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Biologic Rationale for and Ongoing Evaluation of PARP Inhibitors in the Management of Metastatic Prostate Cancer

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Faculty Disclosures

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For which of your patients with metastatic prostate cancer do you generally perform BRCA germline testing?

 EMMANUEL S ANTONARAKIS, MD	All patients
 A OLIVER SARTOR, MD	All patients
 HOWARD I SCHER, MD	All patients
 MATTHEW R SMITH, MD, PHD	All patients
 CORA N STERNBERG, MD	Most patients

For a patient with metastatic prostate cancer and a BRCA germline mutation who does not have a significant family history, how do you approach genetic counseling?

 EMMANUEL S ANTONARAKIS, MD	I refer these patients to a genetic counselor
 A OLIVER SARTOR, MD	Patients are counseled by staff member but not a genetic counselor
 HOWARD I SCHER, MD	I refer these patients to a genetic counselor
 MATTHEW R SMITH, MD, PHD	I refer these patients to a genetic counselor
 CORA N STERNBERG, MD	I counsel these patients myself or refer them to a genetic counselor

Have you or would you prescribe a PARP inhibitor to a patient with metastatic prostate cancer and a….

	gBRCA mutation	Somatic BRCA mutation	ATM mutation
 EMMANUEL S ANTONARAKIS, MD	I have	I have	I have, but will probably stop doing so moving forward
 A OLIVER SARTOR, MD	I have	I have	I haven't and would not
 HOWARD I SCHER, MD	I have	I have	I have
 MATTHEW R SMITH, MD, PHD	I have	I have	I have
 CORA N STERNBERG, MD	I have	I haven't but would for the right patient	I haven't but would for the right patient

Outline

- Frequency of DNA repair mutations in prostate cancer
- Indications for germline genetic testing
- ‘Synthetic lethality’ and biologic rationale for PARP inhibition
- Clinical data with Olaparib in mCRPC
- Clinical data with Rucaparib in mCRPC
- PARP inhibitor combinations (w/ hormonal agents, checkpoint inhibitors)
- Conclusions

Frequency of DNA repair mutations in prostate cancer

Single-stranded (ss) DNA Repair pathways

- Mismatch repair (MMR)
  - Base errors from DNA replication and recombination
  - *MSH2, MSH6, MLH1, PMS2*
- Nucleotide excision repair (NER)
  - DNA damage from UV light, polycyclic aromatic hydrocarbons
  - *XPA-G, ERCC1-8, CSA/B, RPA, RAD23A/B*
- **Base excision repair (BER)**
  - **DNA damage from alkylation, oxidation/ROS, deamination**
  - ***PARP1/2/3, POLβ, MUTYH, XRCC1, MBD4, NTHL1***

Double-stranded (ds) DNA Repair pathways

- **Homologous recombination (HR)**
  - **DNA damage from ionizing radiation or other dsDNA injury**
  - ***FANC* genes, *BRCA1/2*, *ATM*, *PALB2*, *RAD50*, *RAD51*, *NBN*, *MRE11*, *BLM*, *ATR***
- Non-homologous end joining (NHEJ)
  - DNA damage from ionizing radiation or other dsDNA injury
  - *XRCC4/5/6, LIG4, DCLRE1C, PRKDC, NHEJ1, POLL/M*
- Trans-lesion DNA synthesis (TLS)
  - Error-prone recovery mechanism when no DNA template
  - *POLH, POLI, POLK, PCNA, REV1/3* (error-prone DNA polymerases)

DNA Repair Defects in *Localized* Prostate Ca

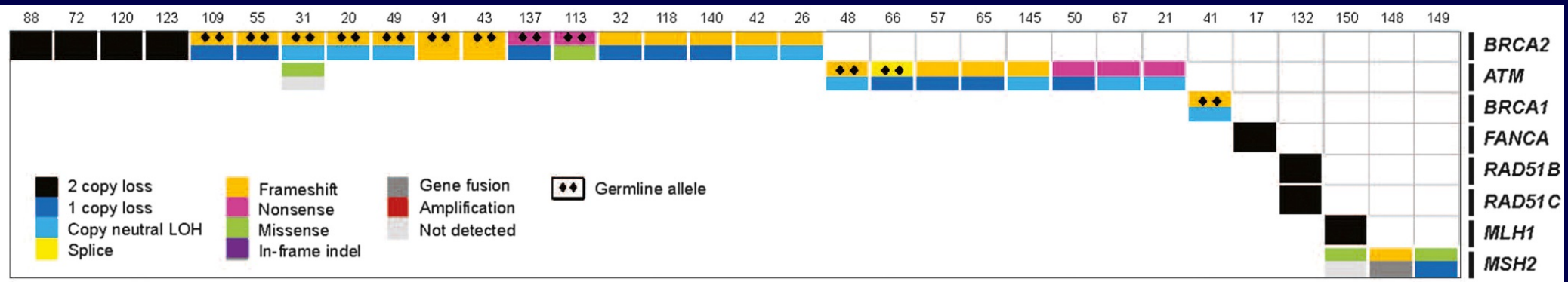
- DNA Sequencing analysis of localized prostate tumors (N = 477)
  - 200 whole-genome sequences, 277 whole-exome sequences
- 47/477 **(9.9%)** tumors had DNA repair mutations
  - *FANCA* (n = 9) 1.9%
  - *ATM* (n = 8) 1.7%
  - *RAD51* (n = 7) 1.5%
  - *CDK12* (n = 6) 1.3%
  - *BRCA2* (n = 5) 1.0%

Fraser M, et al. Nature 2017; 541: 359-364.

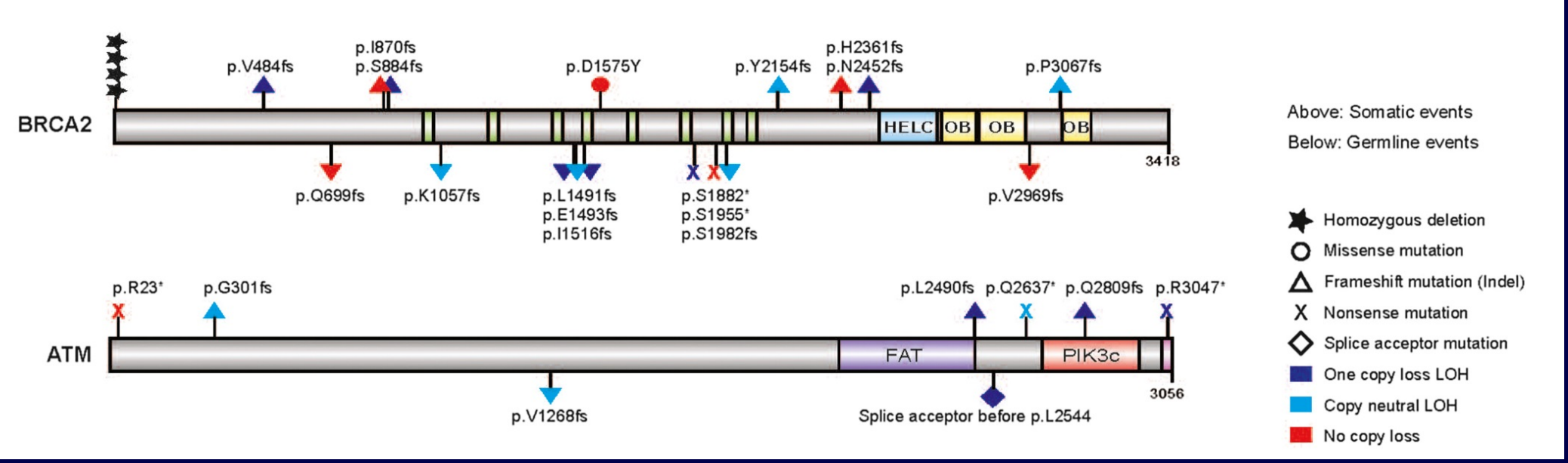
DNA Repair Defects in *Metastatic* CRPC

- 32/150 **(21.3%)** mCRPC pts had bi-allelic DNA repair mutations

All DNA Repair Defects



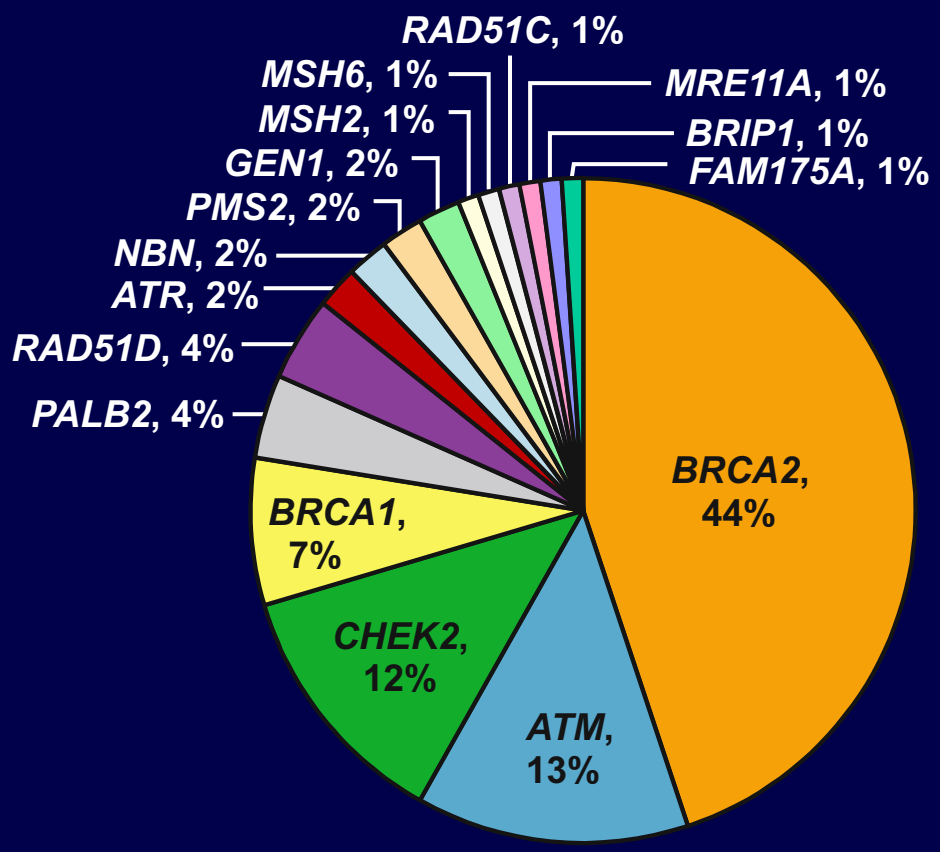
Mutations in *BRCA2, ATM*



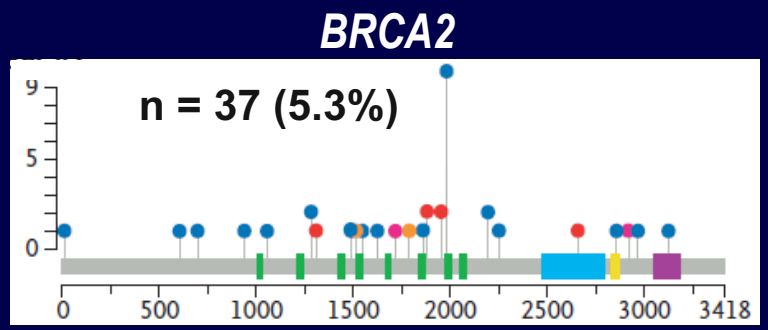
Robinson D, et al. Cell. 2015; 5: 1215-1228.

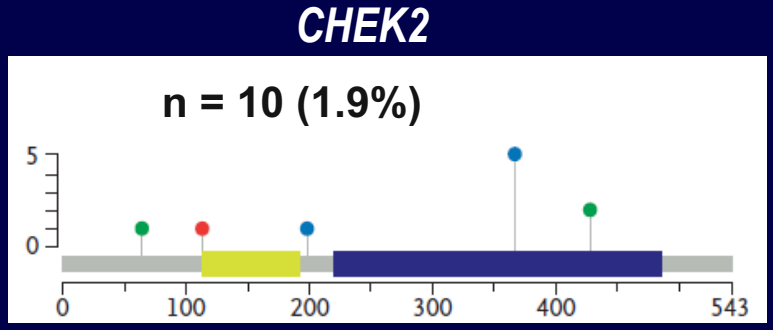
Germline Mutations in Advanced Prostate Cancer

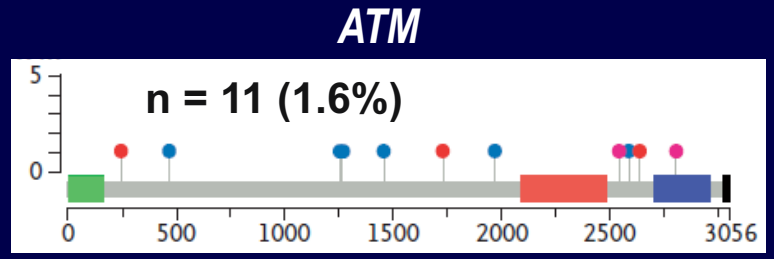
Pathogenic *Germline* Mutations

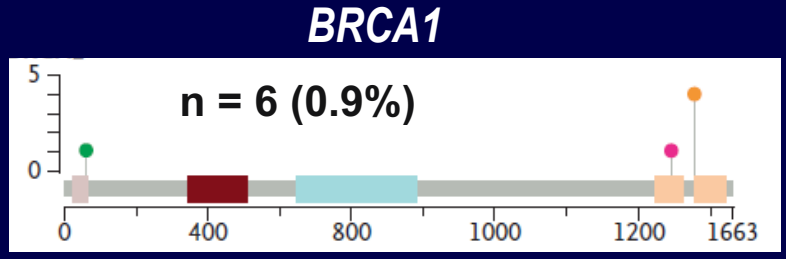


- **11.8%** (82/692) of men with metastatic prostate cancer inherited a germline DNA repair mutation vs 4.6% in localized PCa





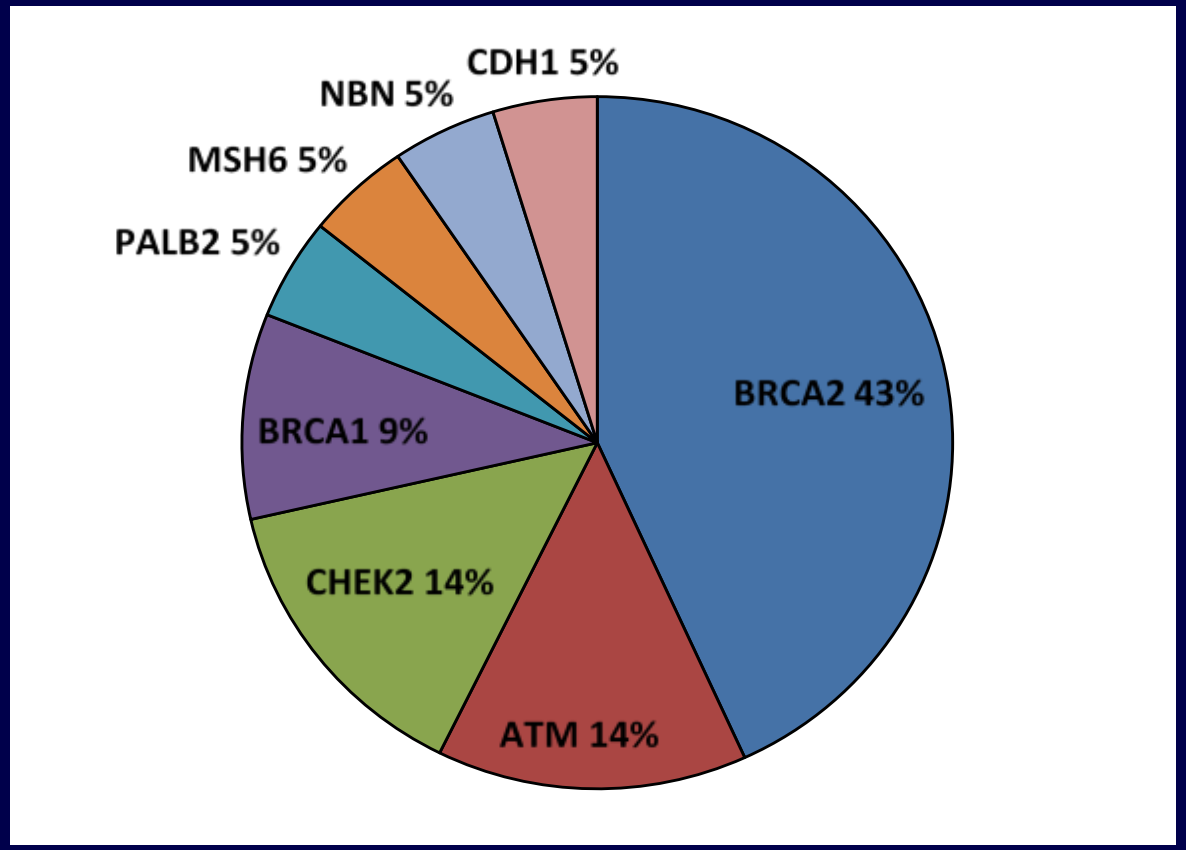




Pritchard CC, et al. N Engl J Med. 2016;375:443-453.

Germline DNA-Repair Defects and Intraductal Ca

Distribution of Germline Mutations



- Germline mutations in **14%** (21/150) of men with recurrent/ advanced prostate cancer
- Men with intraductal histology more likely to have germline mutations

Incidence of Germline Mutations

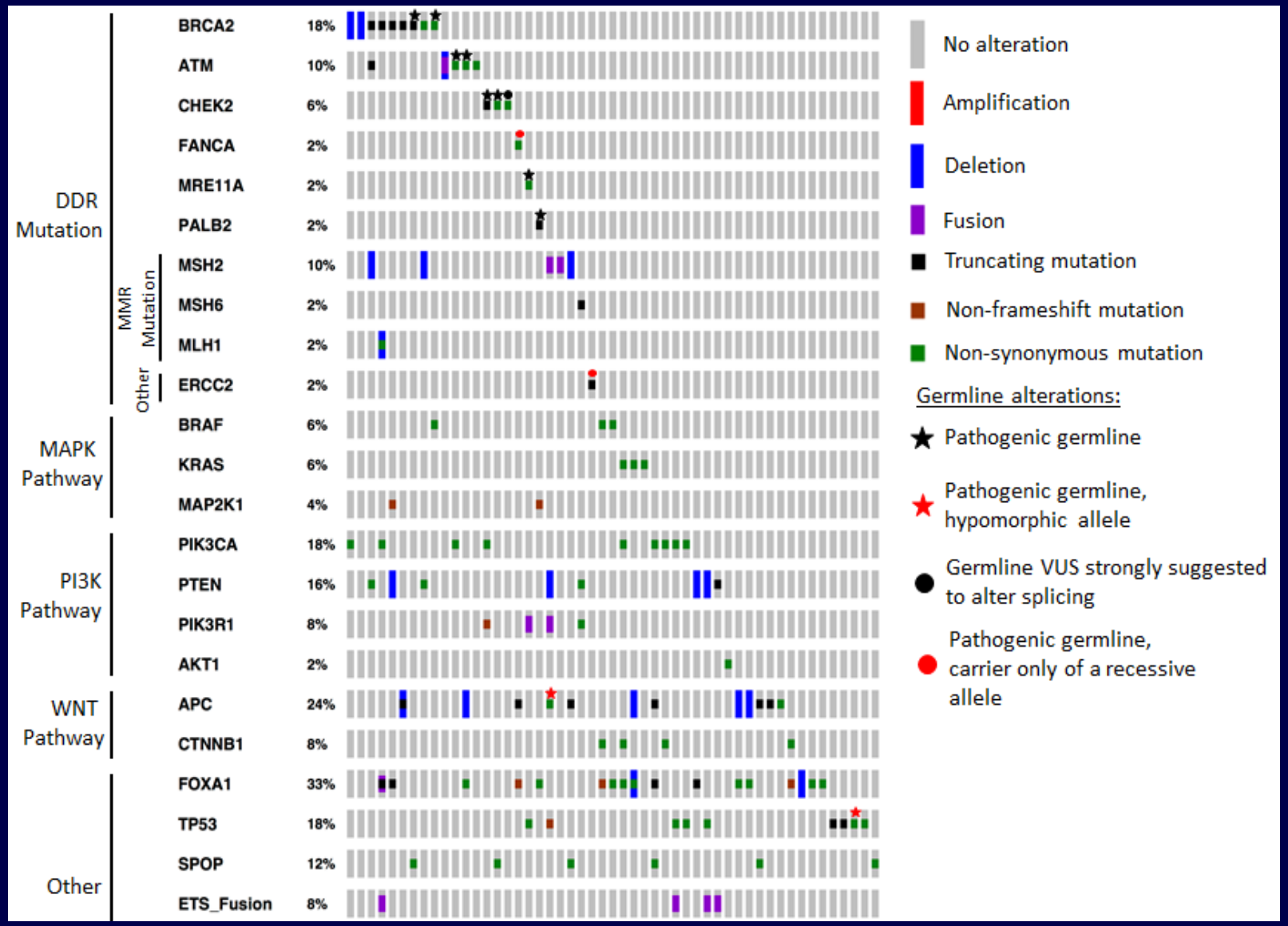
Intraductal Histology	No Intraductal Histology	*P* Value*
40% (10/25)	**9%** (11/125)	*P* = .003

*Fisher's test

Isaacsson Velho P, et al. The Prostate. 2018; 78: 401-407.

DNA Repair Defects and Prostatic Ductal Cancer

- Overall, **49%** had DNA repair gene mutations:
  - MMR mutations 14%
  - HRD mutations **31%**



Schweizer MT, et al. ASCO 2018; abstract 5030.

Indications for germline genetic testing

Germline testing:
2019 NCCN Prostate *vs.* NCCN High-Risk Breast/Ovarian

Prostate Cancer Risk Group	*NCCN 1.2019* Prostate ("Consider germline testing")	*NCCN 2.2019* High-Risk Breast/Ovarian (*BRCA1/2* Testing Criteria)
Gleason score 7, any age	• If brother or father with PCa ≤60 *OR* • If ≥1 relative with breast, ovarian, pancreas Ca *OR* • If ≥1 relative with CRC, endometrial, gastric, ovarian, pancreas, small bowel, urothelial, kidney, bile duct	• Ashkenazi Jewish ancestry • If ≥1 close blood relative with ovarian or breast Ca ≤50 *OR* • If 2 relatives with breast, pancreas, prostate Ca (Gleason ≥7 or metastatic)
Gleason score ≥8, any age	Consider germline testing for all men	• Ashkenazi Jewish ancestry • If ≥1 close blood relative with ovarian or breast Ca ≤50 *OR* • If 2 relatives with breast, pancreas, prostate Ca (Gleason ≥7 or metastatic)
Metastatic (radiographic)	Consider germline testing for all men	Germline testing for all men
Any age, and: • **≥T3a *OR*** • **PSA>20 at diagnosis**	Consider germline testing for all men	No recommendations
Any man with prostate Ca (any grade/stage, PSA level)	• If brother or father with PCa ≤ 60 *OR* • If ≥1 relative with breast, ovarian, pancreas Ca *OR* • If ≥1 relative with CRC, endometrial, gastric, ovarian, pancreas, small bowel, urothelial, kidney, bile duct	No recommendations

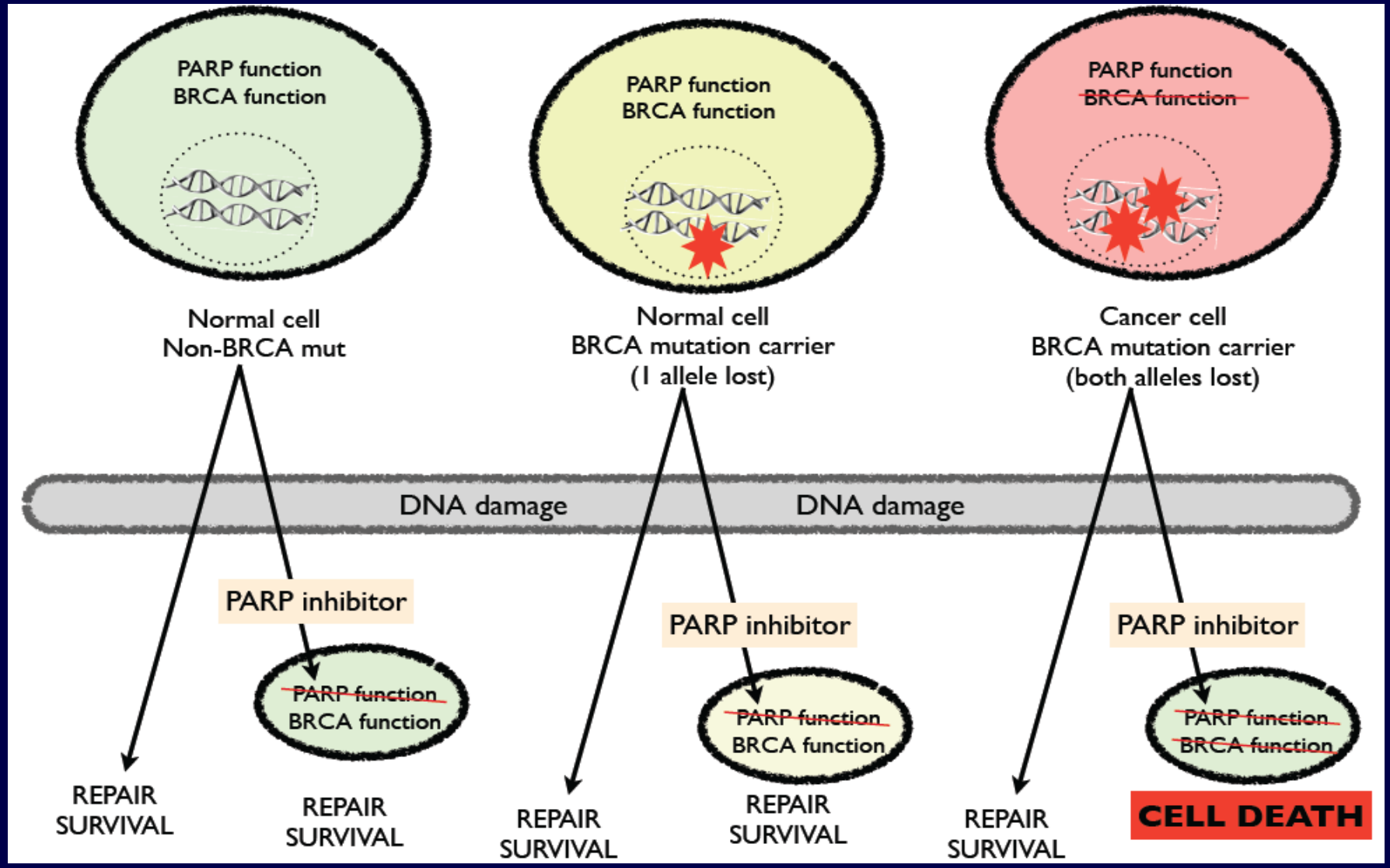
Germline Testing: Merged Referral Criteria

- Metastatic prostate cancer *(both NCCN guidelines agree on this)*
- Men with high-risk or locally-advanced disease
- For very-low to unfavorable-intermediate risk disease:
  - Brother, father, or multiple male relatives diagnosed with prostate cancer <60 yrs
  - FH suggestive of HBOC: >1 relative with breast, ovarian, or pancreatic cancers
  - FH suggestive of Lynch Syndrome: >1 relative with colorectal, endometrial, ovarian, gastric, small bowel, UTUC, bile duct cancers
- If Gleason ≥ 7:
  - FH: ≥ 1 close blood relative with ovarian, pancreatic, met PCa, breast Ca <50
  - FH: ≥ 2 close blood relatives with breast or prostate Ca (any grade) at any age
  - Ashkenazi Jewish ancestry
- *BRCA1/2* mutations detected on somatic tumor profiling

Courtesy of Veda Giri MD, Thomas Jefferson University.

‘Synthetic lethality’ and biologic rationale for PARP inhibition

‘Synthetic Lethality’ Hypothesis

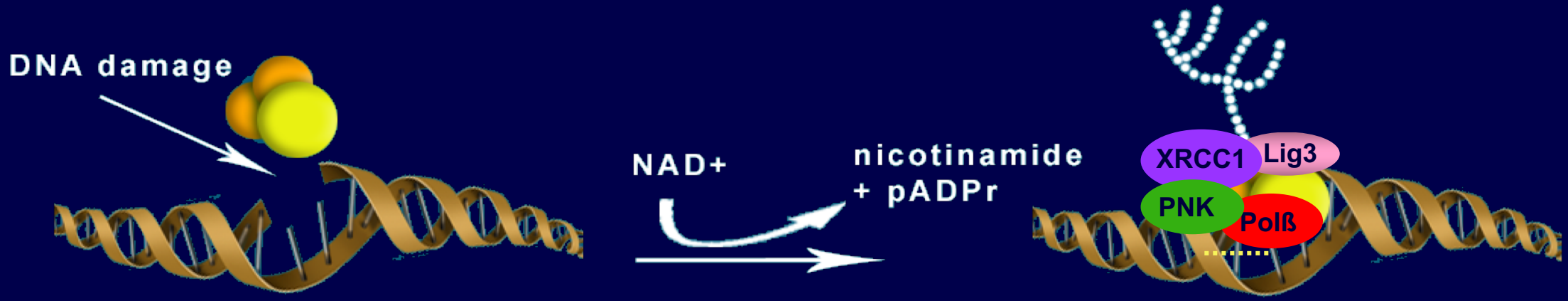


Farmer H, et al. Nature. 2005;434:917-921. Bryant et al. Nature. 2005;434:913-917.

PARP Biology

PARPs play key roles in the repair of ssDNA breaks via BER pathway:

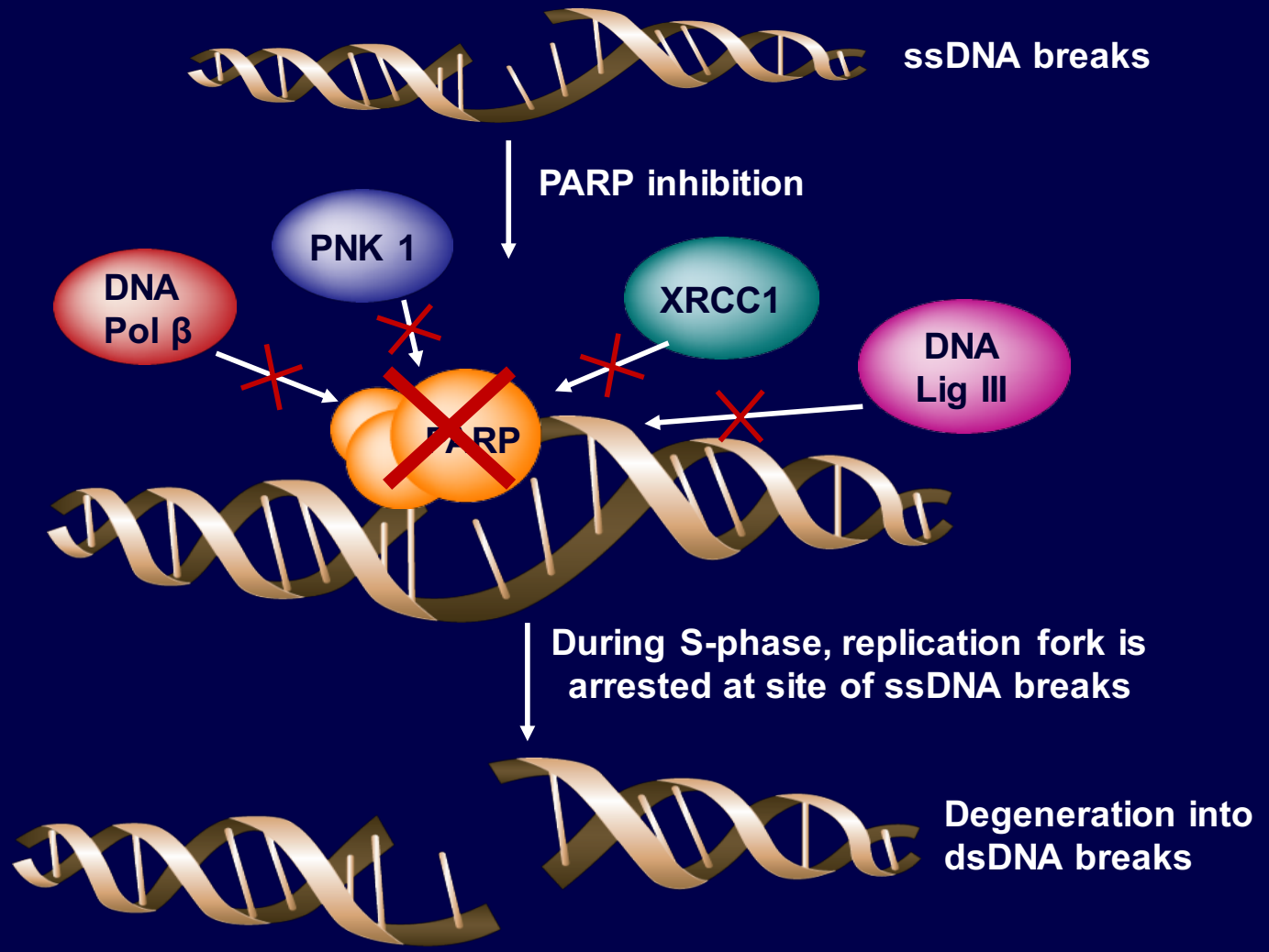
- Binds directly to sites of DNA damage
- Once activated, uses NAD as a substrate to add large, branched chains of poly(ADP-ribose) polymers (*i.e.* PARylation) to itself and interacting partners
- Recruits other DNA repair enzymes to site of damage



Ohmoto A, et al. Onco Targets Ther. 2017; 10: 5195-5208.

PARPi Leads to Increase in dsDNA Breaks

- Inhibition of PARP:
  - Prevents recruitment of DNA repair enzymes to ssDNA breaks
  - Leads to failure of ssDNA repair and accumulation of ssDNA breaks
  - Replication fork is arrested at damage, producing dsDNA breaks

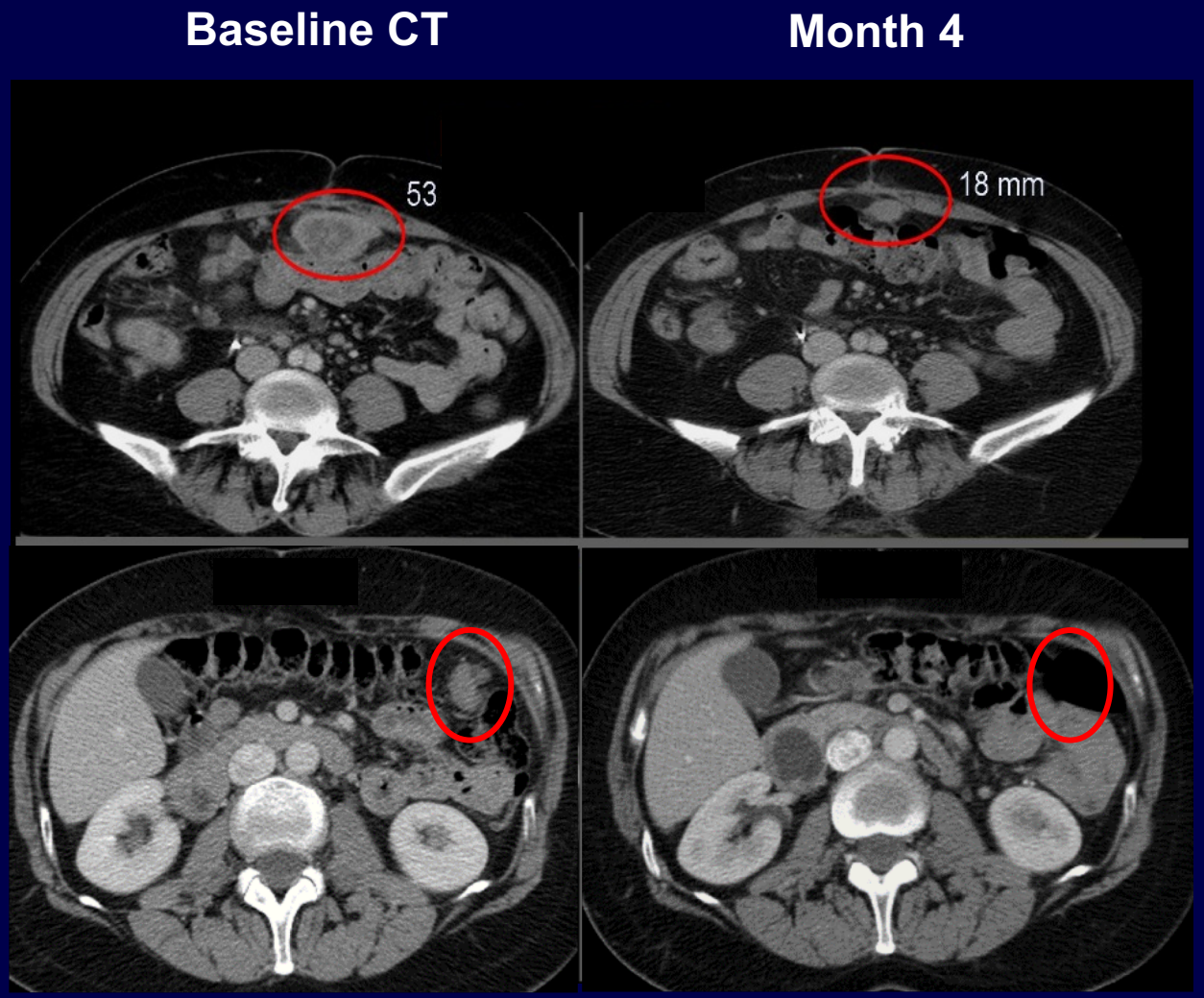


Ohmoto A, et al. Onco Targets Ther. 2017; 10: 5195-5208.

Clinical data with Olaparib in mCRPC

28 January 2016 – Olaparib granted Breakthrough Therapy designation by the FDA for treatment of *BRCA1/2*- or *ATM*-mutated metastatic CRPC

PARPi in germline *BRCA1/2* mutation carriers



- Phase I study of olaparib in patients (N=60) with solid tumors, including prostate cancer
  - 22 *BRCA1/2* mutation carriers
  - 3 prostate cancer pts, 1 with mCRPC and *BRCA2* mutation

Fong PC, et al. N Engl J Med. 2009; 361: 123-134.

TOPARP-A: Unselected phase 2 trial in mCRPC

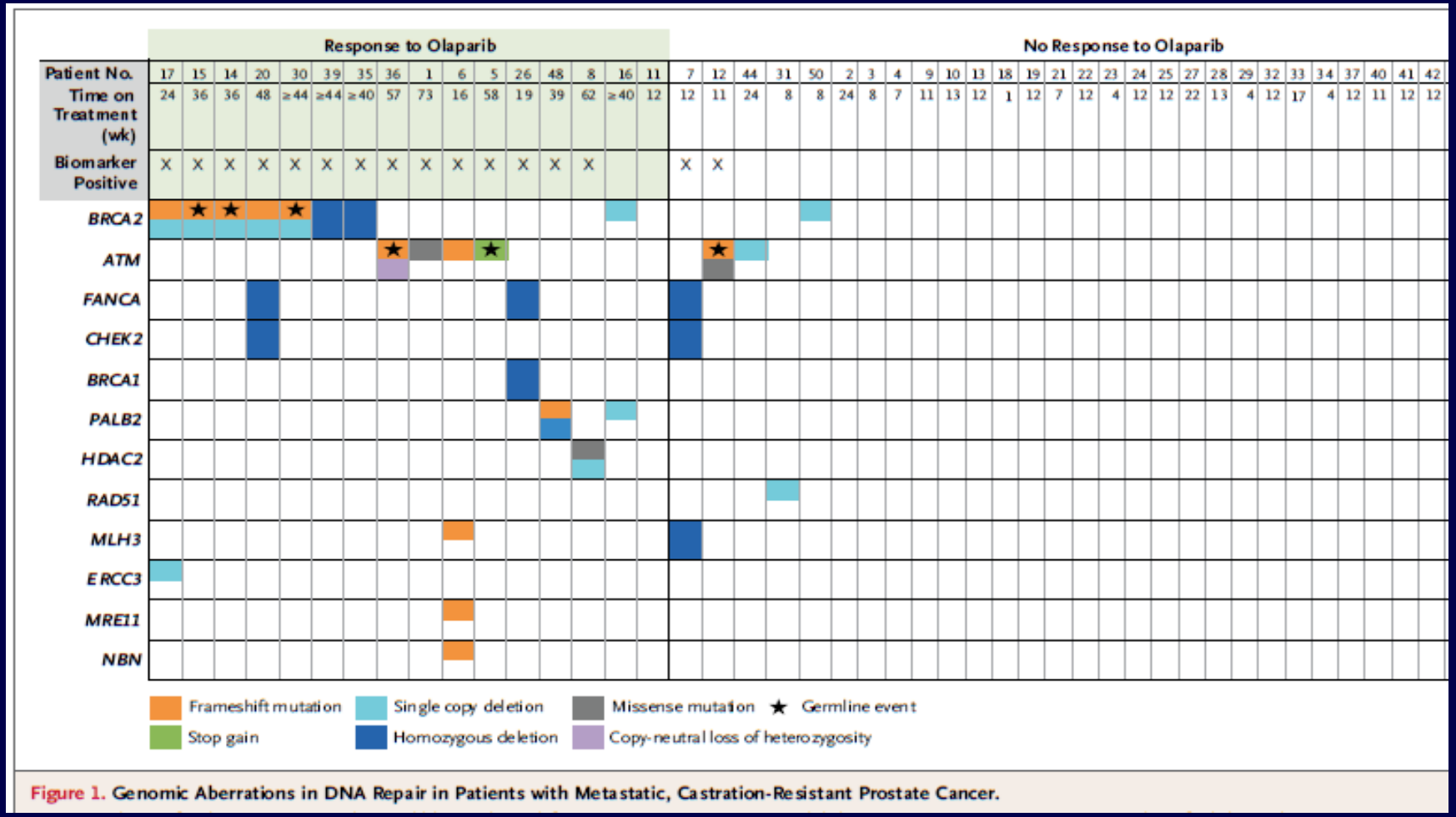
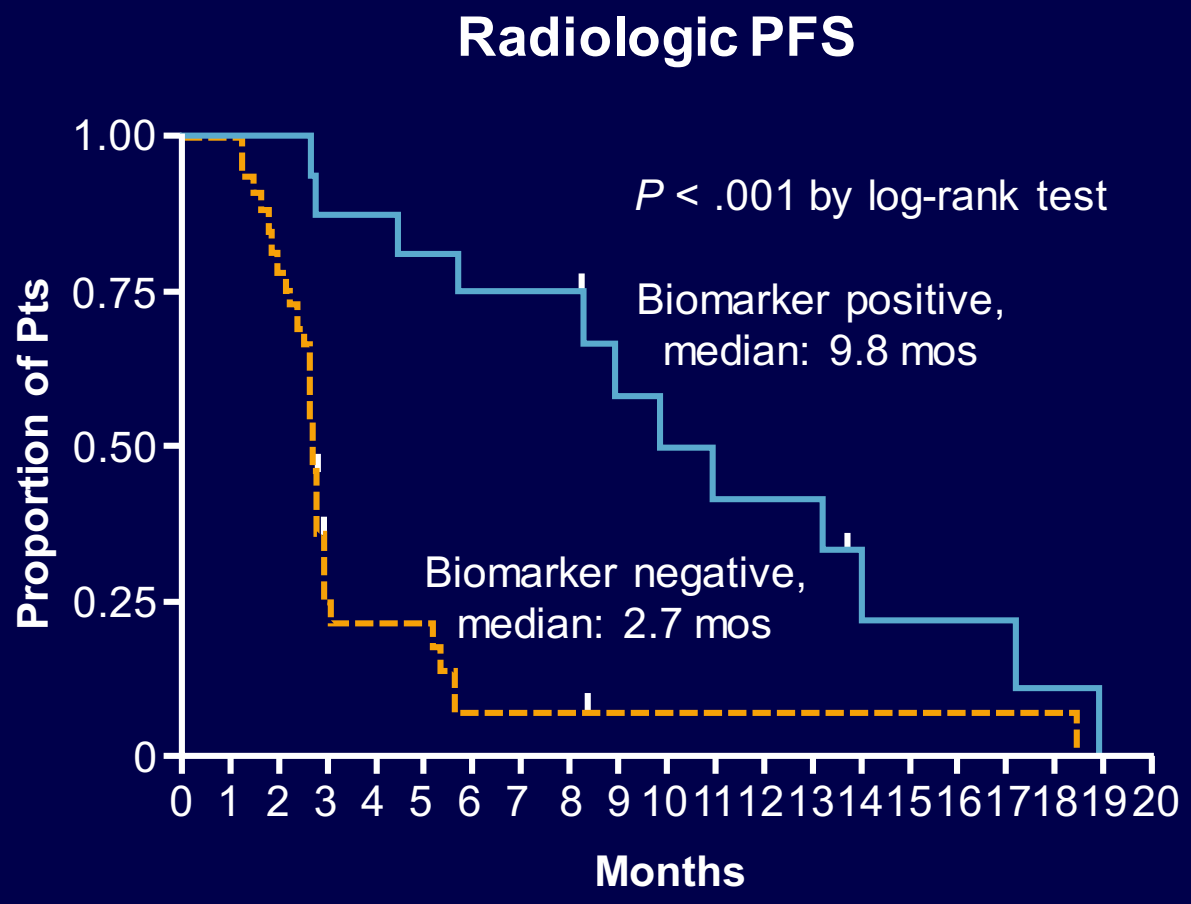


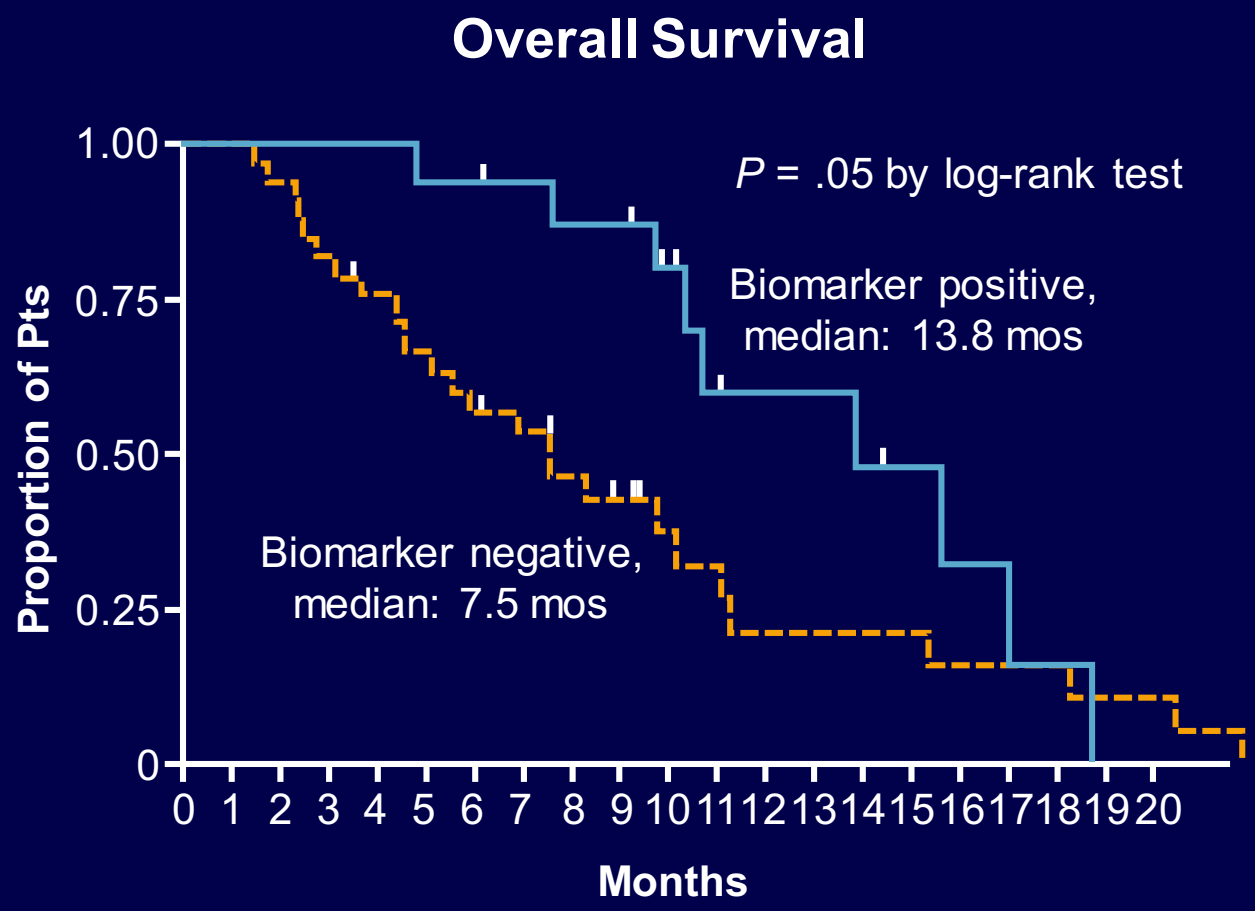
Figure 1. Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer.

- 16 of 49 pts responded to olaparib
  - 14 of 16 (88%) biomarker-positive pts
  - 2 of 33 (6%) biomarker-negative pts

Mateo J, et al. N Engl J Med. 2015; 373: 1697-1708.

TOPARP-A: Survival with Olaparib by HR Deficiency

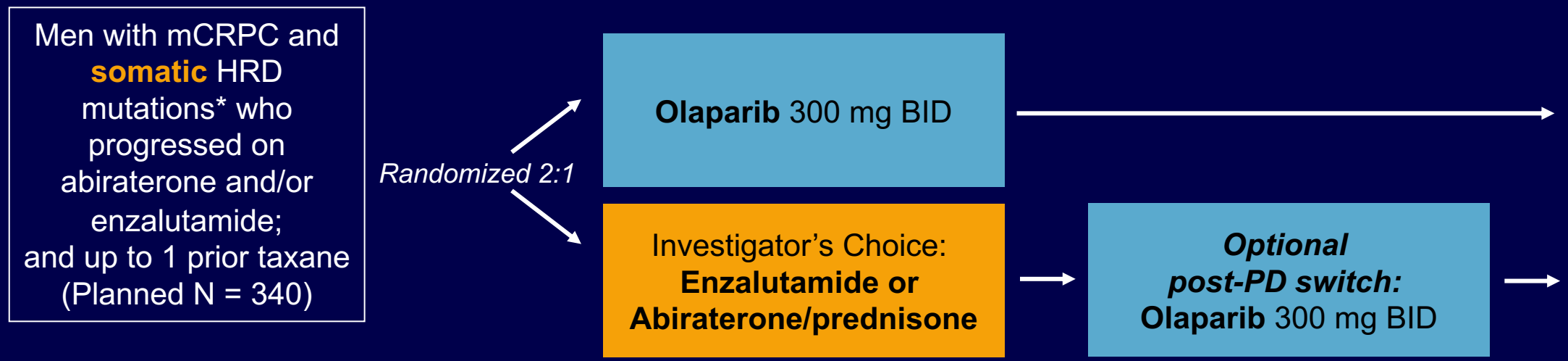




Mateo J, et al. N Engl J Med. 2015; 373: 1697-1708.

PROfound: Olaparib vs Enza or Abi in mCRPC with Somatic HRD Mutations

- Open-label, randomized, phase 3 study with rPFS primary endpoint



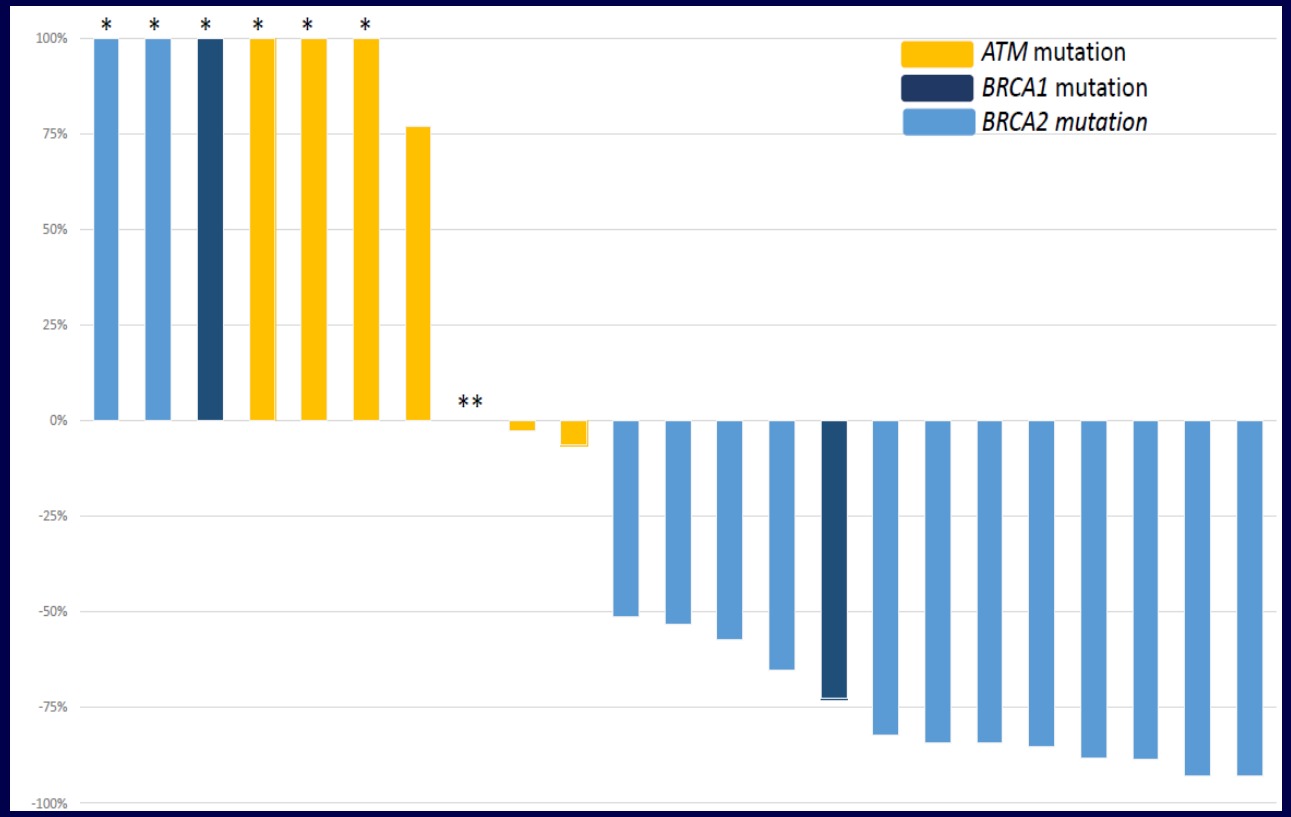
Cohort A: *BRCA1, BRCA2, or ATM*
Cohort B: One of 12 other HRD mutations

- Primary endpoint: rPFS (Cohort A)
- Secondary endpoints: ORR (Cohort A), rPFS (Cohorts A & B), time to pain progression (Cohort A), OS (Cohort A)

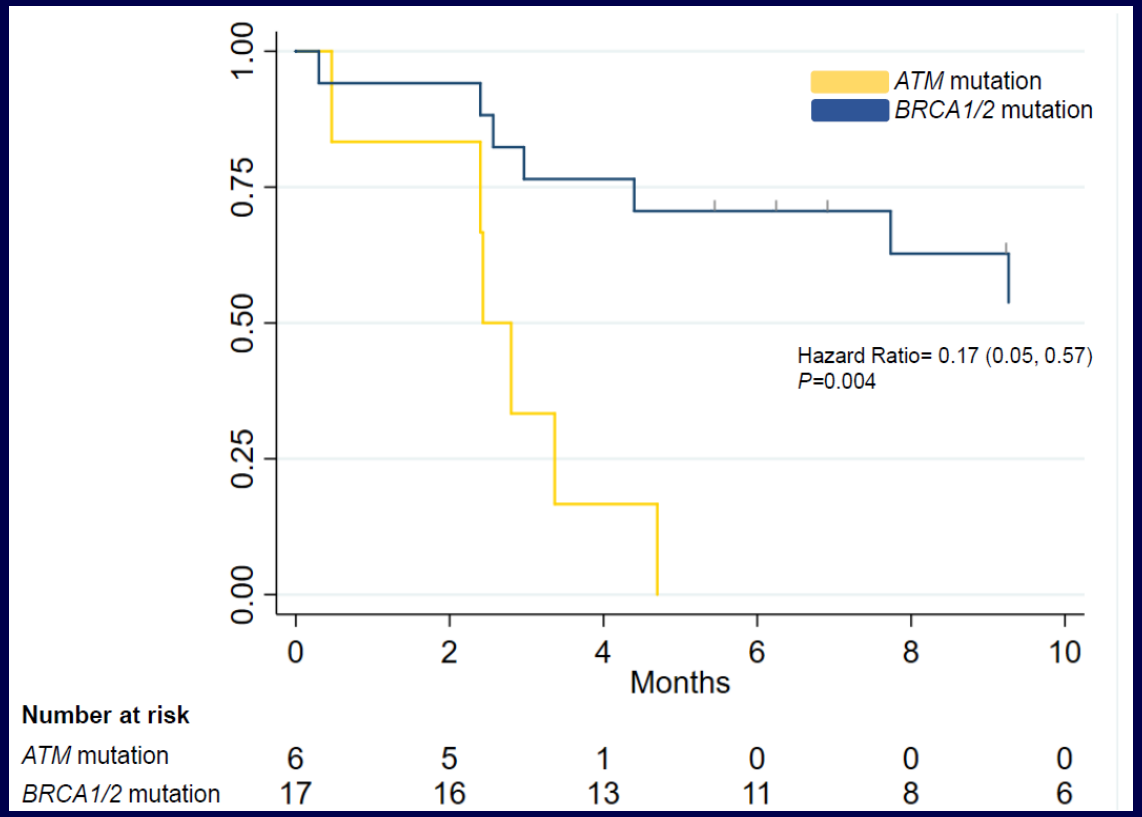
ClinicalTrials.gov. NCT02987543

Olaparib Sensitivity and *BRCA1/2* vs. *ATM*

Best PSA Response



Radiologic PFS



Handy Marshall C, et al. ASCO GU Symposium 2019; abstract 154.

Clinical data with Rucaparib in mCRPC

2 October 2018 – Rucaparib granted Breakthrough Therapy designation by the FDA for treatment of *BRCA1/2*-mutated mCRPC with at least one prior AR-directed therapy and taxane-based chemotherapy

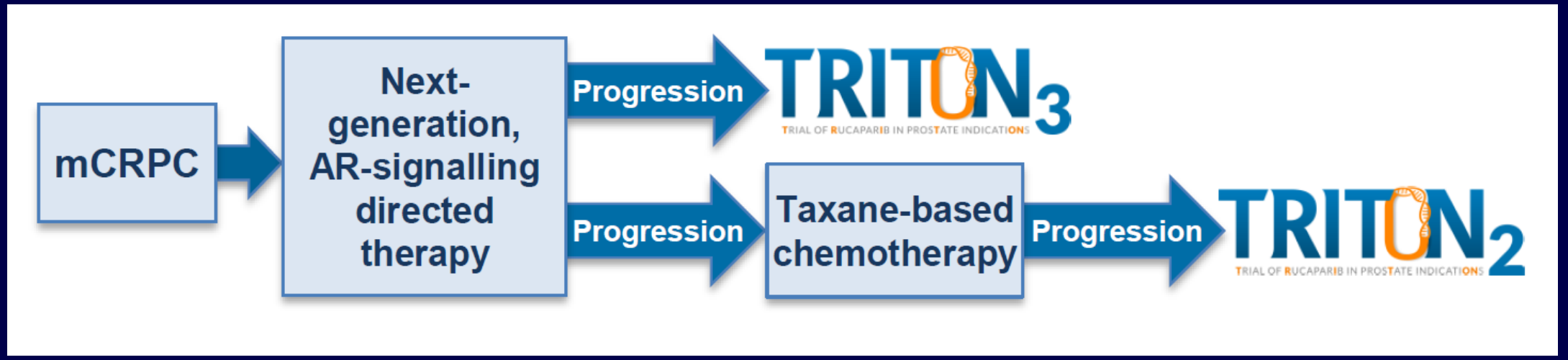
Properties of different PARP inhibitors

Table 1 Properties of PARP inhibitors

	Properties of PARP inhibitors				
	Olaparib	**Veliparib**	**Talazoparib**	**Niraparib**	**Rucaparib**
MW	434.5	244.3	380.8	320.4	323.4
PARP1 IC_{50}	5 nM[b]	1.2 nM[a]	0.56 nM[a]	3.8 nM[b]	0.65 nM[a]
PARP2 IC_{50}	1 nM[b]	0.41 nM[a]	0.15 nM[a]	2.1 nM[b]	0.08 nM[a]
Trapping[b]	++	+	++++	+++	++

Carney B, et al. Nat Commun. 2018; 9: 176.

Rucaparib (TRITON2 and TRITON3)



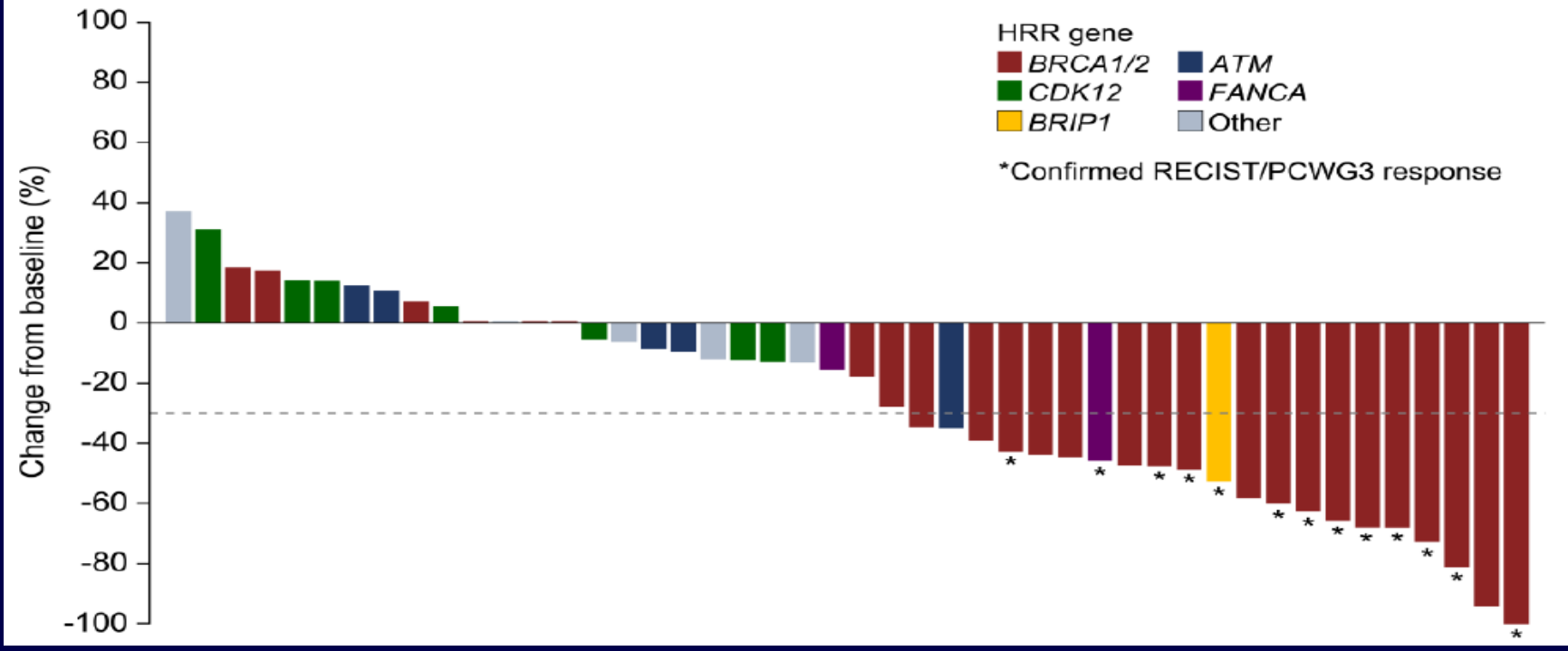
HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*)

Chowdhury S, et al. ESMO 2018; abstract 795PD.

Rucaparib: TRITON2 Interim Results

Table 2. Confirmed Investigator-Assessed ORR in Evaluable Patients

Characteristic	By HRR gene with alteration			
	BRCA1/2 (n=25)	*ATM* (n=5)	*CDK12* (n=8)	Other (n=8)
ORR, n (%) [95% CI][a]	11 (44.0%) [24.4–65.1]	0 [0.0–52.2]	0 [0.0–36.9]	2 (25.0%) [3.2–65.1]
Complete response, n (%)	0	0	0	0
Partial response, n (%)	11 (44.0%)	0	0	2 (25.0%)[b]

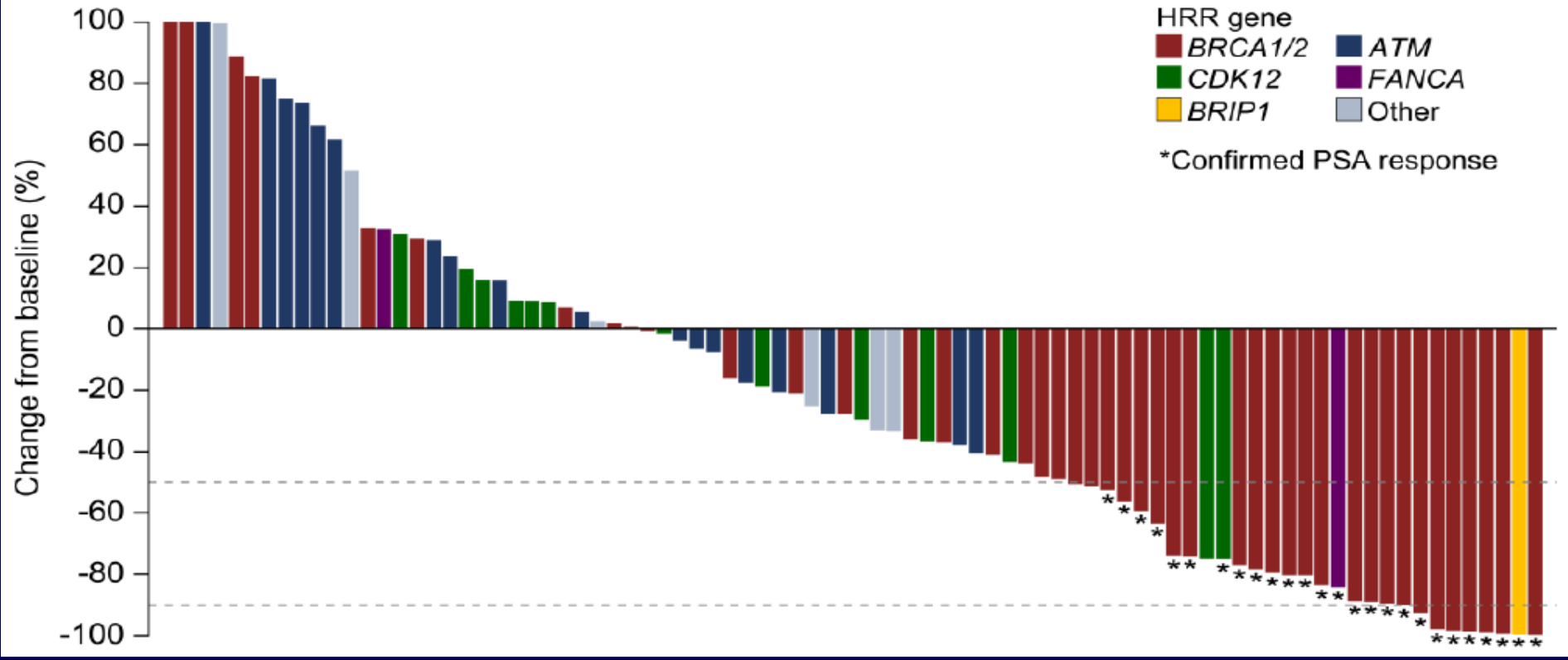


Abida W, et al. ESMO 2018; abstract 793PD.

Rucaparib: TRITON2 Interim Results

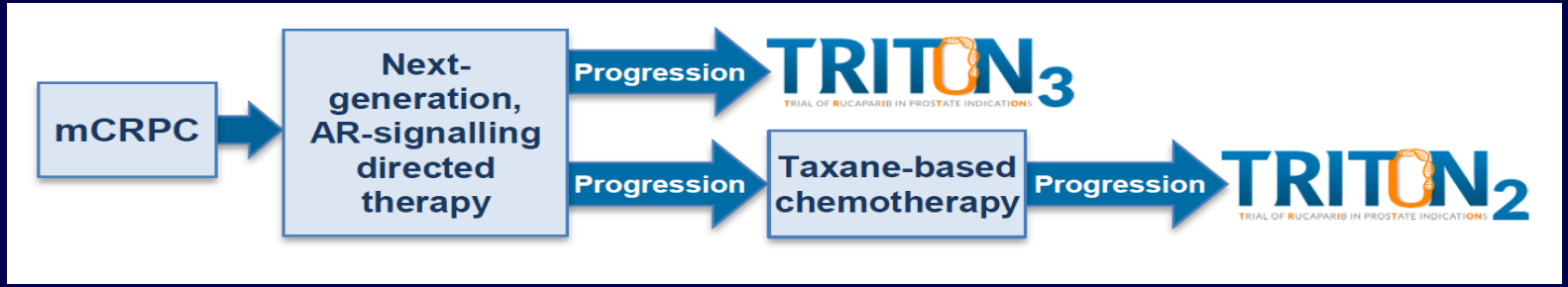
Table 3. Confirmed PSA Response Rates

PSA response rate	By HRR gene with alteration, n/N (%) [95% CI]			
	BRCA1/2	*ATM*	*CDK12*	Other
All evaluable patients	23/45 (51.1%) [35.8–66.3]	0/18 (0%) [0.0–18.5]	1/13 (7.7%)[a] [0.2–36.0]	2/9 (22.2%)[b] [2.8–60.0]



Abida W, et al. ESMO 2018; abstract 793PD.

Rucaparib (TRITON2 and TRITON3)



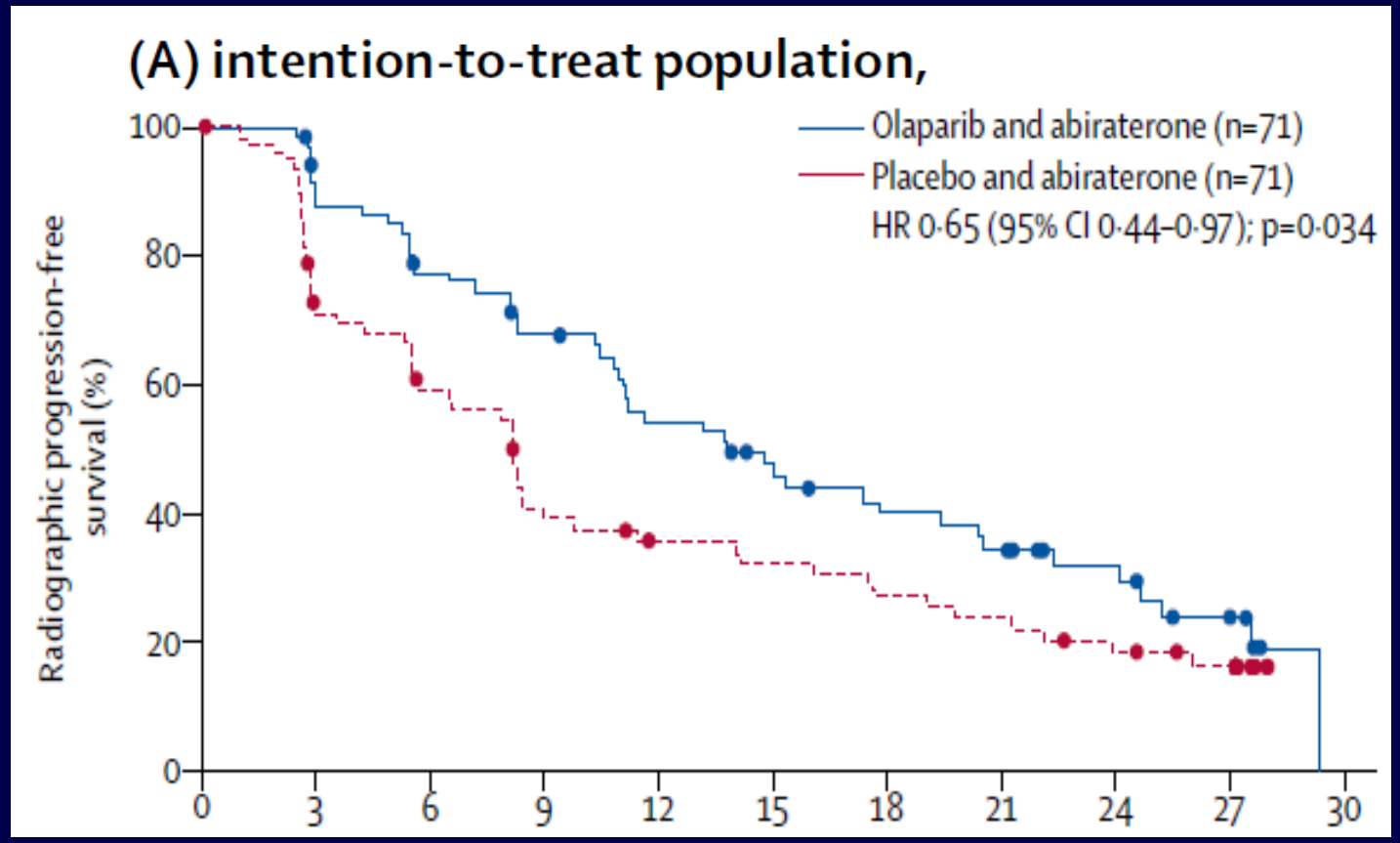
Alteration	Frequency in tissue	
	TRITON2 (n=487)	TRITON3 (n=385)
BRCA1 alteration	1.8%	1.3%
BRCA2 alteration	8.6%	5.5%
ATM alteration	6.6%	5.7%
CDK12 alteration	6.8%	5.4%
TP53 alteration	38.4%	37.1%

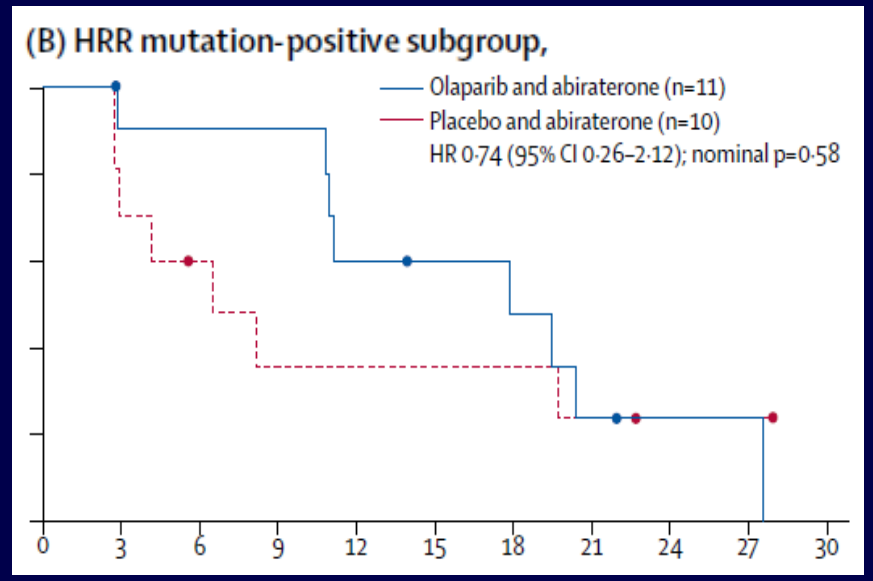
Alteration	Frequency in plasma	
	TRITON2 (n=343)[a]	TRITON3 (n=263)[a]
BRCA1 alteration	2.3%	1.9%
BRCA2 alteration	9.6%	6.8%
ATM alteration	14.6%	8.2%
CDK12 alteration	6.1%	3.1%
TP53 alteration	48.1%	44.9%

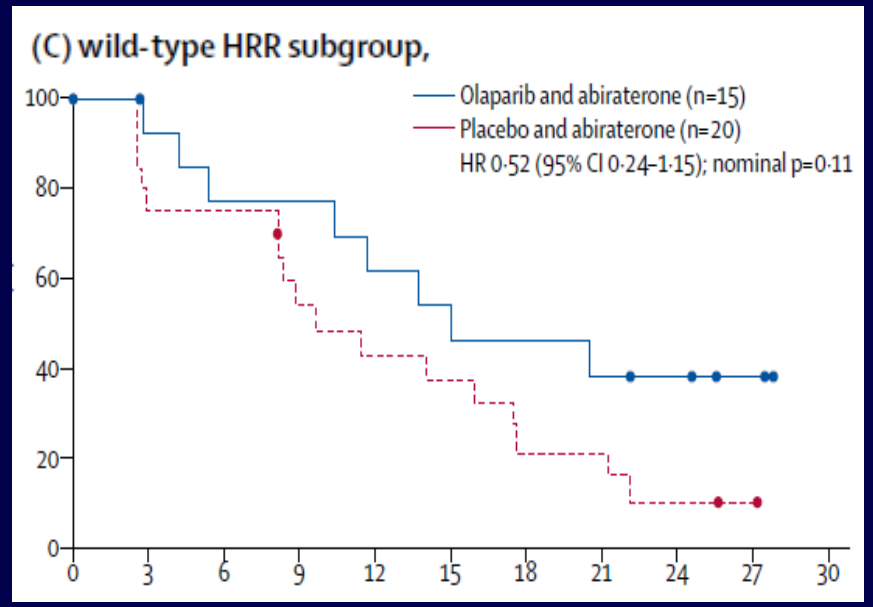
Chowdhury S, et al. ESMO 2018; abstract 795PD.

PARP inhibitor combinations:
(w/ hormonal agents, checkpoint inhibitors)

Olaparib plus Abi in Unselected mCRPC







Clarke N, et al. Lancet Oncol. 2018; 19: 975-986.

Olaparib plus Durvalumab (anti-PDL1) in mCRPC

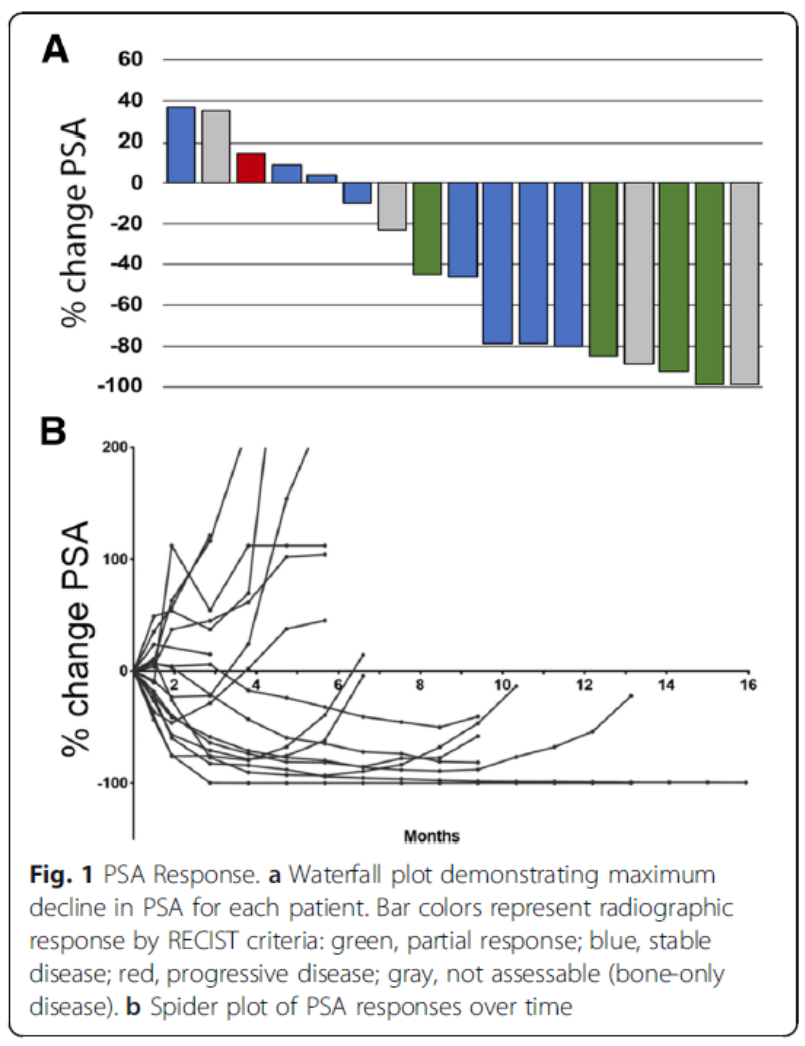
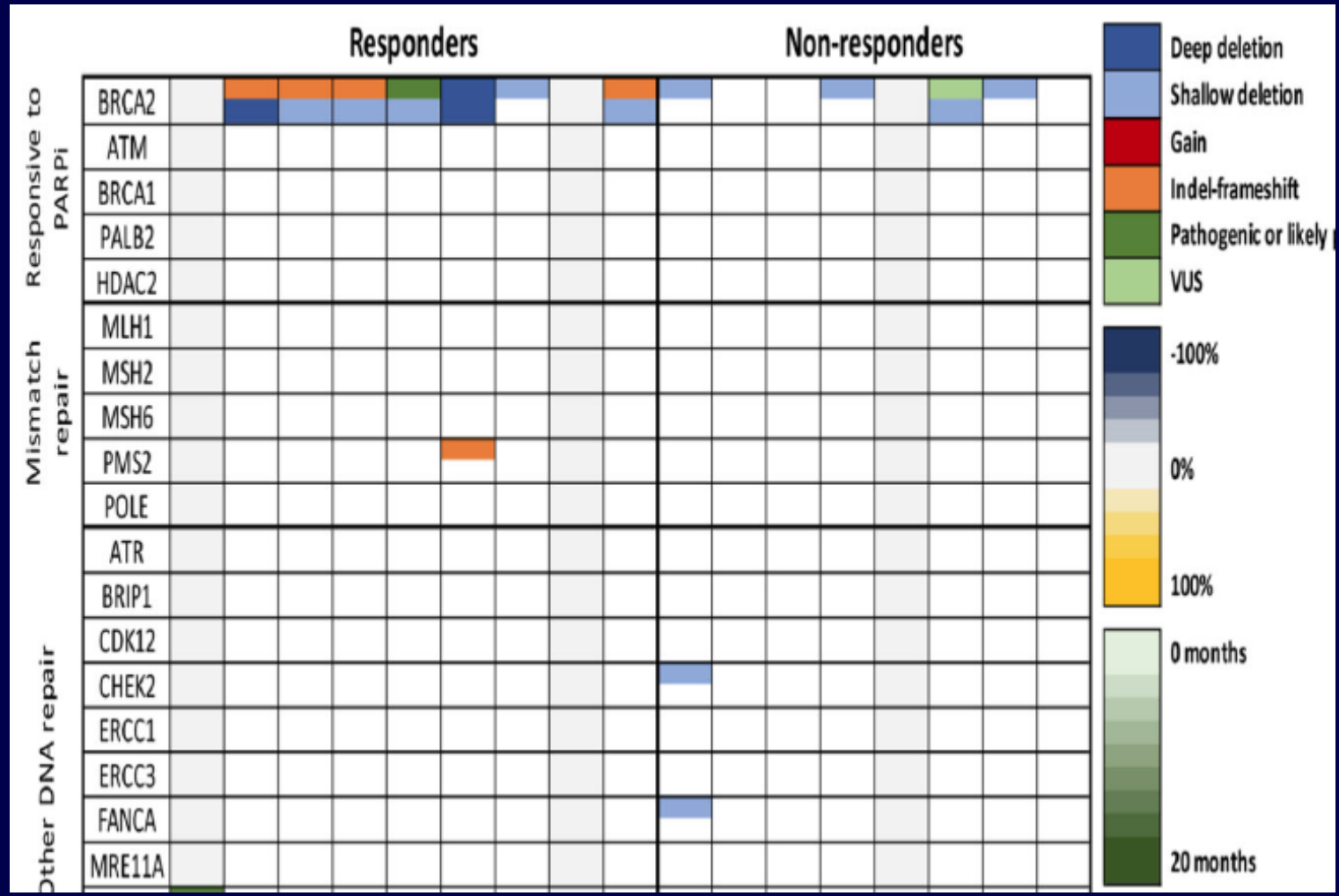


Fig. 1 PSA Response. **a** Waterfall plot demonstrating maximum decline in PSA for each patient. Bar colors represent radiographic response by RECIST criteria: green, partial response; blue, stable disease; red, progressive disease; gray, not assessable (bone-only disease). **b** Spider plot of PSA responses over time



Karzai F, et al. J Immunother Cancer. 2018; 6: 141.

Conclusions

- DNA repair mutations are common in PCa, esp. in mCRPC
- Germline genetic testing is indicated for many PCa patients
- There may be enrichment for HRD mutations in high-grade PCa and in certain histological subtypes
- Not all DNA repair mutations are created equal: *BRCA1/2* mutations (but not *ATM* or *CDK12*) may sensitize to PARPi
- Olaparib and Rucaparib may be the first PARPi to receive FDA approval, and combination studies are now underway
- The role of germline *vs.* somatic, and mono- *vs.* bi-allelic mutations, remains unclear