# The Role of Targeting DNA Repair with PARP

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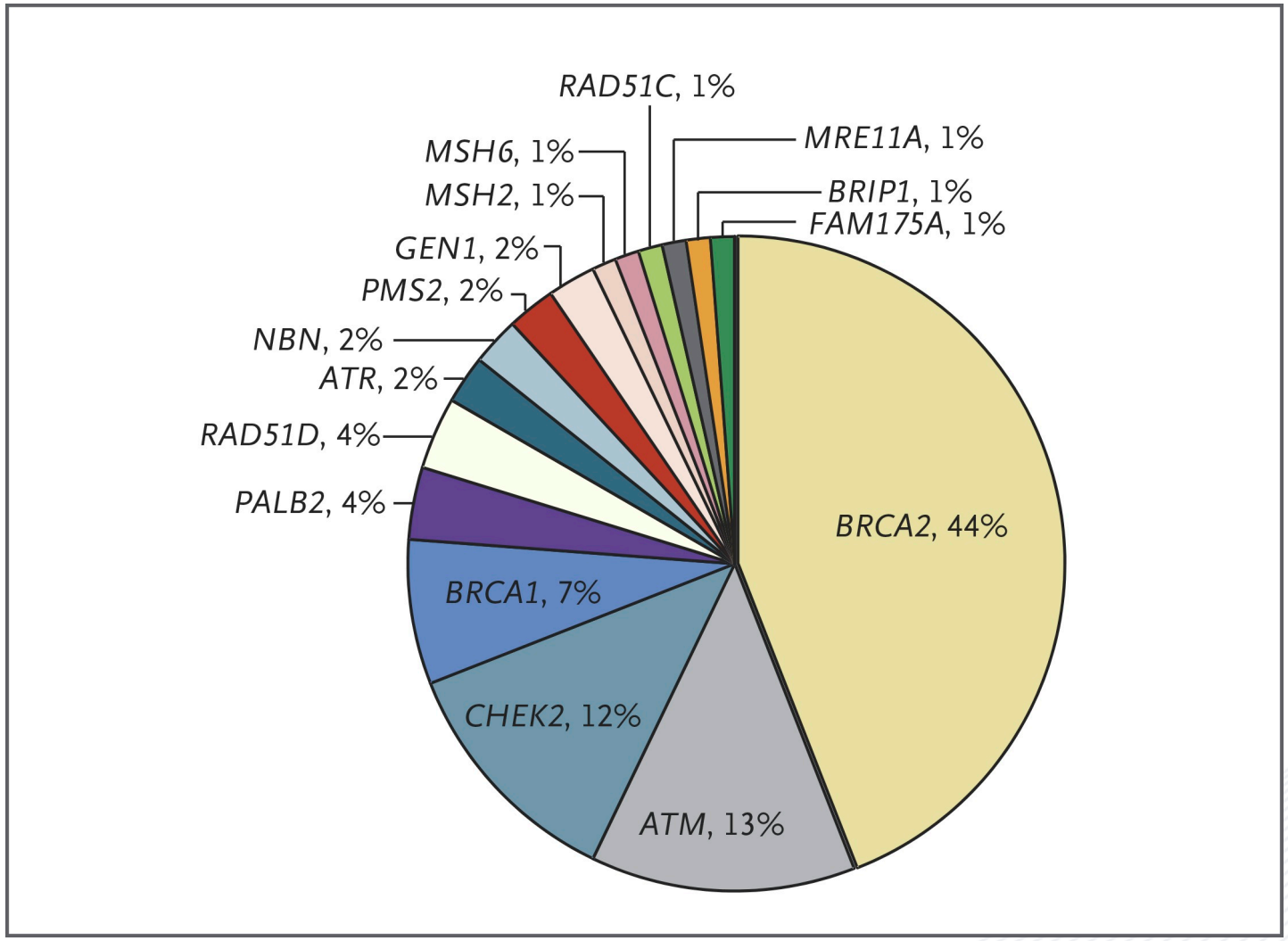
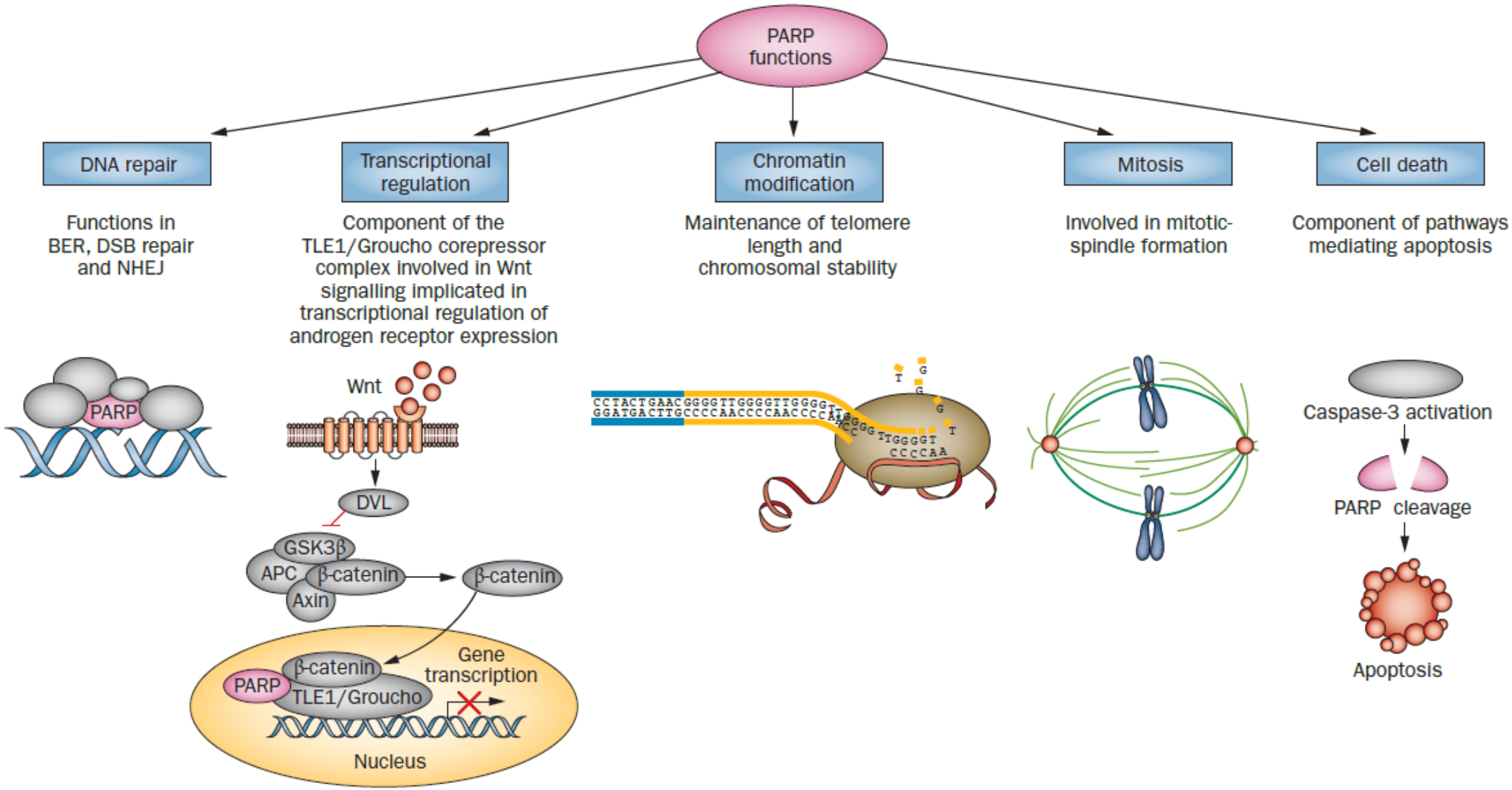
**Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.**

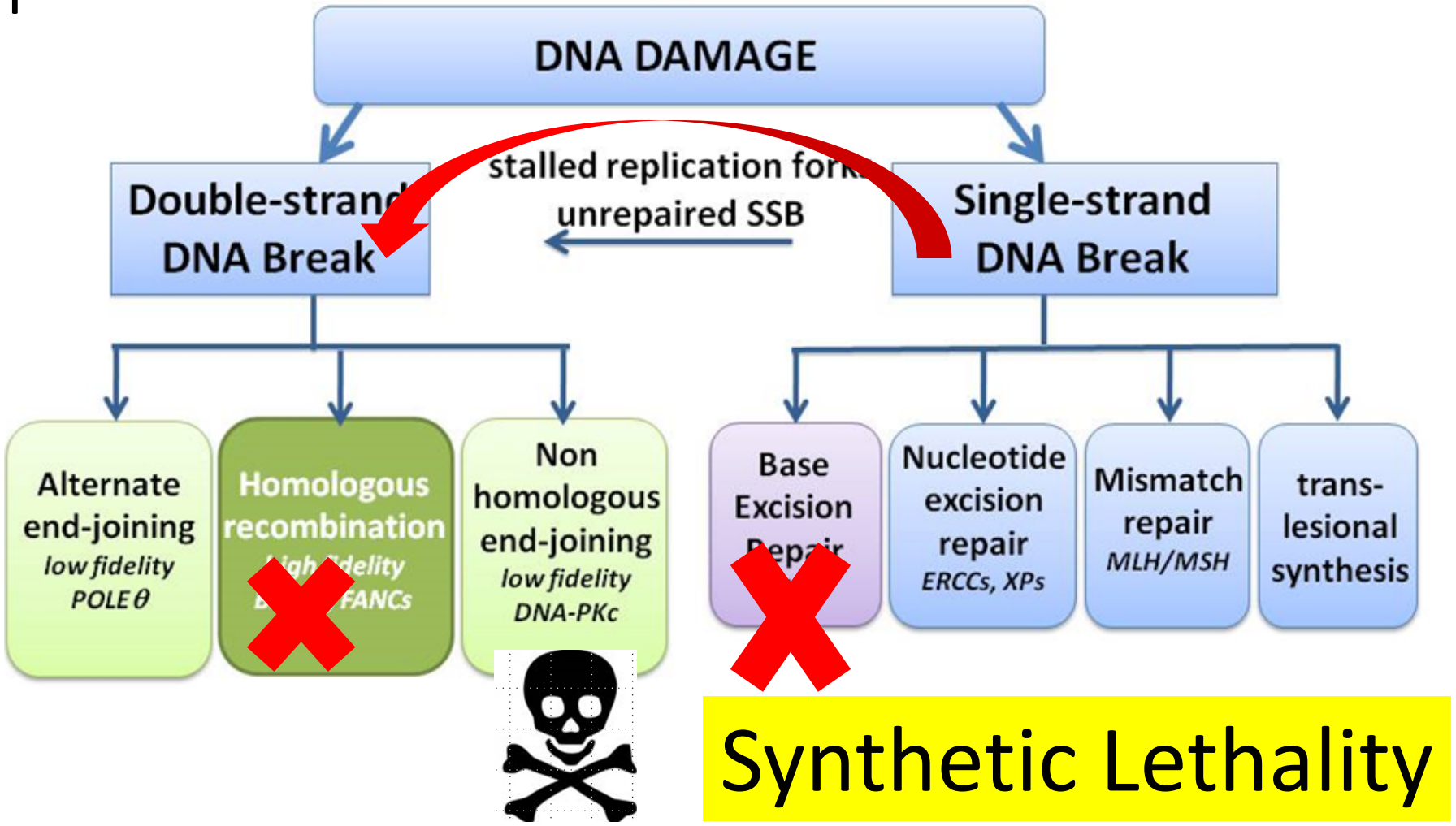
| Case Series | Description | Patients | Patients with Mutations |
|---|---|---|---|
| | | *no.* | *no. (%)* |
| 1 | Stand Up To Cancer–Prostate Cancer Foundation discovery series | 150 | 15 (10.0) |
| 2 | Stand Up To Cancer–Prostate Cancer Foundation validation series | 84 | 9 (10.7) |
| 3 | Royal Marsden Hospital | 131 | 16 (12.2) |
| 4 | University of Washington | 91 | 8 (8.8) |
| 5 | Weill Cornell Medical College | 69 | 7 (10.1) |
| 6 | University of Michigan | 43 | 4 (9.3) |
| 7 | Memorial Sloan Kettering Cancer Center | 124 | 23 (18.5) |
| Total | | 692 | 82 (11.8) |


RAD51C, 1%
MRE11A, 1%
MSH6, 1%
BRIP1, 1%
MSH2, 1%
FAM175A, 1%
GEN1, 2%
PMS2, 2%
NBN, 2%
ATR, 2%
RAD51D, 4%
PALB2, 4%
BRCA2, 44%
BRCA1, 7%
CHEK2, 12%
ATM, 13%




Sonnenblick. Nature Review 2015

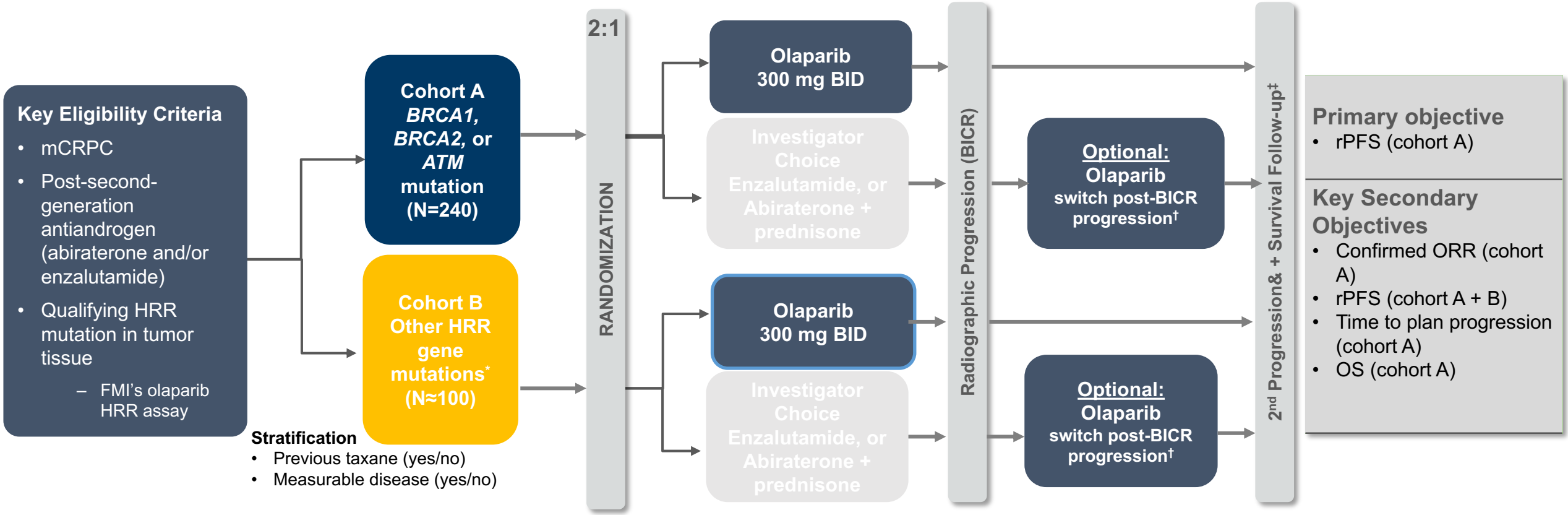
# Synthetic Lethality: PARP inhibition in HRD cancer



# Olaparib in Prostate Cancer

- **TOPARP study: n=49 patients with mCRPC, who are docetaxel-pre-treated.** (Mateo et al. 2015)
  - **32.7 % (16/49**) response rate in “unselected” mCRPC patients.
  - Genomic Analysis of their prospectively obtained tumor samples:
    - **16 (33%)** had mutations in DNA repair pathway (*ATM, BRCA2* and others*)* (biomarker positive)
      - **14 of these patient responded**
    - **33 (67%)** had no such mutations (biomarker negative)
      - **2 o**f these patients responded.

# Phase 3 PROFound: Olaparib vs Enzalutamide or Abiraterone in Men With HRRm mCRPC Who Failed Prior Second-Generation Antiandrogen Treatment




*Cohort B HRR genes include *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L.*

†Subjects randomized to investigator choice arm will be given the opportunity to begin treatment with open-label olaparib (300 mg BID) only after objective radiographic progression by BICR. No intervening systemic anticancer therapy following discontinuation of randomized treatment will be permitted. Subjects may continue on olaparib as long as they show clinical benefit as judged by the investigator.

‡Subsequent anticancer therapy at investigator discretion.

BICR, blinded independent review committee; BID, twice daily.

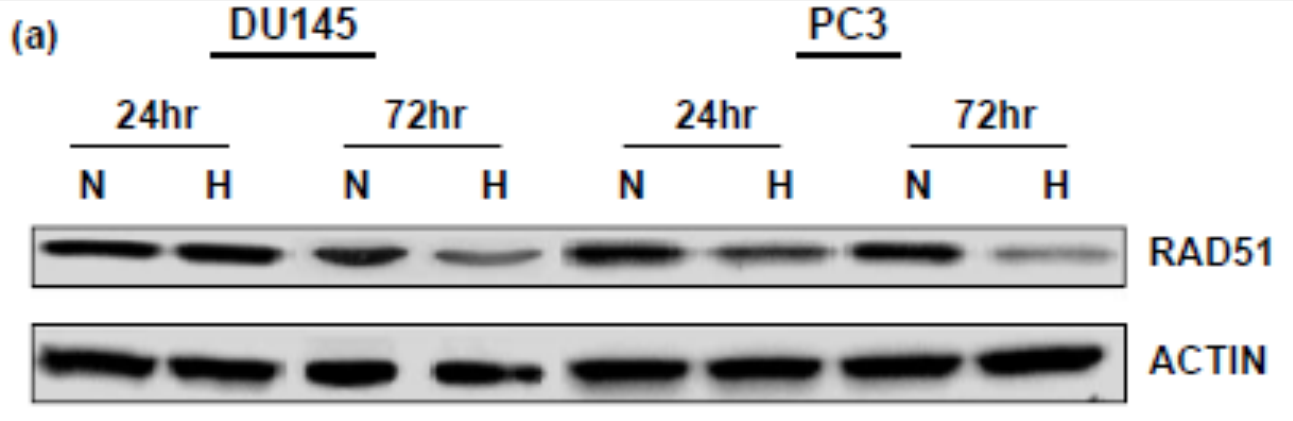
In House Data, AstraZeneca Pharmaceuticals LP. Drug Substance Olaparib. D081DC00007; 2017.

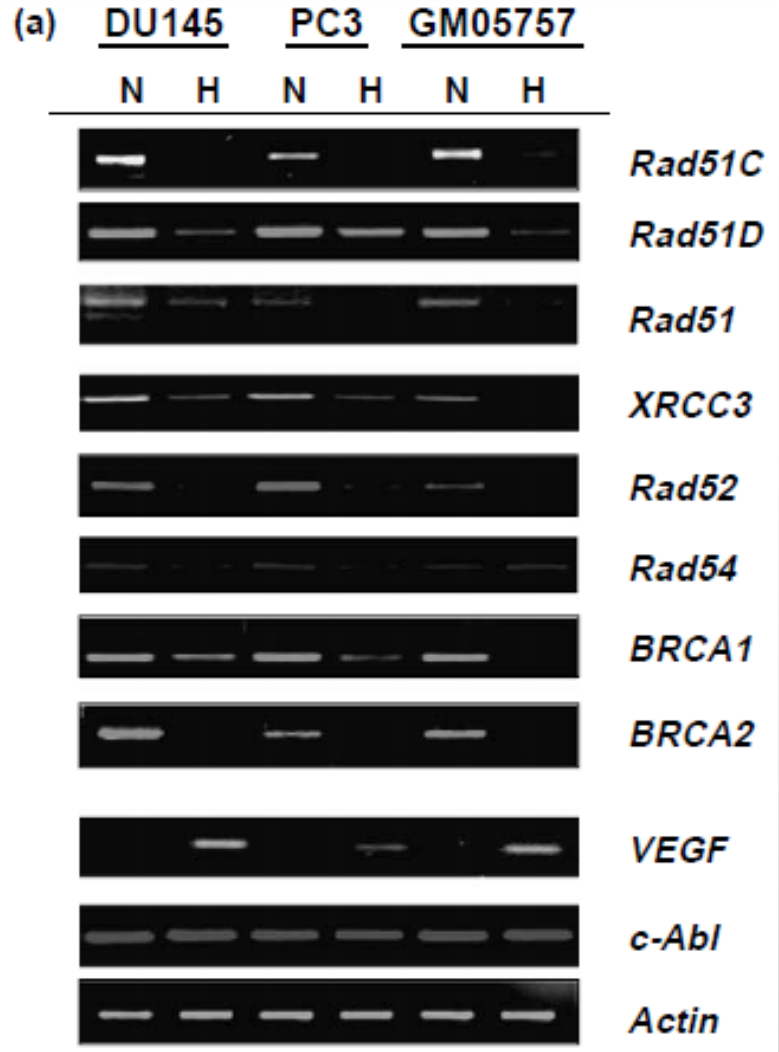
# Ongoing Trials of PARP inhibitor

| Ph | Agent | Setting | Tx Arms | Primary Endpoint | NCT |
|---|---|---|---|---|---|
| **1** | Olaparib | **Intermediate/High Risk Prostate Cancer Before Radical Prostatectomy (CaNCaP03)** | Olaparib +Degarelix vs Olaparib alone | Biomarker endpoint (PARP Inhibition) | NCT02324998 (Not Yet Open) |
| 2 | Rucaparib (Clovis) | HR Deficient mCRPC (deleterious mt inBRCA1/2 or ATM or other HR genes | Rucaparib | ORR and PSA response | TRITON2 NCT02952534 |
| 3 | Rucaparib (Clovis) | mCRPC, HR deficient (BRCA1/2 or ATM) | Rucaparib vs Investigator choice (Doc, Abi, Enz) | rPFS | TRITON3 NCT02975934 (not yet open) |
| 2 | Niraparib | mCRPC (taxaned and AR pre-treated) (Biomarker positive for HR deficient) | Neraparib | Response Rate | NCT02854436 (OPEN) |

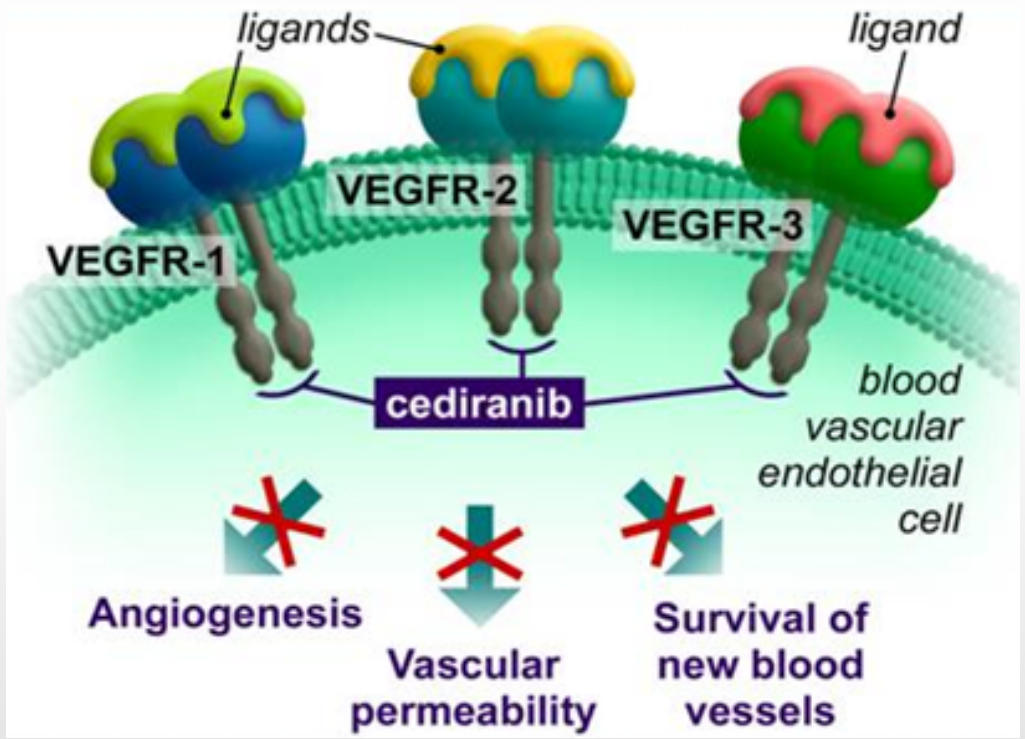
# Hypoxia and DNA repair genes in Prostate Cancer

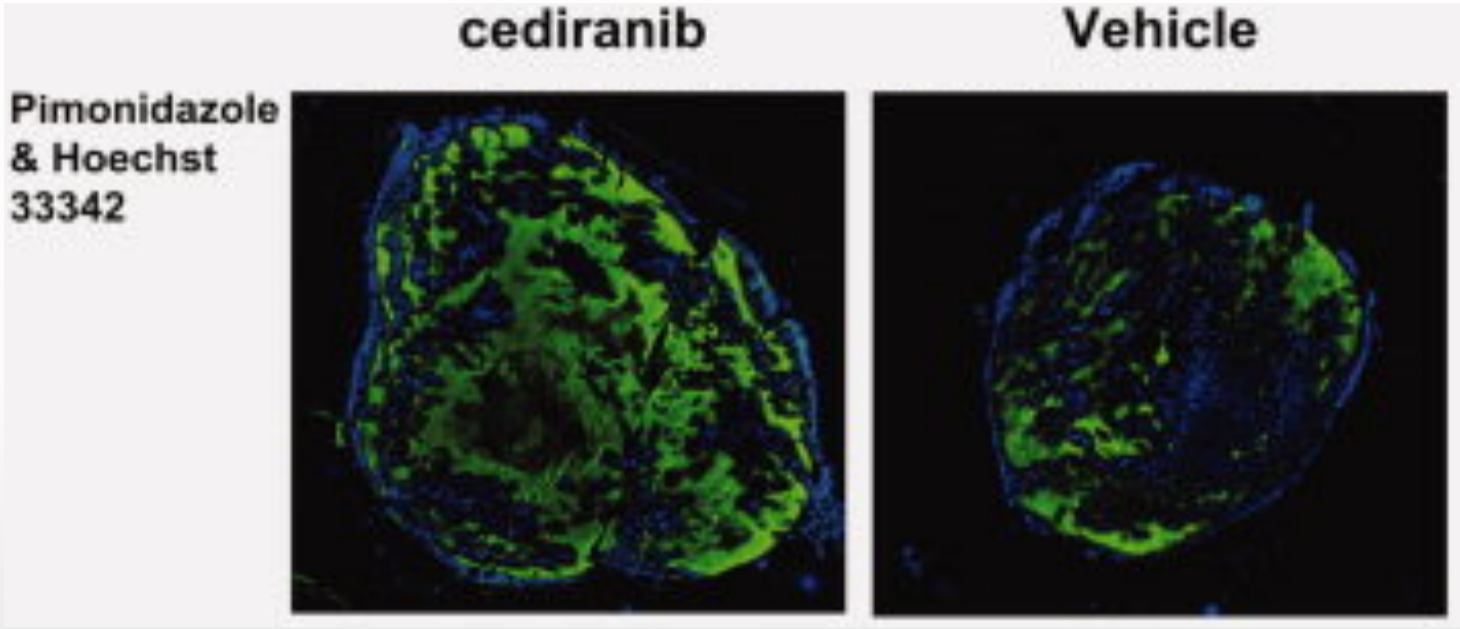
- Hypoxia has been shown to downregulate DNA dsb repair gene expression (*BRCA-2, BRCA-1* and *RAD51* expression in multiple cell lines including prostate cancer (Bindra 2005; Meng AX 2005).



# Cediranib as an inducer of hypoxia




***Pimonidazole adduct (green, hypoxia) and Hoechst 33342 (blue, perfusion) uptake in cediranib- or vehicle treated rat C6 gliomas***

***Burrell JS et al. IJC 2012***

# Summary of Rationale

- Olaparib works in a significant subset of mCRPC, mostly in patients with loss of function mutations in DNA repair pathways.
- Olaparib and cediranib combination may work synergistically even in the absence of mutations in DNA repair pathways via the way of hypoxia-induced homologous recombination DNA repair deficiency by gene-silencing of *BRCA1, BRCA2* and other HR related genes.

- **Hypothesis:** The combination of cediranib/olaparib has higher response rate and progression free survival than olaparib monotherapy in patients with mCRPC

# Study Design: NCI Protocol 9984

Progressive mCRPC.
- 2 prior therapies for mCRPC
- ECOG0-1

**Cediranib +Olaparib (C+O)**

**Olaparib**

**Primary Endpoint: PFS**
**Second Endpoint: OS**

**Paired Biopsies at baseline and 4 weeks:**
1. DNA repair gene panel
2. WES and RNA seq
3. QIF Immune Assays

Statistical Consideration
Power = 90%, one-sided type I error = 10%,
**N = 42 per arm (total N = 84)**

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**OPEN as of 12/23/2016**

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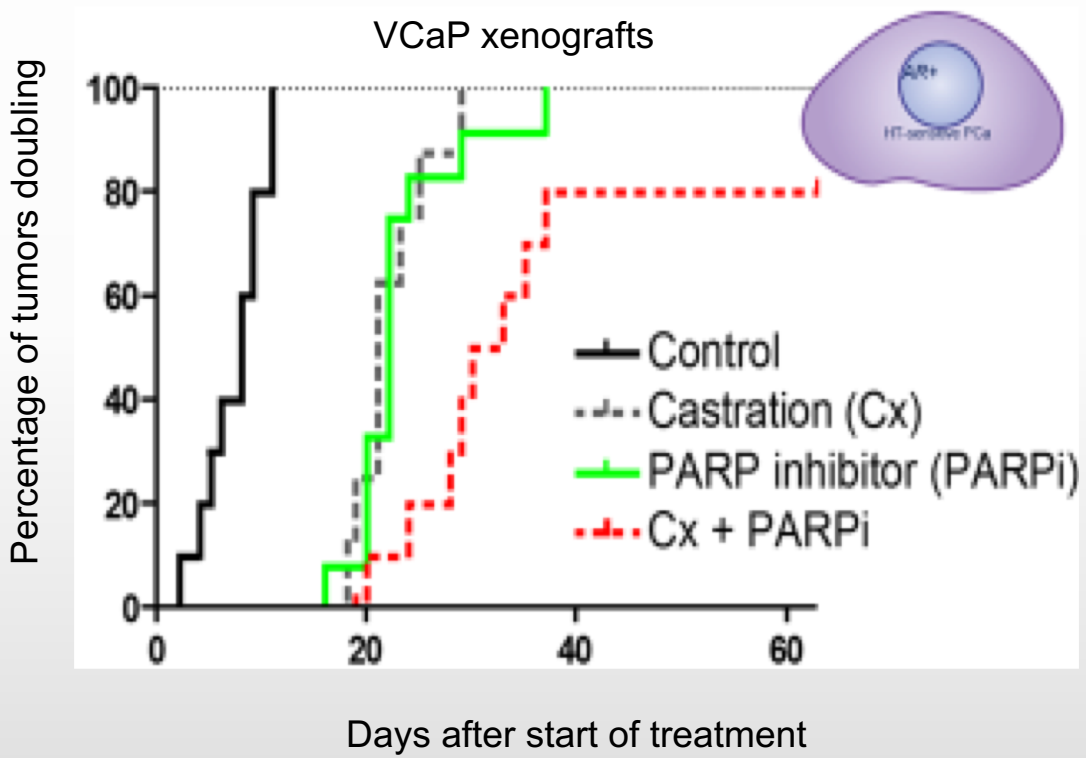
# Rationale for Combining PARPi + AR Targeting

- Preclinical data suggest synergy when a PARPi is combined with agents that inhibit androgen synthesis or function (eg, second-generation antiandrogens), regardless of HRRm status[1,2]

**Cotargeting AR Signaling and DNA Damage Repair[2]**
**PARP inhibition to castration in mouse models of prostate cancer**




1. Asim M, et al. *Nat Commun.* 2017;8:374. 2. Schiewer MJ, et al. *Cancer Discov.* 2012;2:1134-1149.

# Dual Mode of Synergy With Olaparib Plus Second-Generation Antiandrogens[1-4]

- Enhance blockade of AR signaling
  - Failure of AR-dependent localization of PARP to target genes
  - PARP-mediated nucleosome remodeling at targets abolished
  - Transcriptional downregulation of AR targets
- Inducing "*BRCA*ness"
  - Decreased HRR gene expression
  - Decreased DSB repair
  - Radiosensitivity

SGA, second-generation antiandrogen.

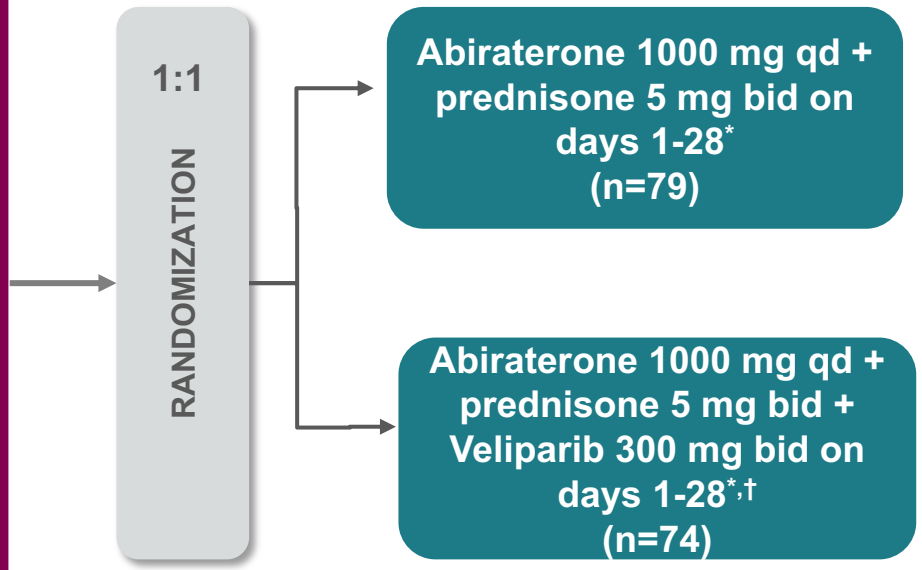
1. Polkinghorne WR, et al. *Cancer Discov.* 2013;3(11):1245-1253. 2. Tarish FL, et al. *Sci Transl Med.* 2015;7(312):312re11. 3. Li L, et al. *Sci Signal.* 2017;10(480). 4. Asim M, et al. *Nat Commun.* 2017;8(1):374.

# Phase 2 NCI 9012 Abiraterone ± Veliparib in mCRPC: Study Design

**Key Eligibility Criteria**

- Histologic or cytologic diagnosis of prostate cancer
- Progressive mCRPC, on androgen-deprivation therapy
- Testosterone <50 ng/dL
- ≤2 prior chemotherapy regimens
  - May include docetaxel; second-generation antiandrogen- and PARPi-naïve
- ECOG PS 0-2

(N=153)




**Stratification**

- Prior ketoconazole and ETS fusion status (positive/negative)

**Primary endpoint**

- Confirmed PSA RR and whether ETS fusions predict response

**Secondary endpoints**

- Safety
- mRR
- PFS
- Molecular biomarker analysis

*Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity.
†Abiraterone and prednisone on day 1 (day 8 of course 1).
mRR, measurable disease response rate; PSA RR, protein-specific antigen response rate; qd, once daily.
Hussain M, et al. *J Clin Oncol.* 2018;36(10):991-999.

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# No Significant Difference in PSA Outcomes Between Abiraterone vs Abiraterone + Veliparib in mCRPC

| Unselected Patients | Abiraterone | Abiraterone + Veliparib | *P*-value |
|---|---|---|---|
| PSA Outcomes<br>ORR, n (%) | (n=72)<br>46 (63.9) | (n=76)<br>55 (72.4) | 0.27 |
| Measurable Disease<br>RECIST ORR, n (%) | (n=40)<br>18 (45.0) | (n=46)<br>24 (52.2) | 0.51 |
| Median PFS, mos | 10.1 | 11 | 0.99 |

**Primary endpoint was not met**

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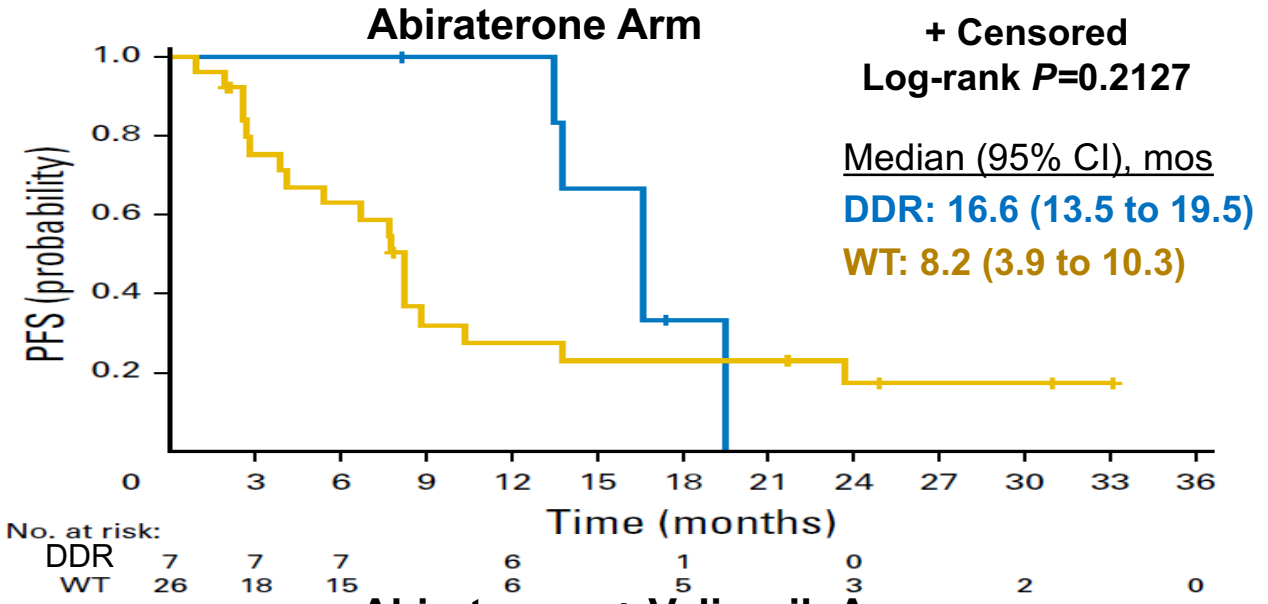
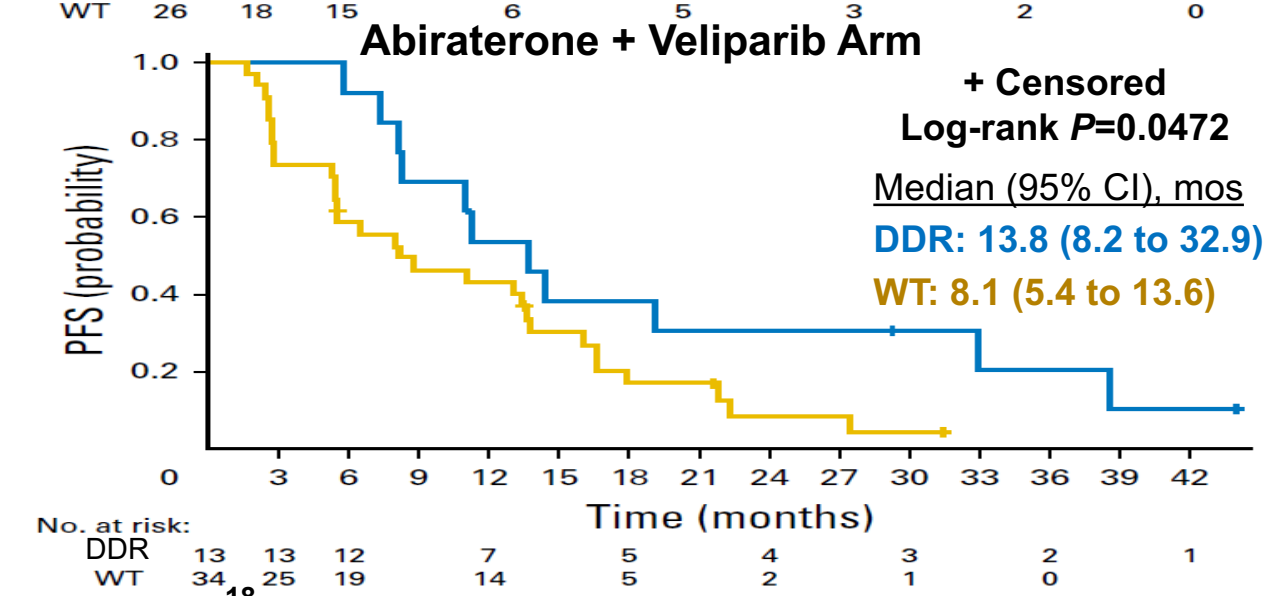
ORR, objective response rate.

Hussain M, et al. *J Clin Oncol.* 2018;36(10):991-999.

# Exploratory Analysis Across Treatment Arms Based on Somatic DDR* Mutations

- Confirmed PSA response (90% vs 56.7%; *P*=0.007)
- PSA decline of ≥90% (75% vs 25%; *P*=0.001)
- Measurable disease RECIST response (87.5% vs 38.6%; *P*=0.001)
- Median PFS (14.5 vs 8.1 months; *P*=0.025)




*Patients with DDR mutations had alterations in *BRCA1, BRCA2, ATM, FANCA, PALB2, RAD51B, or RAD51C*.

Hussain M, et al. *J Clin Oncol*. 2018;36(10):991-999.

# Trial design

- mCRPC
- Prior treatment with docetaxel for mCRPC
- ≤2 prior lines of chemotherapy
- No prior 2nd-generation antihormonal agents

**Randomized 1:1**
**Double-blind**
**N≈140**

Olaparib tablets
300 mg bid
+
abiraterone*
1000 mg od

Placebo
+
abiraterone*
1000 mg od

Treatment until disease progression

**Primary endpoint:**
- Radiologic progression-free survival (investigator-assessed; RECIST 1.1, PCWG2)

**Secondary endpoints:**
- rPFS by HRRm status
- Time to second progression (PFS2)
- Overall survival (OS)
- Objective response rate (ORR)
- CTC-conversion rate
- Safety and tolerability
- Times to first and second subsequent therapies (TFST/TSST)
- Health-related quality of life (HRQoL)

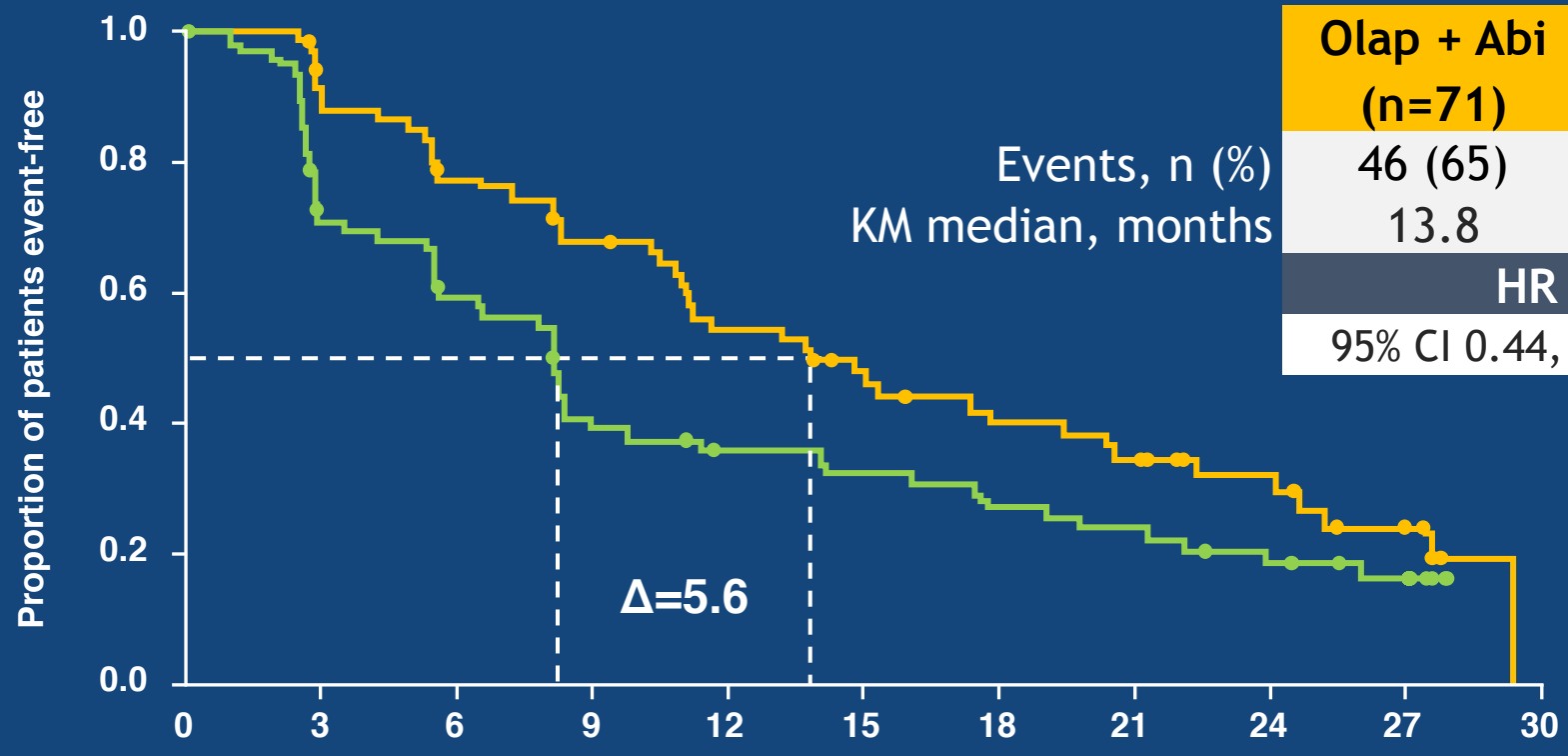
*Prednisone/prednisolone (5 mg) was administered alongside abiraterone as indicated.

# Baseline characteristics

| | Olaparib + Abiraterone (n=71) | Abiraterone (n=71) |
|---|---|---|
| **Median age, years (IQR)** | 70 (65-75) | 67 (62-74) |
| **Caucasian, n (%)** | 67 (94) | 67 (94) |
| **ECOG performance status,* n (%)** | | |
| **0** | 34 (48) | 38 (54) |
| **1** | 36 (51) | 30 (42) |
| **2** | 1 (1) | 1 (1) |
| **Median PSA concentration, µg/L (IQR)** | 86 (23-194) | 47 (21-199) |
| **Median time from diagnosis to first dose, months (IQR)** | 62 (38-93) | 48 (32-76) |
| **Extent of disease, n (%)** | | |
| Bone disease only | 33 (46) | 33 (46) |
| Soft-tissue disease only | 8 (11) | 11 (15) |
| Bone and soft-tissue disease | 30 (42) | 27 (38) |
| **Number of bone metastases, n (%)** | | |
| 0-4 | 32 (45) | 46 (65) |
| 5-9 | 39 (55) | 25 (35) |
| **Prior cabazitaxel treatment, n (%)** | 10 (14) | 9 (13) |
| **Median duration of prior LHRH agonist treatment, months (IQR)** | 53 (32-84) | 37 (28-59) |

*Two abiraterone-arm patients had unknown ECOG performance status. IQR, interquartile range; LHRH, luteinizing hormone-releasing hormone.

# Primary endpoint: investigator-assessed rPFS

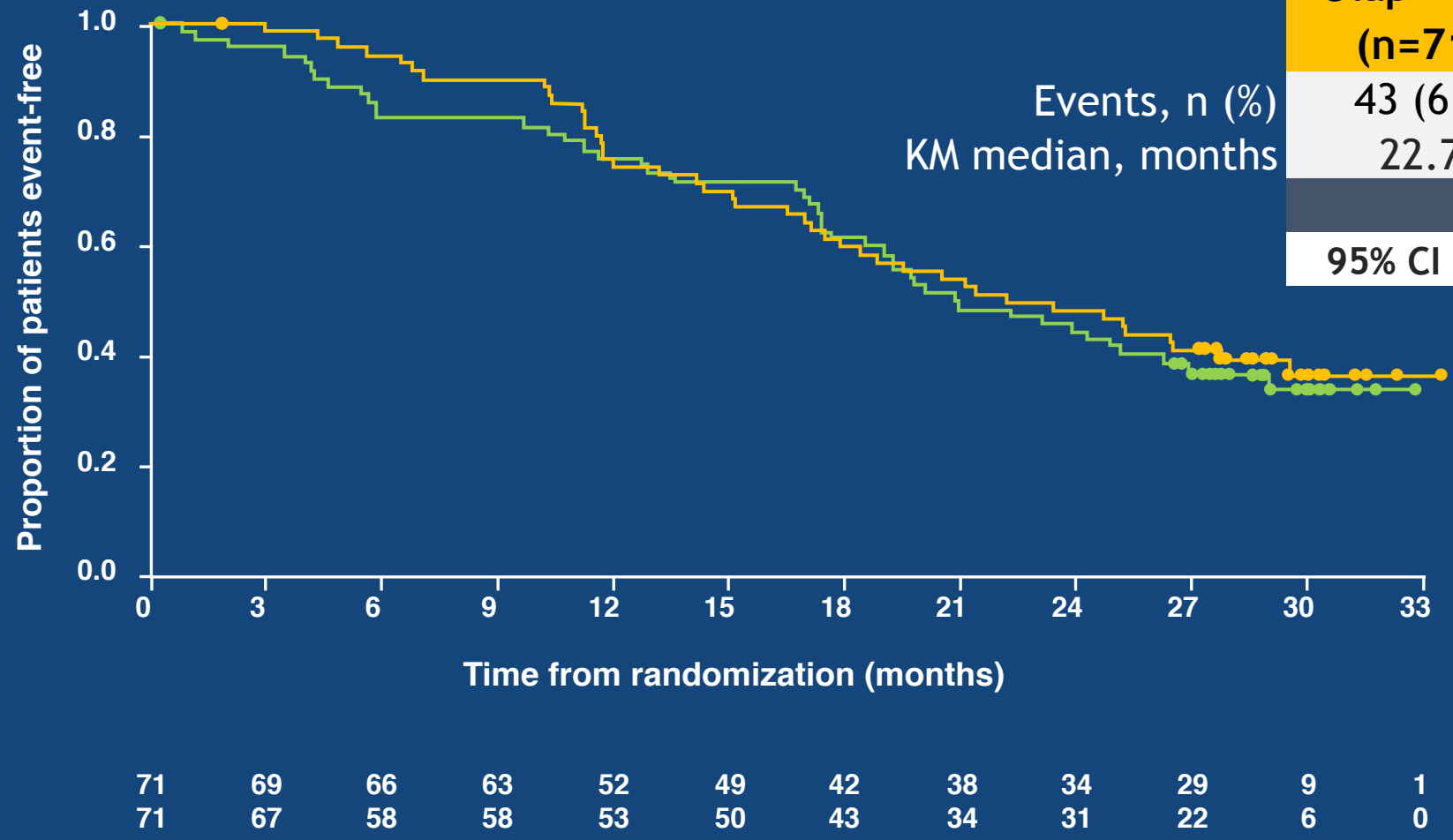



| | Olap + Abi (n=71) | Abi (n=71) |
|---|---|---|
| Events, n (%) | 46 (65) | 54 (76) |
| KM median, months | 13.8 | 8.2 |
| HR 0.65 | | |
| 95% CI 0.44, 0.97; *P*=0.034 | | |

| N at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib + abiraterone | 71 | 58 | 50 | 42 | 33 | 26 | 21 | 18 | 13 | 8 | 0 |
| Abiraterone | 71 | 48 | 39 | 25 | 21 | 19 | 16 | 14 | 10 | 7 | 0 |

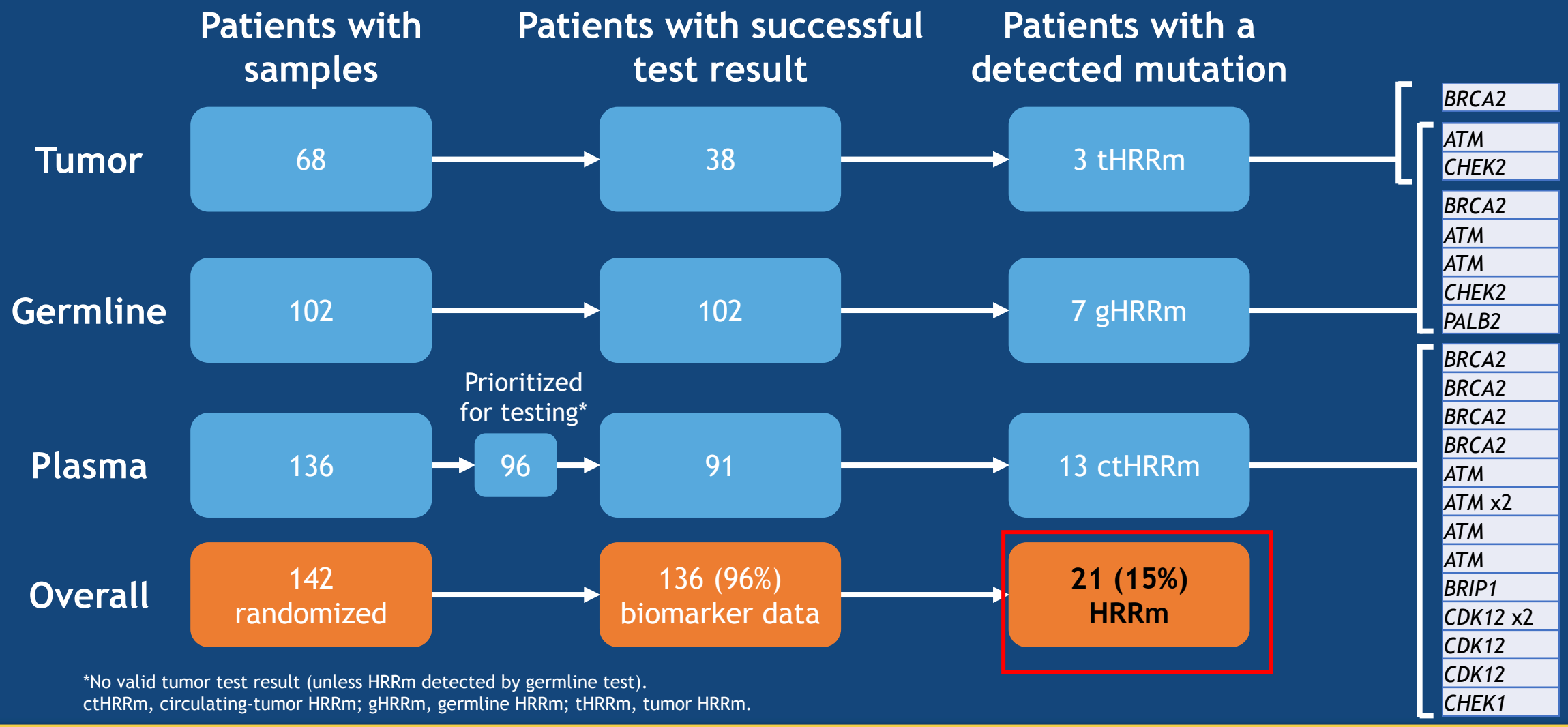
Abi, abiraterone; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; olap, olaparib.

# Secondary efficacy endpoint: OS




| | Olap + Abi (n=71) | Abi (n=71) |
|---|---|---|
| Events, n (%) | 43 (61) | 45 (63) |
| KM median, months | 22.7 | 20.9 |
| HR 0.91 | | |
| 95% CI 0.60, 1.38; *P*=0.66 | | |

# HRR mutation testing




*No valid tumor test result (unless HRRm detected by germline test).
ctHRRm, circulating-tumor HRRm; gHRRm, germline HRRm; tHRRm, tumor HRRm.

# rPFS by HRR mutation status

## HRRm*

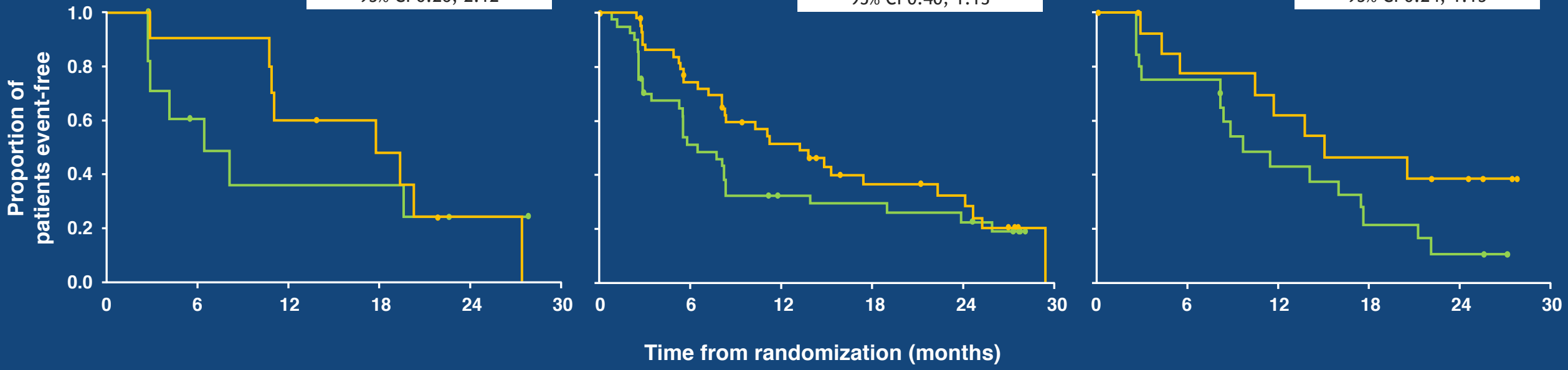
| Events, n (%) / KM median, months | Olap + Abi (n=11) | Abi (n=10) |
|---|---|---|
| | 8 (73) | 7 (70) |
| | 17.8 | 6.5 |
| HR 0.74 | | |
| 95% CI 0.26, 2.12 | | |

## HRRpc†

| Olap + Abi (n=45) | Abi (n=41) |
|---|---|
| 30 (67) | 30 (73) |
| 13.1 | 6.4 |
| HR 0.67 | |
| 95% CI 0.40, 1.13 | |

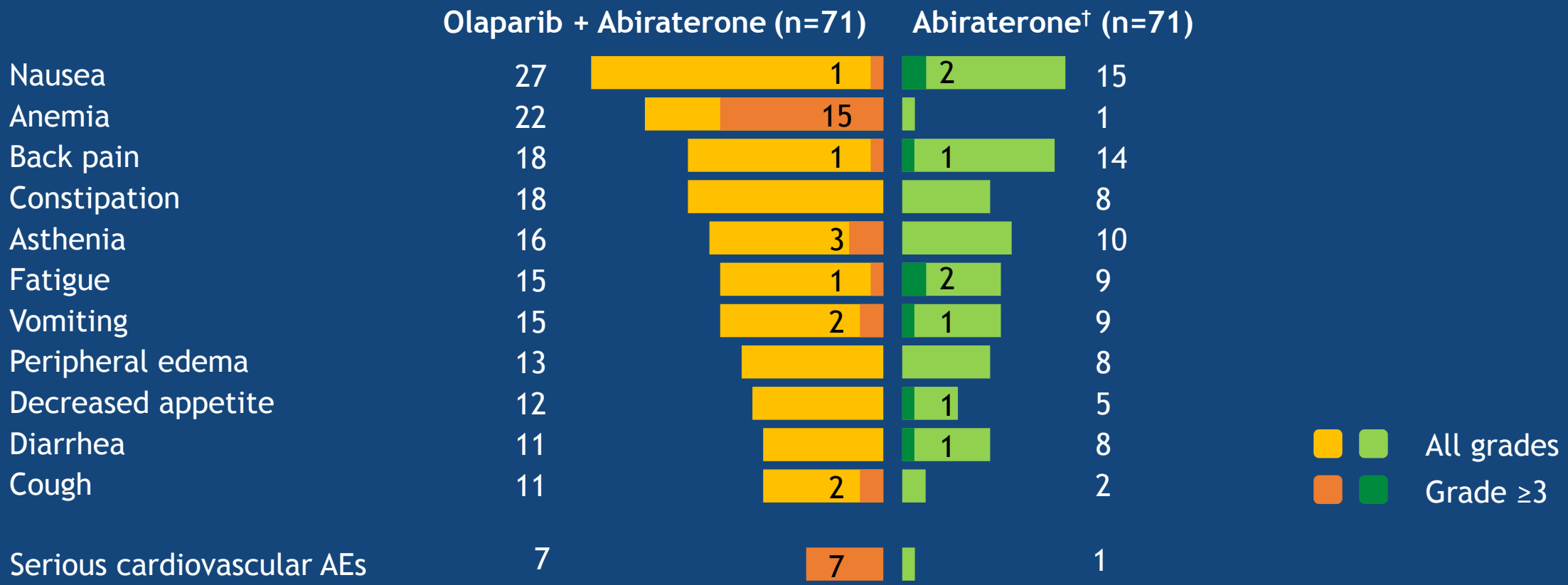
## HRRwt

| Olap + Abi (n=15) | Abi (n=20) |
|---|---|
| 8 (53) | 17 (85) |
| 15.0 | 9.7 |
| HR 0.52 | |
| 95% CI 0.24, 1.15 | |




* There was an 11.3-month rPFS benefit in the HRRm patients treated with olap + abi (17.8 months) vs the HRRm patients treated with abi alone (6.5 months).
†80/86 patients HRRwt by plasma and/or germline testing.
HRRpc, HRR partially characterized; HRRwt, HRR wild-type.

# Adverse events experienced by >10 combination arm patients




**Olaparib + Abiraterone**
Myocardial infarction, n=4; fatal cardiac failure, n=1; chronic cardiac failure, n=1; fatal ischemic stroke, n=1

**Abiraterone**
Thrombotic stroke, n=1

Numbers inside bars indicate grade ≥3 adverse events.

# Combination Trials

| Ph | Agent | Setting | Tx Arms/Cohort | Primary Endpoint | NCT |
|---|---|---|---|---|---|
| 1b/II | Olaparib | mCRPC<br>A: post-docet<br>B: post Ai/Enz<br>C: Post-Abi / naïve to Enz and cheo | A: pembro +Olaparib<br>B: Pembro + Docet/Pred<br>C: Pembro+Enzalutamide | PSA response and toxcity | KEYNOTE-365 |
| R-II | Olaparib | mCRPC (≥ 2 prior lines) | Cediranib plus Olaparib vs Olaparb | rPFS | NCT02893917 |
| I / II | Olapariib | mCRPC, (lung , breast, Ov, CRC) | Durva+Ced<br>Durva+Ola<br>Durva+CO | Safety an dose finding | NCT02484404 |

# Conclusions

- PARP inhibitors  has activity in patients who have aberrant DNA repair pathways.
- Combination studies are evaluating the concept of inducing “BRCAness” in DDR negative patients