Efficacy of olaparib plus abiraterone versus placebo plus abiraterone in patients with metastatic castration-resistant prostate cancer with single homologous recombination repair gene mutations in the PROpel trial

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Objective

- To report gene-by-gene efficacy of olaparib plus abiraterone versus placebo plus abiraterone within the Phase III PROpel trial, to provide more information about olaparib plus abiraterone for patients with metastatic castration-resistant prostate cancer (mCRPC) with a homologous recombination repair gene mutation (HRRm; defined as a mutation in one of the following genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L*).

Conclusions

- PROpel met its primary endpoint and showed a statistically significant and clinically meaningful radiographic progression-free survival (rPFS) benefit in the intention-to-treat (ITT) population of patients with first-line (1L) mCRPC treated with olaparib plus abiraterone versus placebo plus abiraterone.[1]
- At the final prespecified analysis, although not statistically significant, median overall survival (OS) was 42.1 months with olaparib plus abiraterone versus 34.7 months with placebo plus abiraterone, representing a 7.4-month improvement compared with placebo plus abiraterone.[2]
- Post hoc exploratory analysis of patients with an HRRm (based on aggregate test results) has shown improved rPFS and OS with olaparib plus abiraterone versus placebo plus abiraterone.[1,2]
- *BRCA2*, *ATM* and *CDK12* were the most prevalent single gene mutations (with >5 events in either arm for rPFS or OS) and post hoc analysis showed clinical benefit with olaparib plus abiraterone versus placebo plus abiraterone; the greatest treatment benefit was observed in patients with *BRCA2* mutations.
- Other single gene mutations were rare (with <5 events in either arm for rPFS or OS), limiting analysis and interpretation in patients with these alterations (individual patient outcomes are shown in the Supplement).
- The results from PROpel collectively support olaparib plus abiraterone as an important new 1L treatment option for consideration in patients with mCRPC. These findings provide additional information on clinical outcomes in patients with various HRR gene mutations.

Plain-language summary

Why did we perform this research?

- Olaparib and abiraterone, either alone or in combination, are approved to treat certain patients with metastatic castration-resistant prostate cancer (mCRPC).
- In a clinical trial called PROpel, the combination of olaparib plus abiraterone was shown to delay the progression of disease (ie the time between the start of treatment to when patients' cancer grew, spread, or got worse) more than abiraterone alone.
- Also, although not statistically significant, patients who received olaparib plus abiraterone lived an average of 7.4 months longer than patients who received placebo plus abiraterone.
- Based on how olaparib works, it is of interest to understand outcomes for patients with homologous recombination repair (HRR) gene mutations (mutations in genes related to DNA repair).

How did we perform this research?

- In PROpel, patients with mCRPC were randomly assigned to receive either olaparib plus abiraterone or placebo plus abiraterone.
- Patients were enrolled irrespective of HRR gene mutations, but were tested after being assigned to a treatment group.
- The main results from the study have already been published. Here, we looked at outcomes specifically in patients with single HRR gene mutations.

What were the findings of this research?

- In patients with HRR gene mutations, results suggest that olaparib plus abiraterone delays progression of disease and helps patients live longer.
- Clinical benefit of olaparib plus abiraterone was observed in patients identified with the most common HRR mutations: *BRCA2*, *ATM,* and *CDK12*.
- Other single gene mutations were rare, which meant that conclusions could not be made about these gene mutations from the available data (individual patient outcomes are shown in the Supplement).

What are the implications of this research?

- Results were generally consistent with the original findings of the PROpel trial and provide further information on the clinical benefit of olaparib plus abiraterone as an important new treatment option for consideration in patients with mCRPC.

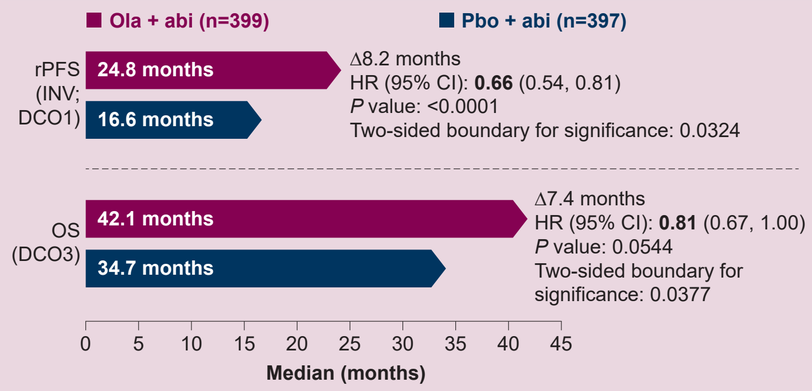
Where can I access more information?

- Information about this study can be found here: NCT03732820.
- Published results from this study can be found here: Clarke N, et al. *NEJM Evid.* DOI: 10.1056/EVIDoa2200043; Saad F, et al. *Lancet Oncol* 2023;24:1094–108.

Introduction

- PROpel met its primary endpoint: olaparib plus abiraterone showed a significant rPFS benefit versus placebo plus abiraterone in the 1L treatment of patients with mCRPC, enrolled irrespective of HRRm or *BRCA1* and/or *BRCA2* mutation (BRCAm) status (**Figure 1**).[1]
- Although not statistically significant, at the final prespecified analysis of OS, median OS was 7.4 months longer with olaparib plus abiraterone than with placebo plus abiraterone (**Figure 1**).[2]
- Post hoc exploratory analysis of patients with an HRRm (based on aggregate test results) has shown improved rPFS and OS with olaparib plus abiraterone versus placebo plus abiraterone, this benefit was especially pronounced in BRCAm patients.[1,2]
  - HRRm
    - Median rPFS not reached with olaparib plus abiraterone versus 13.9 months with placebo plus abiraterone; hazard ratio (HR) 0.50 (95% confidence interval [CI] 0.34, 0.73)
    - Median OS not reached with olaparib plus abiraterone versus 28.5 months with placebo plus abiraterone; HR 0.66 (95% CI 0.45, 0.95).
  - BRCAm
    - Median rPFS not reached with olaparib plus abiraterone versus 8.4 months with placebo plus abiraterone; HR 0.23 (95% CI 0.12, 0.43)
    - Median OS not reached with olaparib plus abiraterone versus 23.0 months with placebo plus abiraterone; HR 0.29 (95% CI 0.14, 0.56).

Figure 1. rPFS and OS in the ITT population



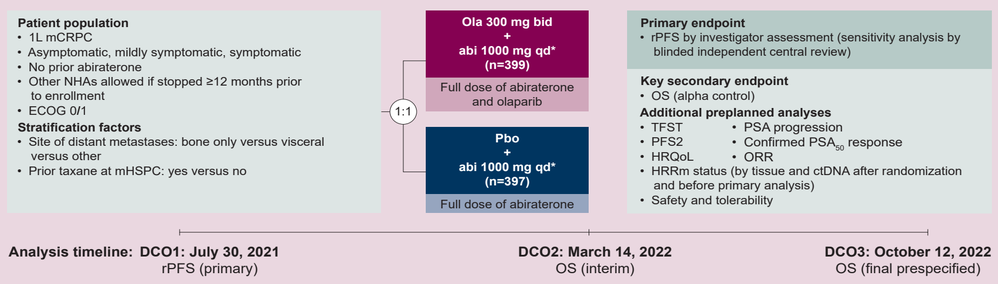
DCO1: July 30, 2021. DCO3: October 12, 2022.
abi, abiraterone; DCO, data cutoff; INV, investigator assessed; ola, olaparib; pbo, placebo.

- Further understanding of clinical outcomes for patients with specific underlying HRR gene mutations is important to identify which non-BRCA HRRm patients are deriving the greatest benefit and to support decision-making in clinical practice.

Methods

- PROpel was a randomized (1:1), double-blind, placebo controlled, Phase III trial (**Figure 2**).
- Patients were enrolled irrespective of biomarker status and received either olaparib or placebo in combination with abiraterone and prednisone/prednisolone.
- rPFS by investigator assessment was the primary endpoint (DCO1: July 30, 2021).
- OS was a key secondary endpoint (DCO3: October 12, 2022).
- Confirmed reduction of 50% of prostate-specific antigen from baseline (PSA_{50}) response was an exploratory endpoint (DCO1: July 30, 2021).
- Following randomization and before primary analysis, HRRm status was assessed by tumor tissue (FoundationOne®CDx) and circulating tumor DNA ([ctDNA] FoundationOne®Liquid CDx) tests and is reported using aggregated results from both tests.
- Genes assessed were *ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.
- In this post hoc analysis, the efficacy of olaparib plus abiraterone versus placebo plus abiraterone was analyzed by single gene mutations; HRs and CIs are not reported in gene subgroups with <5 events in either arm for both rPFS and OS.

Figure 2. PROpel trial design



*In combination with prednisone/prednisolone 5 mg bid.
bid, twice daily; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; mHSPC, metastatic hormone-sensitive prostate cancer; NHA, next-generation hormonal agent; ORR, objective response rate; PFS2, time to second progression or death; PSA, prostate-specific antigen; qd, once daily; TFST, time to first subsequent therapy or death.

Results and interpretation

Baseline characteristics

- Of the 796 patients enrolled in the trial, 226 (28.4%) had an HRRm (**Table 1**).

Table 1. Although patients were not stratified by HRRm/non-HRRm status, there was a similar proportion of patients with an HRRm in each treatment arm

	Ola + abi (n=399)	Pbo + abi (n=397)
Median age (range), years	69 (43–91)	70 (46–88)
ECOG performance status, n (%)		
0	286 (71.7)	272 (68.5)
1	112 (28.1)	124 (31.2)
Missing	1 (0.3)	1 (0.3)
Symptomatic (BPI-SF item #3 score ≥4 and/or opiate use), n (%)	103 (25.8)	80 (20.2)
Site of metastases,* n (%)		
Bone only	349 (87.5)	339 (85.4)
Distant lymph nodes	133 (33.3)	119 (30.0)
Locoregional lymph nodes	82 (20.6)	89 (22.4)
Lung	40 (10.0)	42 (10.6)
Liver	15 (3.8)	18 (4.5)
Docetaxel treatment at mHSPC stage, n (%)		
At mHSPC stage	90 (22.6)	89 (22.4)
Median PSA (IQR), µg/L	17.90 (6.09–67.00)	16.81 (6.26–53.30)
HRRm status (aggregate),† n (%)		
HRRm	111 (27.8)	115 (29.0)
Non-HRRm	279 (69.9)	273 (68.8)
HRRm unknown	9 (2.3)	9 (2.3)

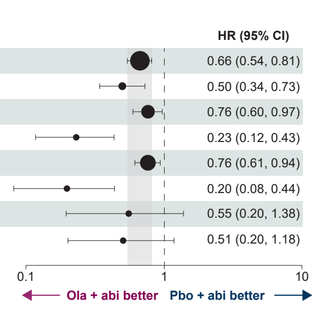
*Investigators could select more than one disease site; †The preplanned tumor tissue and plasma ctDNA testing was conducted after randomization and before primary analysis. Results from tumor tissue and plasma ctDNA were aggregated to determine patients' HRRm status.
BPI-SF, Brief Pain Inventory–Short Form; IQR, interquartile range.

Efficacy endpoints

Figure 4. HR for a) rPFS and b) OS numerically favored olaparib plus abiraterone for the most prevalent single gene mutations, *BRCA2*, *ATM* and *CDK12* (with >5 events in either arm for both rPFS and OS), with the greatest treatment benefit observed in patients with *BRCA2* mutations

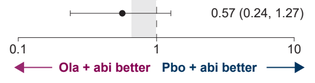
a. rPFS at DCO1

	Events, n/N (%) Ola + abi	Events, n/N (%) Pbo + abi	Median rPFS, months Ola + abi	Median rPFS, months Pbo + abi	HR (95% CI)
All patients	168/399 (42)	226/397 (57)	24.8	16.6	0.66 (0.54, 0.81)
HRRm	43/111 (39)	73/115 (63)	NR	13.9	0.50 (0.34, 0.73)
Non-HRRm	119/279 (43)	149/273 (55)	24.1	19.0	0.76 (0.60, 0.97)
BRCAm	14/47 (30)	28/38 (74)	NR	8.4	0.23 (0.12, 0.43)
Non-BRCAm	148/343 (43)	194/350 (55)	24.1	19.0	0.76 (0.61, 0.94)
***BRCA2* single gene**	8/30 (27)	20/28 (71)	NR	8.4	0.20 (0.08, 0.44)
***ATM* single gene**	6/21 (29)	14/28 (50)	NR	19.9	0.55 (0.20, 1.38)
***CDK12* single gene**	8/19 (42)	14/21 (67)	NR	16.6	0.51 (0.20, 1.18)



b. OS at DCO3

	Events, n/N (%) Ola + abi	Events, n/N (%) Pbo + abi	Median OS, months Ola + abi	Median OS, months Pbo + abi	HR (95% CI)
All patients	176/399 (44)	205/397 (52)	42.1	34.7	0.81 (0.67, 1.00)
HRRm	48/111 (43)	69/115 (60)	NR	28.5	0.66 (0.45, 0.95)
Non-HRRm	123/279 (44)	132/273 (48)	42.1	38.9	0.89 (0.70, 1.14)
BRCAm	13/47 (28)	25/38 (66)	NR	23.0	0.29 (0.14, 0.56)
Non-BRCAm	158/343 (46)	176/350 (50)	39.6	38.0	0.91 (0.73, 1.13)
***BRCA2* single gene**	6/30 (20)	18/28 (64)	NR	23.6	0.20 (0.07, 0.48)
***ATM* single gene**	9/21 (43)	15/28 (54)	NR	31.9	0.79 (0.33, 1.77)
***CDK12* single gene**	9/19 (47)	15/21 (71)	NR	33.7	0.57 (0.24, 1.27)



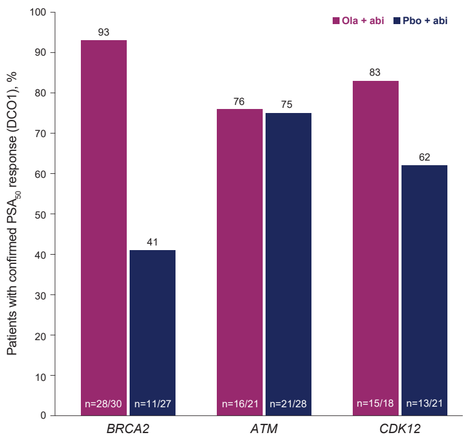
Results are descriptive and not alpha controlled.
HRs and 95% CIs calculated from a Cox proportional hazards model that contains a term for treatment, subgroup factor and a treatment by subgroup interaction. CI calculated using a profile likelihood method.
Only *BRAC2*, *ATM*, *CDK12* and *CHEK2* were included in the Cox proportional hazards model.
BRCAm, *BRCA1* and/or *BRCA2* mutation; NR, not reached.

- In the *CHEK2* population, 5/7 patients in the olaparib plus abiraterone arm and 8/12 patients in the placebo plus abiraterone arm had an rPFS event.
- In the *BRCA1* population, 0/6 patients in the olaparib plus abiraterone arm and 3/3 patients in the placebo plus abiraterone arm had an rPFS event.
- In the *PALB2* population, 1/3 patients in the olaparib plus abiraterone arm and 3/4 patients in the placebo plus abiraterone arm had an rPFS event.
- In the *RAD54L* population, 2/3 patients in the olaparib plus abiraterone arm and 1/2 patients in the placebo plus abiraterone arm had an rPFS event.
- In the *FANCL* population, 3/3 patients in the olaparib plus abiraterone arm and 0/0 patients in the placebo plus abiraterone arm had an rPFS event.
- In the *BARD1* population, 0/0 patients in the olaparib plus abiraterone arm and 1/2 patients in the placebo plus abiraterone arm had an rPFS event.
- Patient-level rPFS for *BRCA2*, *ATM*, *CDK12* and all other single gene populations can be found in the Supplement.

- In the *CHEK2* population, 4/7 patients in the olaparib plus abiraterone arm and 6/12 patients in the placebo plus abiraterone arm had an OS event.
- In the *BRCA1* population, 1/6 patients in the olaparib plus abiraterone arm and 3/3 patients in the placebo plus abiraterone arm had an OS event.
- In the *PALB2* population, 2/3 patients in the olaparib plus abiraterone arm and 3/4 patients in the placebo plus abiraterone arm had an OS event.
- In the *RAD54L* population, 2/3 patients in the olaparib plus abiraterone arm and 0/2 patients in the placebo plus abiraterone arm had an OS event.
- In the *FANCL* population, 2/3 patients in the olaparib plus abiraterone arm and 0/0 patients in the placebo plus abiraterone arm had an OS event.
- In the *BARD1* population, 0/0 patients in the olaparib plus abiraterone arm and 1/2 patients in the placebo plus abiraterone arm had an OS event.
- Patient-level OS for *BRCA2*, *ATM*, *CDK12* and all other single gene populations can be found in the Supplement.

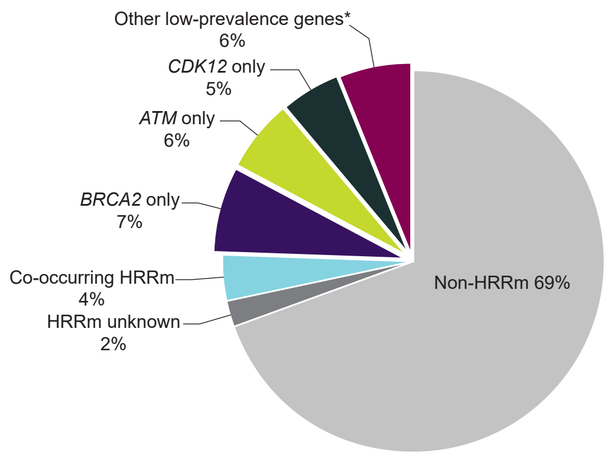
Confirmed PSA_{50} response

Figure 5. Confirmed PSA response for the most prevalent single gene mutations: *BRCA2*, *ATM*, and *CDK12*



Only patients with a PSA measurement at baseline are included.
Confirmed PSA response was defined as a reduction in PSA level of 50% or more on two consecutive occasions at least 3 weeks apart compared with baseline. Patients may have more than one confirmed response but will be counted once for this response rate.

Figure 3. The most prevalent single gene mutations were *BRCA2* (n=58), *ATM* (n=49) and *CDK12* (n=40)



All percentages have been rounded to whole numbers.
*Other low-prevalence genes: *CHEK2* (n=19), *BRCA1* (n=9), *PALB2* (n=7), *RAD54L* (n=5), *FANCL* (n=3), *BARD1* (n=2), *BRIP1* (n=1), *RAD51B* (n=1), *RAD51D* (n=1).

Table 2. Single gene mutations were generally balanced between the arms

n, (%)	Ola + abi (n=399)	Pbo + abi (n=397)
BRCA2 only	30 (8)	28 (7)
ATM only	21 (5)	28 (7)
CDK12 only	19 (5)	21 (5)
CHEK2 only	7 (2)	12 (3)
BRCA1 only	6 (2)	3 (0.8)
PALB2 only	3 (0.8)	4 (1)
RAD54L only	3 (0.8)	2 (0.5)
FANCL only	3 (0.8)	0 (0)
BARD1 only	0 (0)	2 (0.5)
BRIP1 only	0 (0)	1 (0.3)
RAD51B only	0 (0)	1 (0.3)
RAD51D only	0 (0)	1 (0.3)

CHEK1, *RAD51C* (n=0).
Results from tumor tissue and plasma ctDNA were aggregated to determine patients' HRRm status.

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2. Saad F, et al. *Lancet Oncol* 2023;24:1094–108.

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