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ORIGINAL ARTICLE

Efficacy of olaparib in advanced cancers with somatic or germline mutations in *BAP1*, *BARD1*, *BRIP1* and *PALB2*

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Background: Olaparib is registered for use in ovarian, breast, pancreatic and prostate cancers with a *BRCA1/2* mutation and/or mutations in other homologous recombination deficiency (HRD) genes. HRD gene mutations are also found in other cancer types, and these cancers may also benefit from olaparib therapy. We aimed to evaluate the efficacy of olaparib in advanced cancers harboring a (likely) pathogenic germline or somatic mutation in a gene involved in homologous recombination (HR).

Patients and methods: This investigator-initiated, open-label, basket phase II trial evaluates the efficacy of olaparib in patients with advanced tumors harboring HR gene mutations following progression on standard-of-care therapies. Cohorts were stratified based on the presence of either somatic or germline mutations in the same HR-related gene. Although results from the completed cohorts have been previously published, this report presents a case series focusing on cohorts with rare gene alterations.

Results: In patients who harbor a tumor mutation in *ARID1A*, *ATR*, *ATRX*, *BLM*, *CDK12*, *CHEK1*, *DDR2*, *ERCC4*, *FANCE*, *GEN1*, *MRE11A*, *NBN*, *POLE*, *RAD21*, *RAD50*, *RAD51C*, *RAD51D*, *RAD52* and *SLX4*, no responses were observed. In the *BAP1*, *BARD1*, *BRIP1* and *PALB2* cohorts, objective responses were detected.

Conclusion: Olaparib demonstrated meaningful clinical activity across different cancer types with somatic or germline mutations in *BAP1*, *BARD1*, *BRIP1* and *PALB2*.

Key words: olaparib, BAP1, BARD1, BRIP1, PALB2

INTRODUCTION

For many decades, treatment decisions have been guided by patient characteristics, tumor histology and hormone receptor status to guide our treatment decisions. The introduction of next-generation sequencing (NGS) for solid tumors has significantly expanded the spectrum of predictive markers, thereby advancing the development of stratified medicines over the last three decades. Identifying genomic alterations, such as mutations and gene fusions, informs the development and subsequent use of targeted therapies.[1] Genome-driven therapies are typically developed for tumor-specific indications. However, many drug-sensitizing mutations are also present in cancer types beyond those for which treatments are approved. Targeting these drivers in off-label cancer types can yield significant benefit, although the magnitude of response may not always match that observed in the lead indications.

Genomic instability resulting from defects in the DNA damage response represents an actionable genomic alteration.[2] Among these, defects in homologous recombination (HR) are particularly relevant. The HR pathway is crucial for the accurate repair of DNA double-strand breaks and involves numerous genes, including *BRCA1* and *BRCA2*.[3] HR deficiency (HRD) resulting from the inactivation of these genes leads to cancer pathogenesis.[4] But at the same time, HRD renders cancer cells sensitive to synthetic lethality with poly ADP-ribose polymerase inhibitors (PARPis).[5,6]

Olaparib, the first PARPi to be discovered and developed for cancer treatment, was initially registered in first-line advanced ovarian cancer with a pathogenic mutation in the *BRCA1* or *BRCA2* genes, based on the phase III SOLO-1 trial (maintenance olaparib in advanced ovarian cancer with a mutation in BRCA1 or BRCA2).[7] Subsequently, the

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application of olaparib was extended to first-line ovarian cancer treatment based on the results of the phase III PAOLA-1 (Platine, Avastin and OLAparib in 1st line) trial (olaparib in combination with bevacizumab).[8] Currently, olaparib is also available for patients with metastatic breast cancer (Phase III OlympiAD trial, olaparib compared to standard therapy in advanced breast cancer patients with a germline BRCA mutation)[9] and early *BRCA1/2* mutant breast cancer (Phase III OlympiA trial, adjuvant olaparib or placebo for 1 year in early breast cancer patients with a germline BRCA mutation),[10] advanced castration-resistant prostate cancer (Phase III PROpel trial, olaparib in combination with abiraterone versus abiraterone alone in metastatic castration-resistant prostate cancer,[11] phase III PROfound study, olaparib monotherapy in metastatic castration-resistant prostate cancer[12]), and pancreatic cancer (Phase III POLO (Pancreas Olaparib Ongoing) trial, maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer[13]) with pathogenic *BRCA1* or *BRCA2* mutations. Most recently, it has also become available for advanced or recurrent endometrial cancer with proficient mismatch repair in combination with durvalumab (Phase III DUO-E trial, durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer[14]). Olaparib has an NCCN (national comprehensive cancer network) category 2A designation (lower level of evidence but a uniform consensus that the recommendation is appropriate) for patients with cancer with germline *PALB2* mutations, supported by the TBCRC-048 (Translational Breast Cancer Research Consortium 048) trial.[15]

However, other cancer types might carry mutations in the *BRCA1/2* genes, and PARPi responses have also been documented in malignancies lacking *BRCA1/2* mutations,[16] as other causes of HRD may underlie this sensitivity. Mutations in genes implicated in HR have been identified across a wide range of tumor types,[17] indicating that a broader population of patients could potentially benefit from treatment with olaparib.

We are reporting on a phase II basket study conducted within the broader framework of the Belgian Precision Initiative.[18]

PATIENTS AND METHODS

Study design and patient population

The cohorts presented in this report are part of a tumor-agnostic academic, multicenter, phase II basket trial designed to evaluate the efficacy of olaparib across different advanced cancer types characterized by a mutation in HR genes, potentially creating HRD. Excluded were indications for which olaparib was already approved.

The study was approved by the ethical committee (EC) of every participating site (EC number 2018/442). Before entering the study, patients signed a written informed consent form. Patient enrollment started on 1 February 2019 and ended on 1 February 2023. This study was sponsored by the Belgian Society of Medical Oncology. It involved patient recruitment from 12 participating sites across Belgium, comprising university hospitals and large regional institutions with established experience in conducting clinical trials. Tumor sequencing was performed either by the accredited genetics or molecular oncology laboratories of the participating center or by Foundation Medicine, if sequencing was conducted within the framework of the GENEO study (a study to examine the value of broad agnostic NGS (next-generation sequencing) panel testing versus reimbursed organ-directed NGS in Belgium, NCT04641676),[15] a prospective, tumor-agnostic effort involving comprehensive NGS in patients with advanced cancers. In one case, patient 510, we do not have the correct cDNA annotation available. In this case, the information provided is the presence of a genomic rearrangement located within intron 15 of the *BAP1* gene, as reported by Foundation Medicine.

Patients with advanced cancer (stage IV, metastatic disease) with a pathogenic or likely pathogenic germline mutation or a somatic tumor mutation in an HR gene were eligible for the study. The genes considered were as follows: *ATM*, *BRCA1*, *BRCA2*, *CHEK1*, *CHEK2*, *NBN*, *BRIP1*, *MRE11A*, *RAD50*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*, *PALB2*, *BARD1*, *FAM175A*, *CDK12*, *FANCL*, *TP53* (only germline) and *PPP2R2A*. However, the participating investigators could also submit patients with tumor mutations in other genes for which there might be scientific evidence for a role in HR.

The results of the first part of our study, which includes the complete cohorts for *ATM*, *BRCA1*, *BRCA2* and *CHEK2*, were published earlier.[19] Some rare gene cohorts had a limited accrual and no prospect for complete accrual within a reasonable time frame. In this article, we report on incomplete cohorts involving these rarer gene mutations as a case series.

There were no restrictions regarding the number of prior lines of treatment for study participation. Inclusion and exclusion criteria are available in Supplementary File S1, available at https://doi.org/10.1016/j.esmoop.2026.107693.

Study treatment and assessment

The investigational product was administered in the form of film-coated tablets containing either 150 mg or 100 mg of olaparib. Each patient initiated therapy at a continuous dose of 300 mg twice daily. Dose reductions were permitted in cases of toxicity, with a first reduction to 250 mg twice daily and a second dose reduction to 200 mg twice daily.

Clinical visits were scheduled at weeks 2 and 4, followed by monthly assessments and a final visit at the end of treatment. Tumor response was evaluated using clinical assessment and computed tomography imaging according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria, performed by an independent central radiologist, every 2 months during the first year and every 3 months thereafter.

Statistical analysis

A cohort was defined as a group of patients carrying either a somatic or germline mutation in the same gene. Because of the rarity of the mutations, cohort enrollment was incomplete, and therefore, an exploratory analysis was conducted. The primary endpoints are overall response rate (ORR) and clinical benefit rate (CBR). The 95% confidence intervals (CIs) were calculated using the Clopper—Pearson exact method.

RESULTS

A total of 159 patients were included in the study. The distribution of gene mutations accrued in the study are as follows: *ARID1A*: 4, *ATM*: 13, *ATR*: 2, *ATRX*: 6, *BAP1*: 11, *BARD1*: 4, *BLM*: 1, *BRCA1*: 27, *BRCA2*: 35, *BRIP1*: 8, *CDK12*: 2, *CHEK1*: 1, *CHEK2*: 13, *DDR2*: 1, *ERCC4*: 1, *FANCE*: 1, *GEN1*: 1, *MRE11A*: 3, *NBN*: 1, *PALB2*: 8, *POLE*: 1, *RAD21*: 2, *RAD50*: 1, *RAD51C*: 6, *RAD51D*: 3, *RAD52*: 2, *SLX4*: 1.

The completed cohorts (*ATM*, *BRCA1*, *BRCA2* and *CHEK2*) were reported in an earlier article.[19]

Safety

All safety observations were as known in the safety profile of olaparib and have been discussed in the first paper.[19] In the cases reported here, no additional safety signals have been detected.

In the patients that harbor a tumor mutation in the *ARID1A*, *ATR*, *ATRX*, *BLM*, *CDK12*, *CHEK1*, *DDR2*, *ERCC4*, *FANCE*, *GEN1*, *MRE11A*, *NBN*, *POLE*, *RAD21*, *RAD50*, *RAD51C*, *RAD51D*, *RAD52* or *SLX4* genes, no responses were observed.

In the *BAP1*, *BARD1*, *BRIP1* and *PALB2* cohorts, objective responses were observed.

These four cohorts accrued 11, four, eight and eight patients, respectively.

The characteristics of the patients in the four cohorts where responses were observed are shown in Table 1.

BAP1 cohort

The response to therapy with olaparib in the *BAP1* cohort is illustrated in Figure 1. One of 11 patients (renal cell cancer) had a durable response of 33 months. Details on the

Table 1. Clinical characteristics of patients.

Patient number	Pathology	Age	Sex	Prior systemic therapies	Best response	Mutation	G or S
BAP1							
126	Melanoma	37	F	1	SD	NM_004656.3(BAP1): c.1515_1516del	S
203	Hepatocellular carcinoma	54	F	1	SD	NM_004656.3(BAP1):c.592del	S
209	Bladder carcinoma	69	F	2	PD	NM_004656.3(BAP1): c.1984-1G>C	S
215	Breast carcinoma	45	F	3	PD	NM_004656.3(BAP1): c.1117-11_1140dup	S
223	Renal cell carcinoma	59	M	3	PR	NM_004656.3(BAP1): c.1399del	S
230	Head and neck carcinoma	69	F	1	SD	NM_004656.3(BAP1): c.757C>T	S
510	Epithelioid mesothelioma	66	M	1	PD	BAP1: rearrangement intron 15 (< Foundation One)	G
738	Mucinous appendix carcinoma	59	F	1	PD	NM_004656.3(BAP1):c.660-14_681del	S
1105	Uveal melanoma	56	M	2	PD	NM_004656.3(BAP1): c.1063OT	G
1111	Gallbladder carcinoma	43	F	2	PD	NM_004656.3(BAP1): c.717dup	G
1205	Kidney carcinoma	79	M	4	PD	NM_004656.3(BAP1): c.68-1G>A	S
BARD1							
119	Pancreatic adenocarcinoma	78	M	2	PD	NM_000465.4 (BARD1): c.1690C>T	G
220	Head and neck carcinoma	56	M	1	PR	BARD1 (Foundation one)	S
604	Colon carcinoma	53	M	6	PD	NM_000465.3 (BARD1):c.315-1G>C	S
605	Breast carcinoma	75	F	2	SD	NM_000465.3 (BARD1):c.1063G>T	S
BRIP1							
226	Soft tissue sarcoma	68	F	0	CR	NM_032043.3(BRIP1): c.1871C>A	S
229	Breast carcinoma	41	F	3	SD	BRIP1 (Foundation one)	S
305	Pancreatic adenocarcinoma	69	F	3	PD	NM_032043.3(BRIP1):c.2992_2995del	G
505	Breast carcinoma	55	F	4	PD	NM_032043.3(BRIP1): c.359G>C	S
514	Serous ovarian carcinoma	72	F	3	SD	NM_032043.3(BRIP1): c.1201_1204dup	G
725	Pancreatic adenocarcinoma	74	M	4	SD	NM_032043.3(BRIP1): c.1504G>T	G
741	Pancreatic adenocarcinoma	57	F	1	PR	NM_032043.3(BRIP1): c.2990_2993del	G
1114	Cervix carcinoma	45	F	3	PD	NM_032043.3(BRIP1): c.2742_2749del	S
PALB2							
108	Uterine sarcoma	81	F	2	PD	NM_024675.3(PALB2): c.2816T>G	S
109	Breast carcinoma	68	F	5	CR	NM_024675.3 (PALB2): c. 109-12T>A	G
120	Pancreatic adenocarcinoma	71	M	3	PD	NM_024675.3 (PALB2): c. 2201C>A	G
204	Breast carcinoma	54	F	5	PD	NM_024675.3(PALB2): c.712A>T	S
308	Pancreatic adenocarcinoma	70	M	2	SD	NM_024675.3(PALB2): c.3456dup	G
703	Pancreatic adenocarcinoma	59	F	5	PD	NM_024675.3(PALB2):c.1431_1441del and NM_024675.3(PALB2):c.212-1_212delinsTT	S
722	Pancreatic adenocarcinoma	64	F	1	SD	NM_024675.3(PALB2): c.1161del	G
1206	Breast carcinoma	69	F	5	PR	NM_024675.3(PALB2): c.3424del	S

CR, complete response; F, female; G, germline; M, male; PD, progressive disease; PR, partial response; S, somatic; SD, stable disease.

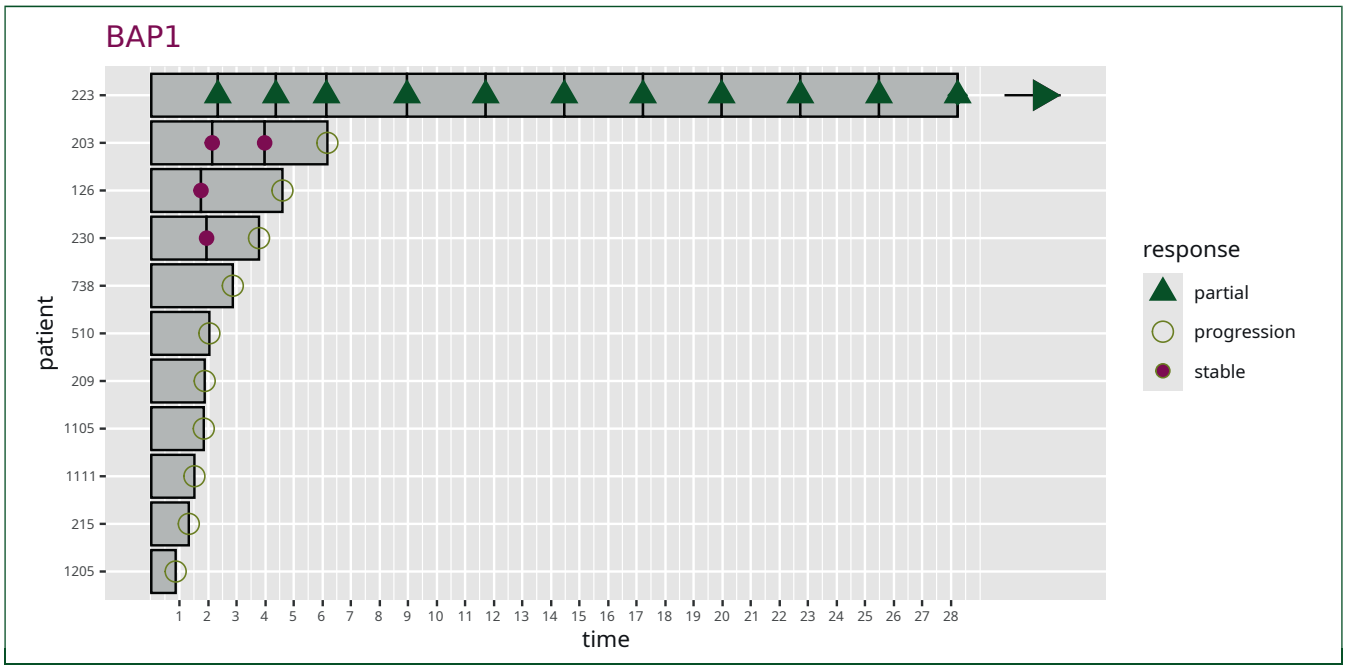

Figure 1. **Swimmer plot of the response to treatment with olaparib in the *BAP1* cohort.**

responding patients with stable disease are provided in Supplementary File S2, available at https://doi.org/10.1016/j.esmoop.2026.107693.

In the *BAP1* cohort ($n = 11$), the objective response rate was 9.1% (CI 0.2-41.3) and the CBR was 36.4% (CI 10.9-69.2).

One of four patients (neuroendocrine head and neck cancer) showed a partial response for 14 months, and one patient with breast cancer had a prolonged stable disease (details in Supplementary File S2, available at https://doi.org/10.1016/j.esmoop.2026.107693). The ORR was 25.0% (CI 0.6-80.6), and the CBR was 50.0% (CI 6.8-93.2).

BARD1 cohort

The response to treatment with olaparib in the *BARD1* cohort is shown in Figure 2.

BRIP1 cohort

The response to therapy with olaparib in the *BRIP1* cohort is illustrated in Figure 3.

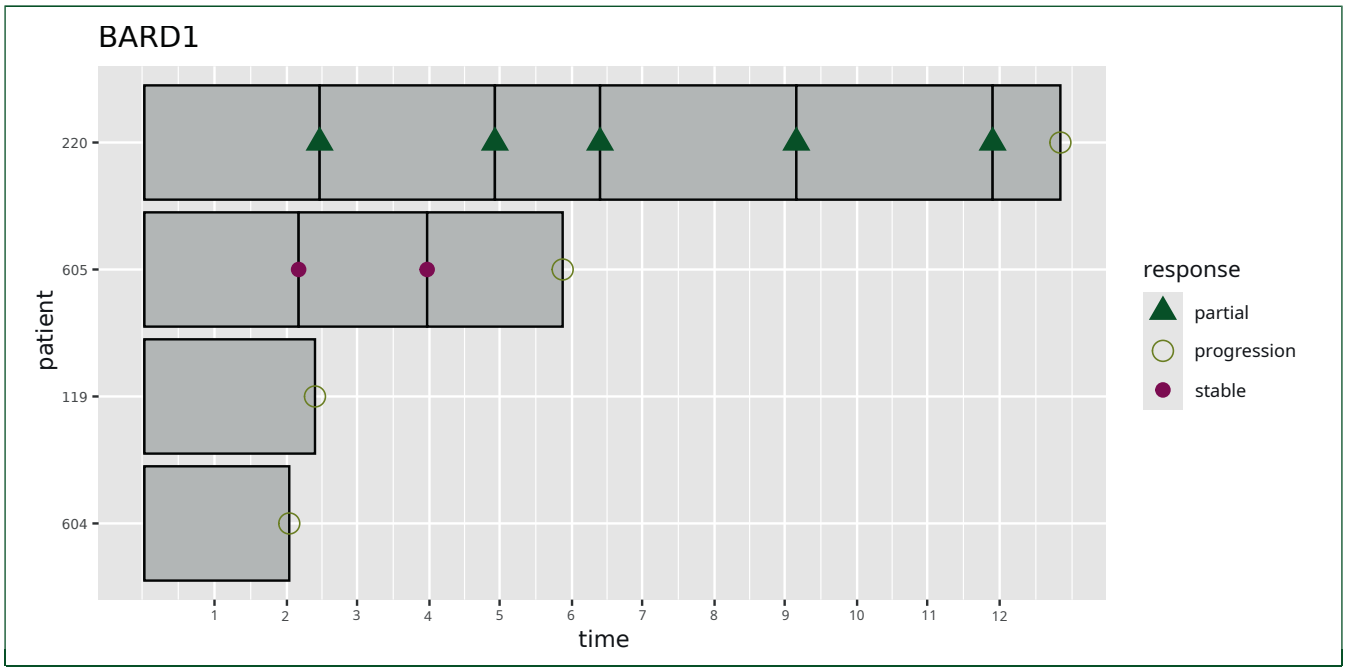

Figure 2. **Swimmer plot showing the response to treatment with olaparib in the *BARD1* cohort.**

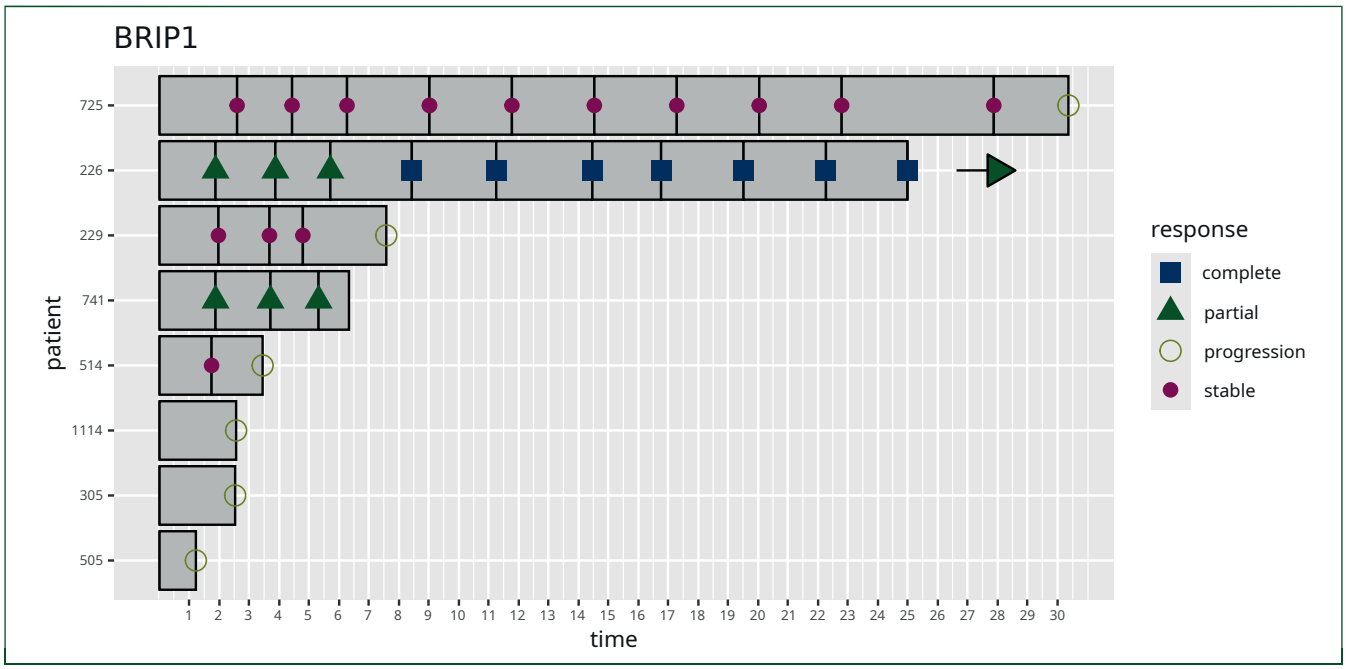

Figure 3. **Swimmer plot showing the response to treatment with olaparib in the *BRIP1* cohort.**

Two of eight patients (sarcoma[20] and pancreatic cancer) responded (ORR 95%, CI 3.2-65.1), and two had prolonged stable disease (CBR 62.5%, CI 24.5-91.5) (more specifics in Supplementary File S2, available at https://doi.org/10.1016/j.esmoop.2026.107693).

PALB2 cohort

The response to treatment with olaparib in the *PALB2* cohort is shown in Figure 4.

In the *PALB2* cohort, the objective response rate was 25.0% (CI 3.2-65.1) and the CBR was 50.0% (CI 15.7-84.3) (details in Supplementary File S2, available at https://doi.org/10.1016/j.esmoop.2026.107693).

DISCUSSION

PARPis may be effective in cancers with somatic or germline mutations in genes involved in HR beyond currently approved indications.

We report on the efficacy of olaparib treatment in 159 patients enrolled in an academic, national open-label basket trial, which included patients with any cancer type and a mutation causing HRD. Only patients with nonapproved

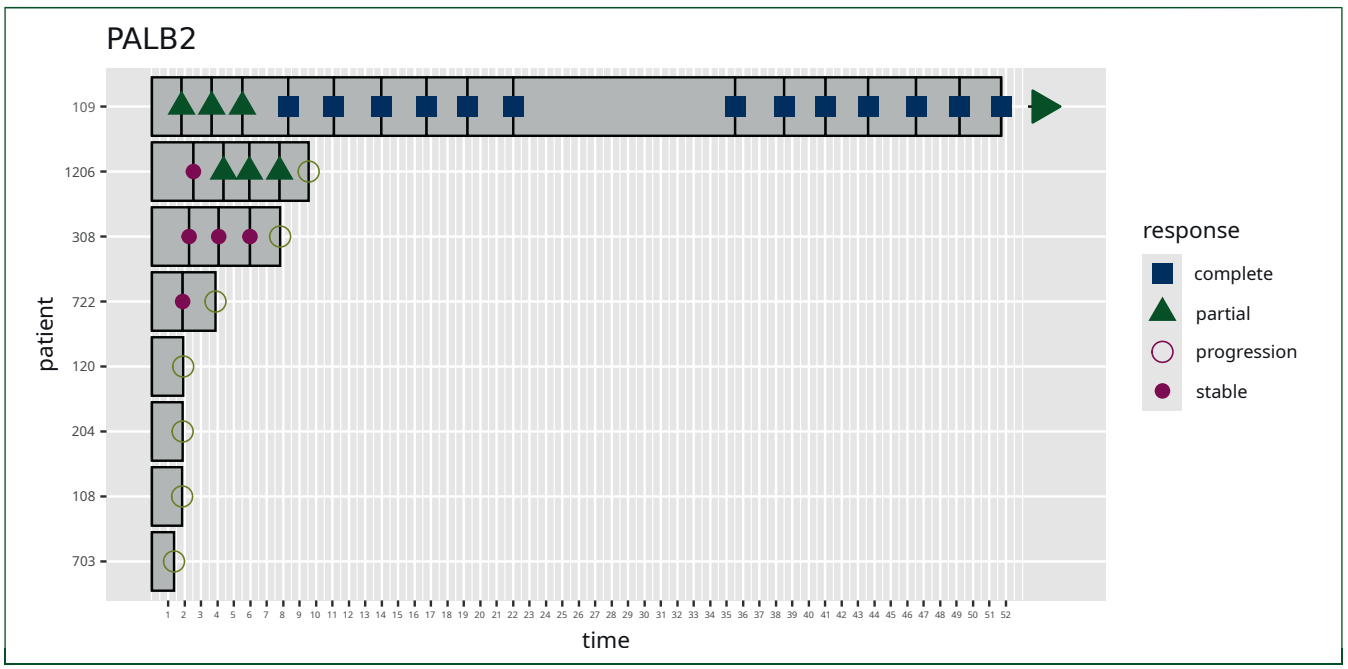

Figure 4. **Swimmer plot showing the response to treatment with olaparib in the *PALB2* cohort.**

tumor type—genotype associations were included. Due to the rarity of these gene alterations, the reported cohorts did not meet their predefined accrual targets and were unlikely to be completed in the future.

In four cohorts (*BAP1*, *BARD1*, *BRIP1* and *PALB2*), objective and durable responses, along with clinical benefit, were observed. Although the small number of patients per cohort limits the statistical power of the study, the findings provide a compelling signal to consider PARPi treatment for patients with mutations in any of these four genes. We also recommend continued documentation of outcomes in such cases to build more robust data. Other limitations include the lack of a control group for contextualizing treatment effects, as well as potential selection bias introduced by restricting enrollment to patients with detectable HR-gene mutations. The data might nevertheless be hypothesis-generating or enlarge the body of evidence when cumulated with other reported cases in these rare cohorts.

Supplementary File S3, available at https://doi.org/10.1016/j.esmoop.2026.107693, provides an overview of the literature of previously reported cases.

Only for *PALB2* and *BAP1*, other case series or phase II studies are available that contain data across different tumor types.

PALB2 (Partner and Localizer of BRCA2) is a tumor suppressor gene involved in HR repair (HRR) through its interaction with both *BRCA1* and *BRCA2*. The TBCR-048 trial (Translational Breast Cancer Research Consortium),[15] an expanded study of olaparib, investigated its efficacy in patients with BRCA-negative breast cancer harboring either germline or somatic mutations in HRR pathway genes. Notably, an objective response rate of 80% was reported among patients with *PALB2* mutations. Ongoing studies in larger cohorts aim to validate these findings.

A phase II study has been published in the literature investigating treatment with olaparib in patients with mesothelioma carrying either a somatic or germline mutation in *BAP1*.[21] The authors concluded that olaparib demonstrated limited efficacy in previously treated patients with mesothelioma who harbored *BAP1* mutations in their tumors.

A second phase II study involving *BAP1*-mutated patients has been published in the literature, investigating a different PARPi, niraparib.[22] Niraparib did not meet the predefined efficacy endpoint for objective response. Nevertheless, clinical benefit was observed in a subset of patients with confirmed *BAP1* mutations, supporting the rationale for further investigation.

Our study also demonstrated responses in patients harboring *BRIP1* or *BARD1* gene alterations.

BRIP1 (BRCA1-interacting protein C-terminal helicase 1) encodes a member of the RecQ DEAH helicase family, which plays a critical role in DNA repair and the maintenance of chromosomal stability. Mutations or alterations in *BRIP1* can impair DNA damage repair mechanisms, thereby increasing the risk of developing breast cancer. A case has been reported in the literature describing a patient with breast cancer with a germline *BRIP1* mutation who showed a favorable response to treatment with olaparib.[23]

Regarding *BARD1*, minimal data are available. One study analyzed various missense variants in *BARD1* among patients with ovarian and breast cancer and observed increased sensitivity to cisplatin and olaparib.[24]

The *ATM* cohort has been previously described in an earlier publication.[19] However, recent literature provides additional insights that are relevant to this cohort. *ATM*, a frequently mutated gene, has been investigated more often, mostly in prostate cancer, and found to have no significant clinical benefit.[25] In a basket trial of the Dutch Drug Rediscovery Protocol, a modest clinical benefit of olaparib was observed in *ATM*-mutant cancers, with an objective response documented in one out of 25 patients.[26]

At present, and in the absence of additional biomarkers, *ATM* mutations do not appear to confer a meaningful clinical benefit. However, recent emerging evidence suggests that PARPi sensitivity may be mutation-specific.[27] A prospective clinical evaluation is therefore warranted.

For the more rarely mutated genes—*ATRX*, *BLM*, *CHEK1*, *DDR2*, *ERCC4*, *FANCE*, *GEN1*, *RAD21*, *RAD52* and *SLX4*—no data on clinical efficacy for PARPis were found in the literature, although for some of these genes, preclinical evidence supports clinical investigation.

With the advent of newer, more selective PARPis, the landscape of gene-specific sensitivity may continue to evolve.

Throughout the course of the study, our understanding of relevant biomarkers evolved.

A unified genomic biomarker for HRD could be instrumental for identifying additional patients who may benefit from PARPi therapy. The HRD signature, a novel genomic scar-based algorithm, has shown promise in predicting PARPi response in HRD-positive tumors.[28] In high-grade serous ovarian cancer[29] and triple-negative breast cancer,[30] the HRD score is a clinically validated biomarker that predicts sensitivity to PARPis and platinum-based chemotherapy. A recent study in patients with sarcoma showed responses with PARPis in HRD-positive cancers.[31] The HRD score is, therefore, a promising biomarker that warrants investigation and validation across multiple tumor types in addition to gene panel mutation analysis.

Conclusion

These data are hypothesis-generating, with the most robust evidence supporting olaparib activity in *PALB2*-mutated cancers. Preliminary signals in *BARD1*, *BRIP1* and *BAP1* require validation in larger, gene- and histology-specific cohorts before they can inform routine clinical decision making.

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DISCLOSURE

The authors have declared no conflicts of interest.

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