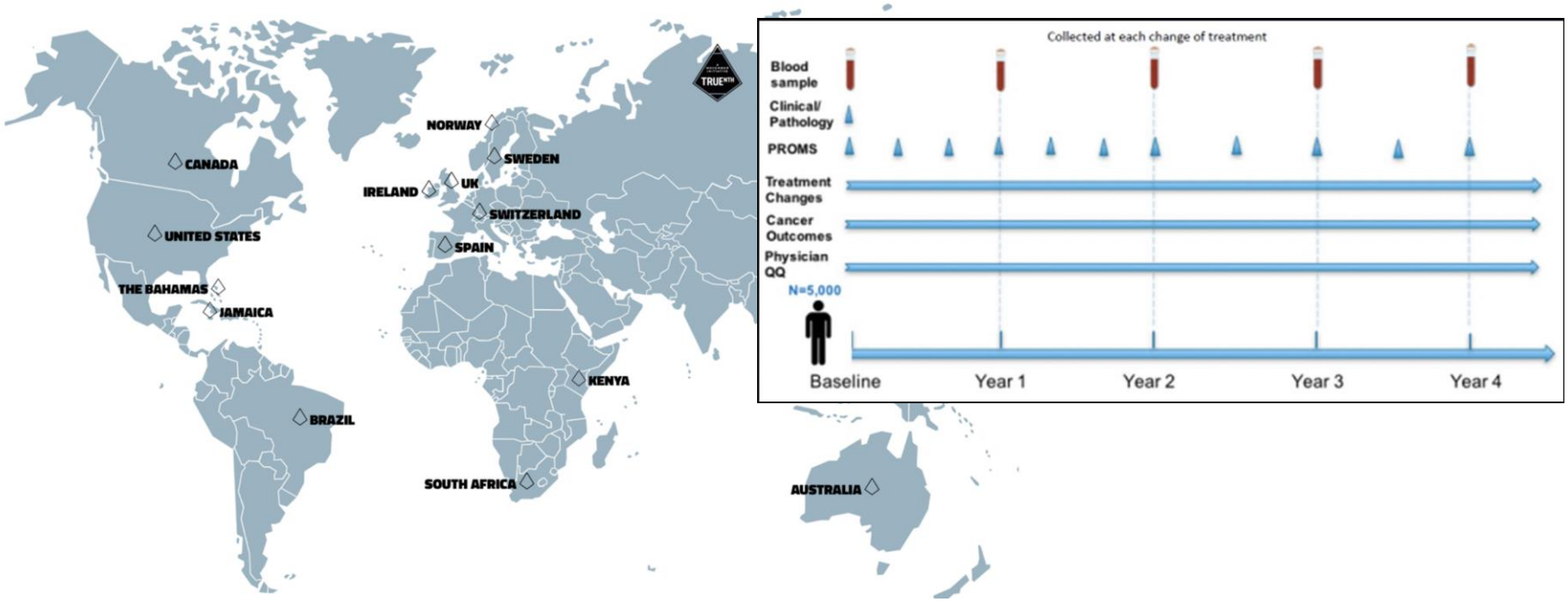


www.clinicatrials.gov. NCT03385655

STRATEGIES IN THE CLINICAL TRIAL DEVELOPMENT

2) Multidisciplinary international collaborations

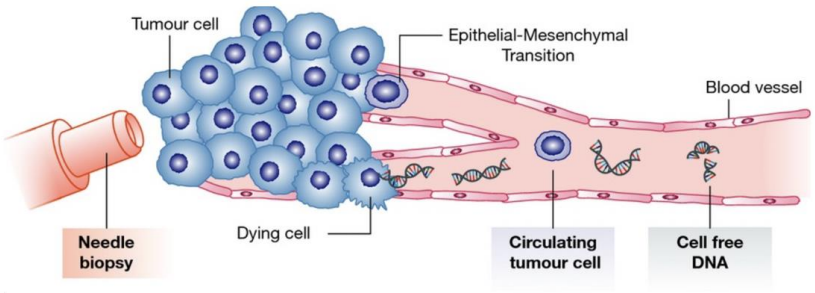
IRONMAN: International Registry for men with advanced PC



Available at: https://ironmanregistry.org/; accessed Aug 2021.

STRATEGIES IN THE CLINICAL TRIAL DEVELOPMENT

3) Incorporate liquid biopsy approach may handle genetic heterogeneity
   - ctDNA seems representative of metastatic tissue biopsies
   - Minimally invasive (bone only disease is frequent in PC)
   - Longitudinal serial sampling
     - Monitoring NEPC transformation
     - Treatment response monitoring
   - Non-specialised centres



4) Window of opportunity trial design (biology evaluation in untreated tumours over a short period of time) can provides a unique view

5) Prospectively collect biological samples and process centrally

6) Randomisation will make possible to investigate the predictive value of biomarkers

Wyatt AW, *et al.* J Natl Cancer Inst 2017;109(12):djx118. Image from Wyatt AW, *et al.* EMBO Mol Med 2015;7:878–894.

DISCLOSURES

- Nieves Martinez Chanza has reported:

Financial Interests:

  - Astellas, Advisory Board, Personal
  - Ipsen, Advisory Board, Personal
  - Janssen, Invited Speaker, Personal
  - Merck, Advisory Board, Personal
  - Merck, Advisory Board, Personal

- Karima Oualla has reported she has no interests to declare
- Irene Moreno Candilejo has reported she has no interests to declare