Adverse events in the placebo arm of SOLO2/ENGOT-Ov21 maintenance trial of olaparib in recurrent ovarian cancer

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HIGHLIGHTS

- Doses were reduced and treatment ceased due to AEs on placebo.
- One quarter of AEs on placebo were attributed by the investigator to treatment.
- AEs reported in screening was not useful to determine AE due to prior treatment.
- Further improvements in AE reporting and AE attribution are needed.

ARTICLE INFO

ABSTRACT

Background. In women with platinum sensitive recurrent ovarian cancer (PSROC) undergoing maintenance treatment, adverse events (AEs) not attributable to the current treatment are not well understood. We used data from SOLO2/ENGOT-Ov21 to evaluate AEs reported in the placebo arm and to explore their longitudinal trajectories.

Methods. SOLO2/ENGOT-Ov21 (NCT01874353) randomly assigned 295 PSROC participants with a *BRCA1/2* mutation to maintenance olaparib tablets ($N = 196$) or matching placebo ($N = 99$). For those assigned to placebo, we analyzed the AE (CTCAE v4.0) data including type, grade, time of onset and resolution, and attribution by investigator.

Results. Amongst 99 participants who received placebo 788 AEs were reported (95 % reporting ≥1 AE). Twenty-two percent of participants reported at least one grade ≥ 3 AE. Grade ≥ 2 AEs that persisted for over 100 days affected 21 % of participants. Recurring grade ≥ 1 AEs were experienced by 44 % of participants. Study

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investigators attributed 25 % of all AEs to the placebo treatment, with neutropenia (88 %), nausea (52 %) and thrombocytopenia (50 %) most attributed. Three percent of participants had a dose reduction, 19 % had treatment delays, and 2 % had permanent treatment discontinuation, due to AEs attributed to placebo.

Conclusion. Virtually all PSROC participants in the SOLO2/ENGOT-Ov21 experienced one or more AE whilst on placebo. Furthermore, study investigators attributed one quarter of AEs to be related to placebo therapy and dose alterations and treatment changes were made based on these AE. Further work is needed to improve measurement and categorization of AEs in trials of maintenance therapy in PSROC.

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1. Introduction

In randomized controlled trials (RCTs) of active maintenance therapy versus blinded placebo in advanced ovarian cancer, the rates of adverse events (AEs) provide valuable information on the comparative difference between treatment arms. They also offer unique insight into the symptom burden of patients on placebo, and the accuracy of investigators' attribution of AE to therapy. A pooled analysis of 13 maintenance trials involving 2224 patients with platinum sensitive recurrent ovarian cancer (PSROC), demonstrated that nearly all (95.2 %) experienced AEs of any grade, and almost one in five (18.2 %) had at least one grade 3 or higher AE when treated with placebo [1].

The observed AEs in maintenance RCTs are likely to be multifactorial in causation. They could include AEs because from the active therapy, residual or persisting AEs from prior treatments such as chemotherapy, symptoms associated with persistent disease or cancer progression, or unrelated events experienced whilst undergoing trial assigned therapy. In patients assigned to receive placebo, AEs will not be the consequence of the interventional therapy. Understanding the types and rates of AEs in the placebo arm may be helpful to better understand the true harms from treatment. This in turn is important to accurately assess the tolerability of novel therapies which is valuable for shared decision-making regarding proceeding with maintenance therapy. Accounting for AEs not attributable to the investigational therapy may also influence the design of future clinical trials, by highlighting the importance of methods beyond investigator attribution to account for these AE, and continuing to demonstrate the value of placebo controlled trial design.

In this analysis, we used data from the placebo arm of the SOLO2/ENGOT-Ov21 RCT [2] to report on types, rates, and timing of onset and resolution of events classified as AEs. We further report on the study investigators' attribution of AEs as related to placebo therapy, placebo dose reduction and placebo treatment cessation consequent of the AE. Our goal is to identify current gaps in data collection, reporting and analysis of harm data in clinical trials which is important for directing future research and practice in measuring and categorizing AE.

2. Methods

SOLO2/ENGOT-Ov21 (NCT01874353) was a RCT of PSROC in patients with a *BRCA1/2* mutation who had received at least two lines of previous chemotherapy and responded to the treatment [2]. Patients were randomly assigned to receive olaparib tablets ($N = 196$) or matching placebo ($N = 99$) as maintenance therapy. Data from SOLO2 are ideal for our study because it was a large international multicenter trial with a double-blind design. Only at the time of cancer progression were study investigators provided with the option of unblinding. SOLO2 was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

In our study, we extracted all data from the placebo arm on the different types of AEs that were reported based on common terminology criteria for adverse events (CTCAE, version 4.0), including grading of severity, dates of onset and cessation, and investigator assessment of relatedness of AE to placebo. All the AE reported were analyzed including: AE occurring during screening prior to placebo commencement, and AE

reported at any point during follow-up, including beyond the thirty days used to define treatment emergent AE for the purposes of the SOLO2 primary publication. We categorized these AEs based on the timing of onset during screening (between 1 and 6 weeks prior to random assignment), during the treatment phase at or after random assignment, or during follow-up following cessation of study therapy. Duration of AE was calculated for those AEs that documented a start and end date, and was calculated as the number of days, inclusive, that the participant reported the presence of the AE. We further reported on types and number of AEs that were recurrent, where recurrence was defined as the same toxicity, each with discrete documented start and end dates occurring more than once in the same participant during the study. We compared AEs due to blood test abnormalities versus AEs associated with symptoms. Specifically, we evaluated symptomatic AEs of special interest with importance in advanced ovarian cancer [3]: fatigue, nausea, vomiting, diarrhea, constipation, bowel obstruction, and abdominal symptom complex including abdominal pain, cramping and bloating.

The data cut-off was September 19, 2016. All analyses were performed using R version 4.2.2.

3. Results

A total of 788 AEs were reported in 95 of the 99 participants in the placebo arm of the SOLO2. There was a total of 19 serious adverse events involving 12 participants (12 %). Most of the AEs reported were low grade (grade 1: $N = 601$ [76 %], grade 2: $N = 146$ [19 %]), but 22 % of participants had grade 3, 4 and 5 AEs (Fig. 1). The median number of AEs reported was 7 events per participant. Only 4 participants (4 %) did not experience any AEs. One participant had 31 AEs; the highest number of AEs recorded by a single individual. Three percent of participants had a dose reduction, 19 % with treatment delays, and 2 % had permanent treatment discontinuation due to AEs arising on placebo. An overview of AE in the olaparib maintenance arm of the SOLO2 trial compared to the placebo arm is provided in Supplementary Table 1. An analysis correlating baseline factors including age, performance status, and number of prior lines of chemotherapy with number of AE reported was undertaken, but we found no strong association between these factors with the frequency of AE (results not shown).

3.1. Grade 2 or higher events with prolonged duration

In 58 % of participants ($N = 58$) there were 187 grade 2 or higher AEs reported. For the 152 (81 %) of these AEs that resolved, the median time to resolution was 11 days. Grade 2 or higher AEs that persisted for over 100 days were observed in 21 (21 %) of participants. Blood test detected AEs accounted for 29 % of these events and included neutropenia, anemia, thrombocytopenia and elevated gamma-glutamyl transpeptidase. Symptomatic AEs that persisted for over 100 days included fatigue, constipation, abdominal pain, back pain, and peripheral neuropathy.

3.2. Grade 3 or higher events

A total of 22 participants (22 %) experienced 41 AEs of grade 3, 4 or 5. Abdominal pain, bowel obstruction, neutropenia, anemia and
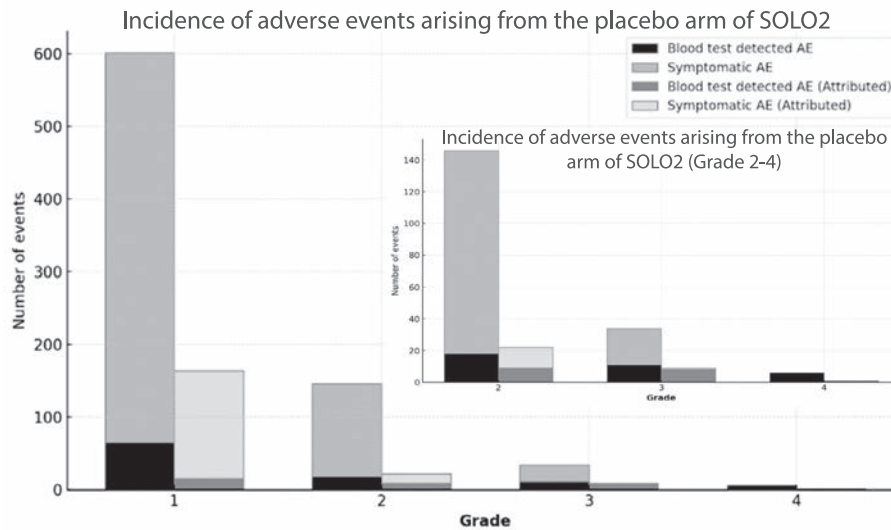
Fig. 1. Incidence of adverse events arising from the placebo arm of SOLO2.
All adverse events (AEs) reported and graded according to common terminology criteria for adverse events (version 4.0). Blood tests detected AEs refers to hematological and biochemical abnormalities only. Attributed AEs refer to toxicities assessed to result in harm arising from placebo by study investigators. Inset figure provides a magnified version of the grade 2–4 events.

constipation were the most common grade 3 events. Of these 41 AEs, myelodysplastic syndrome was the most common grade 4 event (7 %), and 44 % of these AEs were due to blood test abnormalities. The single grade 5 event was acute myeloid leukemia that occurred in follow-up and was attributed as unlikely related to treatment. Table 1 provides a summary of all grade 3 or higher events. A full listing including study investigators' attribution and relationships with dose reduction, and treatment interruption and discontinuation is provided in Supplementary Table 2.

3.3. Recurrent events

A total of 44 participants (44 %) had at least one recurring AE. The majority of recurrent AEs only repeated once (77 %), and the maximum

number of repeat events was 7. Most commonly recurring AEs were fatigue, nausea, abdominal pain, constipation, and diarrhea. Neutropenia and hyperglycemia were the most common recurrent blood test abnormalities.

3.4. Attribution to treatment by study investigators

Of the total 788 AEs in the placebo arm, 25 % were attributed by the study investigators as likely related to treatment (placebo). The most common symptomatic AEs attributed to placebo were nausea (52 %), fatigue (34 %), diarrhea (32 %), and vomiting (31 %). Over half (55 %) of the hematological abnormalities were attributed to treatment with neutropenia (88 %) and thrombocytopenia (50 %) being the most commonly attributed to placebo. Of the 44 % of participants that had at least one recurrent AE, just over one third (36 %) had the attribution of that recurrent AE change on subsequent recurrences. For example, of the seven participants who reported recurrent nausea, four (57 %) were initially attributed to placebo, but attribution was later changed to be unrelated, one (14 %) had nausea initially unrelated, but changed to related on subsequent recurrence. Two participants had consistent attribution on recurrence, one as related to placebo, and one as unrelated. A summary of the rates of attribution for AE of interest is included in Table 2.

3.5. Adverse events during the screening phase

Of the 99 participants 16 % ($N = 16$) recorded at least one AE in the screening phase, these represent 3 % of all AEs reported. Of the recurrent

Table 1
Adverse events of grade 3 or higher in the placebo arm of SOLO2.

Adverse event (G3+)	Number of events	Number of participants	% of G3+ events	Attribution
Abdominal pain	5	4	12 %	Unrelated
Bowel obstruction	4	3	10 %	Unrelated
Neutropenia	4	4	10 %	75 % related
Constipation	3	3	7 %	Unrelated
Myelodysplastic syndrome	3	3	7 %	33 % related
Anemia	3	3	7 %	67 % related
Fatigue	2	2	5 %	Unrelated
Back pain	2	2	5 %	Unrelated
GGT increased	2	2	5 %	50 % related
Insomnia	1	1	2 %	Unrelated
Hypokalemia	1	1	2 %	Unrelated
ALT increased	1	1	2 %	Related
Breast carcinoma	1	1	2 %	Unrelated
Chest pain	1	1	2 %	Unrelated
Deep vein thrombosis	1	1	2 %	Unrelated
Syncope	1	1	2 %	Related
Thrombocytopenia	1	1	2 %	Related
Gastroenteritis	1	1	2 %	Unrelated
Vomiting	1	1	2 %	Unrelated
Hypokalemia	1	1	2 %	Unrelated
Amylase increased	1	1	2 %	Unrelated
Acute myeloid leukemia	1	1	2 %	Unrelated
Total	41			

Percentage (%) of grade 3 or higher (G3+) events uses the total number of grade 3 or higher events ($N = 41$) as the denominator. Attribution refers to assessment of study investigators as likely related to treatment, with the percentage indicating the events attributed to harm arising from placebo.

Table 2
Rates of study investigators' attribution of treatment related adverse events in the placebo arm of SOLO2.

AE of interest	% Attributed being treatment related
Fatigue	34
Nausea	52
Vomiting	31
Diarrhea	32
Constipation	9
Abdominal pain	19
Neutropenia	88
Anemia	36
Thrombocytopenia	50

AE, adverse event.

events, three (7 %) of the 44 participants had an AE that recurred during the treatment phase of the trial following an initial AE reporting during screening. This is in contrast to the vast majority (95 %) of recurrent events which were first reported during the treatment phase of the trial when participants had already commenced on placebo.

3.6. Blood test detected adverse events

For all grades, blood test detected AEs accounted for 12.7 % of all events reported in the placebo arm with hematological AEs comprising almost half (44 %) of these events. During the screening phase, 6 participants (6 %) (12 events, 83 % were G1, 8 % G2, and 8 % G3) had blood test detected AEs. During the treatment phase, blood test AEs were reported in 32 (32 %) of participants (81 events, G1 65 %, G2 20 %, G3 12 %, and G4 2 %). During the treatment phase the median time to onset was 22 days and the median time to AE resolution was 29 days. One participant experienced grade 3 thrombocytopenia leading to treatment interruption and then discontinuation and was later diagnosed with myelodysplastic syndrome. Treatment was interrupted for another 5 participants: 3 due to grade 3 neutropenia, one for grade 4 hypokalemia and one for an episode of liver dysfunction with elevation of alanine transaminase, aspartate aminotransferase, gamma-glutamyl transpeptidase, and alkaline phosphatase.

3.7. Adverse events with associated symptoms

Fatigue was reported 56 times in 43 (43 %) participants. Thirty-seven were grade 1 (66 %), 17 were grade 2 (30 %), 2 were grade 3 (4 %). A total of 77 % of this AE occurred during the treatment phase. The median time to resolution of fatigue was 53.5 days. Fatigue was a recurrent AE in 10 patients (10 %). Despite the participant being on placebo for each occurrence of this AE, in two patients the attribution changed over time, for one patient from related to unrelated, and for another from unrelated to related.

Nausea was reported 44 times in 33 (33 %) participants. Forty-one were grade 1 (93 %) and 3 were grade 2 (7 %). A total of 84 % of this AE occurred during the treatment phase and 52 % were considered related to study therapy. Nausea was recurrent in 7 patients with the attribution changing over time in 5 patients (71 %). For four participants the attribution changed from related to unrelated, and in one participant from unrelated to related.

Vomiting was reported 26 times in 19 (19 %) participants. Twenty-one were grade 1 (81 %), 4 were grade 2 (15 %), 1 was grade 3 (4 %). A total of 81 % of vomiting events occurred during the treatment phase and 31 % were deemed related to study therapy. Five participants had recurrent vomiting and in one of these the attribution changed from related to unrelated to placebo. In one patient the first instance of vomiting was reported in the screening phase.

4. Discussion

In this analysis, we have shown that 95 % of participants in the placebo arm of the SOLO2 had experienced one or more AEs despite not being on active therapy. Whilst the majority of these AEs were grade 1, nearly one quarter were grade 2 or higher in severity. Of those with grade 3 AEs, more than a quarter were due to blood test detected AEs. Of the total 788 AEs reported in the placebo arm, 1 in 4 of these events were attributed by the study investigators as likely related to treatment (placebo). Further, study investigators reduced the dose of placebo treatment in 3 % of participants, 19 % had treatment delays, and 2 % had permanent treatment discontinuation due to perceived harm arising from placebo.

Attribution of AEs as either "likely related to study treatment", or as "unrelated" is required from study physicians in all clinical trials. In SOLO2, 25 % of AEs in the placebo arm were attributed as potentially related to treatment, highlighting the challenges with this process. Some

AEs carried a high rate of attribution, such as neutropenia, which was attributed to treatment in 88 % of participants on placebo in SOLO2. The difficulty of attribution was also illustrated by the significant proportion of recurrent events (36 %) where the attribution changed on recurrence of the AEs. Physicians have acknowledged the complexity and inherent subjectivity in causality assessment, as well as the lack of formal training typically received regarding the attribution process [4,5]. To address these challenges, and since the publication of the primary SOLO2 manuscript, a consensus-building workshop on toxicity attribution with key stakeholders was convened with clear recommendations to improve the process of attribution, and standardization of the attribution reporting to promote international consistency [6]. In keeping with recommendations to improve investigator education, the American Society of Clinical Oncology has developed a decision aid to increase the accuracy of investigator attribution of serious AEs [7]. Whilst these measures may help to improve the accuracy of attribution, the results of our study supports the current CONSORT Harms 2022 recommendation that even where attribution methods are applied, all harms should be reported irrespective of attribution [8].

There is an increased recognition that low- and moderate-grade AE could impact on quality of life and compliance to active therapy. In a recent study evaluating low- and moderate-grade AE, the odds of increased patient side-effect bother and treatment discontinuation were high, particularly when these AEs were associated with symptoms [9]. However, in SOLO2, 95 % of participants on placebo had at least one grade 1 or 2 AE, highlighting that some of the low/moderate grade AEs are not necessarily related to the active therapy. Furthermore, over 12 % of the AEs reported in the placebo arm were blood test abnormalities. Whilst it is possible that some of these events could be symptomatic, for example the three participants with grade 3 anemia, it is anticipated that the majority would not be associated with any symptoms. Whilst the current CONSORT harms 2022 recommended reporting all harms, we propose that this class of events be referred to as "paper-toxicity" (a subset of events that is likely to have minimal bearing on patient outcomes) be reported as separate category in future trials.

In addition, given the large number of mild/moderate AEs reported in the placebo arm of SOLO2, there are ongoing concerns that some of these mild/moderate grade AEs in the active therapy arm might not necessarily be treatment related. When patients and clinicians are presented with AE data from the active therapy arm alone, it could shape patients' perception of treatment tolerability, and could influence clinicians' decision on dose modification or treatment cessation. RCTs with double blinded placebo-controlled design remains crucial in helping patients and clinicians assess harms associated with novel therapies.

It has been suggested that data collection burden could be reduced by gathering data only in the active therapy arm of clinical trial [10]. The argument supporting this suggestion was that there is often already comprehensive clinical experience with the comparator treatment. Our analysis of the AEs in the placebo arm of SOLO2 suggests that this practice should be strongly discouraged as a significant contribution of AEs will not be treatment related. We anticipate that these non-treatment related AE are likely to be present in all treatment arms of any clinical trial population.

When assessing residual AEs from prior therapy, one approach is to quantify baseline 'AEs' prior to commencement of therapy in clinical trials. A subtraction approach or individual change from baseline could provide a more accurate assessment of AEs as to whether they are treatment emergent. However, such an approach relies on study investigators to perform comprehensive baseline data capture for all existing baseline AEs. This is not a current practice, and there is likely underreporting of baseline events during the screening phase of clinical trials [11,12]. In our analysis we have shown that only 3 % of all the AEs reported were reported during the screening phase. Even for recurrent events, only 5 % were first reported in screening. This confirms that the application of a baseline subtraction approach will not be useful.

Universal capture of baseline events during screening phase of clinical trial is recommended, similar to the methodology utilized for Patient Reported Outcome CTCAE (PROCTCAE), since it may permit improved determination of harms arising from treatment, and not due to disease symptoms or residual AEs from prior treatment that are already present at baseline.

Our analysis has several limitations. First, the data have been generated from a single trial. A meta-analysis from multiple trials involving patient level data in the recurrent ovarian cancer will be necessary to provide a more comprehensive review to understand the types, timing of onset and resolution and recurrence of these events. Second, passive data collection with no trial protocol pre-specified types and frequency of collection will underestimate the frequency, duration and recurrence of AEs [13]. In addition, clinician reporting of adverse events has been demonstrated to systematically under-report events experienced by patients compared to patient-reported adverse events [14,15]. The use of PROCTCAE may provide a more accurate representation of symptomatic events on placebo [16] Finally, the rates and severity of AEs occurring in the placebo arm will differ according to severity of the underlying disease where we anticipate more disease related events being reported as AEs occurring in heavily pre-treated women as compared to those who are in the earlier phase of their cancer and hence further studies across different disease stages are required.

Improving the capture of toxicity information in clinical trials is important to allow an understanding of the harms associated with active therapy. Our work outlines the prevalence of AEs being reported in clinical trials that are not related to the current treatment and limitations of current recording of harm data. Further work is needed to measure and categorize the AEs reported in clinical trials. RCTs with double blinded placebo-controlled design remains the best approach in informing harms associated with novel therapies.

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CRediT authorship contribution statement

Katherine Elizabeth Francis: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Conceptualization. **Sandy Simon:** Writing – review & editing, Software, Conceptualization. **Val Gebski:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Florence Joly:** Writing – review & editing, Data curation. **Jonathan A. Ledermann:** Writing – review & editing, Data curation. **Richard T. Penson:** Writing – review & editing, Data curation. **Amit M. Oza:** Writing – review & editing, Data curation. **Jacob Korach:** Writing – review & editing, Data curation. **Nuria Lainez:** Writing – review & editing, Data curation. **Sabrina Chiara Cecere:** Writing – review & editing, Data curation. **Giulia Tasca:** Writing – review & editing, Data curation. **Martina Gropp-Meier:** Writing – review & editing, Data curation. **Keiichi Fujiwara:** Writing – review & editing, Data curation. **Elizabeth S. Lowe:** Writing – review & editing, Data curation. **Michael Friedlander:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Eric Pujade-Lauraine:** Writing – review & editing, Supervision, Data curation. **Chee Khoon Lee:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Data availability

The data underlying this article were provided by AstraZeneca by permission.

Declaration of competing interest

K.E. Francis reports honoraria from Gilead and Janssen; and funding to attend education events from Merck/MSD, BMS and Gilead.

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Appendix A. Supplementary data

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