Olaparib plus Abiraterone for Patients with Metastatic Castration-resistant Prostate Cancer (mCRPC)

Oncologic Drugs Advisory Committee (ODAC) Meeting

FDA Introductory Comments
April 28th, 2023

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Olaparib: Poly-ADP Ribose Polymerase (PARP) Inhibitor

- PARP inhibitors exploit synthetic lethality to target DNA repair defects in cancer cells
- Tumors with mutations in the **homologous recombination repair (*HRR*) pathway** appear especially susceptible to PARP inhibition

***HRR*m**:

Mutation in HRR genes, including *BRCA1*, *BRCA2, ATM, CHEK2, CDK12, etc*.

***BRCA*m**:

Mutation in *BRCA1* and *BRCA2*.

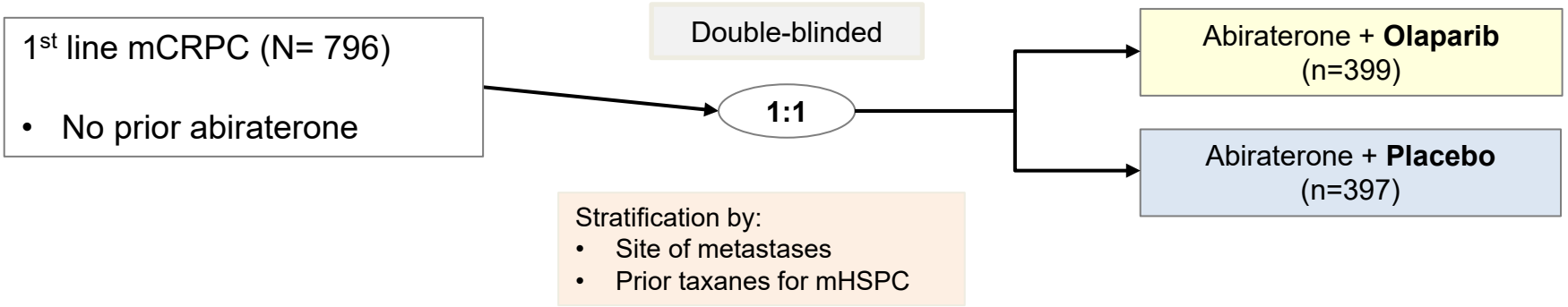
Approved PARP Inhibitors in mCRPC

- PARP inhibitors currently approved as single agents in **selected populations** in mCRPC, in later line of therapy
  - **Olaparib** → approved for homologous recombination repair **(*HRR*) gene-mutated** mCRPC
    - BRCA: most prevalent, most PARP-sensitive mutation
  - **Rucaparib** → approved for ***BRCA*-mutated** mCRPC

Applicant Proposes Broad Indication

- Proposed: **"In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC."**
- First proposed approval of PARP inhibitor for mCRPC population **unselected for *BRCA* or *HRR* mutations**
- ~45,000 patients diagnosed with mCRPC annually
- Early metastatic setting, minimally symptomatic

Primary Evidence of Efficacy: PROpel Study



No stratification or prespecified alpha-controlled analysis by *BRCA*m or *HRR*m

Primary endpoint: radiographic progression-free survival (rPFS) by investigator (inv) assessment

rPFS by blinded independent central review (BICR) for sensitivity analysis

Key secondary endpoint: **overall survival (OS)**

mHSPC: metastatic hormone-sensitive prostate cancer

PROpel Efficacy Results

- Met primary endpoint: **~8 month improvement in rPFS**
- FDA has considered rPFS to be a clinical endpoint
  - Also requires large magnitude, consistent results in other endpoints, acceptable safety profile
- **OS: not statistically significant, trend towards improved OS**

ITT (N=796)	Abiraterone + Olaparib vs Abiraterone + Placebo (median)	HR[a] (95%CI)	P-value
rPFS[b]	25 vs 17 months (Δ: +8 months)	0.66 (0.54, 0.81)	<0.0001
OS[c]	42 vs 35 months	0.81 (0.67, 1.00)	0.054*

[a] Hazard Ratio (HR) and confidence interval (CI) were based on cox proportional hazards model adjusted by metastases, docetaxel treatment at mHSPC stage.
[b] Interim analysis of rPFS by investigator with 83.7% information fraction.
[c] Final OS analysis, *OS difference was not statistically significant (two-sided p-value cut-off = 0.038, using O'Brien-Fleming boundary)
ITT: Intent-to-treat

Main Review Issues for PROpel

- Potential benefit from adding olaparib to abiraterone may be restricted to **small subset of overall population**, i.e. those with ***BRCA* mutations**
- Substantial efficacy in this small subset may disproportionately contribute to efficacy in **overall heterogenous trial population**
- **Modest efficacy, potential harm** in **much larger population** (54% of ITT) with no demonstrated *BRCA* mutation

PROpel Not Stratified by *BRCAm;* No Prespecified Analysis

- PARP inhibitors work well in patients whose **tumors harbor *BRCA* mutations**
  - mCRPC
  - Breast, ovarian cancer
- In PROpel, all patients had testing of both plasma (ctDNA) and tumor tissue for mutations
- Randomization in PROpel **not prospectively stratified** by *BRCA* or *HRR* mutation status, with **no prespecified, alpha-controlled analysis**

ctDNA: circulating tumor DNA

PROpel Results by *BRCA*m Status

ITT- **rPFS HR 0.66** (0.54, 0.81); **OS HR 0.81** (0.67, 1.00)

PROpel Results by *BRCA*m Status

ITT- **rPFS HR 0.66** (0.54, 0.81); **OS HR 0.81** (0.67, 1.00)

11% (N=85) *BRCA*m (either ctDNA or tumor tissue)

rPFS HR 0.24

OS HR 0.3

PROpel Results by *BRCA*m Status

ITT- **rPFS HR 0.66** (0.54, 0.81); **OS HR 0.81** (0.67, 1.00)

11% (N=85) *BRCA*m (either ctDNA or tumor tissue)
rPFS HR 0.24
OS HR 0.3

54% (N=427) Non-*BRCA*m (both ctDNA and tumor tissue)
rPFS HR 0.85
OS HR 1.06

PROpel Results by *BRCA*m Status

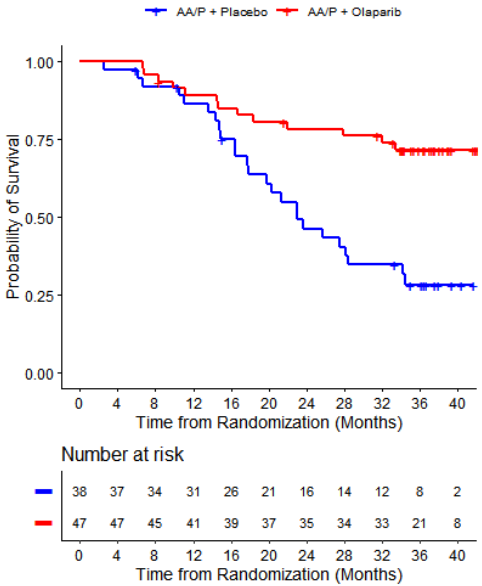
ITT- **rPFS HR 0.66** (0.54, 0.81); **OS HR 0.81** (0.67, 1.00)

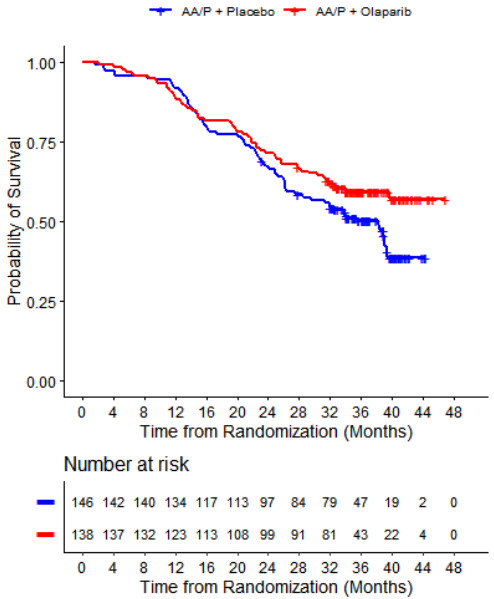
11% (N=85) *BRCA*m (either ctDNA or tumor tissue)	35% (N=284) Undetermined *BRCA*m status	54% (N=427) Non-*BRCA*m (both ctDNA and tumor tissue)
rPFS HR 0.24	rPFS HR 0.66	rPFS HR 0.85
OS HR 0.3	OS HR 0.73	OS HR 1.06

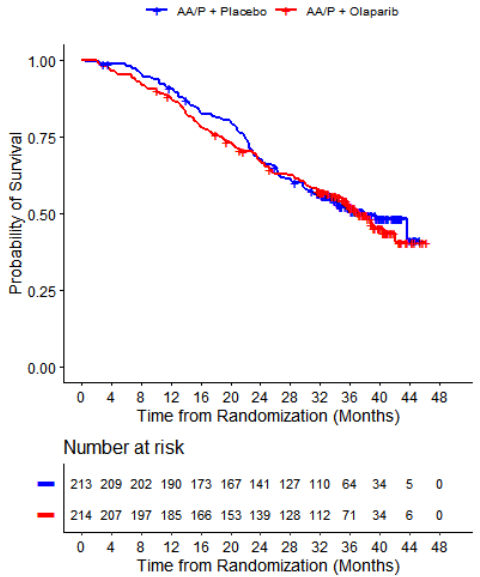
PROpel: OS Subgroup Analysis by *BRCA*m Status

FDA

***BRCA*m** N= 85 (**11%**)	**Undetermined *BRCA*m status** N= 284 (**35%**)	**Non-*BRCA*m** N= 427 (**54%**)







HR = 0.3 (0.15,0.6)	HR = 0.73 (0.52,1.03)	HR = 1.06 (0.81, 1.39)

*BRCA*m ctDNA Testing: Potential False Negatives

- ctDNA testing for *BRCA*m:
  - Best for **RULING IN**, not **RULING OUT** mutation
  - Only identifies ~74-80% of *BRCA* mutations identified with tumor tissue testing
- Patients with negative ctDNA, unknown tumor tissue testing may have **undetected *BRCA* mutations (i.e. false negatives)**
  - Reflex tissue test recommended for negative ctDNA result in the 2nd-line setting

Undetermined *BRCA*m population

ITT- **rPFS HR 0.66** (0.54, 0.81); **OS HR 0.81** (0.67, 1.00)

35% undetermined *BRCA*m status

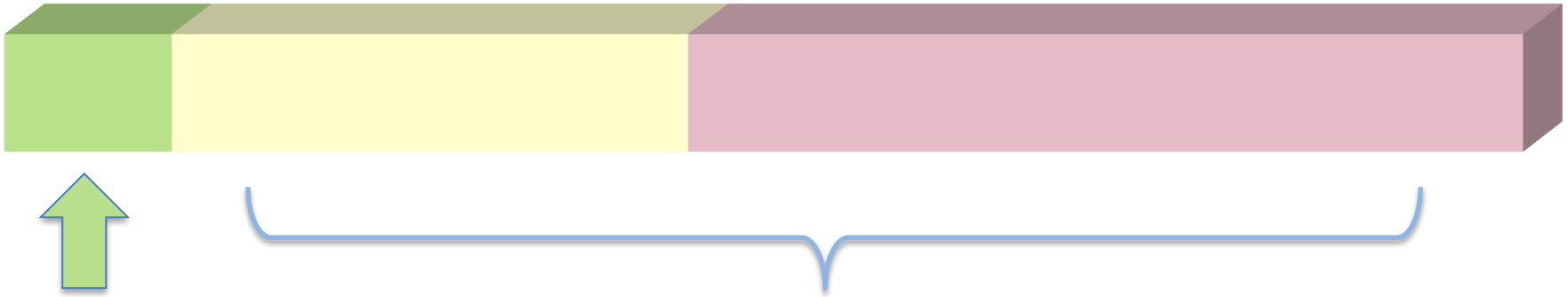
Small number may have undetected *BRCA* mutation

>90% likely truly *BRCA*m negative

Added uncertainty, potential for inclusion of patients who may be truly *BRCA*m negative who will be exposed to harms of add-on therapy

PROpel Results by *BRCA*m Status

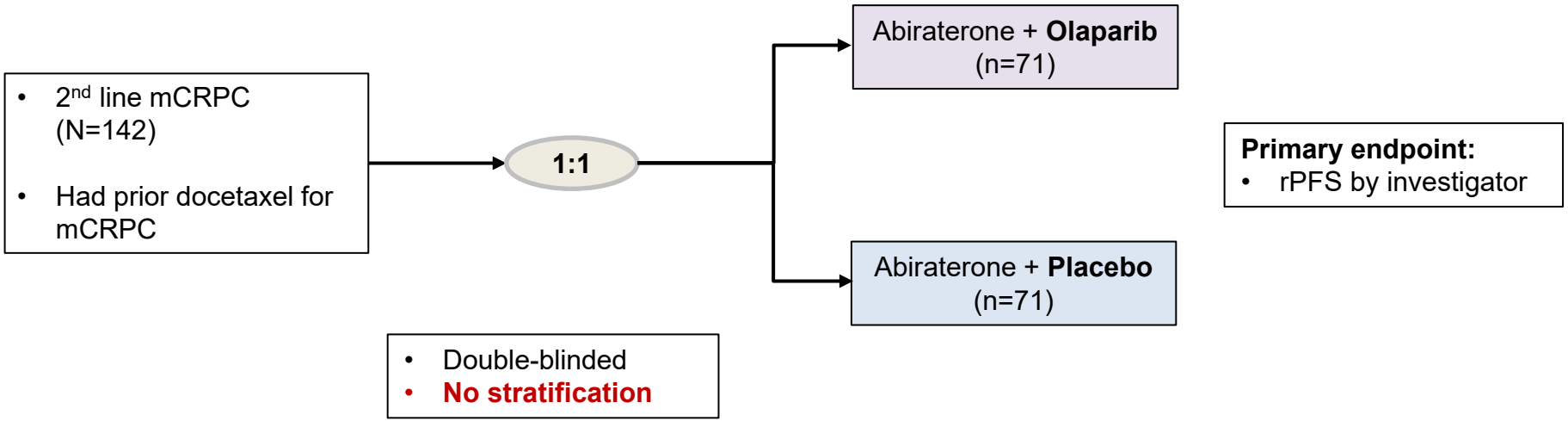
ITT- **rPFS HR 0.66** (0.54, 0.81); **OS HR 0.81** (0.67, 1.00)



11% *BRCA*m
rPFS HR 0.24
OS HR 0.3

89% ITT excluding *BRCA*m
rPFS HR 0.77; 24 vs 19 months (Δ: +5 months)
OS HR 0.92; 40 vs 38 months

Study 8 (small, exploratory study)

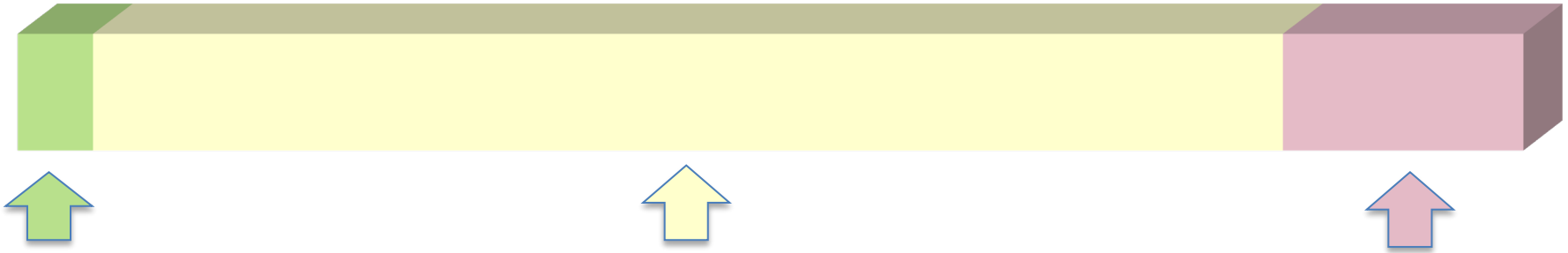


Study 8: Similar Design, Results to PROpel

ITT- **rPFS (inv) HR 0.65 (0.44, 0.97)**; OS HR **0.91 (0.60,1.38)**

Final Study 8 Results: Similar to PROpel

ITT- **rPFS (inv) HR 0.65 (0.44, 0.97)**; **OS HR 0.91 (0.60,1.38)**



5% (N=7) *BRCA*m
rPFS (inv) HR NE
rPFS (BICR) HR NE
OS HR NE

79% (N=112) undetermined *BRCA*m status
rPFS (inv) HR 0.62
rPFS (BICR) HR 0.89
OS HR 0.71

16% (N=23) Non-*BRCA*m
(both ctDNA and tumor tissue)
rPFS (inv) HR 0.88
rPFS (BICR) HR 1.72
OS HR 2.77

NE = Not Evaluable

Adverse Reactions (ARs) Increased in Olaparib Arm on PROpel

ITT population	Olaparib + abiraterone (N=398)	Placebo + abiraterone (n=396)
Grade 3 or greater ARs(%)	**56**	43
Serious ARs (%)	**41**	32
All Grade ARs leading to **discontinuation** of olaparib/ placebo (%)	**17**	9
Fatal ARs (%)	**7**	5
All Grade **myelosuppression*** (%)	**57**	26
Received blood transfusion (%)	**18**	4
All Grade **nausea/vomiting** (%)	**35**	21
All Grade **diarrhea** (%)	**21**	11
All Grade **venous thromboembolism (VTE)** (%)	**9**	3.5

* Anemia, thrombocytopenia, neutropenia, lymphopenia

Population Considerations

- **Many patients** potentially impacted by decision
- **Early** in disease setting, multiple treatment options
- **Long duration of exposure** of treatment
  - Median >20 months overall on olaparib arm in PROpel
  - Paired with abiraterone: very effective therapy, median monotherapy rPFS of ~16 months
- Potential for **added toxicity**- myelosuppression, gastrointestinal toxicity, VTE/ pulmonary emboli
- Different than monotherapy, where lack of efficacy of single agent more immediately apparent

Post-hoc Subgroup Analyses

- Can not be used to "rescue" failed trial with efficacy in a subgroup
- May be used to restrict indication in cases of **limited efficacy and/or potential OS detriment** especially when external data raises concern for harm

  Precedent exists-

  - ***RAS* mutation in colon cancer**- removed from cetuximab, panitumumab indications[1]
  - **Squamous histology in non-small cell lung cancer**- removed from pemetrexed indication[2]
- Burden of proof on Applicant to demonstrate efficacy, safety; if doubt emerges about population not originally accounted for, **can be excluded from indication**
- FDA guidance- if trial demonstrates benefit only in subgroup (e.g. biomarker positive), FDA may approve narrower indication than overall enrolled population[3]

[1] https://ascopost.com/issues/july-15-2012/fda-approves-cetuximab-plus-folfiritherascreen-in-colorectal-cancer; https://ascopost.com/issues/june-10-2014/fda-approves-panitumumab-plus-folfox-for-wild-type-kras-metastatic-colorectal-cancer

[2] Cohen MH, Justice R, Pazdur R. Approval summary: pemetrexed in the initial treatment of advanced/metastatic non-small cell lung cancer. Oncologist. 2009;14(9):930-5

[3] Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry https://www.fda.gov/media/114443/download

PARP Inhibitors in Populations Negative for *HRR*/*BRCA*m

- Ovarian cancer (niraparib Nov 2022, rucaparib Dec 2022)
  - PARP inhibitors **restricted to *BRCA*m populations**
  - Based on **OS detriments** observed in broad populations
- Prostate cancer (niraparib + abiraterone)
  - MAGNITUDE trial **enrolled separate cohorts by *HRR*** mutation status and **stopped early for futility** in non-*HRR*m cohort

Mirza et al. NEJM 2016; USPI for niraparib; www.gsk.com; Coleman et al. Lancet 2017; https://clovisoncology.com;

FDA Conclusions

- Statistically significant **rPFS improvement in ITT population** in PROpel; **attributable to *BRCA*m.**
- As certainty regarding absence of tumor *BRCA*m increases, rPFS benefit appears to decrease.
- **Potential OS detriment** in patients **negative for *BRCA*m by both tumor and ctDNA assays**, comprising over half of the ITT population in PROpel (OS HR 1.06).

FDA Conclusions

- Study 8 also shows **lack of benefit, potential OS detriment in non-*BRCA*m** (OS HR 2.77).
- Patients with non-*BRCA*m tumors are at risk of **prolonged exposure to toxicities** of olaparib.
- Consistency across trials: **attenuated benefit/possible harm in non-*BRCA*m**.

Voting Question

As FDA reviews the proposed indication for olaparib in combination with abiraterone for initial treatment of mCRPC, should the indication be restricted to patients whose tumors have a *BRCA* mutation?

If you feel the combination should not be approved for any indication, please abstain from voting and explain your thinking regarding approvability during the post-voting discussion period.


FDA
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ADMINISTRATION

Olaparib with Abiraterone for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Oncologic Drugs Advisory Committee (ODAC) Meeting

April 28th, 2023

Jaleh Fallah, MD
Clinical Reviewer, Genitourinary malignancies
Division of Oncology 1, Office of Oncologic Diseases

FDA Review Team

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Laleh Amiri-Kordestani, Director, Division of Oncology 1 (DO1)	Erik Bloomquist, Supervisory Mathematical Statistician, DBV
Daniel Suzman, Deputy Division Director, DO1	Mallorie Fiero, Statistical Team Lead, DBV
Chana Weinstock, Supervisory Associate Director (Acting), DO1	Jianjin Xu, Statistical Reviewer, DBV
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Michael Brave, Clinical Reviewer, DO1	Abdelrahmman Abukhdeir, Diagnostic Devices Team Lead, CDRH
Robert Schuck, Pharmacogenomics Team Lead, Division of Translational and Precision Medicine (DTPM)	Anand Pathak, Medical Officer, CDRH
Tien Truong, Pharmacogenomics Reviewer, DTPM	Timothy Schaefer, Reviewer, CDRH

Applicant's Proposed Indication

Proposed indication for olaparib, in combination with abiraterone and prednisone or prednisolone:

Treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC)

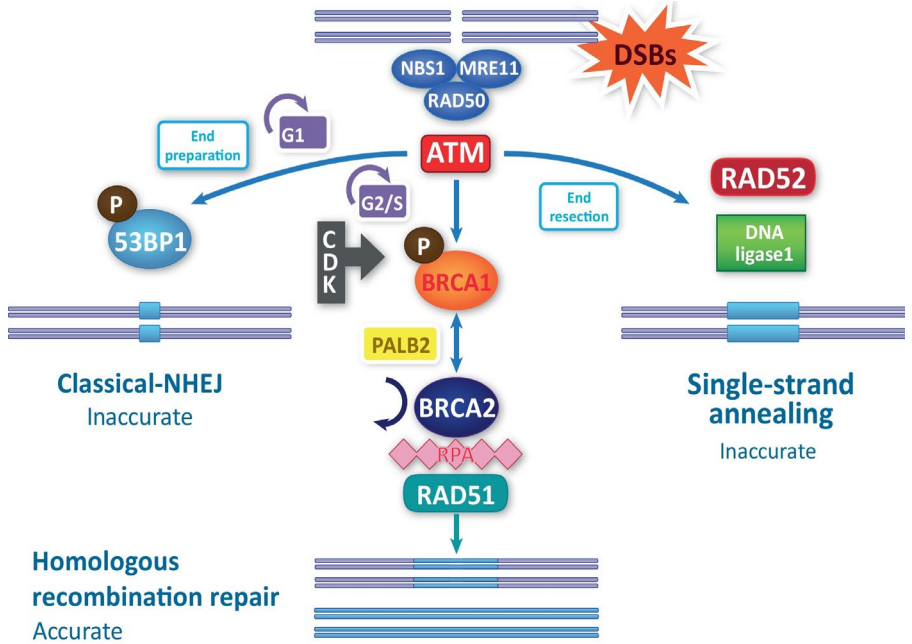
Voting Question

As FDA reviews the proposed indication for olaparib in combination with abiraterone for initial treatment of mCRPC, should the indication be restricted to patients whose tumors have a *BRCA* mutation?

If you feel the combination should not be approved at all, please abstain from voting and explain your thinking regarding approvability during the post-voting discussion period.

HRRm and *BRCA*m

- Homologous recombination repair (HRR) is a DNA repair pathway.
- Several genes are directly or indirectly involved in HRR pathway (e.g., *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *CDK12*, *PALB2*, etc).
- Mutation in *BRCA* and potentially other HRRm genes may sensitize the tumor to PARP inhibition.



HRRm:

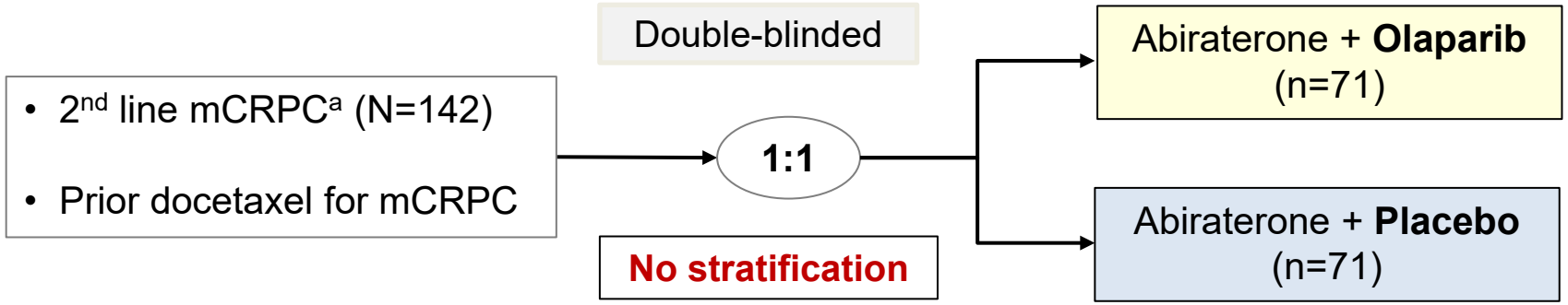
Mutation in HRR genes, including *BRCA1, BRCA2, ATM etc*.

***BRCA*m**:

Mutation in *BRCA1* and *BRCA2*.

Figure from O'kane et al. Trends Mol Med, 2017.; PARP: poly (ADP-ribose) polymerase; PARPi: PARP inhibitor

Study 8 (a small exploratory study)



Primary endpoint:
rPFS by investigator assessment
(sensitivity analysis: rPFS[b] by BICR)

Key secondary endpoints: OS[c]

Study 8: Topline Results (2018)

Study 8 (N= 142)	ITT	HRRm (15%)	Unknown HRRm (61%)	Non-HRRm (25%)
N (olaparib vs placebo)	71 vs 71	11 vs 10	45 vs 41	15 vs 20
rPFS by investigator* HR (95% CI)	**0.65** (0.44, 0.97)	**0.74** (0.26, 2.12)	**0.67** (0.40, 1.12)	**0.52** (0.24, 1.15)
OS	**0.91** (0.60,1.38)	Not provided in 2018.		

2018: Applicant proposed accelerated approval for olaparib in combination with abiraterone for **all-comers**, based on Study 8.

Source: Applicant's analysis

a. ITT: intent to treat; b. rPFS: radiographic progression-free survival; c. OS: overall survival.
* rPFS assessment by blinded independent central review (BICR) was ongoing at the time

Study 8 Regulatory History

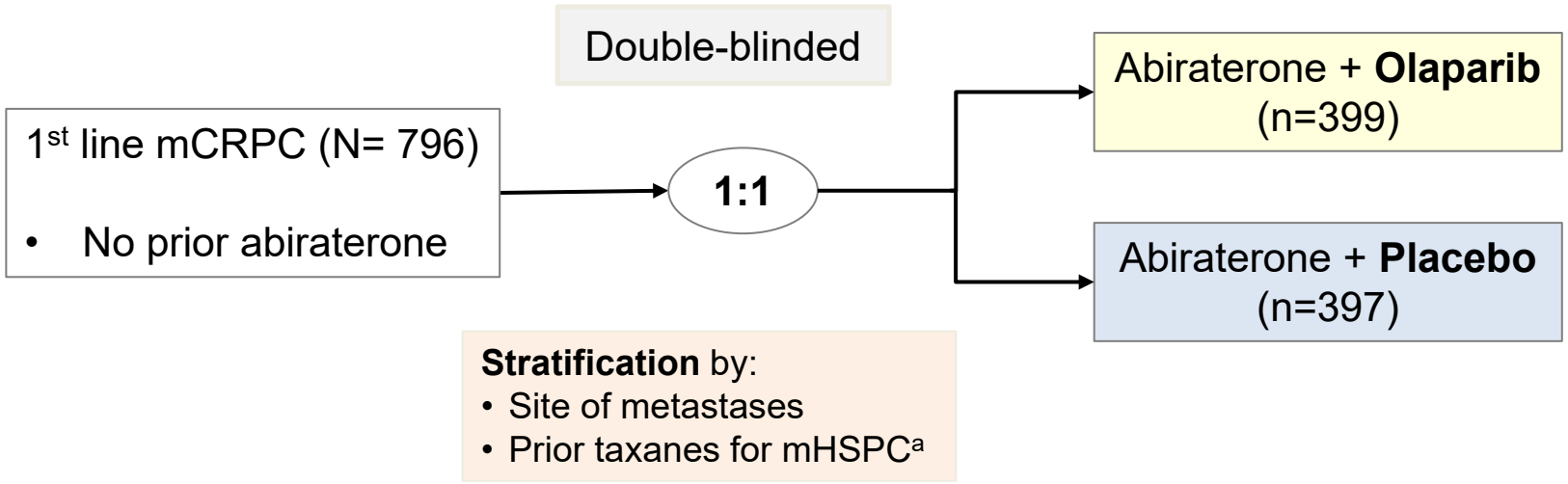
FDA discouraged submission of an application for accelerated approval:

- Study 8 was a small exploratory study => decreased confidence in the results
- Majority of patients had unknown HRRm status => might lead to imbalances between the arms.

The Applicant

- Agreed to not pursue an accelerated approval based on Study 8 alone.
- Acknowledged the need to assess the potential impact of HRRm on efficacy.
- Planned to conduct PROpel (phase 3 randomized trial) to confirm the results of Study 8.

Primary Evidence of Efficacy: PROpel Study



Primary endpoint:
rPFS by investigator assessment
(sensitivity analysis: rPFS by BICR)

Key secondary endpoints: OS[b]

- **Inadequate retrospective assessment of *BRCA*m status.**
- **No stratification by *BRCA*m status.**
- **No pre-specified formal analysis by *BRCA*m status.**

a. mHSPC: metastatic hormone-sensitive prostate cancer; b. OS: overall survival; BICR: blinded independent central review.

Primary Evidence of Efficacy: PROpel Study (Met its Primary Endpoint)

Efficacy results in intent-to-treat (ITT) population in PROpel

ITT (N=796)	Abiraterone + Olaparib (n= 399) vs Abiraterone + Placebo (n= 397)		P-value
rPFS[b]	Median	25 vs 17 mo (**Δ: +8**)	<0.0001
	HR[a] (95%CI)	**0.66** (0.54, 0.81)	
OS[c]	Median	42 vs 35 mo	0.054
	HR[a] (95%CI)	**0.81** (0.67, 1.00)	

[a,] HR and CI were based on cox PH model adjusted by Metastases, docetaxel treatment at mHSPC stage.
[b,] Interim analysis of rPFS by investigator with 83.7% information fraction.
[C,] Final OS analysis, OS difference was not statistically significant (two-sided p-value cut-off = 0.038, using O'Brien-Fleming boundary).

Source: Applicant's analysis

Add-on trial design:

- Large rPFS improvement (8 month), supportive OS (HR for OS <1), and acceptable toxicity
  => positive benefit-risk in a homogenous patient population with mCRPC.

PROpel enrolled a heterogenous patient population with respect to *BRCA*m status and sensitivity to PARPi[a].

a. PARPi: poly (ADP-ribose) polymerase (PARP) inhibitor

Outline

- Key Efficacy Issues
  1. Enrolling a heterogenous population, unstratified by *BRCA*m status
  2. Inadequate determination of *BRCA*m status
  3. Potential harm in non-*BRCA*m subgroup across trials
- Key Safety Issues
- Role of Subgroup Analyses in Regulatory Decision-Making

Outline

- **Key Efficacy Issues**

  1. **Enrolling a heterogenous population, unstratified by *BRCA*m status**

  2. Inadequate determination of *BRCA*m status

  3. Potential harm in non-*BRCA*m subgroup across trials

- Key Safety Issues

- Role of Subgroup Analyses in Regulatory Decision-Making

*BRCA*m as a Predictor of PARPi Efficacy in mCRPC

rPFS analysis in other trials of PARPi in mCRPC

Clinical trial	PARPi	Line	Stratification by HRRm or *BRCA*m	Hazard Ratio (HR) for rPFS (for PARPi arm vs control arm)		
				***BRCA*m**	**HRRm**	**Non-HRRm *(no BRCA*m)**
PROfound[a]	Olaparib	2nd	N/A	0.22	0.49	N/A
TRITON-3[b]	Rucaparib	2nd	Yes	0.50	0.61 (*BRCA* + *ATM*)	N/A
MAGNITUDE[b]	**Niraparib**	**1st**	**Yes**	**0.55**	**0.76**	**Stopped early for futility**
TALAPRO-2[b]	Talazoparib	1st	HRRm only	-	0.46	0.69

Benefit from **PARPi in prostate cancer** appears to be **primarily driven by the effects in the *BRCA*m** subgroup.

[a] sNDA submission for olaparib
[b] ASCO GU 2023

*BRCA*m as a Predictor of Benefit from PARPi in Advanced Ovarian Cancer

Clinical trial	PARPi	Line	Endpoint	Hazard ratio (for PARPi arm vs control arm)		Changes in the labeling
				***BRCA*m**	***Non-BRCA*m**	
NOVA[a-c]	Niraparib	2nd line maintenance	**PFS[d]**	0.26	0.45	Concern for OS detriment => Restriction of indication to g*BRCA*m[e] (Dec 8th, 2022)
			Final OS	0.85	**1.06**	
ARIEL3[f,g]	Rucaparib	2nd line maintenance	**PFS**	0.23	0.44 - 0.58 (for high and low LOH[h])	Concern for OS detriment => Restriction of indication to t*BRCA*m[i] (Dec 21st, 2022)
			Final OS	0.83	**1.08**	

Benefit from **PARPi in ovarian cancer** appear to be **primarily driven by the effects in the *BRCA*m** subgroup.

a. Mirza et al. NEJM 2016; b. USPI for niraparib; c. www.gsk.com; d: Progression-free survival; e. g*BRCA*: germline *BRCA* mutation f. Coleman et al. Lancet 2017; g. https://clovisoncology.com; h. LOH = loss of heterozygosity;; i. t*BRCA*: tumor *BRCA* mutation.

Outline

- **Key Efficacy Issues**
  1. Enrolling a heterogenous population, unstratified by *BRCA* status
  2. **Inadequate determination of *BRCA*m status**
  3. Potential harm in non-*BRCA*m subgroup across trials
- Key Safety Issues
- Role of Subgroup Analyses in Regulatory Decision-Making

PROpel: Retrospective Evaluation of *BRCA*m Status
Concern for False Negative Results

- **FoundationOne CDx**, using tumor tissue
- **FoundationOne Liquid CDx**, using ctDNA[a] (from plasma)

Negative Percent Agreement (NPA) and Positive Percent Agreement (PPA) of ctDNA BRCA test (reference: tissue test)

Study	Tumor type(s)	ctDNA test	PPA % (95% CI)	NPA % (95% CI)
PROpel (olaparib)	Prostate cancer	*BRCA1/2*	**74** (59, 86)	**96** (94, 98)
PROfound (olaparib)	Prostate cancer	*BRCA1/2, ATM*	**80** (72, 86)	**92** (87, 95)

Low PPA => Potential for false negatives => Negative result is not sufficient to rule out

High NPA => Low rate of false positives => Positive result is sufficient to rule in

FDA labeling for FoundationOne tests[b,c]:

- A **negative** tissue test result **does not rule out** the presence of a mutation below the limits of detection of the assay.
- A **negative** ctDNA result **does not rule out** the presence of a mutation (negative ctDNA => reflex to routine biopsy, if feasible).

a. ctDNA: circulating tumor DNA; b. https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019S006C.pdf ; c. https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190032S001C.pdf

PROpel: 3 Subgroups Based on *BRCA*m Certainty

BRCA assay in PROpel		Tumor tissue, n (%)		
		Yes	No	Unknown
ctDNA, n (%)	Yes	34 (4)	18 (**2**)	17 (2)
	No	12 (**2**)	427 (54)	226 (28)
	Unknown	4 (1)	40 (5)	18 (2)

- 2% had negative ctDNA, but positive tumor tissue test.
- 2% had negative tissue test, but positive ctDNA test.
- 33% with unknown tissue test results.
- 8% with unknown ctDNA test results.

PROpel: 3 Subgroups Based on *BRCA*m Certainty

BRCA assay in PROpel		Tumor tissue, n (%)		
		Yes	No	Unknown
ctDNA, n (%)	Yes	34 (4)	18 (**2**)	17 (2)
	No	12 (**2**)	427 (54)	226 (28)
	Unknown	4 (1)	40 (5)	18 (2)

- 2% had negative ctDNA, but positive tumor tissue test.
- 2% had negative tissue test, but positive ctDNA test.
- 33% with unknown tissue test results.
- 8% with unknown ctDNA test results.

***BRCA*m**	1 or 2 positive *BRCA* tests (either tissue or ctDNA)	High certainty for having *BRCA*m	**N= 85 (11%)**
Undetermined *BRCA*m status	1 test is negative/unknown, and the other test is unknown *(Potentially include patients with BRCA*m*)*	Uncertainty about *BRCA*m *status*	**N= 284 (35%)**
Non-*BRCA*m	2 negative *BRCA* tests (both tissue and ctDNA)	High certainty for NOT having *BRCA*m	**N= 427 (54%)**

Key Efficacy Issues

- **Key Efficacy Issues**

  1. Enrolling a heterogenous population, unstratified by *BRCA* status

  2. Inadequate determination of *BRCA*m status

  3. Potential harm in non-*BRCA*m subgroup across trials

- Key Safety Issues

- Role of Subgroup Analyses in Regulatory Decision-Making

PROpel: Subgroup Analysis by *BRCA*m Status

N = 796	***BRCA*m** N= 85 (**11%**) 47 vs 38	**Undetermined *BRCA*m status** N= 284 (**35%**) 138 vs 146	**Non-*BRCA*m** N= 427 (**54%**) 214 vs 213
rPFS (Investigator assessment)			
Median (olaparib vs placebo)	NR[b] , 8	NR , 19	22, 17
HR (95% CI)	**0.24 (0.12, 0.46)**	0.66 (0.46, 0.94)	**0.85 (0.66, 1.11)**
OS			
Median (olaparib vs placebo)	NR , 23	NR , 38	37 , 38
HR (95% CI)	**0.3 (0.15, 0.6)**	0.73 (0.52, 1.03)	**1.06 (0.81, 1.39)**

Source: FDA's analysis

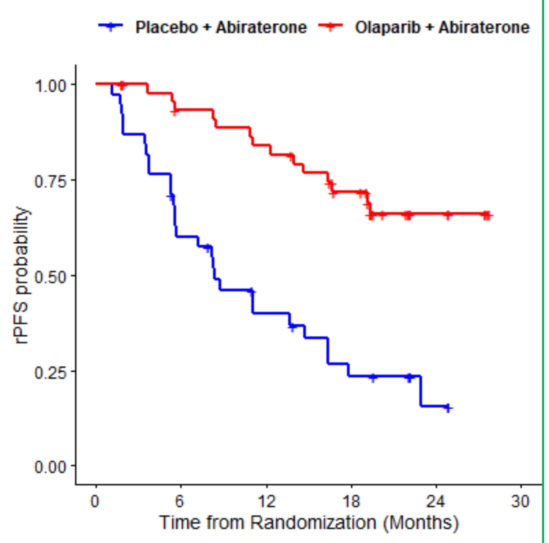
Efficacy is largely attributed to the effects of *BRCA*m.

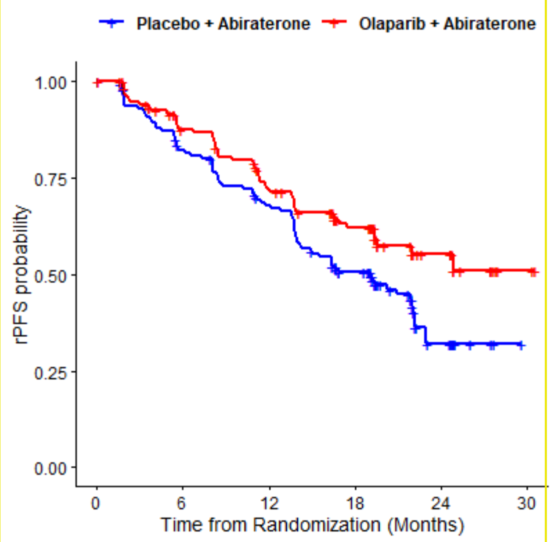
a. rPFS by investigator assessment
b. NR= not reached

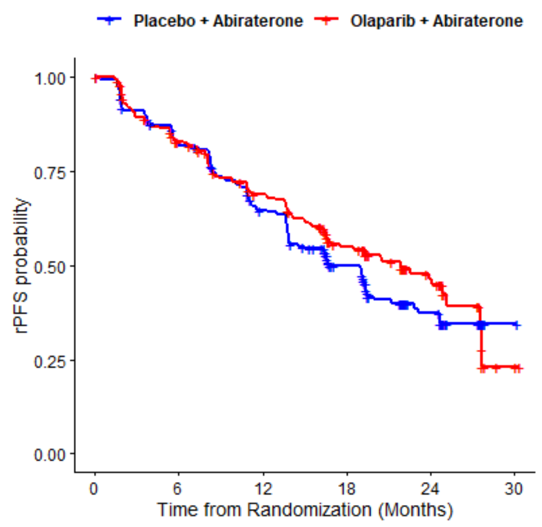
PROpel: rPFS and OS Subgroup Analysis by *BRCA*m Status

***BRCA*m** N= 85 (**11%**)	**Undetermined *BRCA*m status** N= 284 (**35%**)	**Non-*BRCA*m** N= 427 (**54%**)

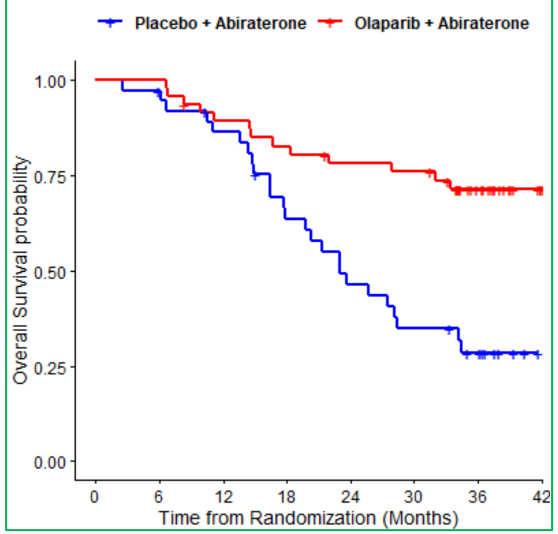
rPFS
(by investigator assessment)

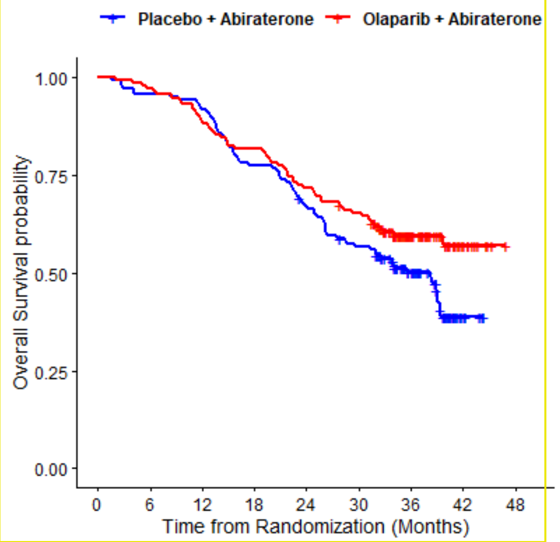


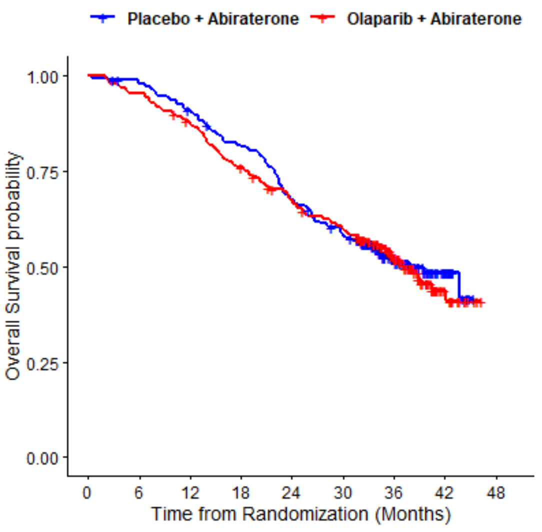




OS







Prognostic Factor Balance by *BRCA*m Subgroup

- Well-balanced baseline prognostic factors in Undetermined *BRCA*m and non-*BRCA*m subgroups:
  - Large sample size
  - Individual prognostic factors were balanced
  - Validated mCRPC Halabi prognostic score model[a] shows balanced risk score

- Some imbalance of prognostic factors in *BRCA*m subgroup:
  - Slight imbalance in favor of olaparib arm
  - Small sample size
  - Adjustment methods for imbalance have little impact on observed treatment effect

No overall changes in conclusions of rPFS and OS analyses for all the three subgroups after adjustment.

a. Halabi et al. Journal of Clinical Oncology, 2014. 8 prognostic factors: disease site, Eastern Cooperative Oncology Group performance status, opioid use, prostate-specific antigen, lactate dehydrogenase high, albumin, hemoglobin, alkaline phosphatase

PROpel: rPFS and ORR by BICR

N = 796	*BRCA*m	Undetermined *BRCA*m status	Non-*BRCA*m
rPFS by BICR	N= 85 (11%)	N= 284 (35%)	N= 427 (54%)
Median (olaparib vs placebo)	NR[a] vs 8 mo	NR vs 19 mo	**20 vs 17 mo**
HR (95% CI)	**0.19** (0.1, 0.37)	**0.59** (0.41, 0.85)	**0.82** (0.62, **1.08**)
ORR by BICR[b]			
Patients with evaluable disease at baseline (olaparib vs placebo)	N= 20 vs 18	N= 50 vs 51	N= 92 vs 81
ORR, n (%)	60% vs 28% (Δ = 32%)	60% vs 43% (Δ = 17%)	**52% vs 48%** (**Δ = 4%**)

Source: FDA's analysis

In **non-*BRCA*m** subgroup:

- ΔrPFS by BICR is equal to imaging intervals → actual rPFS difference could be smaller than 3 months.
- Overall similar ORR between treatment arms in an add-on trial.

a. NR: not reached; b. ORR: Confirmed objective response rate, ORR result is based on data cut-off 2.

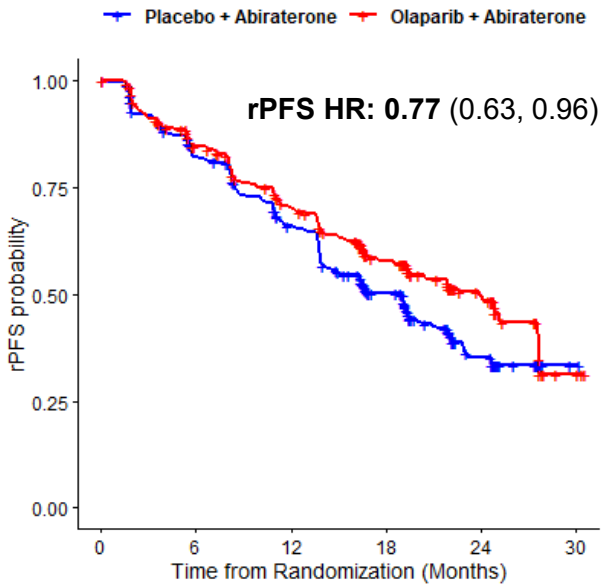
PROpel: Analysis of Two *BRCA*-Based Subgroups

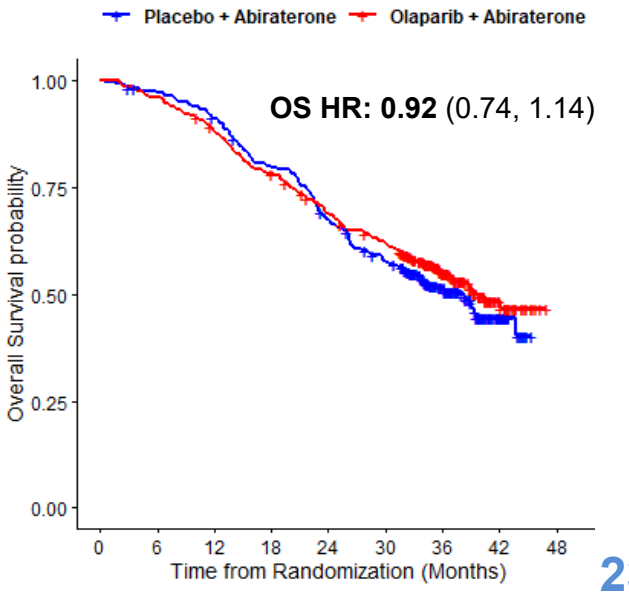
N = 796		***BRCA*m** N= 85 (11%)	**All Others** (Potentially include patients with *BRCA*m) N= 711 (89%)
rPFS (Investigator assessment)	HR (95% CI)	**0.24** (0.12, 0.46)	**0.77** (0.63, 0.96)
	Median (months)	NR , 8	Olaparib: 24 vs Placebo: 19 (**Δ: 5 mo**)
OS	HR (95% CI)	**0.3** (0.15, 0.6)	**0.92** (0.74, 1.14)
	Median (months)	NR , 23	Olaparib: 40 vs Placebo: 38

Source: FDA's analysis

For patients without demonstrated *BRCA*m:

- >1.5 year of treatment with olaparib for 5 month improvement in rPFS (per investigator assessment).
- Is 5 months rPFS improvement with no OS benefit clinically meaningful in an add-on trial?
- What is the impact of patients with unidentified *BRCA*m (false negatives) on results in this subgroup?





NR= not reached

Overestimation of rPFS by BICR in All Others

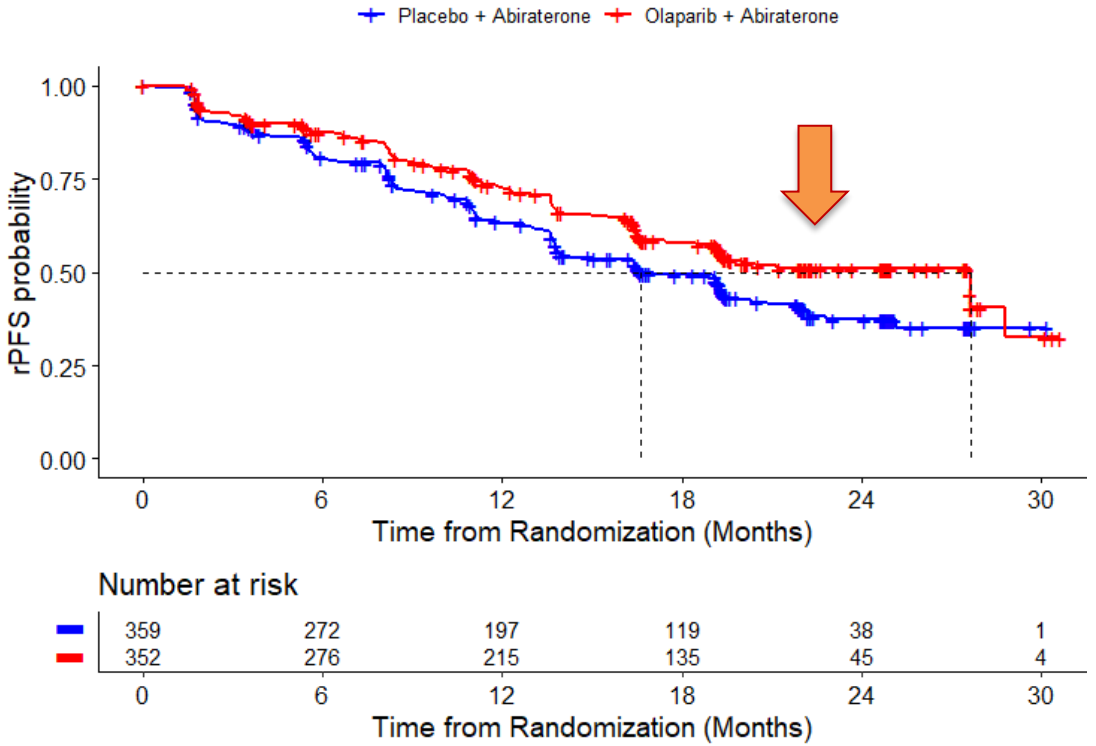
N = 796		*BRCA*m N= 85 (11%)	All Others (Potentially include patients with *BRCA*m) N= 711 (89%)
rPFS (**BICR assessment**)	HR (95% CI)	**HR = 0.19** (0.10, 0.37)	**HR = 0.73** (0.59, 0.9)
	Median (months)	NR, 8	Olaparib: 28 vs Placebo: 17 (**Δ: 11 mo**)

Source: FDA's analysis

The 11-month improvement of rPFS by BICR is **overestimated** and **unstable:**

- Median estimated towards the tail end of the Kaplan Meier curve for the olaparib arm.
- Final pre-specified rPFS analysis at DCO2 shows median rPFS difference by BICR of 8 months.
- Largely attributed to the undetermined *BRCA*m subgroup (rPFS difference in non-*BRCA*m is only 3 months).

rPFS by BICR in All Others subgroup at DCO1



NR: not reached; DCO: data cut-off

Study 8: Initial Results

2018: The Applicant proposed accelerated approval for olaparib in combination with abiraterone for treatment of patients with mCRPC (all-comers) based on Study 8.

2022: The Applicant proposed to add the following results to the olaparib label:

Primary Efficacy Result – Study 8 (investigator-assessed)

	Olaparib/abiraterone N=71	Placebo/abiraterone N=71
Radiological Progression-Free Survival (rPFS)		
Number of events (%)	46 (64.8)	54 (76.1)
Median, months	13.8	8.2
Hazard ratio (95% CI)	0.65 (0.44, 0.97)	
p-value	0.034	

Source: Applicant's proposed labeling

Study 8: Final Results

(rPFS by BICR and OS for subgroups were submitted with the sNDA)

N= 142	ITT	*BRCA*m (5%)	Undetermined *BRCA*m status (79%)	Non-*BRCA*m (16%)
n (olaparib vs placebo)	**71 vs 71**	**2 vs 5**	**56 vs 56**	**13 vs 10**
rPFS (Investigator assessment)	**0.65** (0.44 , 0.97)	NE[a]	0.62 (0.39 , 0.98)	0.88 (0.33 , **2.37**)
rPFS (BICR assessment)[b]	**0.95 (0.62 , 1.44)**	NE	0.89 (0.56 , 1.41)	**1.72 (0.56 , 5.76)**
OS	0.91 (0.60 ,1.38)	NE	0.71 (0.43 , 1.16)	**2.77 (1.06 , 8.06)**

a. NE: not estimable; b. median rPFS by BICR in ITT: 11.1 months in olaparib arm and 8.2 months in placebo arm (Δ <3 months).

*** Follow-up assessments were performed every 12 weeks (±1 week) from the date of randomization (every 24 weeks after Week 72)**

Source: Applicant's analysis

- **Concern for lack of benefit and potential harm in non-*BRCA*m subgroup**.
- Consistent pattern for lack of efficacy and potential OS detriment across two trials: PROpel and Study 8 (**external consistency**).

Outline

- Key Efficacy Issues
  1. Enrolling a heterogenous population, unstratified by *BRCA* status
  2. Inadequate determination of *BRCA*m status
  3. Potential harm in non-*BRCA*m subgroup across trials
- **Key Safety Issues (Increases toxicity and symptom burden)**
- Role of Subgroup Analyses in Regulatory Decision-Making

PROpel: Higher Level of Toxicity from Adding Olaparib to Abiraterone

ITT population	Olaparib + abiraterone (N=398)	Placebo + abiraterone (n=396)
Grade 3-4 adverse reactions (ARs) (%)	**56**	43
Serious ARs (%)	**41**	32
Fatal ARs (%)	**7**	5
All Grade **ARs leading to discontinuation** of olaparib/placebo (%)	**17**	9
All Grade **myelosuppression**[a,b] (%)	**57**	26
Received **blood transfusion** (%)	**18**	4
All Grade **nausea/vomiting** (%)	**35**	21
All Grade **diarrhea** (%)	**21**	11
All Grade **venous thromboembolism** (%)	**9**	3.5

a. Anemia, thrombocytopenia, neutropenia, lymphopenia; b. **1 patient in the olaparib arm developed myelodysplastic syndrome (MDS).**

PROpel: Patient-Reported Outcomes (PRO)

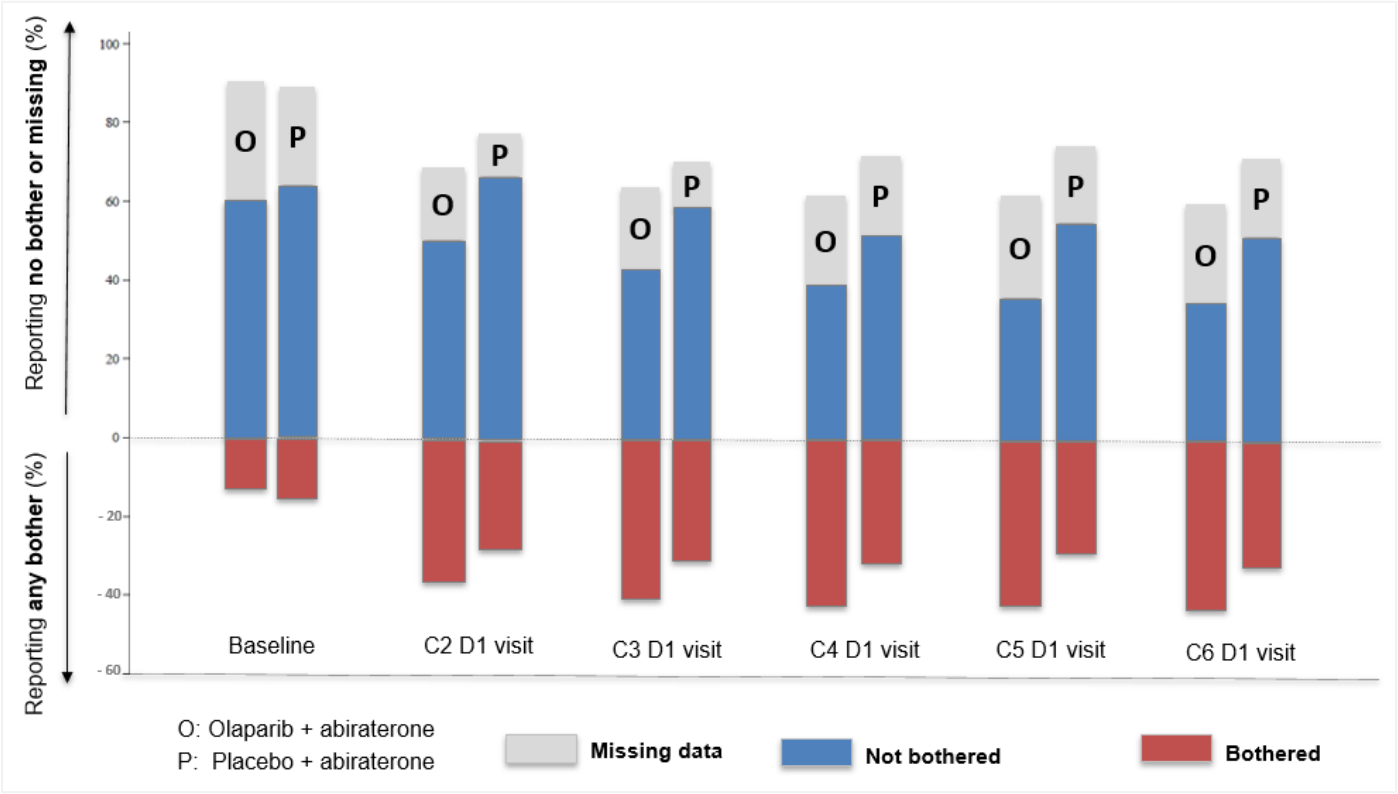
FACT-P GP5[a] item to **assess treatment tolerability**

"I am bothered by side effects of treatment"

0: Not at all;
1: A little bit;
2: Somewhat;
3: Quite a bit;
4: Very much

Previous experience in a prostate cancer trial[b]:

Minimal side effect impact of ARPI (apalutamide) monotherapy vs placebo observed.



FDA assessment of descriptive, exploratory PRO results:

- Adequate **completion rate (~70%)** through the first 6 months of treatment.
- Minimal "severe" bother (GP5 score 3-4) observed in both arms.
- **Higher proportion of patients in the olaparib arm were bothered by the side effects of treatment.**

a. Functional Assessment of Cancer Therapy (https://www.facit.org/measures/FACT-P); b. Saad, et al. Lancet Oncol, 2018.

Concern for Harm in Non-*BRCA*m Subgroup

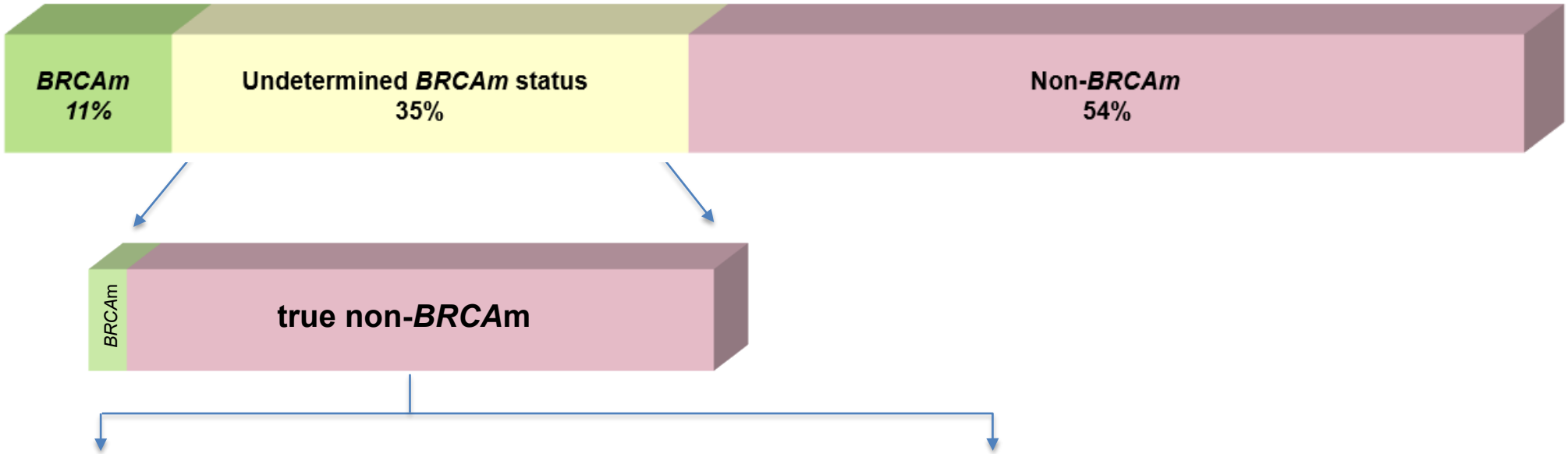
Concerns for overtreatment with olaparib in non-*BRCA*m subgroup:

- **A large patient population**
- **Early disease setting (mostly asymptomatic or minimally symptomatic)**
- **Exposure to olaparib for > 1 year without evidence of efficacy**
  - Higher risk of **myelosuppression** and need for **blood transfusion (1 in 5 patients)**
  - Higher risk of **thromboembolic events**
  - Higher incidence of **gastrointestinal toxicity**
  - Higher need for **admission to the hospital**
  - Increased **symptom** and **side effect burden**
  - **Potential OS detriment**

Concern for Harm in Undetermined *BRCA*m Status Subgroup

Heterogenous population due to lack of prospective tumor tissue *BRCA*m determination (likely >90% with non-*BRCA*m)

- Blindly adding olaparib to abiraterone in patients with Undetermined *BRCA*m status
  - → Potential harm to majority of the patients in this subgroup
  - → Substantial benefit to a very small proportion in this subgroup



Undetected *BRCA*m
(small proportion)
Benefit > Risk

True non-*BRCA*m
(Likely **>90%**)

Concern for harm
- Lack of efficacy
- Added toxicity
- Potential OS detriment

Outline

- Key Efficacy Issues
  1. Enrolling a heterogenous population, unstratified by *BRCA* status
  2. Inadequate determination of *BRCA*m status
  3. Potential harm in non-*BRCA*m subgroup across trials
- Key Safety Issues
- **Role of Subgroup Analyses in Regulatory Decision-Making**

Role of Subgroup Analyses in Regulatory Decision-Making

ICH-E17 Guideline:

- **Assessment of consistency of treatment effects** should be done with diligence to inform regulatory decision-making.
- The **credibility of subgroup findings** should take into consideration:
  - **Biological plausibility**
  - **Internal consistency**
  - **External consistency**
  - **Strength of evidence**
  - **Clinical relevance**
  - **Statistical uncertainty**

Subgroup analyses cannot be used to salvage a failed trial, but can be used to narrow the indication when there are safety/efficacy concerns, and strong biologic rationale, particularly when there is also external consistency across trials.

ICH: The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

Examples of Indication Restriction by FDA Based on Subgroup Analyses

Year of approval	Drug	Enrolled Population (ITT)	Approved Indication	Limitation of Use
2008	Pemetrexed	Patients with metastatic NSCLC	**Non-squamous** NSCLC	Squamous NSCLC
2012	Cetuximab	Patients with mCRC	**Wild-type *KRAS*** mCRC	*RAS* mutant mCRC
2014	Panitumumab	Patients with mCRC	**Wild-type *KRAS*** mCRC	*RAS* mutant mCRC
2020	Olaparib	Patients with metastatic ovarian cancer	Metastatic ovarian cancer with **HRD**	-
2023	Pembrolizumab	Patients with resected stage IB (T2a ≥4 cm), II, or IIIA NSCLC	Adjuvant treatment **following** resection and **platinum-based chemotherapy**	-
2023	Elacestrant	Patients with ER+, HER2- metastatic breast cancer	***ESR1*-mutated** metastatic breast cancer	-

Source: https://www.accessdata.fda.gov/scripts/cder/daf/

NSCLC: non-small cell lung cancer; mCRC: metastatic colorectal cancer; HRD: homologous recombination deficiency; ER: estrogen-receptor.

FDA Conclusions

1. Despite the suboptimal design of PROpel to assess the efficacy by mutation status, the **rPFS improvement** in all-comers is **attributed to efficacy in the *BRCA*m** subgroup

2. **Potential OS detriment** in patients with **negative *BRCA*m** by both tumor and ctDNA assays (>50% of the ITT)

3. **Minimal impact of lack of stratification** and consistent results in *BRCA* subgroups after adjustment for baseline prognostic factors

4. **Internal consistency** between primary and secondary endpoints, showing modest efficacy from adding olaparib in patients with non-*BRCA*m tumors

5. **External consistency** with Study 8, PARPi class in prostate cancer and other tumor types

6. Patients with non-*BRCA*m tumors are at **risk of exposure to toxicities** of olaparib for **longer than 1 year**, without demonstrated efficacy

- **We are concerned that the addition of olaparib to abiraterone may harm patients who do not have a demonstrated tumor *BRCA* mutation**

Voting Question

As FDA reviews the proposed indication for olaparib in combination with abiraterone for initial treatment of mCRPC, should the indication be restricted to patients whose tumors have a *BRCA* mutation?

If you feel the combination should not be approved at all, please abstain from voting and explain your thinking regarding approvability during the post-voting discussion period.

Back up slides

*BRCA*m as a Predictor of PARPi Efficacy in mCRPC

Clinical trial	PARPi	Line	Stratification by HRRm or *BRCA*m	Hazard Ratio (HR) for rPFS (for PARPi arm vs control arm)	
				***BRCA*m**	**HRRm**
PROfound[a]	Olaparib	2nd	N/A	**0.22**	**0.49**
PROpel[a]	Olaparib	1st	No	**0.24**	**0.52**
TRITON-3[b]	Rucaparib	2nd	Yes	**0.50**	**0.61** (*BRCA + ATM*)
MAGNITUDE[b]	Niraparib	1st	Yes	**0.55**	**0.76**

	Endpoint	***BRCA*m (n=85)**	**HRRm (n=226)**	**non-*BRCA*m/HRRm (n=141)**
PROpel	**rPFS** (Investigator assessment)	0.24 (0.12, 0.46)	0.52 (0.36,0.76)	0.8 (0.5,1.27)
	OS	0.3 (0.15,0.6)	0.65 (0.45,0.94)	**1.02** (0.65,1.59)

[a] sNDA submission for olaparib; [b] ASCO GU 2023

PROpel: 3 subgroups based on likelihood of having *BRCA*m

BRCA assay in PROpel		Tumor tissue, n (%)		
		Yes	**No**	**Unknown**
ctDNA, n (%)	**Yes**	34 (4)	18 (**2**)	17 (2)
	No	12 (**2**)	427 (54)	**226 (28)**
	Unknown	4 (1)	**40 (5)**	**18 (2)**

- Proportion of potential *BRCA*m in Undetermined *BRCA*m subgroup
  - 2.7% x 226 ~6 patients
  - 4% x 40 ~ 2 patients
  - 13% x 18 ~ 3 patients
  - ~11 patients (4% of 284) may have a *BRCA*m with 95% CI: 2% to 7%
- Negative predictive value of tumor tissue or ctDNA: 96-97%

Issues to consider:

- NPV estimate may be biased because tissue test is not a standard reference.
- 2-7% is an estimate, however, it is not possible to find out the exact number.

PROpel: Post-discontinuation Anticancer Therapy

- In PROpel, 7 patients (**2 patients in the Olaparib arm** and **5 patients in the Placebo arm**) received post-trial PARPi.

post-discontinuation therapy			
		Olaparib	Placebo
PARPi	*BRCA*m	1	1
	Undetermined	0	3
	non-*BRCA*m	1	1
Platinum compounds	*BRCA*m	1	4
	Undetermined	2	5
	non-*BRCA*m	8	6

Source: CSR submitted by the Applicant

Approved Drugs[1] for 1st Line mCRPC Labeled for rPFS

Trial	Drug	Disease setting	Median rPFS (months)	rPFS HR (95% CI)	OS HR (95% CI)	Exploratory Median rPFS Analysis by Investigator Assessment[2,3]
COU-AA-302	Abiraterone	1st line mCRPC	NR (11.7, NR) vs 8 (8.1, 8.5)	**0.43** (0.35, 0.52)	**0.81** (0.70, 0.93)	**∆=8.2** (16.5 vs 8.3)
PREVAIL	Enzalutamide	1st line mCRPC	NR (13.8, NR) vs 3.7 (3.6, 4.6)	**0.17** (0.14, 0.21)	**0.77** (0.67, 0.88)	**∆=14.6** (20 vs 5.4)

1. drugs@fda; 2: Ryan et al. NEJM, 2013; 3. Beer et al, Eur Urol, 2017.

Approved Drugs[1] for Other Metastatic Prostate Cancer Settings

Labeled for rPFS

Trial	Drug	Disease setting		Median rPFS (months) (Δ compared to control)	rPFS HR (95% CI)	OS HR (95% CI)
TITAN	Apalutamide	mCSPC[2]		NR (NR, NR) vs 22 (18, 33)	**0.48** (0.39, 0.60)	**0.65** (0.53, 0.79)
ARCHES	Enzalutamide	mCSPC		NR (NR, NR) vs NR (49.7, NR)	**0.39** (0.30, 0.50)	**0.66** (0.53, 0.81)
CARD	Cabazitaxel	2nd/3rd line mCRPC		4.3 (8 vs 3.7)	**0.54** (0.40 to 0.73)	**0.64** (0.46; 0.89)
PROfound	Olaparib	2nd+ line mCRPC	Cohort A	3.8 (7.4 vs 3.6)	**0.34** (0.25, 0.47)	**0.69** (0.50, 0.97)
			Cohort A+B	2.3 (5.8 vs 3.5)	**0.49** (0.38, 0.63)	-

1. drugs@fda; 2. mCSPC: metastatic castration sensitive prostate cancer