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Case series

Rucaparib for PARP inhibitor-pretreated ovarian cancer: A GEICO retrospective subgroup analysis from the Spanish Rucaparib Access Program

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ABSTRACT

The poly(ADP-ribose) polymerase inhibitor (PARPi) rucaparib is approved as maintenance therapy for patients with platinum-sensitive recurrent high-grade ovarian cancer (HGOC). The efficacy and safety of rucaparib after PARPi therapy are largely unknown; therefore, we analyzed outcomes in the subgroup of PARPi-pretreated patients from Spanish hospitals participating in the Rucaparib Access Program. This post hoc subgroup analysis explored baseline characteristics, treatment exposure, safety, effectiveness, and subsequent therapy among women receiving rucaparib 600 mg twice daily after at least one prior PARPi for HGOC. Of 14 women eligible for the analysis, 11 (79%) had tumors harboring *BRCA1/2* mutations. Patients had received a median of 5 (range 3–8) treatment lines before rucaparib. Twelve patients (86%) had previously received olaparib and two (14%) niraparib; 12 patients received rucaparib as treatment for platinum-resistant HGOC, one as treatment for platinum-sensitive HGOC, and one as maintenance therapy. Progression-free survival was 0.2–9.1 months. One of seven patients assessable for response by RECIST achieved stable disease. Adverse events occurred in 11 patients (79%; grade 3 in 29%), leading to treatment interruption in eight patients (57%), dose reduction in six (43%), but treatment discontinuation in only one (7%). No new safety signals were observed. This is one of the first reported series of real-world data on rucaparib after prior PARPi for HGOC. In this heavily pretreated population, rucaparib demonstrated meaningful activity in some patients and tolerability consistent with previous prospective trials. Future investigation should focus on identifying patients who may benefit from rucaparib after prior PARPi exposure.

1. Background

The therapeutic class of poly(ADP-ribose) polymerase (PARP) inhibitors (PARPis) has transformed the treatment of several solid tumor types. Initially these agents were developed as treatment for *BRCA*-mutated ovarian and breast cancers, but their use has extended across biomarker subgroups and treatment settings, and into prostate and pancreatic cancers (Rubraca (rucaparib) Prescribing Information, 2022;

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Table 1
Baseline characteristics ($n = 14$).

Characteristic		Prior PARPi ($n = 14$)
Median (range) age, years	At diagnosis	56 (37–74)
	At first dose of rucaparib	63 (42–78)
Diagnosis, *n* (%)	Epithelial ovarian cancer	13 (93)
	Fallopian tube cancer	1 (7)
Histology, *n* (%)	Serous	14 (100)
ECOG performance status, *n* (%)	0	4 (29)
	1	8 (57)
	Unknown	2 (14)
***BRCA* mutation status, *n* (%)**	*BRCA1* mutated*	9 (64)
	BRCA2 mutated†	2 (14)
	BRCA1/2 wild type	2 (14)
	Unknown	1 (7)
Previous bevacizumab therapy, *n* (%)		13 (93)
Median (range) number of treatment lines before first PARPi		3 (2–5)
Number of prior lines of therapy before rucaparib	Median (range)	5 (3–8)
	3, *n* (%)	2 (14)
	4, *n* (%)	3 (21)
	5, *n* (%)	3 (21)
	≥6, *n* (%)	6 (43)
Rucaparib indication, *n* (%)	Maintenance	1 (7)
	Treatment for platinum-sensitive disease	1 (7)
	Treatment for platinum-resistant disease	12 (86)
Measurable disease (investigator assessed), *n* (%)		11 (79)
First PARPi, *n* (%)	Olaparib	12 (86)
	Niraparib	2 (14)

ECOG: Eastern Cooperative Oncology Group. PARPi: poly(ADP-ribose) polymerase inhibitor.
*All germline mutations. †One somatic and one germline mutation.

Lynparza (olaparib) Prescribing Information, 2022; Zejula (niraparib) Summary of Product Characteristics, 2023). PARPis are established as maintenance therapy following response to platinum-based therapy for ovarian cancer (Rubraca (rucaparib) Prescribing Information, 2022; Lynparza (olaparib) Prescribing Information, 2022; Zejula (niraparib) Summary of Product Characteristics, 2023). Rucaparib is currently approved as maintenance therapy for patients with (platinum-sensitive) recurrent high-grade ovarian cancer in complete or partial response to platinum-based therapy based on results from the ARIEL3 trial (Coleman et al., 2017), regardless of *BRCA1/2* mutation status by the European Medicines Agency (EMA) (Rubraca (rucaparib) Summary of Product Characteristics, 2022), and limited to patients with ovarian cancer associated with *BRCA* mutation by the US Food and Drug Administration (FDA) (Rubraca (rucaparib) Prescribing Information, 2022). However, when the study reported here was designed, rucaparib was also approved by the FDA and EMA as third-line therapy for *BRCA*-mutated ovarian cancer, an indication that was subsequently withdrawn, and as maintenance therapy for recurrent ovarian cancer irrespective of *BRCA* mutation by the FDA.

Until the introduction of targeted therapies for ovarian cancer, chemotherapy agents were typically used in succession, with re-use of platinum if patients had a relatively long relapse-free period between treatment lines. More recently, this dogma has been revised and platinum rechallenge may be considered even after early relapse based on numerous other variables, such as tumor biology, histology, and molecular changes in the tumor (Baert et al., 2021). The approval of bevacizumab – initially in newly diagnosed ovarian cancer and subsequently in recurrent disease – raised the possibility of re-treatment with anti-angiogenic therapies. Subsequently the MITO16b/MANGO–OV2/ENGOT–ov17 randomized phase III trial provided evidence that bevacizumab is beneficial after progression in patients previously treated with bevacizumab (Pignata et al., 2021). Similarly, as PARPis have become standard of care in additional treatment settings, the role of PARPi rechallenge has become an increasingly important unanswered question.

In Spain, the Rucaparib Access Program (RAP), initiated in September 2018, provided patients with the opportunity to receive rucaparib treatment for *BRCA*-mutated platinum-sensitive recurrent ovarian cancer or as maintenance therapy for recurrent ovarian cancer regardless of *BRCA* status according to the approved indications at the time, or as treatment for *BRCA*-mutated platinum-resistant ovarian cancer with no therapeutic alternatives. An observational retrospective study conducted by the Grupo Español de Investigación en Cáncer de Ovario (GEICO) analyzed outcomes among 51 patients treated in 22 GEICO-associated hospitals to evaluate the effectiveness and safety of rucaparib in an unselected population treated in the real-world setting within the RAP (Yubero et al., 2022). Rucaparib demonstrated clinical outcomes consistent with those observed in pivotal clinical trials, even in patients with heavily pretreated disease.

Prior PARPi therapy was an exclusion criterion in ARIEL3 (Coleman et al., 2017) and ARIEL4 (Kristeleit et al., 2022); consequently, the efficacy and safety of rucaparib after prior PARPi therapy are largely unknown. Therefore, we identified the subgroup of PARPi-pretreated patients receiving rucaparib in the GEICO-associated hospitals of the RAP. Here we describe characteristics and outcomes for this subgroup.

2. Methods

The parent study is described in detail elsewhere (Yubero et al., 2022); briefly, patients treated with rucaparib in any of 22 GEICO-associated hospitals in Spain between September 2018 and March 2020 were included. These women had high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer and received rucaparib 600 mg orally twice daily as maintenance therapy after at least two prior lines of therapy ($n = 18$) or as treatment for *BRCA*-mutated platinum-sensitive or platinum-resistant disease after at least three prior lines of therapy ($n = 33$). Main efficacy parameters were investigator-assessed best response in patients receiving rucaparib in the treatment setting (investigator-assessed radiological response by Response Evaluation Criteria In Solid Tumors [RECIST] version 1.1 and biological best response by Rustin criteria), duration of response and investigator-assessed progression-free survival (PFS) in patients receiving rucaparib in the treatment setting, and PFS in patients receiving maintenance rucaparib. In this real-world retrospective observational study, all parameters were assessed according to routine clinical practice at each site. Data were extracted from source medical records available at

Table 2
Details of prior PARPi and rucaparib treatment setting and outcome.

Patient	*BRCA* mutation status	Prior PARPi				Rucaparib		
		PARPi	Setting	Treatment duration, months	Reason for treatment discontinuation	Setting	Treatment duration, months	Reason for treatment discontinuation
1	g*BRCA1*mut	Olaparib	MNT in 4L	18.0	PD	Tx Pt-R as 8L	4.4	PD
2	Unknown	Olaparib	MNT in 3L	18.0	PD	Tx Pt-R as 7L	9.4	PD
3	g*BRCA1*mut	Olaparib	MNT in 4L	16.4	PD	Tx Pt-S as 6L	2.6	PD
4	g*BRCA2*mut	Olaparib	MNT in 2L	23.4	PD	Tx Pt-R as 4L	1.0	PD
5	g*BRCA1*mut	Olaparib	MNT in 2L	3.0	PD	Tx Pt-R as 4L	0.2	PD
6	g*BRCA1*mut	Olaparib	MNT in 5L	17.2	PD	Tx Pt-R as 9L	6.9	PD
7	g*BRCA1*mut	Olaparib	MNT in 3L	4.5	Toxicity	Tx Pt-R as 6L	1.3	PD
8	g*BRCA1*mut	Olaparib	MNT in 3L	6.0	PD	Tx Pt-R as 6L	0.5	PI decision
9	g*BRCA1*mut	Olaparib	MNT in 2L	9.5	PD	Tx Pt-R as 7L	0.8	PD
10	g*BRCA1*mut	Niraparib	MNT in 3L	6.0	Toxicity	Tx Pt-R as 6L	2.8	PD
11	Wild type	Niraparib	MNT in 3L	3.0	PD	Tx Pt-R as 4L	2.0	PD
12	s*BRCA2*mut	Olaparib	MNT in 4L	2.8	PI decision (not PD)	Tx Pt-R as 5L	11.5	Toxicity
13	Wild type	Olaparib	MNT in 2L	10.0	PD	MNT in 4L	2.7	PD
14	g*BRCA1*mut	Olaparib	MNT in 3L	39.5	PD	Tx Pt-R as 5L	3.2	PD
		Olaparib	MNT in 4L	4.0	PD			

mut: mutated. MNT: maintenance. L: line. PARPi: poly(ADP-ribose) polymerase inhibitor. PD: disease progression. PI: principal investigator. Tx Pt-R: treatment for platinum-resistant disease. Tx Pt-S: treatment for platinum-sensitive disease.

participating sites. The study protocol was approved by the referral ethics committee of the 22 participating sites and performed according to local laws and regulations. Accessible patients provided written informed consent. In accordance with Spanish laws, informed consent was not required from inaccessible patients.

This post hoc subgroup analysis explored baseline patient and tumor characteristics, prior treatment, rucaparib treatment exposure, adverse events (AEs), effectiveness, and subsequent therapy in women treated in the RAP who had received previous treatment with a PARPi before rucaparib, irrespective of treatment setting or specific drug. The data cutoff date was March 31, 2021.

3. Results

Fourteen women were identified as eligible for this subgroup analysis. Their median age at initiation of rucaparib was 63 (range 42–78) years, 13 (93%) had epithelial ovarian cancer, and 11 (79%) had tumors harboring *BRCA1/2* mutations (Table 1). Patients had received a median of five (range 3–8) treatment lines before rucaparib (three [range 2–5] before first PARPi). The prior PARPi (given in the maintenance setting in all cases) was olaparib in 12 patients (86%) and niraparib in two patients (14%); one patient had received two prior lines of olaparib before rucaparib (Table 2). Twelve patients (86%) received rucaparib as treatment for platinum-resistant disease, one as treatment for platinum-sensitive disease, and one as maintenance therapy.

3.1. Treatment exposure

All but one patient started rucaparib at a dose of 600 mg twice daily. Eight patients (57%) required a dose interruption and six (43%) had a

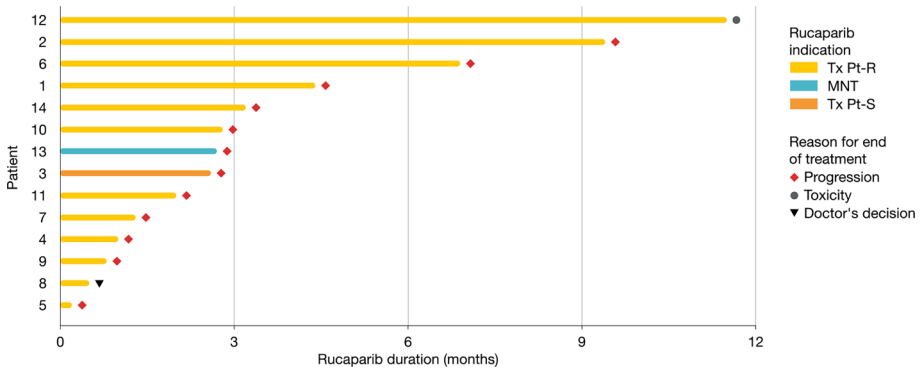

Fig. 1. Rucaparib treatment exposure following PARPi. MNT: maintenance. PARP: poly(ADP-ribose) polymerase inhibitor. Tx Pt-R: treatment for platinum-resistant disease. Tx Pt-S: treatment for platinum-sensitive disease.

dose reduction. In all but one patient, the dose was interrupted only once and only one dose reduction was required. In the remaining patient (who started rucaparib at a dose of 500 mg twice daily), rucaparib was interrupted numerous times and the dose was reduced twice (for asthenia and decreased platelet count). Ultimately, this patient discontinued treatment because of persistent asthenia. One additional patient discontinued treatment because of investigator decision. The remaining 12 patients (86%) continued treatment until disease progression (Table 2).

3.2. Effectiveness

Median PFS was 2.5 months (95% confidence interval: 1.0–4.4 months; range 0.2–9.1 months) (Supplementary Fig. 1). PFS on rucaparib exceeded 6 months in three patients (21%) (Fig. 1). Best response (according to RECIST version 1.1, assessable in seven patients) was stable disease in one patient (7%) and disease progression in six patients (43%). The best biological response (assessable in six patients) was stable disease in three patients (21%) and disease progression in three (21%).

3.3. Safety

AEs (any grade) occurred in 11 patients (79%), the most common being fatigue (36%), platelet count decreased (29%), anemia (21%), nausea (14%), and vomiting (14%). All other AEs each occurred in only one patient (7%) (Supplementary Table 1). Grade 3 AEs occurred in four patients (29%); there were no grade 4 AEs. One patient died from colonic obstruction, considered unrelated to rucaparib. The only grade 3 AEs occurring in more than one patient were anemia and decreased platelet count (each in two patients; 14%). No new safety signals were observed.

3.4. Subsequent therapy

Information on treatment after rucaparib was available for nine patients at the data cutoff, and included platinum-containing therapy in two patients (Table 3). A durable response was observed in one patient treated with paclitaxel after rucaparib treatment for platinum-resistant disease.

4. Discussion

This is one of the first reported series of real-world data on rucaparib after prior PARPi therapy. Real-world data provide valuable insights into treatment practice and clinical outcomes in a less selected, more heterogeneous population of patients than is typically treated in prospective trials with extensive exclusion criteria. In this series, most patients had *BRCA*-mutated platinum-resistant ovarian cancer, a setting in which there is limited evidence for PARPis except for the ARIEL4 trial (Kristeleit et al., 2022), which excluded patients previously treated with a PARPi, and the OCTOVA trial (Nicum et al., 2021), which enrolled a predominantly platinum-resistant population, including 31 patients (across three randomized treatment arms) previously treated with a PARPi; however, only 30% of the entire population had germline *BRCA* mutations. Despite extensive prior therapy, rucaparib demonstrated notable activity in some patients and a safety profile consistent with previous prospective trials in PARPi-naïve patients. Hematologic effects represented the most common grade $\geq$ 3 AEs in the present series, ARIEL3 (Coleman et al., 2017), and ARIEL4 (Kristeleit et al., 2022), as well as in the more recently published ATHENA-MONO trial evaluating rucaparib as maintenance therapy for newly diagnosed ovarian cancer (Monk et al., 2022).

This study adds to the body of data describing PARPi activity in patients with PARPi-pretreated ovarian cancer, including a retrospective case series from the US in which 12 (55%) of the 22 patients had received veliparib combined with chemotherapy (nine in the front-line setting, three in the platinum-sensitive setting) as their first PARPi but without continuation as maintenance therapy (Essel et al., 2021). The second PARPi (typically given as maintenance therapy) was most frequently niraparib. In the series reported by Essel et al., 59% of patients had tumors harboring *BRCA* mutations and 55% had received bevacizumab as part of their front-line therapy (Essel et al., 2021). The median platinum-free interval at first recurrence was 15 months, indicating a highly platinum-sensitive population. Nevertheless, only three patients achieved a partial response to the second PARPi (no complete responses), and all of these had tumors harboring *BRCA* mutations and no evidence of disease after first PARPi given as part of front-line therapy. In the single-arm QUADRA study of niraparib as fourth- or later-line therapy, a subgroup analysis of patients with prior PARPi exposure (in any setting; monotherapy or combination therapy) showed only minimal activity (6% response rate despite *BRCA* mutations in 62% and homologous repair deficiency in 81%) (Rimel et al., 2020). Another recent retrospective study reported on 29 patients treated with PARPi after maintenance PARPi; all but two patients received olaparib or niraparib as their first PARPi, resulting in a complete radiological response in 31% (Moubarak et al., 2022). Likewise, the second PARPi was olaparib or niraparib in all but two patients (who received rucaparib after olaparib). Outcomes were best in patients with a clear response to their last platinum-based therapy. PFS with second PARPi appeared to be longer in patients without *BRCA* mutations. The inconsistent findings in these case series may reflect chance findings because of the very small sample sizes or may reflect differences between treatments and disease biology.

Most recently, results were reported from the randomized phase III OReO/ENGOT Ov-38 trial evaluating olaparib as maintenance therapy

Table 3
Subsequent therapies (n = 9).

Patient	Rucaparib indication	*BRCA* status	No. of subsequent lines	Subsequent treatment	Best response	Duration, months
1	Tx Pt-R	g*BRCA1*Mut	2	Carboplatin-paclitaxel	NA	2.8
				Cisplatin-gemcitabine	PD	3.0
2	Tx Pt-R	Unknown	1	Paclitaxel	PR	5.3
3	Tx Pt-S	g*BRCA1*Mut	1	Tamoxifen	PD	2.5
5	Tx Pt-R	g*BRCA1*Mut	1	Gemcitabine	PD	4.4
6	Tx Pt-R	g*BRCA1*Mut	1	Paclitaxel	NA	11.1
7	Tx Pt-R	g*BRCA1*Mut	1	PLD	NA	1.0
11	Tx Pt-R	Wild type	1	Weekly paclitaxel	SD	3.9
12	Tx Pt-R	s*BRCA2*Mut	1	Bevacizumab-oral cyclophosphamide	NA	6.2*
14	Tx Pt-R	g*BRCA1*Mut	3	Carboplatin-paclitaxel	PD	1.6
				PLD-trabectedin	PD	1.9
				Topotecan	NA	3.0*

Mut: mutated. NA: not assessable. PD: disease progression. PLD: pegylated liposomal doxorubicin. PR: partial response. SD: stable disease. Tx Pt-R: treatment for platinum-resistant disease.
*Ongoing at data cutoff.

after PARPi exposure (Pujade-Lauraine et al., 2021). Eligible patients had shown sustained disease control with prior PARPi therapy and a complete or partial response to the most recent platinum-containing regimen (or no evidence of disease in patients undergoing optimal cytoreductive surgery before chemotherapy), thus representing a population selected for platinum sensitivity, regardless of *BRCA* mutation status. The prior PARPi was almost exclusively olaparib in the cohort of patients with *BRCA*-mutated tumors, and most commonly niraparib, followed by olaparib, in the cohort without *BRCA* mutations. PFS was significantly improved with maintenance olaparib in patients previously treated with a PARPi, irrespective of *BRCA* mutation status.

Ongoing prospective trials evaluating the effect of alternative PARPi re-treatment strategies include the Korean GOG 3056/NIRVANA-R (NCT04734665) single-arm phase II study evaluating niraparib and bevacizumab maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer previously treated with a PARPi, and the MITO 35b (NCT05255471) randomized phase III trial comparing outcomes with olaparib versus platinum-based chemotherapy after first-line maintenance PARPi and secondary cytoreductive surgery.

Data on rucaparib in a predominantly platinum-resistant population distinguish our results from previous reports of a PARPi after previous PARPi therapy. Another unique feature of our analysis is the information on subsequent therapy, showing disease stabilization or even response to chemotherapy after multiple lines of treatment and PARPi retreatment. Further research to understand the molecular characteristics of patients sensitive to multiple lines of PARPi and chemotherapy will help to unravel the complexities of disease and improve patient selection for repeated PARPi administration.

The main limitations of this analysis are the small sample size and the heterogeneity of the population in terms of prior treatment, therapeutic decision-making, tumor testing, and assessment of clinical outcomes. However, the population reflects the real-world treatment setting and thus provides important insights into everyday practice, especially when there are limited treatment options available for patients. AEs may be under-reported in a retrospective observational study compared with prospective clinical trials, but there is no reason to expect worse tolerability with PARPi re-treatment compared with clinical experience, especially given the results of the recently presented OReO/ENGOT Ov-38 trial (Pujade-Lauraine et al., 2021).

5. Conclusions

This is one of the first reported series of real-world data on rucaparib after prior PARPi for high-grade serous ovarian cancer. In this heavily pretreated population, meaningful activity was observed in a subset of patients receiving rucaparib in the treatment setting for platinum-resistant ovarian cancer, and tolerability was consistent with previous prospective trials. Future investigation should focus on identifying patients who may benefit from rucaparib after prior PARPi exposure.

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of HM Hospitales (Code: 20.05.1633-GHM) and performed according to the Declaration of Helsinki and local laws and regulations. Patients provided written informed consent. Informed consent was not required from inaccessible patients according to Spanish laws. The IRB that waived the need for informed consent from inaccessible patients was CEIm HM Hospitales: 20.05.1633-GHM. A declaration form waiving the need for informed consent was signed by the corresponding investigator.

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CRediT authorship contribution statement

Alfonso Yubero: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Purificación Estévez:** Investigation, Resources, Writing – review & editing. **Aránzazu Barquín:** Investigation, Resources, Writing – review & editing. **Luisa Sánchez:** Investigation, Resources, Writing – review & editing. **Ana Santaballa:** Investigation, Resources, Writing – review & editing. **Bella Pajares:** Investigation, Resources, Writing – review & editing. **Piedad Reche:** Investigation, Resources, Writing – review & editing. **Carmen Salvador:** Investigation, Resources, Writing – review & editing. **Luis Manso:** Investigation, Resources, Writing – review & editing. **Raúl Márquez:** Investigation, Resources, Writing – review & editing. **Antonio González-Martín:** Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

AY reports consulting/advisory roles for Clovis Oncology, GSK, AstraZeneca, MSD, PharmaMar, and Roche and receipt of travel/accommodation/expenses from MSD, GSK, and PharmaMar. PE reports consulting fees and honoraria for lectures, presentations, and speaker bureaus from MSD, GSK, AstraZeneca, Clovis Oncology, and PharmaMar. LS reports consulting/advisory roles for GSK–Tesaro, Clovis Oncology, AstraZeneca, MSD, and Roche, and travel/accommodation/expenses from GSK, MSD, and PharmaMar. AS reports consulting fees and honoraria for lectures, presentations, and speaker bureaus from MSD, GSK, AstraZeneca, Clovis Oncology, Pfizer, Lilly, and Novartis. BP reports consulting/advisory roles for Clovis Oncology, Novartis, and AstraZeneca, and travel/accommodation from AstraZeneca. CS reports consulting/advisory roles for PharmaMar and travel/accommodation/expenses from GSK, MSD, Pfizer, and AstraZeneca. LM reports consulting/advisory roles for Roche/Genentech, AstraZeneca, Novartis, Pfizer, Tesaro, Eisai, Lilly, Clovis Oncology, Pierre Fabre, and GlaxoSmithKline, speakers' bureaus for Roche/Genentech, Novartis, Pfizer, AstraZeneca, and Lilly, and research funding from Tesaro. AGM reports advisory/consultancy roles for Alkermes, Amgen, AstraZeneca, Clovis Oncology, Genmab, GSK, ImmunoGen, Merck Sharp & Dohme, MacroGenics, Novartis, Oncoinvent, Pfizer/Merck, PharmaMar, Roche, Sotio Biotech, and Sutro Biopharma, speaker bureaus for AstraZeneca, PharmaMar, Roche, GSK, and Clovis Oncology, research grant/funding from Roche and Tesaro/GSK, and travel/accommodation/expenses from AstraZeneca, PharmaMar, Roche, and Tesaro/GSK. AB, PR, and RM declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to data protection laws but are available from the corresponding author on reasonable request and with permission from GEICO.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2023.101211.

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