Lynparza olaparib

Zoladex goserelin

New age Management of Prostate Cancer: a focus on PARP inhibitors

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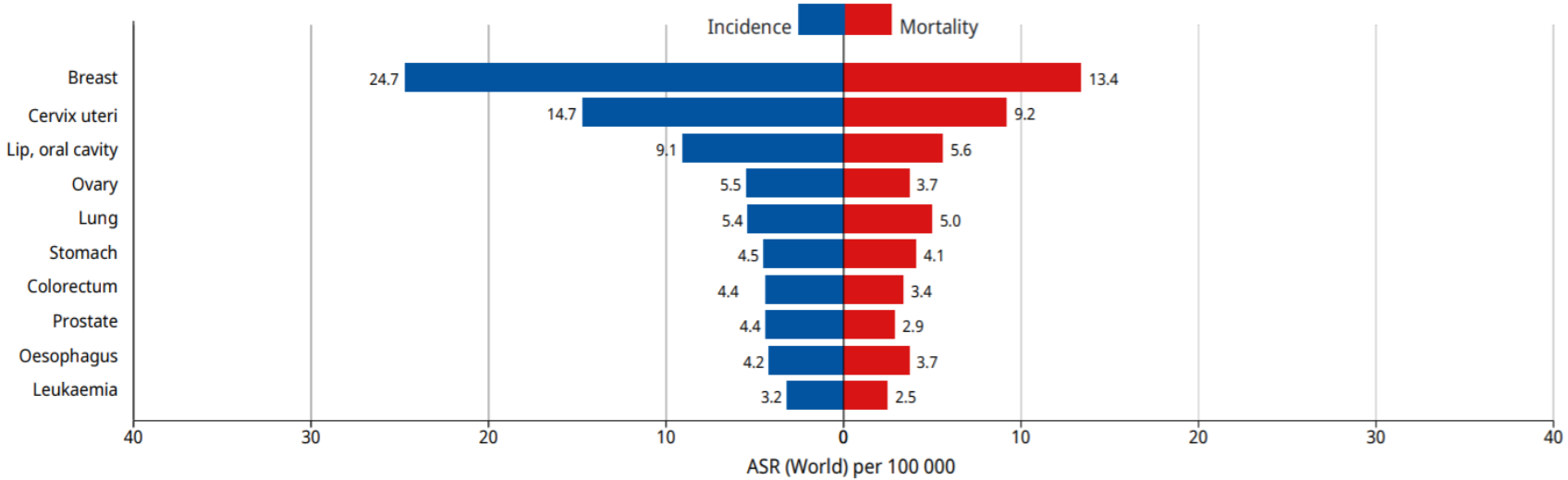
IN-8645

profound
OLAPARIB IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Epidemiology – Prostate Cancer

- Prostate cancer ranks 12th incidence wise in India, with a reported incidence of 34 540 cases and causes 16 783 deaths as per GLOBOCAN 2020. [1]
- Almost all patients with metastatic prostate cancer (mPC) go on to develop castration-resistant prostate cancer (CRPC). [2]
- Overall prognosis of metastatic castration-resistant prostate cancer (mCRPC) remains poor with a median survival of 1–2 years.



1. GLOBOCAN 2020 2. Saad F, Fizazi K. Androgen Deprivation Therapy and Secondary Hormone Therapy in the Management of Hormone-sensitive and Castration-resistant Prostate Cancer. *Urology*. 2015;86(5):852-861. doi:10.1016/j.urology.2015.07.034

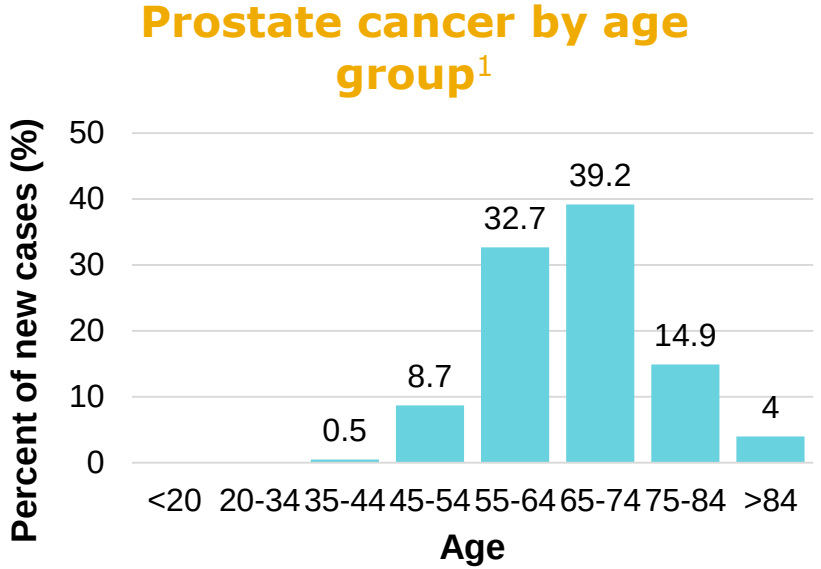
Risk of developing prostate cancer increases with age, however incidence is increasing in young men

Prostate cancer is most frequently diagnosed in men between the age of 65-74, with a median age of 66 years[1]

1 in 9 (US)[2] and 1 in 14 (globally)[3] males may develop prostate cancer in his lifetime

Worldwide incidence continues to increase in young men[4]

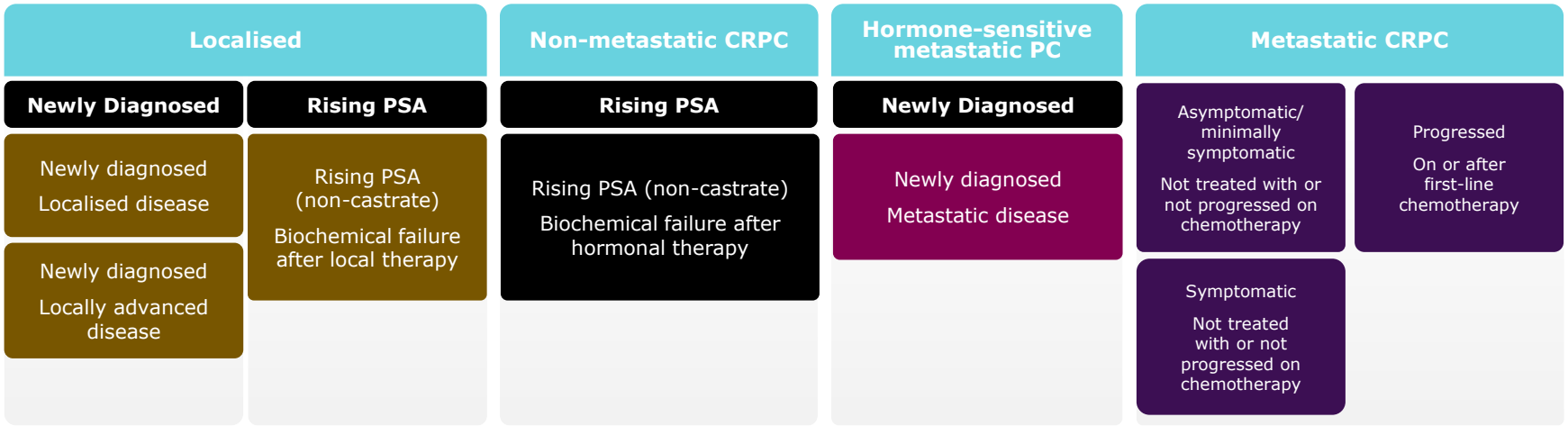
- From 1990-2017 there has been a 2.0 annual percent change in global incidence for all men between 15-39 years



With more young men being diagnosed with prostate cancer, the importance of overall survival outcomes and quality of life increases

1. SEER, National Cancer Institute. https://seer.cancer.gov/statfacts/html/prost.html. Accessed Jan 21, 2020; 2. American Cancer Society, Cancer Facts and Figures 2019. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed Jan 21, 2020; 3. Fitzmaurice C et al. *JAMA Oncol*. 2017;3(4):524-548; 4. Bleyer A et al. *Cancer*. 2020;126:46-57.

Prostate cancer is comprised of multiple disease states

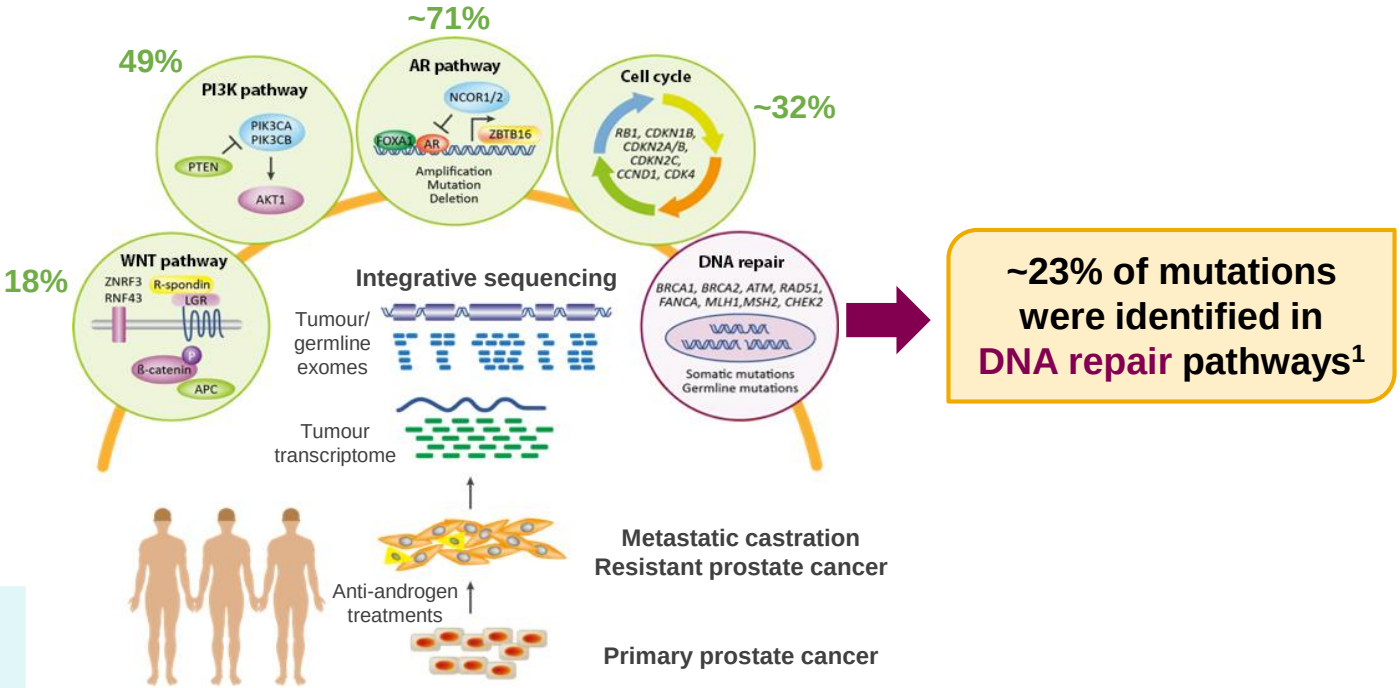


CRPC, castrate-resistant prostate cancer; PSA, prostate-specific antigen.
Adapted from Scher H et al. *PLoS One.* 2015;10(10):1-12.

Metastatic prostate cancer is biologically heterogeneous

Approximately 90% of mCRPC patients have genomically aberrant pathways involving AR, PI3K, DDR, WNT and cell cycle related signalling[1]

In a multi-institutional study profiling N=150 tumours from mCRPC patients:



~23% of mutations were identified in DNA repair pathways[1]

Percentage of cases that harboured alterations in each pathway are shown in **green**

AR=androgen receptor; DDR=DNA damage repair; mCRPC=metastatic castrate-resistant prostate cancer; PI3K=phosphoinositide 3-kinase.

1. Robinson D et al. *Cell.* 2015;161:1215–1228.

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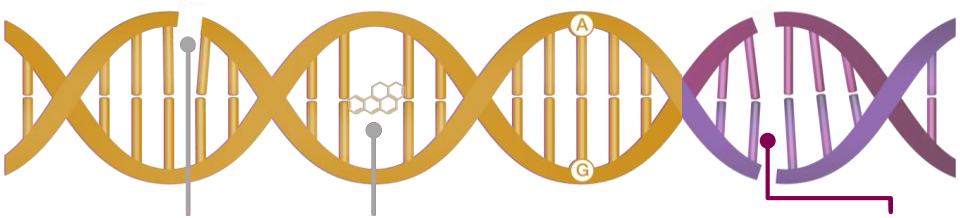
Mutations in DNA repair pathways can lead to genetic instability and drive tumour growth[1,2]



	DNA single strand breaks	Bulky adducts	Base mismatches, insertions & deletions	DNA double strand breaks
Repair pathway	Base excision repair (BER)	Nucleotide excision repair (NER)	Mismatch repair ***(including MSH2 MLH1)***	Non-homologous end joining (NHEJ); **Homologous recombination repair (HRR)** ***including ATM, BRCA1/2, PALB2, CHEK1/2, RAD51***

Homologous recombination repair (HRR)
is a key mechanism for the repair of DNA double strand breaks[1,2]

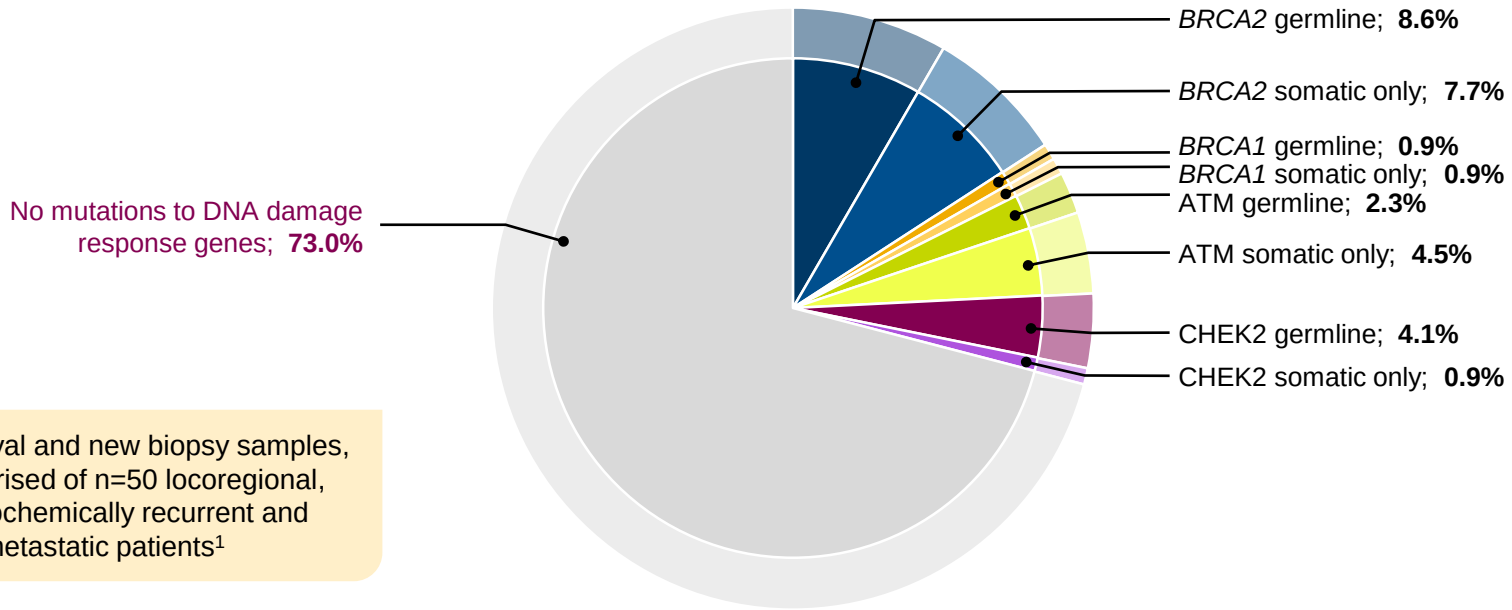
ATM=ataxia telangiectasia mutated; BER=base excision repair; *BRCA1/2*=breast cancer gene 1/2; *CHEK1/2*=checkpoint kinase 1/2; HRR=homologous recombination repair; *MLH2*=MutL Homolog 1; *MSH2*=MutS protein homolog 2; NER=nucleotide excision repair; NHEJ= non-homologous end joining; *PALB2*=partner and localizer of *BRCA2*.

1. Lord CJ and Ashworth A. *Nature.* 2012;481:287–293; 2. O'Connor MJ. *Mol Cell.* 2015;60:547–560.

DNA repair gene aberrations are enriched in patients with loco-regional, biochemically recurrent and metastatic prostate cancer[1]

BRCA2 is usually the most frequently altered DNA repair gene in prostate cancer

Germline and somatic alteration frequencies (n=451) patients[1]



Archival and new biopsy samples, comprised of n=50 locoregional, 53 biochemically recurrent and 348 metastatic patients[1]

NCCN Guidelines® acknowledge prostate cancer heterogeneity

Thus highlighting the need to consider tumor HRRm and MSI/dMMR testing in patients with regional or metastatic prostate cancer[1]

Risk group	Very low[a]	Low[a]	Favourable intermediate[a]	Unfavourable intermediate[a]	High	Very high	Regional	Metastatic[b]
Germline testing	Recommended if FH positive[c,i] or intraductal histology				Recommended[c,d]		Recommended[c,d]	
Molecular and biomarker testing of tumor[e]	Not indicated	Consider if life expectancy ≥10 years[f]		Not routinely recommended			Consider testing for HRR gene mutations and MSI/dMMR[g,h]	

- ESMO guidelines (2015) and EAU guidelines (2017) do not currently provide any recommendations for genetic testing[2,3]
- The Philadelphia Consensus Conference 2017 supported consideration of *BRCA2* testing in screening, management and informing prognosis/treatment[4]

Footnotes for NCCN guidelines available in the slide notes.
BRCA2=breast cancer gene 2; dMMR=deficient mismatch repair; EAU=European Association of Urology; ESMO=European Society for Medical Oncology; FH=family history; HRR=homologous recombination repair (mutation); MSI=microsatellite instability.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.4.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed [August 19, 2019]. To view the most recent and complete version of the guideline, go online to NCCN.org.; 2. Parker C et al. Ann Oncol. 2015;26(Suppl_5):v69–v77; 3. EAU Prostate Cancer Guidelines. https://uroweb.org/guideline/prostate-cancer/. Accessed Apr 30, 2019. 4. Giri VN et al. J Clin Oncol. 2018;36:414–424

Background and rationale of use of PARPi in mCRPC

- Despite significant progress in systemic therapy, metastatic castration-resistant prostate cancer (mCRPC) continues to be lethal
- mCRPC is molecularly heterogeneous; up to 30% of mCRPC harbour deleterious alterations in DNA damage repair genes, including those with direct or indirect roles in homologous recombination repair (HRR)[1–3]
- These gene alterations can confer sensitivity to poly(adenosine diphosphate-ribose) polymerase (PARP) inhibition; of which *BRCA1*, *BRCA2* and *ATM* are the most well characterised[4–7]
- Anti-tumour activity has been reported with the PARP inhibitor olaparib in patients with prostate cancer harbouring HRR alterations[6,7]

HRR=homologous recombination repair; mCRPC=metastatic castration-resistant prostate cancer

1. Robinson D *et al. Cell* 2015;161:1215–28; 2. Pritchard CC *et al. N Engl J Med* 2016;375:443–53; 3. Abida W *et al. JCO Precis Oncol* 2017; 4. Abida W *et al.* Presented at ESMO 2018, 19th – 23rd October, Munich Abstract 793PD; 5. Smith MR *et al. J Clin Oncol* 2019;37:abstract 202; 6. Mateo J *et al. N Engl J Med* 2015;373:1697-708; 7. Mateo J *et al. J Clin Oncol* 2019;37:abstract 5005

The PROfound trial

PROfound is the first randomised Phase III study evaluating the efficacy and safety of olaparib vs. new hormonal agents (NHAs) in patients with HRRm mCRPC[1–3]

Eligibility criteria ***only required failure of prior treatment with an NHA for mPC*** *(including mHSPC and mCRPC)* ***and/or CRPC*** *(including nmCRPC and mCRPC)*[1,2]

- Documented evidence of mCRPC
- Qualifying HRR mutation in tumour tissue (central review)
- Investigator-assessed radiographic progression on prior NHA (e.g. abiraterone acetate and/or enzalutamide) for mPC and/or CRPC
- ECOG PS 0–2
- No prior treatment with a PARPi or any DNA-damaging cytotoxic chemotherapy for prostate cancer

COHORT A*

BRCA1/2 or *ATM*

2:1

- Olaparib (300 mg BID tablets)
- Physician's choice†

Optional olaparib at BICR progression

Open-label

COHORT B*

Other HRRm Tail

2:1

- Olaparib (300 mg BID tablets)
- Physician's choice†

Optional olaparib at BICR progression

Second progression and survival follow-up
Subsequent anti-cancer therapy at investigator's discretion

Primary endpoint:

- rPFS by BICR in Cohort A, using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria

Key secondary endpoints:

- BICR-confirmed ORR (Cohort A)
- rPFS by BICR (Cohort A + B)
- Time to pain progression (Cohort A)
- Overall survival (Cohort A)
- Safety and tolerability

Patient randomisation will be stratified by:

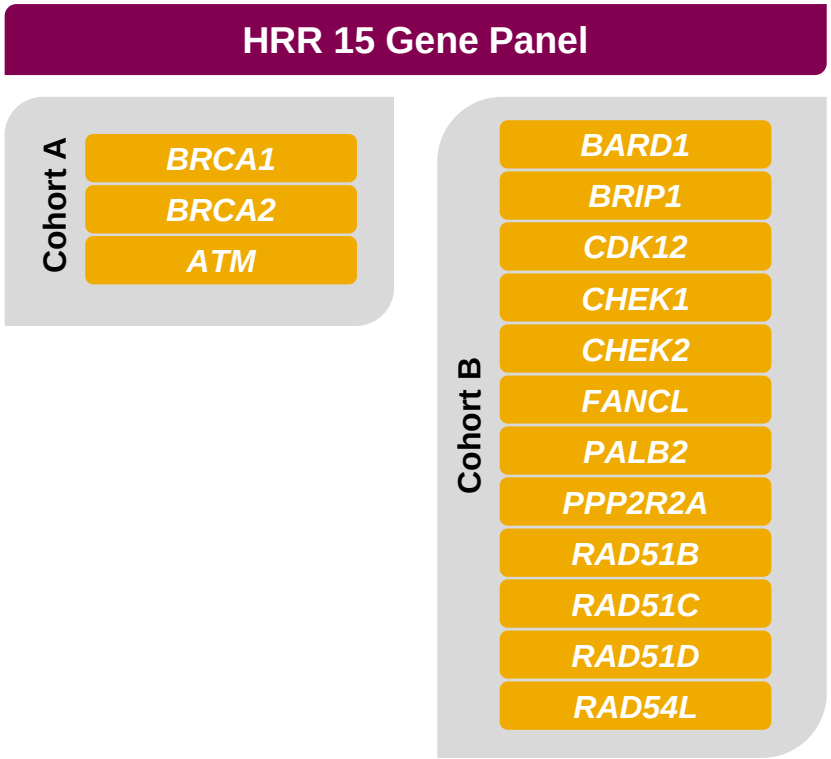
- Prior taxane therapy (yes/no)
- Measurable disease at baseline (yes/no)

BICR=blinded independent central review; ECOG=Eastern Cooperative Oncology Group; HRR=homologous recombination repair; PSA=prostate specific antigen; rPFS=radiological progression free survival

1. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440; 2. AstraZeneca Data on File (2020)

The PROfound trial

The qualifying HRR gene alteration was identified by prospective tissue testing using a pre-specified panel of 15 genes involved directly or indirectly in HRR1



- The 15 genes tested are a subset of the genes covered in the **FoundationOne®** comprehensive cancer panel of cancer-related genes[1]
- **Genes were selected based** on mechanistic role in HRR, clinical efficacy data, hereditary cancer risk, preclinical evidence of sensitivity to PARP inhibition, prevalence across solid tumour types, and genetic reversion events that restore gene function in tumours from patients who have developed clinical resistance to PARP inhibitors[2-5]
- *BRCA1, BRCA2*, and *ATM* are the **best characterized** and/or frequently mutated HRR genes in prostate cancer and hence were included in Cohort A which was used for the primary endpoint and key secondary endpoints
- Genes in Cohort B were considered **exploratory**

BICR=blinded independent central review; HRR=homologous recombination repair; mCRPC=metastatic castration resistant prostate cancer; PARP=poly(ADP ribose) polymerase

1. de Bono JS et al. Poster presented at: ASCO Annual Congress; June 2–6, 2017; Chicago, IL. Abstract TPS5091. 2. Robinson D *et al. Cell* 2015;161:1215–28; 3. Abida W et al. *JCO Precis Oncol.* 2017;doi 10.1200/PO.17.00029 4. Chung JH *et al. JCO Precis Oncol* 2019;3:doi:10.1200/PO.18.00283; 5. Armenia J et al. Nat Genet 2018;50:645–51.

Baseline characteristics were generally well balanced between arms[1]

Patients ≥85 years were included in both arms and the majority of patients had Gleason ≥8. More patients had visceral metastases in the physician's choice arm, whilst more patients had an ATM alteration in the olaparib arm.[1]*

		Cohort A		Cohorts A+B	
		Olaparib (N=162)	Physician's choice (N=83)	Olaparib (N=256)	Physician's choice (N=131)
Age at randomisation, years, median age (range)		**68 (47–86)**	**67 (49–86)**	**69 (47–91)**	**69 (49–87)**
Age ≥65 years at randomisation, n (%)		**108 (66.7)**	**60 (72.3)**	**174 (68.0)**	**97 (74.0)**
Metastatic disease at initial diagnosis, n (%)		**38 (23.5)**	**19 (22.9)**	**66 (25.8)**	**25 (19.1)**
Metastases at baseline, n (%)	Bone only	57 (35.2)	23 (27.7)	86 (33.6)	38 (29.0)
	Visceral (lung/liver)	46 (28.4)	32 (38.6)	68 (26.6)	44 (33.6)
	Other	49 (30.2)	23 (27.8)	88 (34.4)	41 (31.3)
Gleason score ≥8,* n (%)		**105 (66.9)**	**54 (67.5)**	**183 (72.9)**	**95 (74.8)**
Patients with alteration(s) in a single gene,† n (%)	*BRCA1*	8 (4.9)	5 (6.0)	8 (3.1)	5 (3.8)
	BRCA2	80 (49.4)	47 (56.6)	81 (31.6)*	47 (35.9)
	ATM	60 (37.0)	24 (28.9)	62 (24.2)	24 (18.3)
	CDK12	–	–	61 (23.8)	28 (21.4)
Patients with co-occurring alterations, n (%)		14 (8.6)	7 (8.4)	17 (6.6)	11 (8.4)

*A multivariate rPFS (BICR) analysis adjusting for previous taxane, measurable disease, PSA, location of metastases at baseline, ECOG, metastatic disease at initial diagnosis (yes/no) did not support confounding impact of these factors on study outcomes[2]

BICR=blinded independent central review; ECOG=Eastern Cooperative Oncology Group; HRR=homologous recombination repair; PSA=prostate specific antigen; rPFS=radiological progression free survival

1. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440; 2. AstraZeneca Data on File (2020)

Baseline characteristics were generally well balanced between arms[1]

Approximately 1/3 patients were taxane naïve; ~1/5 received 2 prior taxanes and ~1/5 received 2 prior NHAs before randomisation (heavily pre-treated). Just over a half patients had measurable disease at baseline and the majority were PS 0–1.There was a higher median baseline PSA in the physician's choice arm, however the interquartile range was balanced between arms.[1]

		Cohort A		Cohorts A+B*	
		Olaparib (N=162)	Physician's choice (N=83)	Olaparib (N=256)	Physician's choice (N=131)
Baseline PSA, µg/L median (Q1, Q3)		**62.2 (21.9, 280.4)**	**112.9 (34.3, 317.1)**	**68.2 (24.1, 294.4)**	**106.5 (37.2, 326.6)**
Measurable disease at baseline, n (%)		**95 (58.6)**	**46 (55.4)**	**149 (58.2)**	**72 (55.0)**
ECOG performance status, n (%)	0	84 (51.9)	34 (41.0)	131 (51.2)	55 (42.0)
	1	67 (41.4)	46 (55.4)	112 (43.8)	71 (54.2)
	2	11 (6.8)	3 (3.6)	13 (5.1)	4 (3.1)
Prior new hormonal agent, n (%)	Enzalutamide only	68 (42.0)	40 (48.2)	105 (41.0)	54 (41.2)
	Abiraterone only	62 (38.3)	29 (34.9)	100 (39.1)	54 (41.2)
	Abiraterone + enzalutamide	32 (19.8)	14 (16.9)	51 (19.9)	23 (17.6)
Previous taxane use, n (%)	**Yes**	**106 (65.4)**	**52 (62.7)**	**170 (66.4)**	**84 (64.1)**
	Docetaxel only	74 (45.7)	32 (38.6)	115 (44.9)	58 (44.3)
	Cabazitaxel only	2 (1.2)	0 (0.0)	3 (1.2)	0 (0.0)
	Docetaxel + cabazitaxel	**29 (17.9)**	**20 (24.1)**	**51 (19.9)**	**26 (19.8)**
	Paclitaxel only	**1 (0.6)**	**–**	**1 (0.4)**	**–**

A multivariate rPFS (BICR) analysis adjusting for previous taxane, measurable disease, PSA, location of metastases at baseline, ECOG, metastatic disease at initial diagnosis (yes/no) did not support confounding impact of these factors on study outcomes[2]

BICR=blinded independent central review; ECOG=Eastern Cooperative Oncology Group; HRR=homologous recombination repair; PSA=prostate specific antigen; rPFS=radiological progression free survival

1. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440; 2. AstraZeneca Data on File (2020)

BRCA2, *ATM* and *CDK12* were the most prevalent genes of qualifying gene alterations in randomised patients reported

Patients, n (%)*	Cohort A		Cohort B		Cohorts A + B	
	Olaparib (N=162)	Physician's choice (N=83)	Olaparib (N=94)	Physician's choice (N=48)	Olaparib (N=256)	Physician's choice (N=131)
BRCA1	10 (6.2)	5 (6.0)	0	0	10 (3.9)	5 (3.8)
BRCA2	91 (56.2)	52 (62.7)	1 (1.1)	1 (2.1)	92 (35.9)	53 (40.5)
ATM	64 (39.5)	26 (31.3)	2 (2.1)	0	66 (25.8)	26 (19.8)
BARD1	2 (1.2)	0	1 (1.1)	1 (2.1)	3 (1.2)	1 (0.8)
BRIP1	0	0	2 (2.1)	2 (4.2)	2 (0.8)	2 (1.5)
CDK12	3 (1.9)	2 (2.4)	64 (68.1)	30 (62.5)	67 (26.2)	32 (24.4)
CHEK1	0	0	2 (2.1)	1 (2.1)	2 (0.8)	1 (0.8)
CHEK2	4 (2.5)	1 (1.2)	7 (7.4)	5 (10.4)	11 (4.3)	6 (4.6)
FANCL	0	0	0	0	0	0
PALB2	0	0	4 (4.3)	4 (8.3)	4 (1.6)	4 (3.1)
PPP2R2A	1 (0.6)	3 (3.6)	6 (6.4)	5 (10.4)	7 (2.7)	8 (6.1)
RAD51B	1 (0.6)	1 (1.2)	4 (4.3)	1 (2.1)	5 (2.0)	2 (1.5)
RAD51C	0	0	0	0	0	0
RAD51D	1 (0.6)	0	1 (1.1)	0	2 (0.8)	0
RAD54L	1 (0.6)	0	3 (3.2)	2 (4.2)	4 (1.6)	2 (1.5)

Table shows the prevalence of qualifying gene alterations in randomised patients reported for the total number of alterations in any gene

*Patients with multiple genes are included across more than one gene

†Twenty-eight patients (21 patients in Cohort A and seven patients in Cohort B) had mutations in more than one gene. Four patients were incorrectly assigned to Cohort B (one *BRCA2* [olaparib], one *BRCA2+CDK12* [control] and two *ATM* [both olaparib])

HRR=homologous recombination repair

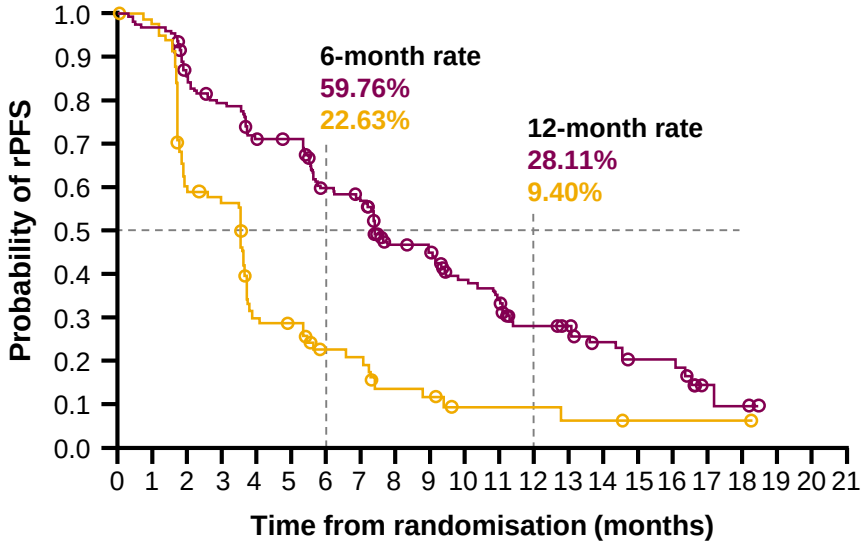
1. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

Cohort A

PROfound met its primary endpoint

Lynparza significantly improved rPFS by BICR in patients with alterations in *BRCA1, BRCA2* or *ATM* (Cohort A) vs. physician's choice[1,2]

Olaparib reduced the risk of progression or death by 66% vs. physician's choice. In Cohort A, the median rPFS for patients with BRCAm or ATMm mCRPC was doubled in the olaparib arm vs. physician's choice. Separation of the curves occurs at approximately 8 weeks, which corresponds with the first scan

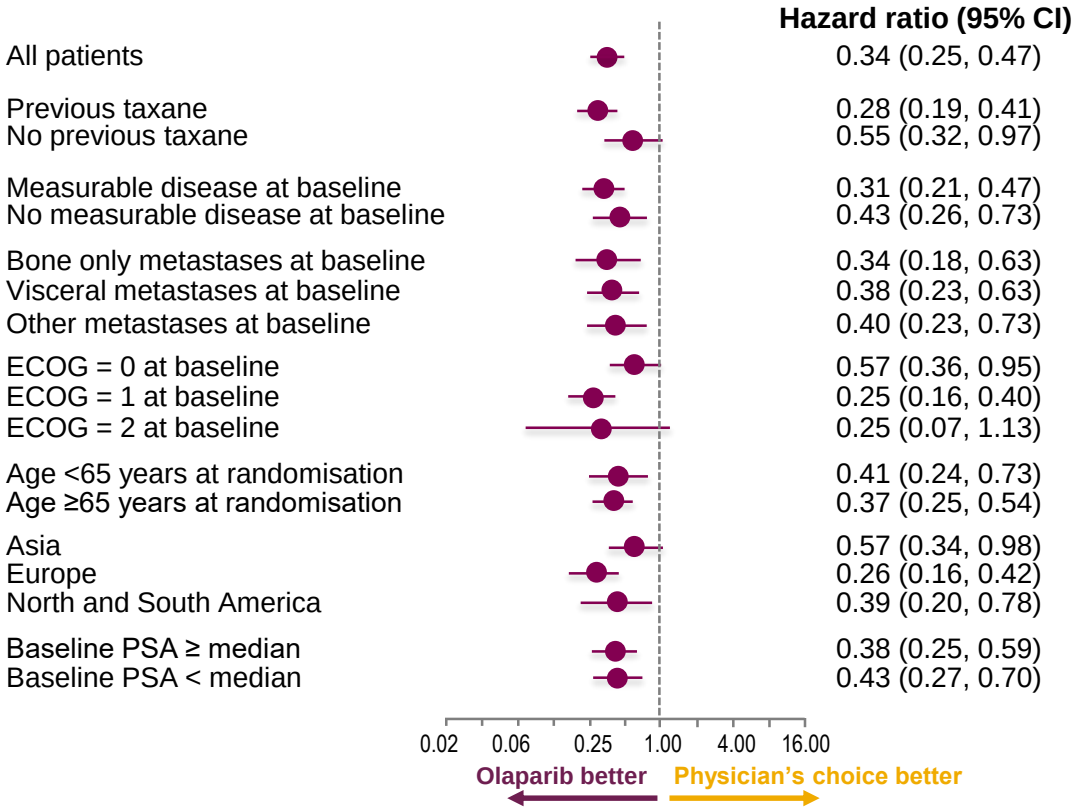


	Olaparib (n=162)	Physician's choice (n=83)
Events, n (%)	106 (65.4)	68 (81.9)
Median PFS, months (BICR)	7.39	3.55
Median difference, months	+3.84	
	HR=0.34 95% CI (0.25, 0.47) *P*<0.001	

BICR=blinded independent central review; ECOG=Eastern Cooperative Oncology Group; HRR=homologous recombination repair; PSA=prostate specific antigen; rPFS=radiological progression free survival

1. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440; 2. AstraZeneca Data on File (2020)

rPFS benefit with olaparib was seen across prespecified subgroups in patients with alterations in *BRCA1*, *BRCA2* or *ATM* (Cohort A)[1,2]

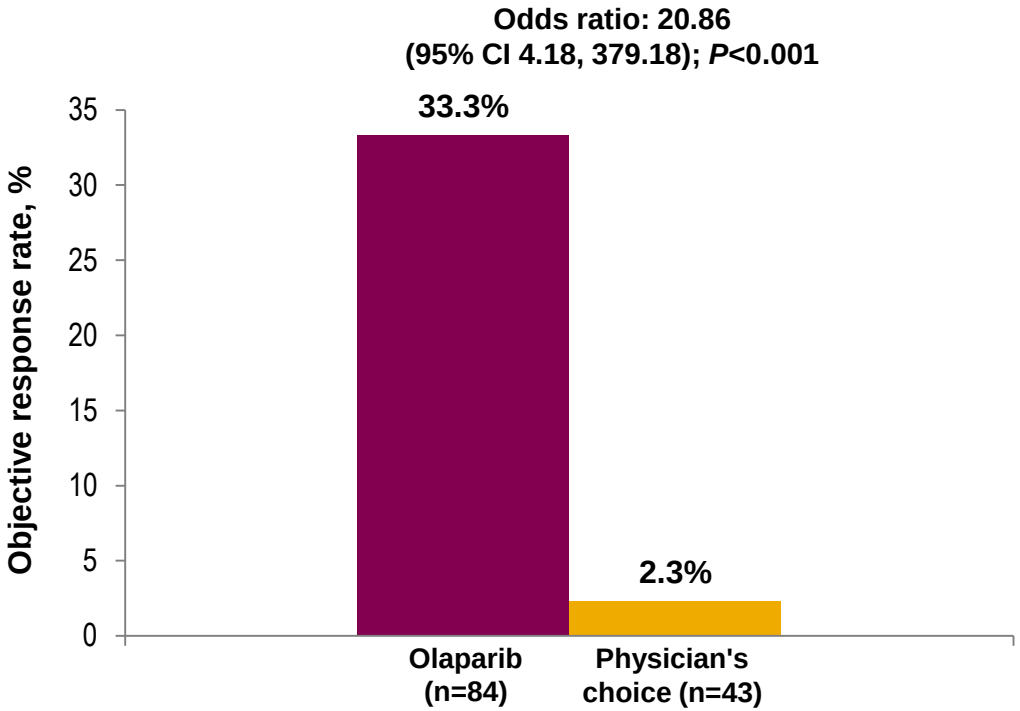


- The benefit of olaparib over physician's choice of NHA was **maintained across all pre-defined subgroups**, with clinically meaningful reductions in the risk of progression or death in olaparib-treated patients
- PROfound however was **not powered to demonstrate differences between subgroups**

Cohort A

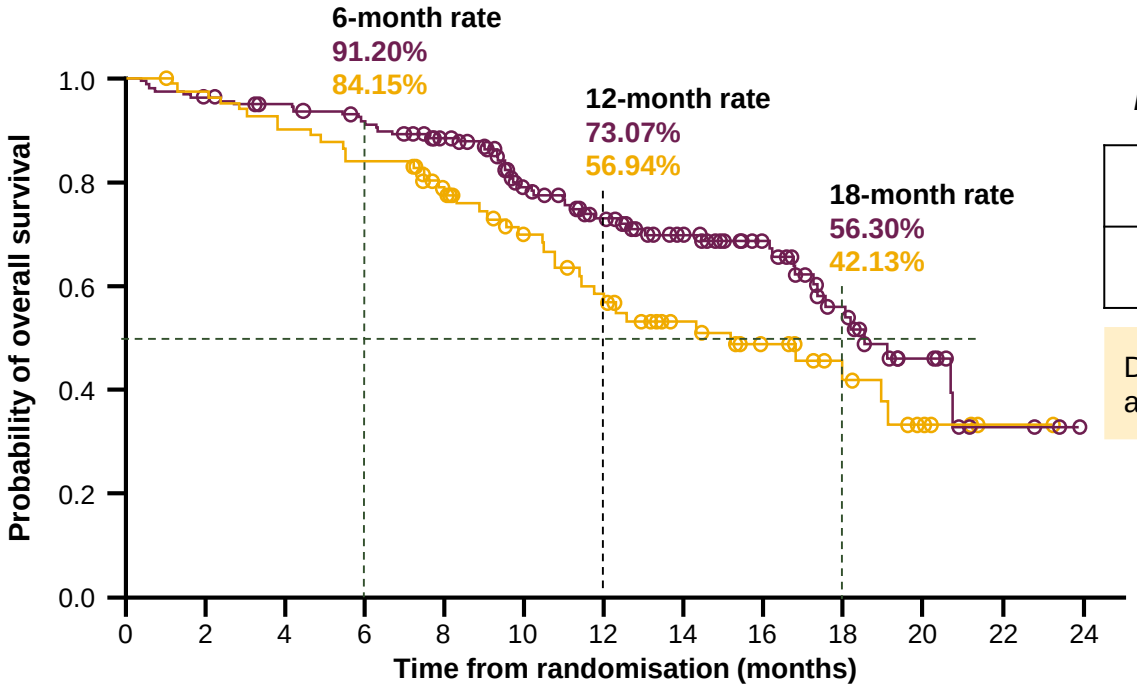
Significantly more patients with alterations in *BRCA1, BRCA2* or *ATM* (Cohort A) had an objective response whilst on olaparib vs. physician's choice (RECIST v1.1)[1]

One-third of patients in the olaparib arm achieved an objective response, a 21-fold increase in the odds ratio of olaparib compared with physician's choice



Cohort A

At interim analysis, olaparib had a favourable trend in OS in patients with alterations in *BRCA1, BRCA2* or *ATM* (Cohort A) despite >80% cross-over for eligible patients*[1,2]

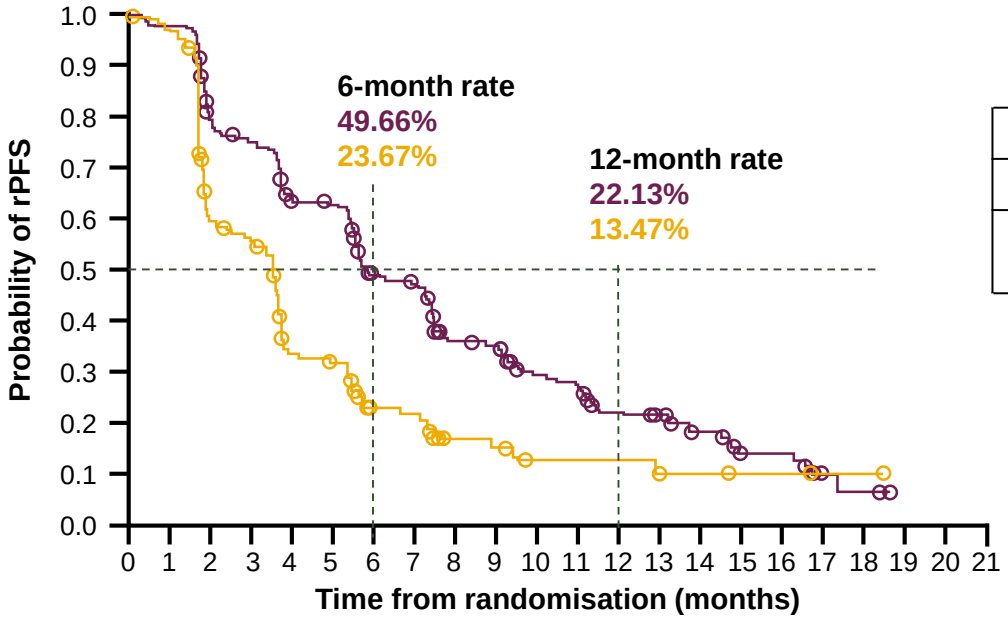


Cohort A *Part of MTP*	Olaparib (N=162)	Physician's choice (N=83)
Median OS (months)	18.50	15.11
Hazard ratio (95% CI)	**0.64** (0.43, 0.97) *P*<0.02†	

Differential of over 3 months was seen between arms in OS at interim

Statistically significant and clinically meaningful improvement was seen for BICR-assessed rPFS in olaparib vs. physician's choice-treated patients (Cohort A+B)[1,2]

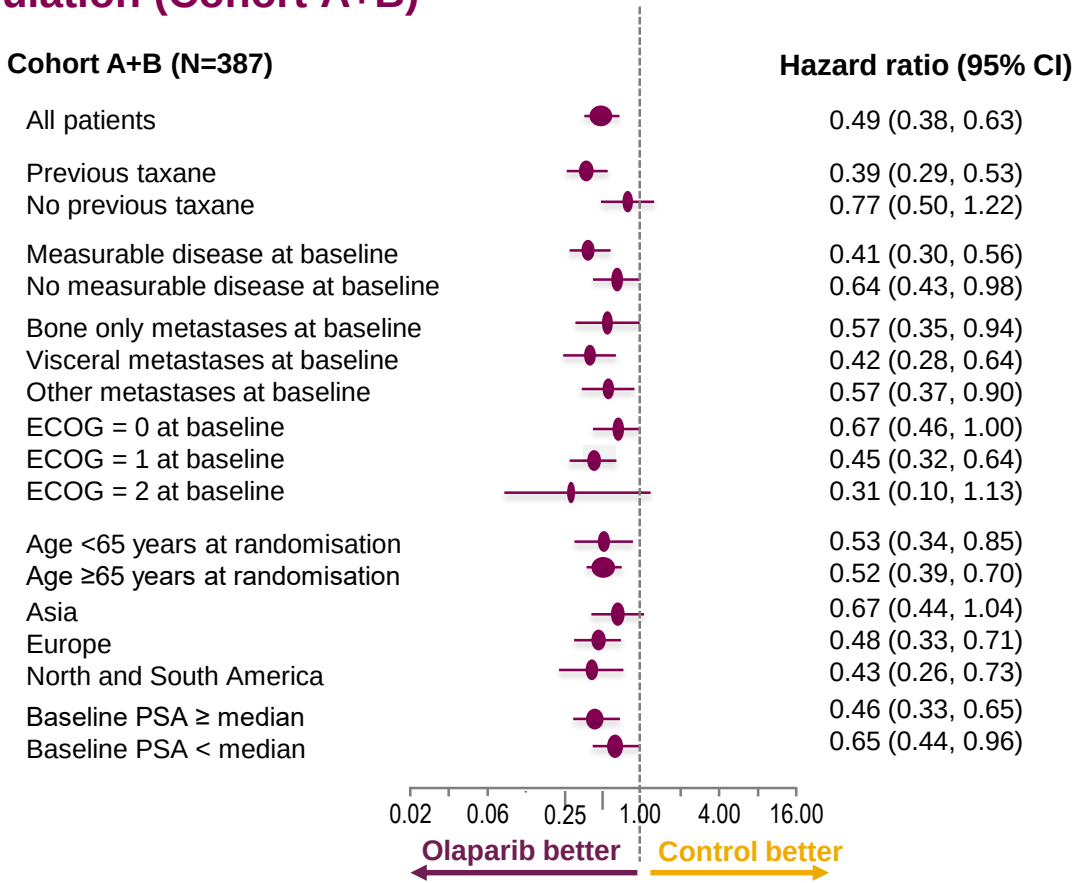
rPFS in the overall population including all qualifying gene alterations was a key secondary objective with alpha control



	Olaparib (n=256)	Physician's choice (n=131)
Events, n (%)	180 (70.3)	99 (75.6)
Median PFS, months	5.82	3.52
Median difference, months	+2.3	
	HR=0.49; 95% CI (0.38, 0.63); *P*<0.001	

- Olaparib reduced the risk of progression or death by 51% vs. physician's choice. Benefit was seen at 6 months and 12 months
- Patients with a qualifying HRRm experienced a significant improvement in median rPFS (+2.3 months)

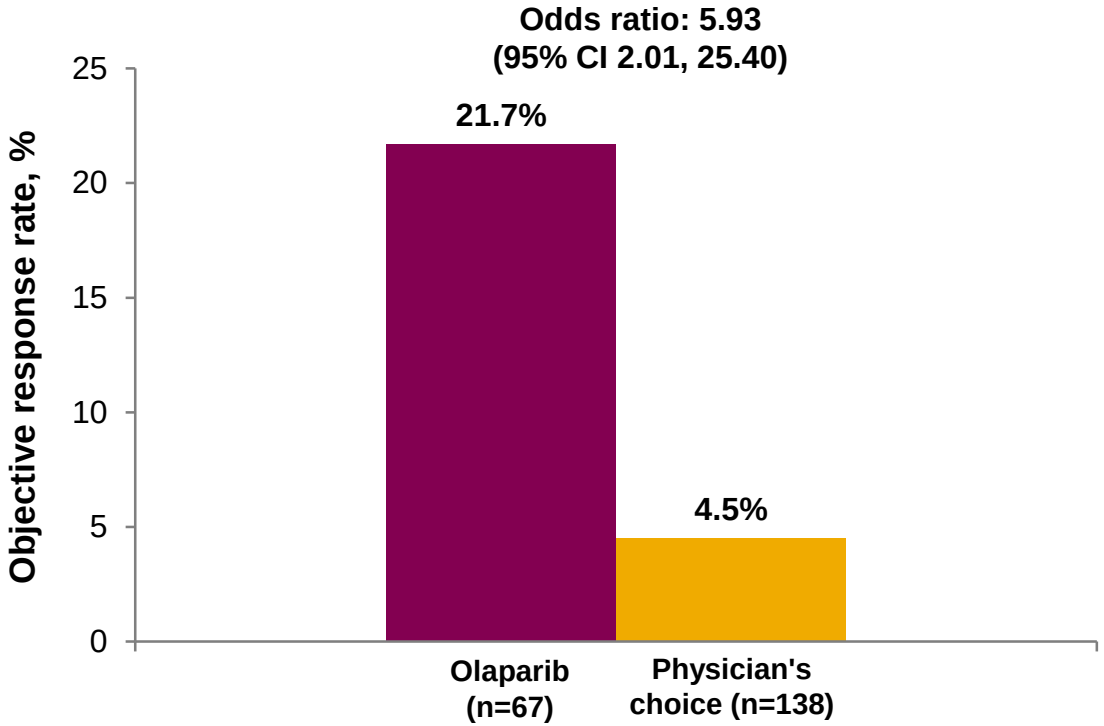
rPFS benefit with olaparib was also seen across prespecified subgroups in the overall population (Cohort A+B)[1]



CI=confidence interval; ECOG=Eastern Cooperative Oncology Group rPFS=radiological progression free survival; PSA=prostate specific antigen

1. de Bono J, et al. Article and supplementary appendix . *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

Significantly more patients with a qualifying alteration in the ITT (Cohort A+B) had an objective response to olaparib vs. physician's choice

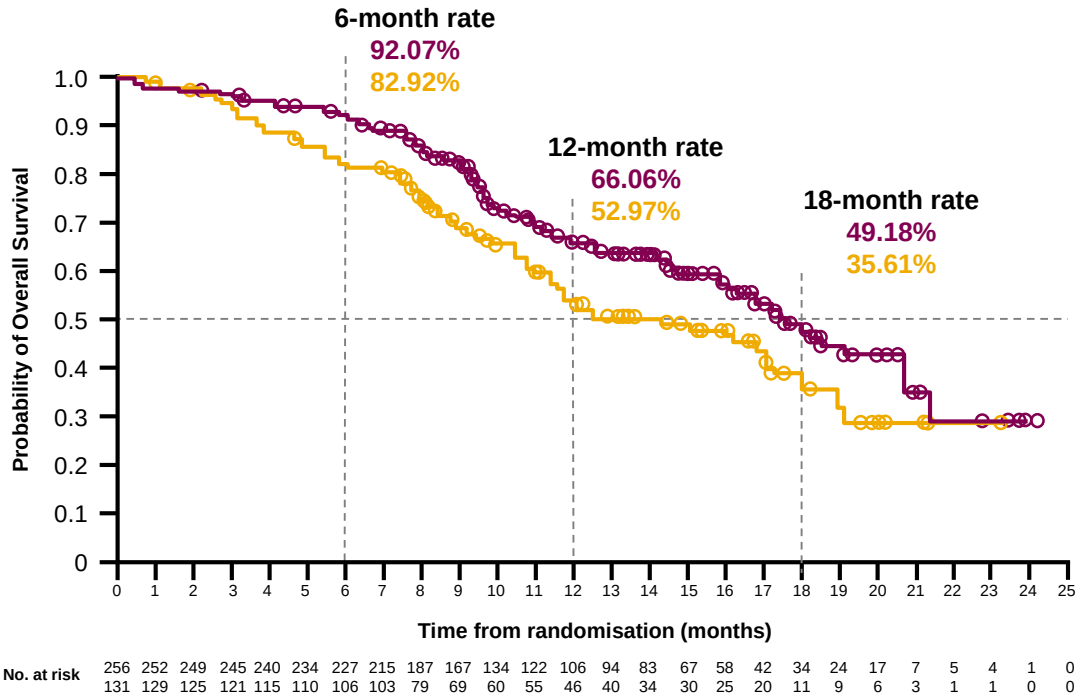


CI=confidence interval; CTC=circulating tumour cell; ITT=intention to treat; PSA=prostate-specific antigen

de Bono J, et al. Article and supplementary appendix. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

Cohort A+B

At interim analysis,* olaparib showed a favourable trend in OS in patients in the ITT population (Cohort A + B) despite >80% crossover for eligible patients



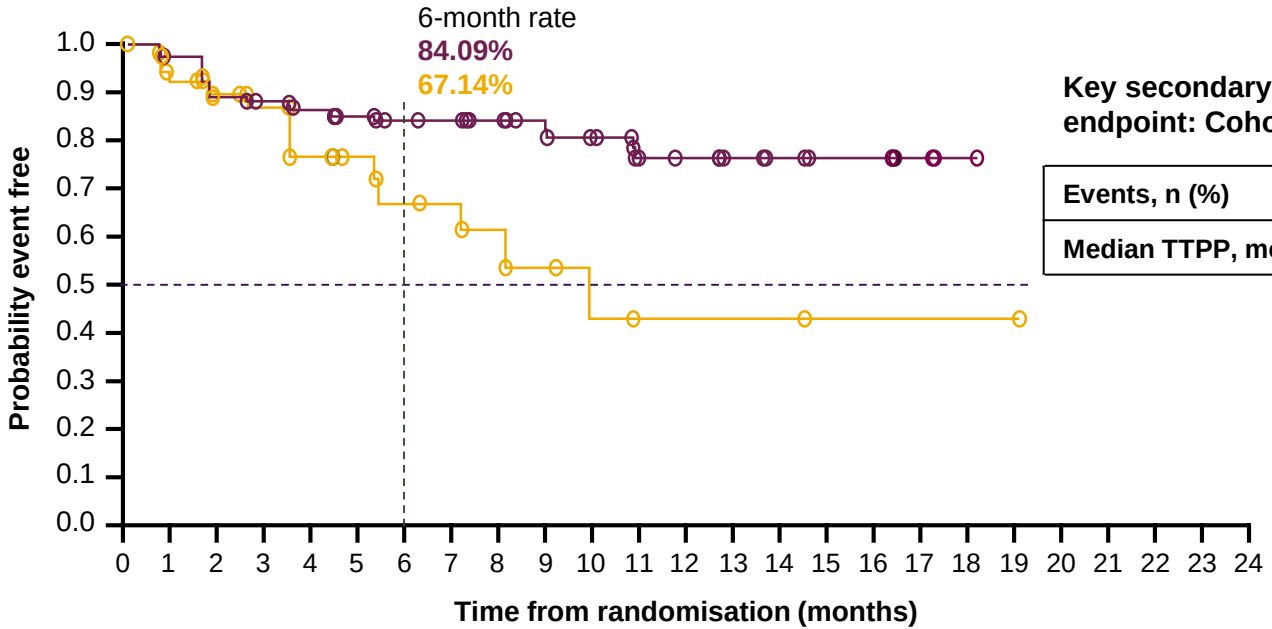
Cohort A+B	Olaparib (N=256)	Physician's choice† (N=131)
Median OS (months)	17.51	14.26
Hazard ratio (95% CI)	**0.67** (0.49, 0.93)	

*41% maturity in Cohort A+B; final analysis planned after ~146 deaths in Cohort A (60% maturity). †Of the physician's choice arm patients who were eligible for cross-over based on radiographic progression and meeting eligibility criteria for olaparib, 81.8% from Cohort A+B crossed over to olaparib. †Alpha spend at interim was 0.01; statistical significance not reached
CI=confidence interval; ITT=intention to treat; OS=overall survival

de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

Median time to pain progression (TTPP)* was significantly increased for olaparib vs. physician's choice in patients with alterations in *BRCA1, BRCA2* or *ATM* (Cohort A)[1,2]

TTPP was assessed using the Brief Pain Inventory-Short Form worst pain item and opioid use.
Statistical significance in TTPP allowed evaluation of interim OS as part of the multiplicity testing procedure



Key secondary endpoint: Cohort A	Olaparib (n=162)	Physician's choice (n=83)
Events, n (%)	21 (13.0)	14 (16.9)
Median TTPP, months	NR	9.92
	HR=0.44 95% CI (0.22, 0.91) *P*=0.0192	

A sensitivity analysis including death as an event in the absence of pain progression yielded similar results

AML=acute myeloid leukaemia; MDS=myelodysplastic syndromes

1. Lynparza SmPC. Accessed April 2020; 2. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

Adjustment for crossover showed a directional improvement in favour of olaparib

72 patients in total in PROfound crossed over to olaparib from the control arm. The median duration of olaparib post crossover was 3.5 months

	Cohort A	Cohort B	Cohort A+B
Sensitivity analyses from crossover effect on overall survival results*			
Patients switching to olaparib from control arm, n (%)	51 (61.4)	24 (50.0)	75 (57.3)
Hazard ratio (95% CI)			
Full analysis without treatment switch adjustment	0.64 (0.43, 0.97)	0.73 (0.45,1.23)	0.67 (0.49, 0.93)
Treatment switch adjusted – RPSFTM (Method a)**	0.45 (0.22, 0.94)	0.40 (0.09,1.79)	0.45 (0.24, 0.85)
Treatment switch adjusted – RPSFTM (Method b)***	0.57 (0.34, 0.96)	0.57 (0.23,1.42)	0.60 (0.40, 0.90)

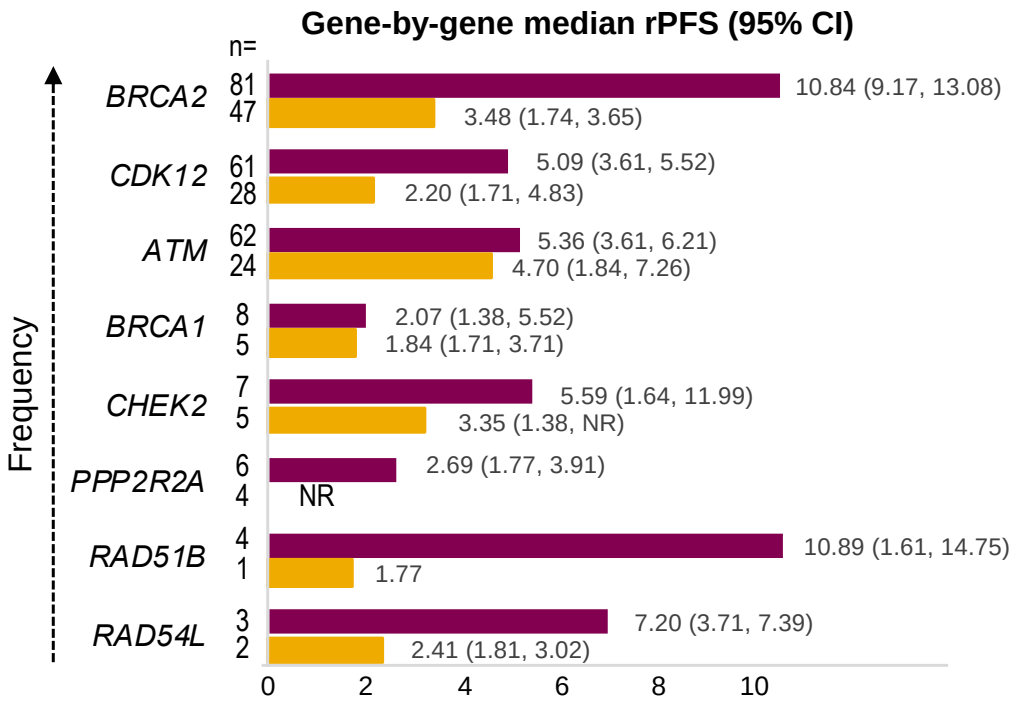
Switching analyses performed to adjust for crossover showed a **further directional improvement in HR for OS in favour of olaparib** in both Cohort A and the ITT population (Cohort A + B)

AML=acute myeloid leukaemia; MDS=myelodysplastic syndromes

1. Lynparza SmPC. Accessed April 2020; 2. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

There is evidence of clinical activity of olaparib in patients with alterations in genes other than BRCA

97% of patients were randomised based on alterations in 8/15 single genes. 7/15 genes had alteration frequencies too low for descriptive statistics (<5 patients)



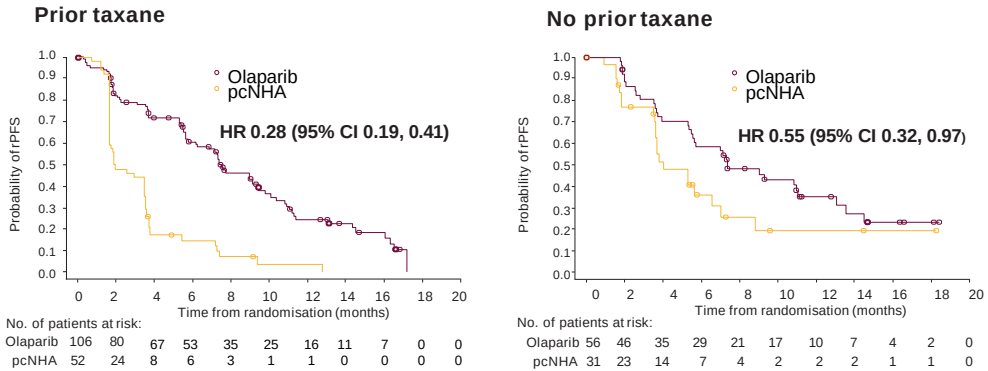
- Exploratory analyses suggest that patients with BRCA alterations derived the most benefit, however, there is evidence of clinical activity of olaparib in patients with alterations in non-BRCA HRR genes
- But, gene-level analysis is complex and exploratory – comparisons may be confounded by small sample size, low power, lack of stratification at the gene level and limited knowledge of the performance on prior, and standard of care therapies

AML=acute myeloid leukaemia; MDS=myelodysplastic syndromes

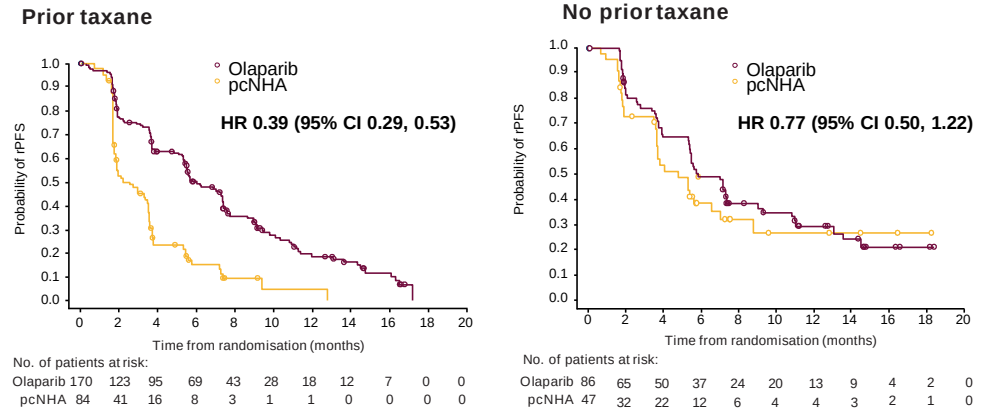
1. Lynparza SmPC. Accessed April 2020; 2. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

rPFS (BICR) benefit was greater for olaparib vs. physician's choice of NHA in Cohort A and Cohort A+B, regardless of prior taxane use

rPFS (BICR) Cohort A



rPFS (BICR) Cohort A+B



Subgroup analyses of rPFS by prior taxane status in patients

	Prior taxane	Number of events, n (%)		Median rPFS, months	
		Olaparib	pcNHA	Olaparib	pcNHA
Cohort A	Yes	72 (67.9)	47 (90.4)	7.4	1.9
	No	34 (60.7)	21 (67.7)	7.4	4.1
Cohort A+B	Yes	124 (72.9)	70 (83.3)	5.8	2.6
	No	56 (65.1)	29 (61.7)	5.8	4.8

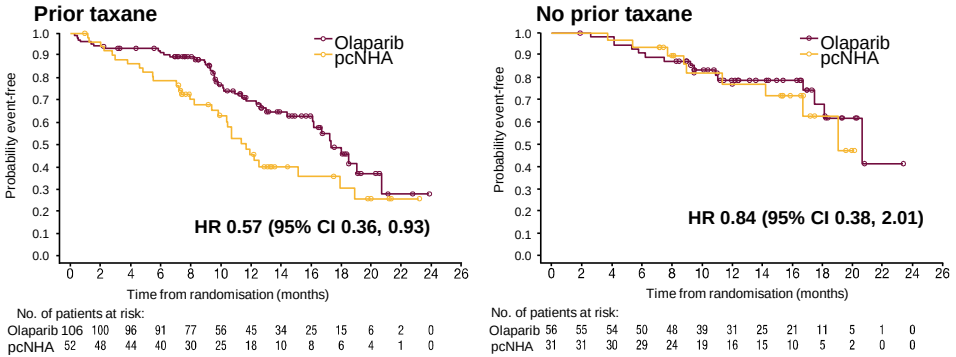
AML=acute myeloid leukaemia; MDS=myelodysplastic syndromes

1. Lynparza SmPC. Accessed April 2020; 2. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

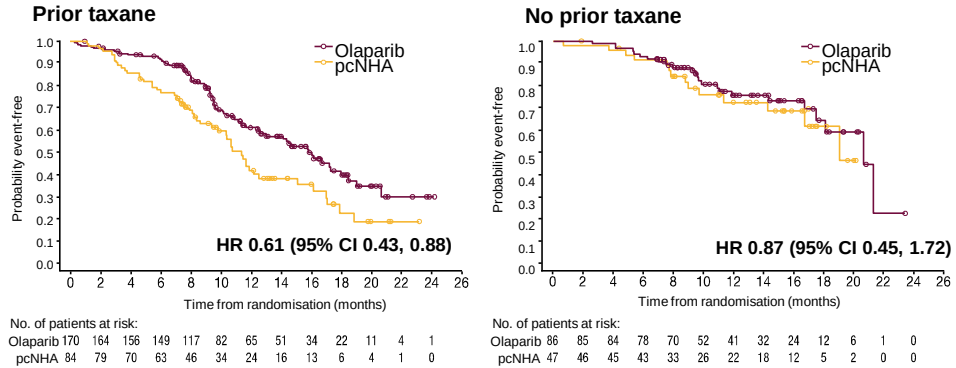
OS benefit was greater for olaparib vs. physician's choice of NHA in Cohort A and Cohort A+B, regardless of prior taxane use

*OS data is currently immature, however there was >80% crossover to olaparib from physician's choice upon disease progression for eligible patients**

OS Cohort A



OS Cohort A+B



Subgroup analyses of OS by prior taxane status in patients

	Prior taxane	Number of events, n (%)		Median OS, months	
		Olaparib	pcNHA	Olaparib	pcNHA
Cohort A	Yes	39 (36.8)	30 (57.7)	17.3	11.7
	No	15 (26.8)	9 (29.0)	20.7	19.1
Cohort A+B	Yes	73 (42.9)	49 (58.3)	15.8	11.4
	No	24 (27.9)	14 (29.8)	20.7	19.1

AML=acute myeloid leukaemia; MDS=myelodysplastic syndromes

1. Lynparza SmPC. Accessed April 2020; 2. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

The median duration of treatment with olaparib in Cohort A + B was nearly double that of the physician's choice arm

Approximately 1/5 patients were still receiving study drug in the olaparib arm at data cut off vs. ~1/10 patients in the physician's choice arm

Median treatment duration with olaparib was 7.4 months vs. 3.9 months with physician's choice

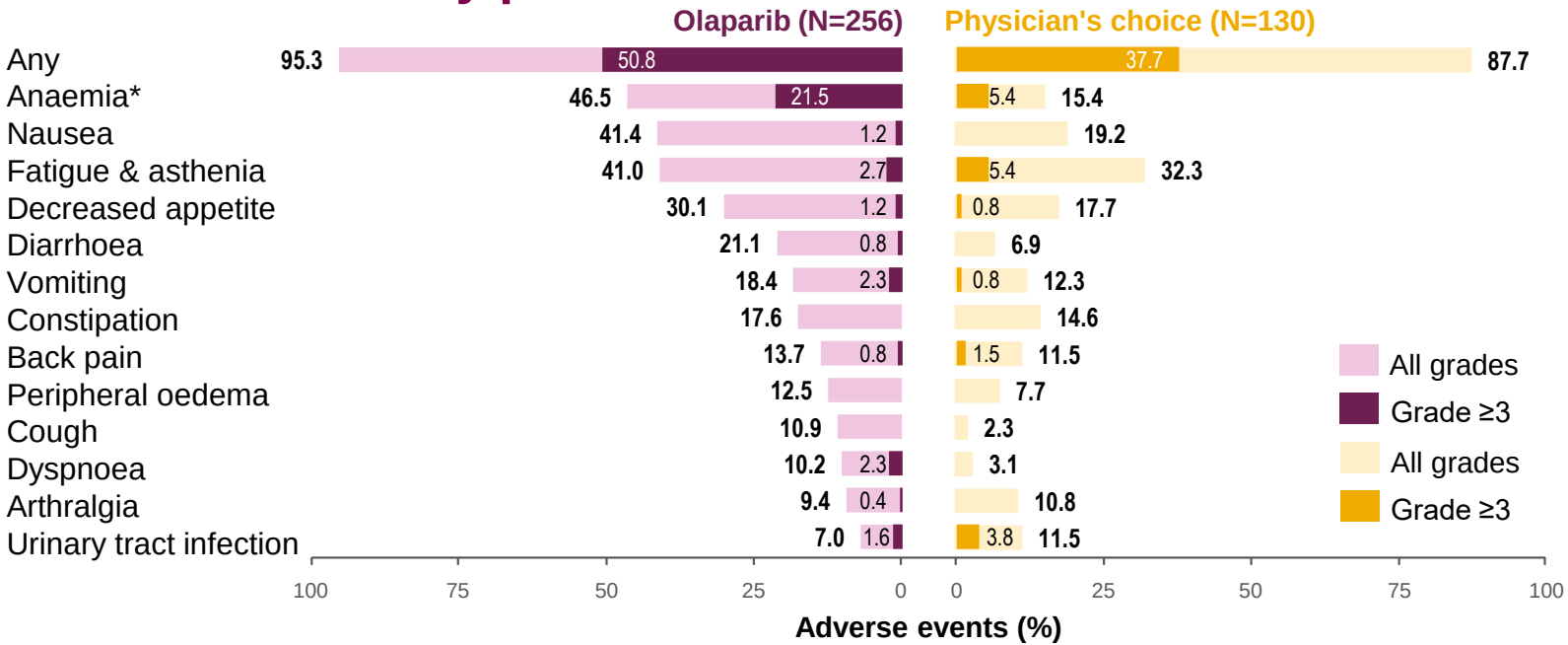
	Olaparib (N=256)	Physician's choice (N=130)
Any AE, n (%)	244 (95.3)	114 (87.7)
Any AE of CTCAE grade 3 or higher, n (%)	130 (50.8)	49 (37.7)
Interruption of intervention due to AE, n (%)	115 (44.9)	24 (18.5)
Dose reduction due to AE, n (%)	57 (22.3)	5 (3.8)
Discontinuation due to AE, n (%)	46 (18.0)	11 (8.5)
Death due to AE*, n (%)	10 (3.9)	5 (3.8)
Reported to be related to study treatment	1 (0.4)	1 (0.8)

Patients **received olaparib for nearly twice as long as the control arm**, which may have contributed to the higher rate of grade ≥3 AEs and AEs leading to discontinuation in the olaparib arm

AML=acute myeloid leukaemia; MDS=myelodysplastic syndromes

1. Lynparza SmPC. Accessed April 2020; 2. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

The adverse event profile for olaparib was generally consistent with the known safety profile[1,2]



- The most common adverse events were **anaemia, nausea and fatigue**
- **4.3%** of patients on olaparib experienced **pulmonary embolism** vs. **0.8%** with physician's choice
- There were **no reports of MDS or AML**

AML=acute myeloid leukaemia; MDS=myelodysplastic syndromes

1. Lynparza SmPC. Accessed April 2020; 2. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

~50% of patients on olaparib who developed a pulmonary embolism, the Grade assessment was 1–2, and most patients did not change olaparib dosing as a consequence of the diagnosis[1]

- Of the 11 (4.3%) pulmonary embolism events reported in the olaparib arm, five were Grade 1 or 2, five were Grade 3, and one was Grade 4; none were fatal
- Eight out of 11 patients continued olaparib at unchanged dose and had no repeated pulmonary embolism events
- The event in the control arm was Grade 3

- Pulmonary embolism is not a recognised complication of olaparib treatment and the significance of the occurrence of these events is difficult to interpret

- With over half of these events denoted Grade 1 to 2, and continuation of olaparib therapy in most cases, the significance of the occurrence of these events is difficult to interpret in this patient population

- Following assessment of cases, there was no plausible biological explanation for the imbalance seen and no pattern of time to event onset, therefore it was concluded that no causal association can be established

de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

Adverse events of special interest for olaparib were generally consistent with the known safety profile[1,2]

Haematological toxicity

- Haematological toxicity is a recognised complication of olaparib
- In PROfound, 21.5% of patients treated with olaparib experienced ≥ Grade 3 anaemia, 3.9% ≥ Grade 3 neutropenia and 3.5% ≥ grade 3 thrombocytopenia[1]

Myelodysplastic syndrome (MDS) / Acute Myeloid Leukaemia (AML)

- The overall incidence of MDS/AML in patients in clinical trials with olaparib monotherapy including long term survival follow up was <1.5%[1]
- In PROfound, with current follow up, no patients were identified with MDS/AML[2]

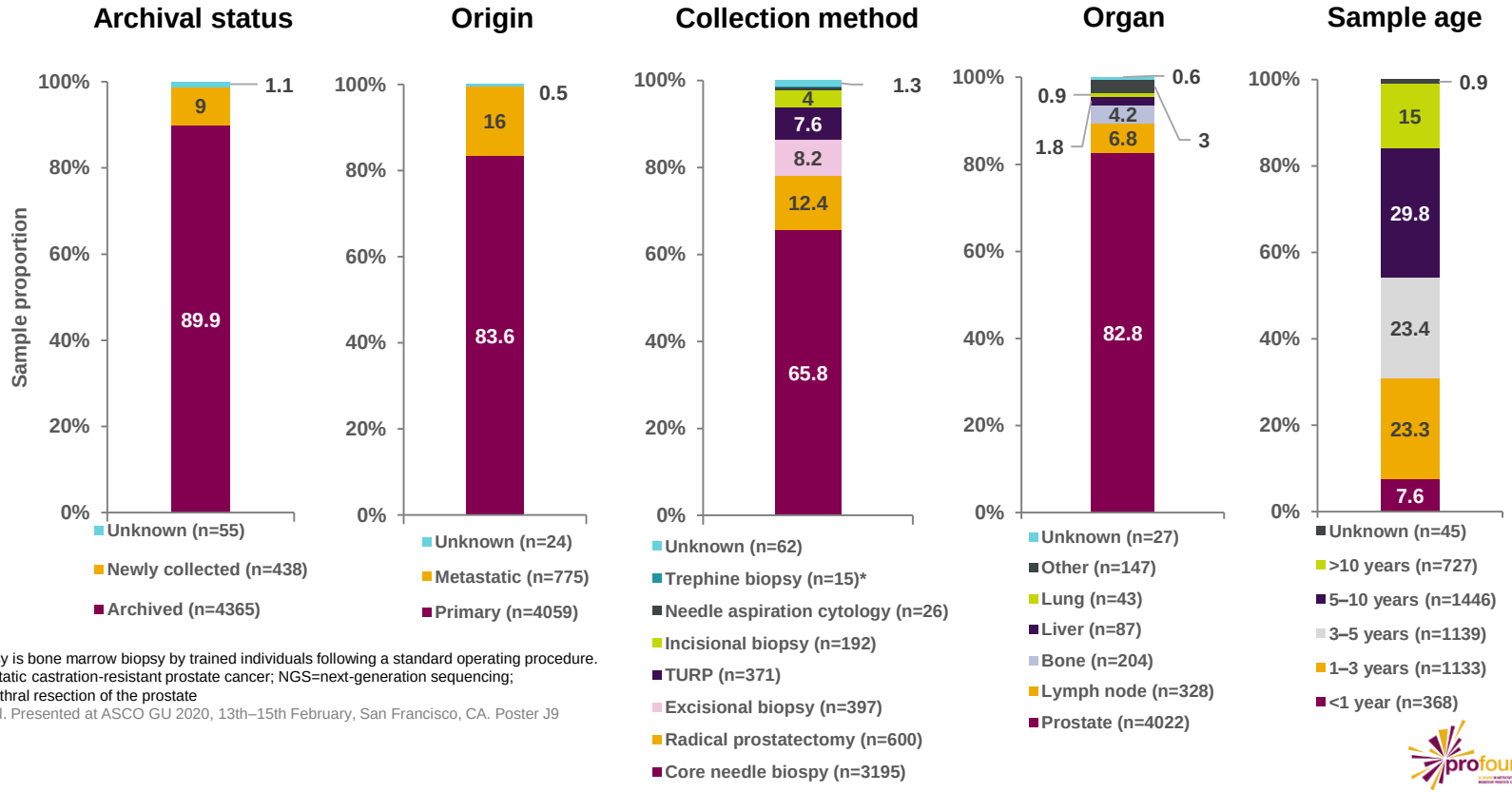
Pneumonitis

- Pneumonitis including events with fatal outcome has been reported in <1.0% of patients treated with olaparib[1]
- In PROfound, pneumonitis was reported in four patients treated with olaparib; two had resolved at data cut-off for this analysis vs. two in the control arm that did not resolve[2]

AML=acute myeloid leukaemia; MDS=myelodysplastic syndromes

1. Lynparza SmPC. Accessed April 2020; 2. de Bono J, et al. Article and supplementary appendix online ahead of print. *New Engl J Med*. 2020. doi 10.1056/NEJMoa1911440

The majority of samples assessed in the study were from archived core biopsies derived from the primary tumour



*Trephine biopsy is bone marrow biopsy by trained individuals following a standard operating procedure.
mCRPC=metastatic castration-resistant prostate cancer; NGS=next-generation sequencing;
TURP=transurethral resection of the prostate

Hussain M, et al. Presented at ASCO GU 2020, 13th–15th February, San Francisco, CA. Poster J9

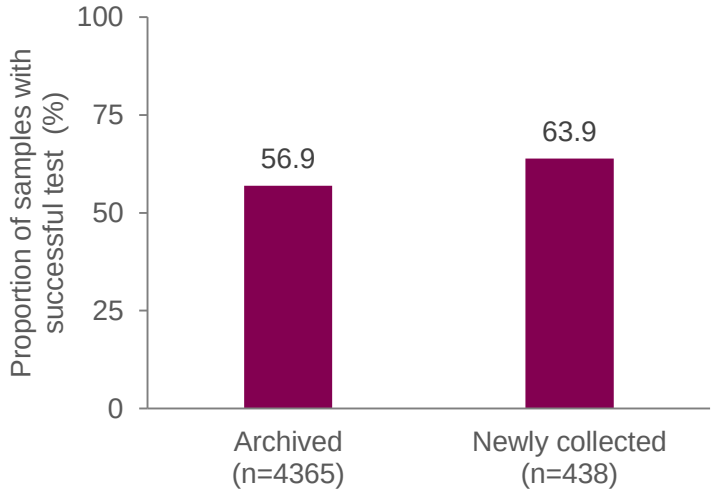
Test success rates were higher with newly collected vs. archived samples and samples from metastatic sites vs. primary tumour origin

During screening for the PROfound study, a total of 4,858 samples were tested and reported by FMI. The majority of samples were derived from archived tissue (N=4365) and from the primary tumour (N=4059)

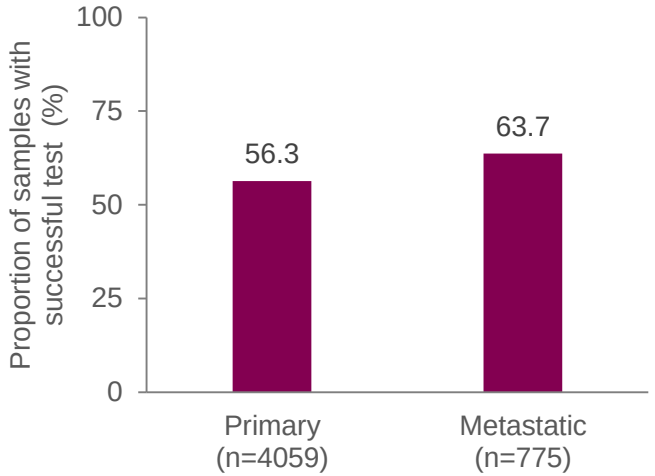
The most common reasons for test failure were different depending on the age of the sample:

1. **Archived samples were more likely to fail at the stage of DNA extraction**
2. **Newly collected samples were most likely to fail at pathology review**

Archived vs. newly collected samples



Primary vs. metastatic samples

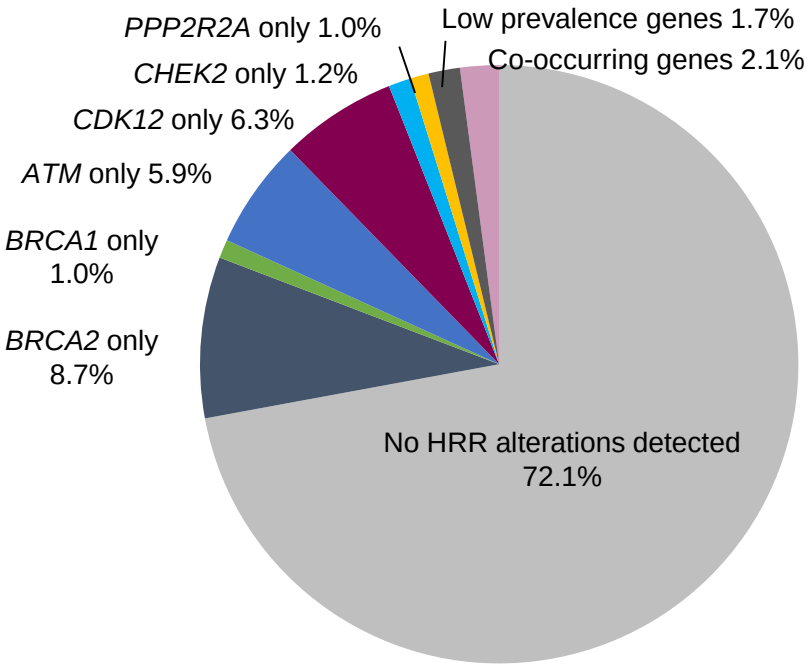


DNA=deoxyribose nucleic acid; FMI=Foundation Medicine, Inc

Hussain M, et al. Presented at ASCO GU 2020, 13th–15th February, San Francisco, CA. Poster J9

PROfound: HRRm prevalence in the screened population

A qualifying HRR alteration was observed in 27.9% of patients with a successful test result



- Prevalence of HRRm in genes included in Cohort A was ~16% (*BRCA2* was highest prevalence at 8.7%)
- CDK12 (Cohort B) contributed ~6%
- Remaining 11 genes of Cohort B contributed ~6% HRRm
- The distribution of alterations in HRR genes within the randomised population reflected that observed in the screened population
- 7.2% of HRRm randomised patients had a mutation in more than one gene (most frequently with *BRCA2* or *CDK12*)

de Bono J M et al. Presented at ESMO 2019, 27th September – 1st October, Barcelona Abstract 847PD

PROfound: Prevalence of HRR gene alterations in primary and metastatic tumour tissue

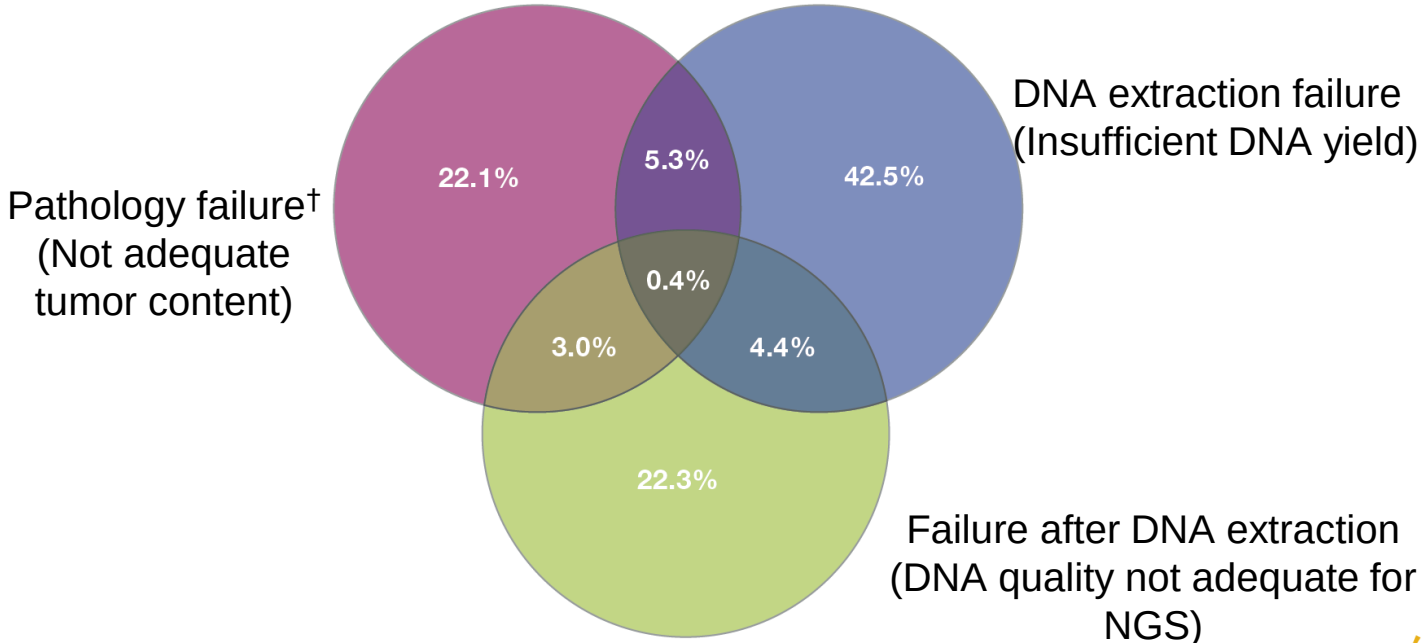
	HRR gene alteration prevalence (%)
All patients	27.9
All primary tumours	**27.2**
Archived primary	27.1
Newly collected primary	28.9
All metastatic tumours	**31.8**
Archived metastatic	33.2
Newly collected metastatic	29.5

A higher prevalence of HRR gene alterations was found in metastatic tumour tissue (31.8%) vs primary tumour (27.2%)

De Bono et al. Poster no. 847PD *Presented at ESMO Annual Meeting, 27 September–1 October 2019, Barcelona, Spain*

PROfound: Test failure is a possibility, why does this happen?

The most frequent reason for test failure was DNA extraction failure: insufficient DNA yield to proceed with testing



*Patients could have more than one tissue sample tested and samples may have failed at different stages of the next generation sequencing testing process.
†Samples does not meet pathology requirements for the test if there is ≤20% tumour content or <5–7.5 mm^2 viable nucleated tissue.

de Bono J M et al. Presented at ESMO 2019, 27th September – 1st October, Barcelona Abstract 847PD

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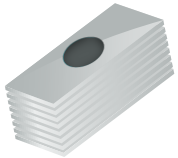
An algorithm for the use of more than one diagnostic option is likely to be needed in prostate cancer

If used in isolation, each of the diagnostic options present challenges for physicians and patients



The lack of an adequate tissue sample is a common challenge in mCRPC

- The diagnostic biopsy is typically the source of tumour tissue for genetic testing in men with mCRPC[1] and may have insufficient sample for both diagnosis and molecular testing[2]
- Obtaining adequate tumour from metastatic sites is particularly difficult in prostate cancer[3]
    - Bone is the principal metastatic site, and not only are biopsy yields low, but the need for decalcification during tissue processing can hamper DNA quality

Sample inadequacy may mean that tissue testing proves to be unsuccessful in up to 30% of cases[4,5]

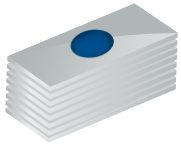
Plasma ctDNA testing may result in a false-negative outcome in some individuals since not all tumours shed sufficient DNA for detection. This aspect of tumour biology is less well characterised in prostate, but in non-small-cell lung cancer, for example, plasma ctDNA testing for EGFR mutations has a **sensitivity of 60-80%**[6-8]

Blood testing may **miss ~50%*** of those harbouring HRRm, simply because it will only detect germline mutations, and not those that are somatic[9,10]

*The ratio of germline to somatic mutations varies by HRR gene but overall is approximately 50%.

1. Vandekerhove G et al. Eur Urol 2019; 75(6):667-675. 2. Pritzker KPH et al. Arch Pathol Lab Med. doi: 10.5858/arpa.2018-0463-RA. 3. Tao D et al. JCO Precis Oncol 2017, 4. de Bono J M et al. Presented at ESMO 2019, 27th September – 1st October, Barcelona Abstract 847PD; 5. Mateo J et al. Lancet Oncol 2019 doi:10.1016/S1470-2045(19)30684-9; 6. Oxnard GR et al. J Clin Oncol 2016 34:3375-3382 45. 7. Jenkins S et al. J Thoracic Oncol 2017;12(7): 1061-1070. 8. Thress K et al. Lung Cancer 2015; 90:509–515; 9. Cheng HH et al. J Natl Compr Canc Netw 2019;17:515-521 10. Pritchard CC. Presented at: APCCC; August 29, 2019; Basel, Switzerland.

The preferred algorithm - initial tissue testing followed by germline mutation testing if insufficient sample/no tissue, in absence of validated ctDNA testing



Tissue as the primary modality

Access to robustly validation Plasma ctDNA test is a challenge

Tissue testing

Test Unsuccessful or tissue not available

Plasma ctDNA testing

Test successful

Blood testing is capability well established

Clinical decision

Blood germline testing

NCCN recommendations

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

GENETIC AND MOLECULAR BIOMARKER ANALYSIS FOR ADVANCED PROSTATE CANCER[c]

Risk Group	Clinical/Pathologic Features	Germline Testing[c]	Molecular and Biomarker Analysis of Tumor[c]	Initial Therapy
Regional	Any T, N1, M0	Recommended	Consider tumor testing for homologous recombination gene mutations (HRRm) and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR)	See PROS-9
Metastatic[ee]	Any T, Any N, M1	Recommended	Recommend tumor testing for HRRm and consider tumor testing for MSI or dMMR	See PROS-13

PROS-8

- Metastatic risk group, changed: ~~Consider~~ *Recommend* tumor testing for HRRm and *consider tumor testing* for MSI or dMMR.

PROS-H

- Systemic Therapy for M1 CRPC added:
  - *Mitoxantrone with prednisone*
  - *Cabazitaxel at 25 mg/m² with concurrent steroid improved radiographic PFS and reduced the risk of death compared with abiraterone or enzalutamide in patients with prior docetaxel treatment for mCRPC in the CARD study.*
  - *Consider inclusion of olaparib in men who have an HRRm and have progressed on prior treatment with enzalutamide and/or abiraterone regardless of prior docetaxel therapy.*

Germline Testing

- The panel recommends inquiring about family and personal history of cancer and family history for known germline variants at time of initial diagnosis. In cases when a patient says he was tested and had negative results, the clinician should inquire about the details of testing. Direct-to-consumer genetic tests do not test for all known relevant variants.
- Germline genetic testing is recommended for patients with prostate cancer and any of the following:
  - High-risk, very-high-risk, regional, or metastatic prostate cancer
  - Ashkenazi Jewish ancestry
  - Family history of high-risk germline mutations (eg, *BRCA1/2*, Lynch mutation)
  - A positive family history of cancer:

- Genetic counseling resources and support is critical and pre-test counseling is preferred when feasible, especially if family history is positive.
- Post-test genetic counseling is recommended if a germline mutation (pathogenic variant) is identified. Cascade testing for relatives is critical to inform the risk for familial cancers in male and female relatives.
- If no pathogenic variant mutations or only germline variants of unknown significance (VUS) are identified but family history is positive, genetic counseling is recommended to discuss possible participation in family studies and variant reclassification studies.

Somatic Tumor Testing

- Recommend evaluating tumor for alterations in homologous recombination DNA repair genes, such as *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*, and *CDK12,* in patients with metastatic prostate cancer. This testing can be considered in men with regional prostate cancer.
  - At present, this information may be used for genetic counseling, early use of platinum chemotherapy, olaparib (category 2B), and/or eligibility for clinical trials (eg, PARP inhibitors). Clinical trials may include additional candidate DNA repair genes under investigation as molecular biomarkers.
  - If mutations in *BRCA1, BRCA2, ATM, PALB2,* and *CHEK2* are found and/or there is a strong family history of cancer, refer to genetic counseling for confirmatory germline testing.
  - Somatic testing may require repetition when prostate cancer progresses after treatment.
  - Patients should be informed that somatic tumor sequencing has the potential to uncover germline findings. However, virtually no somatic NGS test is designed or validated for germline assessment. Therefore, overinterpretation of germline findings should be avoided. If a germline mutation is suspected, the patient should be recommended for follow-up with genetic counseling and dedicated germline testing.

 NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer, Version 1.2020

Abbreviated Prescribing information

For the use of registered oncologist only

Olaparib Tablets

LYNPARZA® 100 mg and 150 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION: Each 150 mg film-coated tablet contains 150 mg of Olaparib | Each 100 mg film-coated tablet contains 100 mg of olaparib.

INDICATIONS: LYNPARZA is indicated in:

Ovarian Cancer: for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy; for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy ; for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy; Lynparza in combination with bevacizumab is indicated for the: maintenance treatment of adult patients with advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy with bevacizumab

Breast Cancer: In patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment

Prostate cancer: Lynparza is indicated as monotherapy for the: treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene mutations (germline and/or somatic) who have progressed following a prior new hormonal agent

Adenocarcinoma of the pancreas: Lynparza is indicated as monotherapy for the: maintenance treatment of adult patients with germline BRCA-mutated metastatic adenocarcinoma of the pancreas whose disease has not progressed on first-line platinum-based chemotherapy

DOSAGE & ADMINISTRATION: The recommended dose of LYNPARZA is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction.

DURATION OF TREATMENT: Maintenance treatment of newly diagnosed advanced ovarian cancer: can continue treatment for 2 years or until disease progression. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years. **Advanced gBRCA-mutated Ovarian Cancer** :Continue treatment until disease progression or unacceptable toxicity. **Platinum-sensitive relapsed ovarian cancer**: it is recommended that treatment be continued until progression of the underlying disease **Maintenance treatment of newly diagnosed advanced ovarian cancer in combination with bevacizumab**: patients can continue treatment for 2 years or until disease progression. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years. **Metastatic HER2-negative breast cancer**: it is recommended that treatment be continued until progression of the underlying disease. **HRR-gene mutated metastatic castration-resistant prostate cancer**: it is recommended that treatment be continued until progression of the underlying disease. **Maintenance following first-line treatment of metastatic adenocarcinoma of the pancreas**: It is recommended that treatment be continued until progression of the underlying disease

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Abbreviated Prescribing information

CONTRAINDICATIONS: None.
WARNINGS & PRECAUTIONS: Haematological toxicity: Haematological toxicity has been reported in patients treated with LYNPARZA including generally mild or moderate anaemia, neutropenia, thrombocytopenia and lymphopenia. If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with LYNPARZA should be interrupted. **Myelodysplastic Syndrome/Acute Myeloid Leukaemia**: The incidence of MDS/AML in patients treated in clinical trials with LYNPARZA monotherapy was <1.5% and majority of events had a fatal outcome. If MDS and/or AML are confirmed while on treatment with LYNPARZA, it is recommended that LYNPARZA should be discontinued and the patient be treated appropriately. **Pneumonitis**: Pneumonitis has been reported in <1.0% patients treated with LYNPARZA monotherapy in clinical studies. If pneumonitis is confirmed, LYNPARZA treatment should be discontinued and the patient treated appropriately. **Embryofoetal toxicity**: Based on its mechanism of action (PARP inhibition), LYNPARZA could cause foetal harm when administered to a pregnant woman. LYNPARZA should not be taken during pregnancy. **Breast-feeding**: The excretion of olaparib in milk has not been studied in animals or in breast-feeding mothers. **Interactions with other medicinal products**: Co-administration of LYNPARZA with strong or moderate CYP3A inhibitors is not recommended. If a strong or moderate CYP3A inhibitor must be co-administered, the dose of LYNPARZA should be reduced. Co-administration of LYNPARZA with strong or moderate CYP3A inducers is not recommended.
UNDESIRABLE EFFECTS: The most commonly reported adverse drug reactions (ADRs), reported in more than 10% of the patients and greater than placebo/ active comparator were: Anemia, Neutropenia and/or Leukopenia, Decreased apetite, Dizzyness, Headache, Cough, Dysguesia, Vomiting, Nausea and Diarrhoea, Fatigue.
INTERACTIONS: Concomitant use of itraconazole as well as other strong CYP3A inhibitors is not recommended with LYNPARZA due to an increase in Cmax and AUC. CYP3A inducers could substantially diminish the clinical efficacy of LYNPARZA and concomitant use of strong inducers is not recommended.
PHARMACOLOGICAL PROPERTIES:
Mechanism of action : Olaparib is a potent inhibitor of human poly (ADP ribose) polymerase enzymes (PARP 1, PARP 2, and PARP 3), and has been shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo either as a standalone treatment or in combination with established chemotherapies
Pharmacokinetic properties: The pharmacokinetics of olaparib at the 300 mg tablet dose is characterized by an apparent plasma clearance of ~7 L/h, an apparent volume of distribution of ~158 L and a terminal half-life of 15 hours. The in vitro plasma protein binding is approximately 82% at 10 µg/mL. CYP3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib. Post administration, ~86% of the dose was recovered within a 7-day collection period, ~44% via the urine and ~42% via the faeces. Majority of the material was excreted as metabolites.
PHARMACEUTICAL PARTICULARS
PRESENTATION & STORAGE: LYNPARZA 150 mg tablet is a green to green/grey, oval, bi-convex tablet debossed with 'OP150' on one side and plain on the reverse. LYNPARZA 100 mg tablet is a yellow to dark yellow, oval, bi-convex tablet debossed with 'OP100' on one side and plain on the reverse. This medicinal product does not require any special temperature storage conditions.
SHELF LIFE: Please refer outer carton.

For Further information contact: AstraZeneca Pharma India Ltd., Block N1, 12th Floor, Manyata Embassy Business Park, Rachenahalli, Outer Ring Road, Bengaluru – 560 045 | www.astrazenecaindia.com

For more information, refer full prescribing information Version 6, dated 25th Aug 2020. API Version 5 Dated 25th Aug 2020.

Confidentiality Notice

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