How Long is Long Enough? An International Survey Exploring Practice Variations on the Recommended Duration of Maintenance Therapy with PARP Inhibitors in Patients with Platinum Sensitive Recurrent Ovarian Cancer and Long-Term Outcomes.

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Abstract

Objective: There are no data, and thus no consensus, on the optimal duration of poly(ADP-ribose) polymerase (PARP) inhibitor maintenance therapy for exceptional responders (here defined as progression-free for 5 years or longer) with platinum sensitive recurrent ovarian cancer. The current licence is to continue PARP inhibitors until progression or toxicity, however international practice varies considerably. The risks of late progression and late-onset myeloid malignancies, defined as occurring beyond 5 years of PARP inhibition, are unknown. This study aims to examine the practice patterns and opinions regarding the management and surveillance protocols of exceptional responders with platinum sensitive recurrent ovarian cancer.

Methods: An online international survey of experts from June 2023 to June 2024, disseminated at Gynaecologic Cancer Intergroup meetings and by Chairs of Cooperative Groups.

Results: 210 responses were received from 26 countries, including Australia (27 respondents), Germany (24), United Kingdom (21), The Netherlands (16), France (13), Spain (12), Canada (12), Italy (11), Japan (11), and other countries (63). Most respondents did not have institutional or trials group guidelines regarding duration of PARP inhibitors (154, 73.3%). For the minority with guidelines, recommendations varied: 1 year (2), 2 years (13), 3 years (4) and indefinite treatment (22). Individual practice varied considerably for those without guidelines: most (116, 76.3%) recommended ≥5 years of PARP inhibition, of which 73 (48.0%) recommended indefinite PARP inhibition. Sixty-six respondents (31.4%) reported having patients with late progression, and 46 (22.0%) had cases with late-onset myeloid malignancies. Surveillance practices varied widely across all respondents.

Conclusions: This international survey highlights the diverse practice variations and disparate views on the optimal duration of maintenance therapy with PARP inhibitors in platinum sensitive recurrent ovarian cancer. The responses suggest a notable risk of late progression and myelodysplastic syndrome /acute myeloid leukaemia among exceptional responders which needs confirmation. Detailed individual patient data is required to draw more reliable conclusions: another study is underway addressing this.

Key Messages

- **What is already known on this topic:** PARP inhibitors improve outcomes for patients with platinum sensitive recurrent ovarian cancer and are approved as maintenance therapy after response to platinum-based chemotherapy. A subset of these patients are exceptional responders without disease progression >5 years after commencing maintenance PARP inhibitors.
- **What this study adds:** this is the first study to examine practice patterns for exceptional responders with platinum sensitive recurrent ovarian cancer. The key findings are that there is wide variation internationally in clinical practice and recommendations regarding treatment duration and follow-up practices. These results suggest that risks of late relapse and myeloid malignancies may persist in

exceptional responders, however this finding requires confirmation with individual patient data.

- **How this study might affect research, practice or policy:** further research analysing individual patient data is underway to examine in depth the late clinical outcomes of exceptional responders with platinum sensitive recurrent ovarian cancer which will inform clinical practice guidelines.

Introduction

Maintenance therapy with poly(ADP-ribose) polymerase (PARP) inhibitors has been approved for patients with platinum sensitive recurrent ovarian cancer following response to platinum-based chemotherapy. Prior response to platinum-based chemotherapy is likely a surrogate for functional homologous recombination deficiency and PARP inhibitor response. Five phase 3 studies have demonstrated a progression-free survival benefit with maintenance PARP inhibitors: SOLO2 (olaparib), ARIEL3 (rucaparib), NOVA and NORA (niraparib), and FZOCUS (fuzuloparib).[1-5] SOLO2 only included patients with a *BRCA* mutation,[1] while the others included patients regardless of homologous recombination repair status.[2-5] While benefit has been demonstrated across all subgroups, the degree of benefit is greater in those with *BRCA1/2* mutations. In Study 19, a randomised phase 2 trial of olaparib versus placebo, median progression-free survival in those with a *BRCA1/2* mutation was 11.2 months with olaparib versus 4.3 months with placebo, while in those without a *BRCA1/2* mutation, median progression-free survival was 7.4 months with olaparib versus 5.5 months with placebo. In 2022, the Food and Drug Administration restricted the indication of niraparib to patients with *BRCA* mutations only, due to lack of a statistically significant overall survival benefit being seen in the NOVA trial, however licencing remains unchanged in other countries as the trial was not powered to detect overall survival differences.[6] Importantly, in these trials, treatment was continued until disease progression or unacceptable toxicity, which is reflected in the current licence for these medications.

A subset of patients on these trials are “exceptional responders,” defined here as remaining progression-free ≥5 years (Table 1). There are a growing number of these patients due to the rapid uptake of maintenance therapy after regulatory approval of these drugs (Table 2). In SOLO2, 22% (n=43) continued olaparib for ≥5 years,[7] while in ARIEL3, 4% (n=15) continued rucaparib at a median follow-up of 6.4 years.[3, 8] Study 19 was a smaller study: 11% (n=15) continued olaparib beyond 6 years.[9] There is shorter follow-up for the NOVA trial, in which 13% (n=49) remained on niraparib for >3 years. PARP inhibitors increase the risk of acute myeloid leukaemia and myelodysplastic syndrome, both of which are often fatal complications. In a recent meta-analysis of 28 randomised controlled trials, the incidence of myelodysplastic syndrome/acute myeloid leukaemia in patients with any cancer type treated with PARP inhibitors was 0.73%, compared to 0.47% with placebo.[10] However, the trials included in this meta-analysis had a median follow-up of 24 months, so the incidence of late-onset myelodysplastic syndrome/acute myeloid leukaemia may be underestimated. The longest follow-up data comes from Study 19 which reported two cases of myelodysplastic syndrome/acute myeloid leukaemia with olaparib (1.5%) and 1 case with placebo (0.8%).[9, 11] Long-term data from SOLO2, with median follow-up of 65.7 months, reported an incidence of

myelodysplastic syndrome/acute myeloid leukaemia of 8% in the olaparib group, compared to 4% with placebo.[7] In addition, the incidence of myelodysplastic syndrome/acute myeloid leukaemia was 3.5% with niraparib at the final analysis of NOVA, with median follow-up of 67 months, compared to 1.7% with placebo.[12] There are no studies that we are aware of specifically examining the incidence of late-onset of myelodysplastic syndrome/acute myeloid leukaemia in exceptional responders.

The long-term outcome of these exceptional responders is uncertain, as is the optimal duration of PARP inhibitors: specifically whether patients should continue indefinitely or cease treatment after a number of years. Significant variability exists internationally in practice recommendations and no consensus exists regarding the optimal duration of PARP inhibitors. Some practitioners recommend cessation of PARP inhibitors after an arbitrary duration (e.g. 2-5 years), while others continue PARP inhibitors indefinitely. In addition, the optimal surveillance schedule and practices for these patients is unknown. Hence, this study aims to document the current practice patterns and treatment recommendations for exceptional responders with platinum sensitive recurrent ovarian cancer internationally.

Methods

A purpose-built electronic survey in English was developed by the authors (Supplementary Appendix 1) as no suitable prior validated questionnaires were available. Feeback on the survey was obtained from international experts at the 2023 Gynaecologic Cancer Intergroup and the 2023 European Society of Gynaecological Oncology annual meetings, and minor modifications were made to improve clarity prior to distribution. Clinicians who had experience in managing patients with platinum sensitive recurrent ovarian cancer were invited to complete the survey. The survey was distributed at the annual meetings of the following groups: Gynaecologic Cancer Intergroup, Australia and New Zealand Gynaecological Oncology Group, Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom Germany, and European Society of Gynaecological Oncology. In addition, Chairs of Cooperative Groups within Gynaecologic Cancer Intergroup distributed the survey to experienced clinicians within their network. Reminders were sent via email. Survey participation was voluntary. Respondents were encouraged to complete all questions but were allowed to skip questions and were able to edit or return to previous questions before submission. All responses were anonymous, and participants were not asked to identify their institution.

The data was analysed using descriptive statistics in Statistical Package for the Social Sciences version 29.0. Ethics approval was obtained from South Eastern Sydney Local Health District Human Research Ethics Committee (2023/ETH01573). The Institutional Review Board waived the requirement for written informed consent as there was no identifiable data. In accordance with the journal's guidelines, the authors will provide these research data for independent analysis by a selected team for the purposes of additional data analysis or for the reproducibility of this study in other centres if such is requested.

Results

The survey was conducted between June 2023 and June 2024. 210 responses were obtained, 195 of which were complete (92.9%). The number of persons who received the survey, and hence the survey response rate, is unknown. Results were obtained from 26 countries (Table 3), with most responses being from Europe (n=120, 57.1%), followed by Oceania (n=35, 16.7%), Asia (n=27, 12.9%), and North America (n=25, 11.9%). Australia was the country with the largest number of respondents (n=27, 12.9%). 70 respondents were gynaecologic oncologists (33.3%), 138 (65.7%) were medical oncologists and data were missing for 2 respondents (1.0%). The primary place of work was for most respondents a university affiliated teaching hospital (n=134, 63.8%), followed by a comprehensive cancer care centre (n=48, 22.9%), a regional hospital (n=22, 10.5%), and private practice (n=6, 2.9%). 229 responses were received for trials group membership, which exceeded the total number of responses as some respondents belonged to multiple groups. The most frequent trials groups represented were Australia and New Zealand Gynaecological Oncology Group (n=29, 12.7%), Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom Germany (n=24, 10.5%) Grupo Espanol de Investigacion en Cancer de Ovario (n=12, 5.5%) and Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (n=12, 5.5%) (Supplementary Appendix 2).

Most respondents had cared for 1-5 exceptional responders (106, 50.5%), while 37 (17.6%) had cared for 6-10 exceptional responders and 11 (5.2%) had cared for ≥11 exceptional responders. 36 respondents (17.1%) had not cared for any exceptional responders and data were missing for 20 (9.5%). A notable minority of respondents (66, 31.4%) reported that they had patients with late disease progression, defined as disease progression occurring ≥5 years of maintenance therapy with PARP inhibitors. Most of these respondents (57, 27.1%) had cared for 1-5 patients with late relapse, however 9 respondents (4.3%) had cared for >5 patients with late relapse.

Most respondents did not have institutional or collaborative trials group guidelines regarding the management of exceptional responders (n=154, 73.3%), 41 (19.5%) did have guidelines and data were missing for 15 respondents (7.1%). The next two questions assessed respondents' recommendations on the duration of PARP inhibitors (Table 4). Some respondents who did not have guidelines gave responses to how long their institutional guidelines recommended continuing therapy for (n=31), and some respondents who did have guidelines responded to the question intended to assess the practice of those without guidelines (n=20). As these responses were contradictory, the results were excluded from the analysis. For those with institutional guidelines, most (n=22, 53.7%) recommended continuing PARP inhibitors indefinitely, while 4 (9.8%) recommended 3 years, 13 (31.7%) recommended 2 years and 2 (4.9%) recommended 1 year of maintenance PARP inhibitors. Similarly, most respondents who did not have institutional guidelines (n=73, 47.4%) recommended indefinite treatment. 173 respondents (82.4%) supported patients' wishes to continue PARP inhibitors if they chose to do so. 85 respondents (40.5%) estimated that

fewer than half of their patients would accept their recommendation to cease PARP inhibitors if advised to do so, in the current setting of drug approval until disease progression.

89 respondents (42.4%) had cared for PARP inhibitor treated patients diagnosed with myelodysplastic syndrome/acute myeloid leukaemia. 46 (22.0%) had cared for patients with late-onset myelodysplastic syndrome/acute myeloid leukaemia, defined as occurring >5 years of PARP inhibitor use. 34 of these late-onset cases were taking PARP inhibitors at the onset of myelodysplastic syndrome/acute myeloid leukaemia.

Follow-up practices were highly varied as illustrated in Table 5. Most respondents ordered imaging routinely (n=130, 61.9%), while others conducted imaging only if the patient was symptomatic or the CA125 was rising (n=31, 14.8%).

Discussion

Summary of Main Results:

This study explored international practice patterns, attitudes and experience of global experts regarding the duration of maintenance therapy with PARP inhibitors in exceptional responders with platinum sensitive recurrent ovarian cancer, and experience with late outcomes, including recurrence and myeloid malignancies. 210 oncologists from 26 countries were surveyed, revealing that most institutions and collaborative trial groups lacked practice guidelines on the duration of maintenance therapy with PARP inhibitors in patients with platinum sensitive recurrent ovarian cancer, as may be expected given that there are no phase 3 trials that have defined the optimal treatment duration. There was substantial variability in the recommendations provided with no clear consensus on the optimal treatment duration or surveillance schedule. Importantly, this research suggests concerning risks of late disease recurrence and late-onset myeloid malignancies, with 31.4% of respondents having cared for a patient with late recurrence after 5 years of PARP inhibition, and 22.0% having cared for a patient with late-onset myelodysplastic syndrome/acute myeloid leukaemia. These findings need to be confirmed as we cannot be certain of the reliability of these responses or what proportion of exceptional responders will experience late relapse or diagnosed with myelodysplastic syndrome/acute myeloid leukemia.

Results in the Context of Published Literature:

This is the first study exploring practice patterns for exceptional responders with platinum sensitive recurrent ovarian cancer treated with maintenance PARP inhibitors. Several manuscripts have explored real-world outcomes of patients with platinum sensitive recurrent ovarian cancer treated with maintenance PARP inhibitors,[13-18] without reporting on the outcomes of those with long-term response, and others have examined the molecular profile of long-term responders, without providing data on practice patterns or clinical outcomes.[19-22] To our knowledge, no regulatory or health authority guidance exists providing recommendations regarding the optimal duration of PARP inhibitors in this context. . Reimbursement is based on regulatory approvals which allow for continuation of therapy

until disease progression, consistent with the design of the phase 3 registration trials, and to the best of our knowledge there are no restrictions on duration of therapy due to reimbursement restrictions.

Myelodysplastic syndrome and acute myeloid leukaemia are known consequences of PARP inhibitors which confer poor prognosis.[10, 23] The effect of PARP inhibitor duration on this risk is currently unknown. Two meta-analyses have examined the incidence of myeloid malignancies in patients treated with PARP inhibitors. Morice *et al.* (2021) observed that PARP inhibition was associated with an increased odds of myelodysplastic syndrome/acute myeloid leukaemia compared to placebo (odds ratio 2·63, p=0·026).[10] In contrast, Nitecki *et al.* 2021 did not observe an association between PARP inhibitors and myelodysplastic syndrome/acute myeloid leukaemia in the overall population, but did note an association in those treated in the front line setting and in those who had < 2 lines of prior chemotherapy.[24] Differences between the two analyses are likely due to differences in methodology, such as the included trial designs and the type of meta-analysis used. In the phase 3 trials of maintenance PARP inhibitors for platinum sensitive recurrent ovarian cancer, rates of myelodysplastic syndrome/acute myeloid leukaemia in the intervention group ranged from 3.8-8%, compared to 0-4% with placebo.[4, 7, 8, 25] .[7] Furthermore, it is thought that resistance mechanisms that emerge due to PARP inhibition, such as *BRCA* reversion mutations, can limit response to platinum-based chemotherapy.[26] It is unknown whether the duration of PARP inhibitors affects the development of resistance to PARP inhibitors and cross-resistance to platinum.

This survey highlights the heterogeneity in follow-up practices, which underscores the need for more reliable data to support the development of guidelines to inform practice. There is little evidence to guide follow-up practices in exceptional responders with platinum sensitive recurrent ovarian cancer, with the evidence-base for surveillance practices predating the use of maintenance PARP inhibitors.[30-32] In clinical trials, patients underwent blood tests including CA125 and imaging every 8-12 weeks. In this study, 61.9% of practitioners obtained routine imaging at intervals varying between 3-12 months, while 14.8% obtained imaging based on clinical features or CA125 increases.

Strengths and Weaknesses:

This research provides the first data on real-world practice patterns and anecdotal reported long-term outcomes in exceptional responders with platinum sensitive recurrent ovarian cancer. The selection of participants by invitation ensured that the data provided were from expert clinicians who were experienced in using PARP inhibitors. The main limitations of this work are the risk of recall bias, which may lower the accuracy of providers' estimates on the number of participants they have cared for with late relapse or late-onset myeloid malignancies, and selection bias, whereby practitioners who have cared for cases with adverse outcomes may be more likely to respond to the survey than those who have not experienced adverse outcomes. Two respondents indicated they would cease maintenance

PARP inhibitors in the relapsed setting after only 1 year of therapy, which is surprising as the risk of relapse remains substantial at this timepoint and cessation after 1 year of maintenance is not standard of care**.** Furthermore, given the lack of patient-level data in this study, we were not able to determine whether the occurrence of late progression or late-onset myeloid malignancies was related to the duration of PARP inhibitor received: this question will be examined in the cohort study. While a benefit of the survey was its global distribution, it is possible that language barriers may have limited respondents' understanding of some of the questions. Another limitation is that some regions were not adequately represented in the sample, including the United States, South America, Africa and China, and hence this data may not be generalisable to those populations. Finally, we do not have any demographic information on those who received but did not respond to the survey, and we were not able to determine whether the recommended duration was influenced by the tumour genotype.

Implications for Practice and Future Research:

This survey is the first to address how oncologists, in the absence of relevant data, address the optimal duration of maintenance PARP inhibitors in exceptional responders with platinum sensitive recurrent ovarian cancer. The reporting on late recurrences and delayed myelodysplastic syndrome/acute myeloid leukaemia need to be examined closely in further research to inform the risk-benefit profile of extended PARP inhibition in these exceptional responders. It will also be important to explore in future work the relationship between homologous recombination repair status and the development of treatment related myeloid malignancies. An international cohort study is underway examining the outcomes of exceptional responders with platinum sensitive recurrent ovarian cancer which we expect will generate data to inform patients of risks and to help with future guideline development. As PARP inhibitors have now shown benefit in the first line maintenance setting, and hence are being widely used in this context, it is likely that the number of patients treated with PARP inhibitors in the recurrent setting who have not had prior PARP inhibitor exposure will diminish significantly in future . We have not explored practices of PARP-post-PARP inhibitor therapy in platinum sensitive recurrent ovarian cancer, which is an important area of future research.

Conclusion

This study provides insights into the wide variations in practice patterns for exceptional responders with platinum sensitive recurrent ovarian cancer treated with maintenance PARP inhibitors. Most practitioners reported that there were no guidelines on how these patients should be managed. There was significant variability in the recommendations regarding the optimal duration of PARP inhibitors, and in the follow-up for these patients. Importantly, a substantial subset of practitioners had cared for individual patients with late relapse after 5 years of maintenance PARP inhibitors, suggesting that despite long term remission, a subset of patients will relapse whereas a proportion may be cured. Furthermore, a substantial minority of practitioners had cared for patients with late-onset myeloid malignancies. An international cohort study is underway to examine the outcomes of these exceptional

responders in more detail in order to guide future practice recommendations and guideline development.

COI Summary

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- SCC: meeting/travel support from AstraZeneca, MSD and GSK, and participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, MSD and GSK.
- SP: research funding from MSD, Roche, AstraZeneca, GSK, Pfizer and honoraria from MSD, AstraZeneca, GSK, Novartis, Pfizer, Pharmamar and Roche.
- YCL: institutional research grant from BeiGene, honoraria from AstraZeneca, participation on Advisory Board for AstraZeneca.

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Tables

Table 1: Extended PARP Inhibitor Use in Pivotal Clinical Trials.

Trial	Year of trial opening	PARPi Studied	Total patients, n	Patients on PARPi, n (%)	Patients continuing on PARP beyond 5 years, n (%)	Total number withmyelodysplastic syndrome/ acute myeloid leukaemia, n (%)
STUDY 19[9]	2008	Olaparib	265	136 (53%)	18 (13%)	2 cases (1.5%) with olaparib, 1 with placebo (0.8%).
SOLO 2[33]	2013	Olaparib	295	196 (66%)	43 (22%)	16 cases with olaparib (8.2%), 4 cases with placebo (4.0%).
NOVA[2, 12]	2013	Niraparib	553	372 (67%)	Not reported. 49 (13%) remained on niraparib and 9 (5%) on placebo for >3 years.	14 cases (3.6%) with niraparib, 3 cases (1.7%) with placebo.7.4% of g BRCA cases (n=136) were diagnosed vs 3.1% on placebo (n=65)
NORA[5, 34]	2017	Niraparib	265	177	17 (9.6%)	3 cases (1.7%) with niraparib, vs 0% with placebo
ARIEL3[3, 8]	2014	Rucaparib	564	375 (67%)	Not reported. 15 (4%) remained on rucaparib vs 0 on placebo with a median duration of	14 cases (3.8%) with rucaparib, 6 cases (3.2%) with placebo

					follow-up of 6.4 years.	
FZOCUS[4]	2019	Fuzuloparib	252	167 (66.3%)	NA – maximum follow-up 14.1 months	0 cases in either group.

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Table 2: Year of Regulatory Approvals of PARP Inhibitors Globally

	Regulatory Approvals
USA[12]	2014: olaparib approved. 2016: rucaparib approved. 2017: niraparib approved
Canada[35]	2016: olaparib approved. 2020: niraparib approved.
Europe[12]	2014: olaparib approved. 2017: niraparib approved. 2018: rucaparib approved.
UK	2016: olaparib approved. 2018: niraparib approved. 2019: rucaparib approved.
Australia[36]	2016: olaparib approved. 2019: niraparib approved.

Table 3: Geographical Distribution of Respondents

Continent	Country	Number of responses (%)
Oceania	Australia	27 (12.9%)
	New Zealand	8 (3.8%)
Asia	Japan	11 (5.2%)
	Israel	7 (3.3%)
	Singapore	5 (2.4%)
	India	1 (0.5%)
	Taiwan	1 (0.5%)
	South Korea	1 (0.5%)
	Hong Kong	1 (0.5%)
Europe	Germany	24 (11.4%)
	United Kingdom	21 (10.0%)
	The Netherlands	16 (7.6%)
	France	13 (6.2%)
	Spain	12 (5.7%)
	Italy	11 (5.2%)
	Austria	9 (4.3%)
	Switzerland	3 (1.4%)
	Denmark	3 (1.4%)
	Ireland	2 (1.0%)
	Czech Republic	2 (1.0%)
	Norway	2 (1.0%)
	Belgium	1 (0.5%)
	Hungary	1 (0.5%)
North America	Canada	12 (5.7%)

	United States of America	7 (3.3%)
	Mexico	6 (2.9%)

Table 4: Recommendations Regarding the Duration of Maintenance PARP Inhibitors in Participants with or without Institutional Guidelines

Recommended Duration of PARP Inhibitor	Participants with Guidelines, n (%) 41 (19.5%)	Participants without Guidelines, n (%) 154 (73.3%)
1 year	2 (4.9%)	0 (0%)
2 years	13 (31.7%)	16 (10.5%)
3 years	4 (9.8%)	17 (11.2%)
4 years	0 (0%)	3 (2.0%)
5 years	0 (0%)	31 (20.4%)
6 years	0 (0%)	1 (0.7%)
7 years	0 (0%)	3 (2.0%)
8 years	0 (0%)	0 (0%)
9 years	0 (0%)	0 (0%)
10 years	0 (0%)	8 (5.3%)
Indefinite	22 (53.7%)	73 (48.0%)

Table 5: Follow-Up Practices

Frequency	Reviews, n (%)	Laboratory Tests, n (%)	Imaging, n (%)
Monthly	3 (1.4%)	11 (5.2%)	0
2 monthly	3 (1.4%)	4 (1.9%)	0
3 monthly	80 (38.1%)	86 (41.0%)	11 (5.2%)
4 monthly	1 (0.5%)	1 (0.5%)	3 (1.4%)
6 monthly	68 (32.4%)	57 (27.1%)	65 (31.0%)
12 monthly	10 (4.8%)	51 (24.3%)	51 (24.3%)
Other	6 (2.9%)	3 (1.4%)	31 (14.8%)