

ORIGINAL ARTICLE

Health-related quality of life in patients with a germline BRCA mutation and metastatic pancreatic cancer receiving maintenance olaparib

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Background: Patients with metastatic pancreatic cancer often have a detriment in health-related quality of life (HRQoL). In the randomized, double-blind, phase III POLO trial progression-free survival was significantly longer with maintenance olaparib, a poly(ADP-ribose) polymerase inhibitor, than placebo in patients with a germline *BRCA1* and/or *BRCA2* mutation (gBRCAm) and metastatic pancreatic cancer whose disease had not progressed during first-line platinum-based chemotherapy. The prespecified HRQoL evaluation is reported here.

Patients and methods: Patients were randomized to receive maintenance olaparib (300 mg b.i.d.; tablets) or placebo. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item module at baseline, every 4 weeks until disease progression, at discontinuation, and 30 days after last dose. Scores ranged from 0 to 100; a ≥ 10 -point change or difference between arms was considered clinically meaningful. Adjusted mean change from baseline was analysed using a mixed model for repeated measures. Time to sustained clinically meaningful deterioration (TSCMD) was analysed using a log-rank test.

Results: Of 154 randomized patients, 89 of 92 olaparib-arm and 58 of 62 placebo-arm patients were included in HRQoL analyses. The adjusted mean change in Global Health Status (GHS) score from baseline was < 10 points in both arms and there was no significant between-group difference [-2.47 ; 95% confidence interval (CI) $-7.27, 2.33$; $P = 0.31$]. Analysis of physical functioning scores showed a significant between-group difference (-4.45 points; 95% CI $-8.75, -0.16$; $P = 0.04$). There was no difference in TSCMD for olaparib versus placebo for GHS [$P = 0.25$; hazard ratio (HR) 0.72; 95% CI 0.41, 1.27] or physical functioning ($P = 0.32$; HR 1.38; 95% CI 0.73, 2.63).

Conclusions: HRQoL was preserved with maintenance olaparib treatment with no clinically meaningful difference compared with placebo. These results support the observed efficacy benefit of maintenance olaparib in patients with a gBRCAm and metastatic pancreatic cancer.

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Key words: pancreatic cancer, health-related quality of life, olaparib, BRCA, metastatic

Introduction

Pancreatic cancer is the 13th most common cancer and 7th most common cause of cancer death worldwide [1]. Patients often present with advanced disease with worldwide 5-year survival rates of 9%, reducing to 3% for metastatic pancreatic cancer [2]. Median progression-free survival (PFS) with standard-of-care first-line treatments is around 6 months and disease progression can result in deterioration in health-related quality of life (HRQoL) [3, 4]. As a consequence, patients with metastatic pancreatic cancer have reduced HRQoL due to high emotional burden, symptom burden (in particular pain, fatigue, vomiting and diarrhoea), and poor prognosis [5–10]. When evaluating the best treatment option for patients with metastatic pancreatic cancer, it is important to not only assess survival, which is relatively short, but also ensure that there are no detrimental effects of treatment on HRQoL. Indeed, American Society for Clinical Oncology guidelines on treatment of metastatic pancreatic cancer recommend that clinicians should proactively discuss quality of life issues such as pain, fatigue, and loss of appetite, which tend to be overlooked yet have significant impact on daily life, with their patients [11].

In the international, randomized, placebo-controlled phase III POLO trial patients with metastatic pancreatic cancer and a germline *BRCA1* and/or *BRCA2* mutation (gBRCAm) whose disease had not progressed on first-line platinum-based chemotherapy derived a statistically significant and clinically meaningful improvement in PFS from maintenance treatment with the poly(ADP-ribose) polymerase inhibitor olaparib versus placebo [12]. The aim of maintenance treatment is to prolong PFS, and ultimately overall survival, delaying the need for subsequent cytotoxic chemotherapy. In addition, maintenance treatment should seek to preserve HRQoL, which may be improved following effective first-line chemotherapy [13]. First-line treatment with FOLFIRINOX has been shown to improve overall HRQoL and lead to a decrease in some symptoms, including pain, for patients with metastatic pancreatic cancer [13]. A prespecified secondary objective of the POLO trial was to evaluate the effect of olaparib on HRQoL, specifically the adjusted mean change from baseline in Global Health Status (GHS) score using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item module (EORTC QLQ-C30).

Methods

Patient population and study design

Details of this randomized double-blind, placebo-controlled phase III trial have been reported previously [12]. Briefly, patients aged ≥ 18 years with histologically or cytologically confirmed pancreatic

adenocarcinoma and a documented deleterious or suspected deleterious gBRCAm were eligible. Patients had received ≥ 16 weeks of continuous first-line platinum-based chemotherapy for metastatic pancreatic cancer, although duration was unlimited as long as no evidence of disease progression was noted by the investigator at randomization. Patients were randomized in a 3 : 2 ratio to receive maintenance olaparib tablets (300 mg twice daily) or matching placebo, initiated 4–8 weeks after the last dose of first-line chemotherapy and continued until objective radiologic disease progression (investigator-assessed according to modified Response Evaluation Criteria in Solid Tumors v1.1) or unacceptable toxicity [14]. Crossover to olaparib was not permitted during the trial.

Study outcome measures

A prespecified secondary objective of the POLO study was to assess HRQoL using the EORTC QLQ-C30 questionnaire. Additional HRQoL data were collected using the pancreatic cancer specific EORTC QLQ-PAN26 questionnaire (data not reported here). These questionnaires are considered appropriate to assess the pancreatic cancer patient experience [15]. The EORTC QLQ-C30 includes a two-item GHS scale, five multi-item functioning scales, three multi-item symptom scales, five single-item symptom scales, and a single-item financial impact scale [16]. Raw scores were transformed on to a scale ranging from 0 to 100; transformed scores are reported here. For GHS and functioning scales, a higher score is indicative of better quality of life whereas for symptom scales a higher score is indicative of more severe symptoms. A change from baseline of ≥ 10 points was predefined as clinically meaningful, based on the published literature [17–19]. Assessments were undertaken at baseline, every 4 weeks until disease progression, at discontinuation of study treatment, and 30 days after last dose. The primary HRQoL end point was adjusted mean change from baseline in GHS score. Best HRQoL response (improvement, no change, or deterioration), the proportion of patients with a clinically meaningful change (defined as a ≥ 10 -point change from baseline) and time to sustained clinically meaningful deterioration (TSCMD) were secondary HRQoL end points. A TSCMD event was defined as a ≥ 10 -point decrease (GHS and functioning subscales) or increase (symptom subscales) from baseline (or a patient being too ill to complete the questionnaire) sustained at the next scheduled visit with no response of ‘improved’ or ‘no change’ in between the two visit responses of ‘deterioration’, or death. In addition to the GHS score evaluation, exploratory analyses of functioning scores (physical, role, cognitive, emotional, and social) and patient-reported symptoms (pain, fatigue, nausea and vomiting, appetite loss and insomnia) were prespecified. Results from datasets considered to be most clinically relevant (GHS, physical functioning, and symptom subscales) are reported here.

Statistical analysis

HRQoL data were analysed in the subset of patients in the intention-to-treat population who had an evaluable baseline EORTC QLQ-C30 or QLQ-PAN26 form [patient-reported outcome (PRO) analysis set]. An evaluable form was defined as one on which at least one subscale baseline score could be determined.

For the adjusted mean change from baseline in GHS score analysis, only visits with at least 25% non-missing values in each treatment arm were included; study treatment discontinuation and 30 days following last dose of study treatment visits were excluded. The analysis was carried out using a linear mixed model for repeated measures, adjusted for score

at baseline, time, and treatment-by-time interaction to estimate the cumulative effect of olaparib versus placebo on GHS. Between-group differences were compared using adjusted mean estimates for each treatment group with a between-group difference of ≥ 10 points defined as clinically meaningful, based on published literature [17–19]. A change of ≥ 10 points from baseline was also predefined as clinically meaningful [17–19]. TSCMD was analysed by log-rank test [hazard ratio (HR) < 1 favours olaparib] in all patients with a baseline score ≥ 10 (GHS and functioning subscale analyses) or ≤ 90 (symptom subscales). HRQoL improvement rates were analysed using a logistic regression model [odds ratio (OR) > 1 favours olaparib].

Results

Population characteristics

Baseline characteristics of randomized patients are reported in the primary manuscript [12].

Of 154 randomized patients, 89 of 92 who received olaparib and 58 of 62 who received placebo were included in the PRO analysis set; the remaining seven patients had missing baseline forms. HRQoL scores were well-balanced between treatment groups at baseline with overall high scores for GHS and physical functioning scales, and low scores for symptom scales (supplementary Figure S1, available at *Annals of Oncology* online).

Questionnaire compliance

The overall compliance rate for EORTC QLQ-C30 was high, 100% at baseline and 96.6% and 94.8% overall in the olaparib and placebo groups, respectively, based on the PRO analysis set (supplementary Figure S2, available at *Annals of Oncology* online).

Global Health Status

Mean baseline scores for GHS were high compared with those from other metastatic pancreatic cancer trials [13]; 70.4 in the olaparib and 74.3 in the placebo group (supplementary Figure S1A, available at *Annals of Oncology* online). GHS scores remained relatively stable over time for both treatment groups (Figure 1A). There was no statistically significant difference in overall between-group adjusted mean change from baseline for GHS score [between-group difference -2.47 ; 95% confidence interval (CI) $-7.27, 2.33$; $P=0.31$] calculated across the first 6 months of treatment (Figure 2A). The median TSCMD for GHS score was 21.2 months for olaparib and 6.0 months for placebo (HR 0.72; 95% CI 0.41, 1.27; $P=0.25$) (Figure 3). A similar proportion of patients in each arm reported improvement in GHS score: 26/89 (29.2%) in the olaparib and 13/58 (22.4%) in the placebo group (OR 1.43; 95% CI 0.67, 3.15; $P=0.36$) (Figure 4).

Physical functioning

Mean baseline physical functioning scores were similarly high in both treatment groups and improved over time (supplementary Figure S1A, available at *Annals of Oncology* online; Figure 1B). The between-group difference in adjusted mean change from baseline for physical functioning was -4.45 points (95% CI

$-8.75, -0.16$; $P=0.04$) (Figure 2A). There was no statistically significant between-group difference in TSCMD for physical functioning (medians not reached; HR 1.38; 95% CI 0.73, 2.63; $P=0.32$) (Figure 3B). The proportion of patients with best HRQoL responses of 'improved' or 'deterioration' for physical functioning was similar between arms (Figure 4). Analyses of role, emotional, cognitive and social functioning showed no between-group differences in adjusted mean change from baseline of ≥ 10 -points and no statistically significant differences in TSCMD between arms.

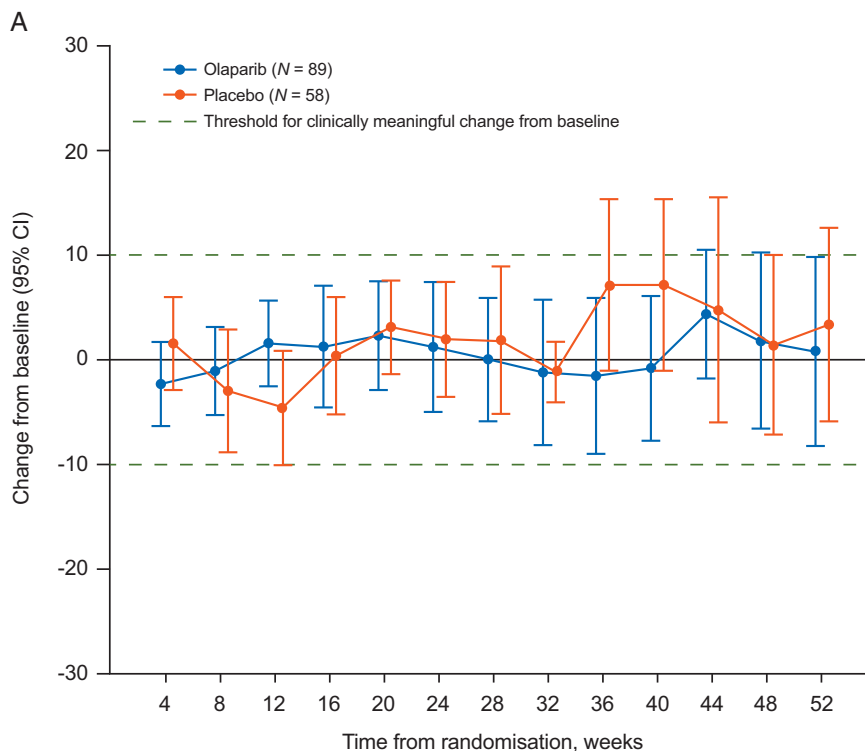
Symptom subscales

Mean symptom scale scores were low at baseline, reflecting a low symptom burden (supplementary Figure S1B, available at *Annals of Oncology* online). For the symptom scales of fatigue, nausea and vomiting, and appetite loss between-group differences were statistically significant in favour of placebo. For fatigue, and nausea and vomiting the between-group difference was < 10 points, whereas for appetite loss the between-group difference was 10.11 points (Figure 2B). There were no between-group differences in TSCMD for any symptom scores, except for nausea and vomiting, and constipation for which there were significant differences in favour of placebo (Figure 3B). Best HRQoL responses for symptom subscales are shown in Figure 4.

Discussion

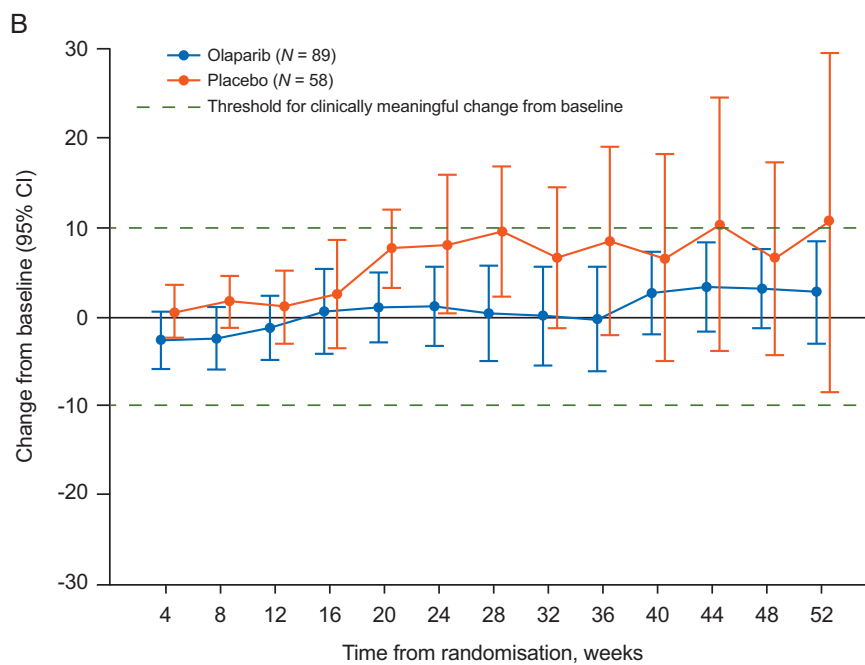
Metastatic pancreatic cancer, which is the initial diagnosis for 50%–60% of pancreatic cancer patients, has a poor prognosis [20]. Therefore, treatment should focus not only on prolonging disease progression or improving survival but should also consider preserving or improving quality of life, because symptoms such as fatigue, pain, appetite and weight loss, and decreased functional status all have a detrimental impact on HRQoL for patients with this disease.

Patients were randomized into the POLO study following a minimum of 4 months of first-line platinum-based chemotherapy (although there was no maximum limit to the duration of platinum-based treatment) and patients whose disease had progressed during first-line chemotherapy were not eligible for this maintenance trial. With the exception of alopecia, peripheral neuropathy and anaemia, toxic effects from previous treatments must have resolved to grade 1 before randomization [12]. The majority of patients (84%) had received variants of FOLFIRINOX, which is known to significantly improve GHS over the first 6 months of treatment [12, 13]; in the seminal phase III study FOLFIRINOX improved mean GHS score from 53.8 at baseline to 68.3 at the end of 6 months of treatment [13]. It is therefore not surprising that patients in the POLO study had consistently higher baseline GHS and physical functioning scores and lower symptom severity than the general population of patients with gastrointestinal cancers, reflecting low disease burden following first-line chemotherapy [21]. The mean GHS score was 70.4 in the olaparib arm at baseline, consistent with expectations based on FOLFIRINOX data. Preservation of HRQoL is a major therapeutic goal in the maintenance setting and further improvement in comparison with placebo may not be expected.



Number of patients at risk:

Olaparib	83	74	66	55	48	41	38	35	32	29	27	23	21
Placebo	54	39	36	23	19	13	9	7	7	7	7	6	5



Number of patients at risk:

Olaparib	83	74	67	55	47	43	38	35	32	29	27	23	21
Placebo	54	39	36	23	19	13	9	7	7	6	7	6	5

Figure 1. Mean change from baseline in EORTC QLQ-C30 scores across timepoints, by treatment group for (A) Global Health Status and (B) physical functioning scores. A change from baseline of ≥ 10 points was predefined as clinically meaningful. Error bars denote 95% confidence intervals.

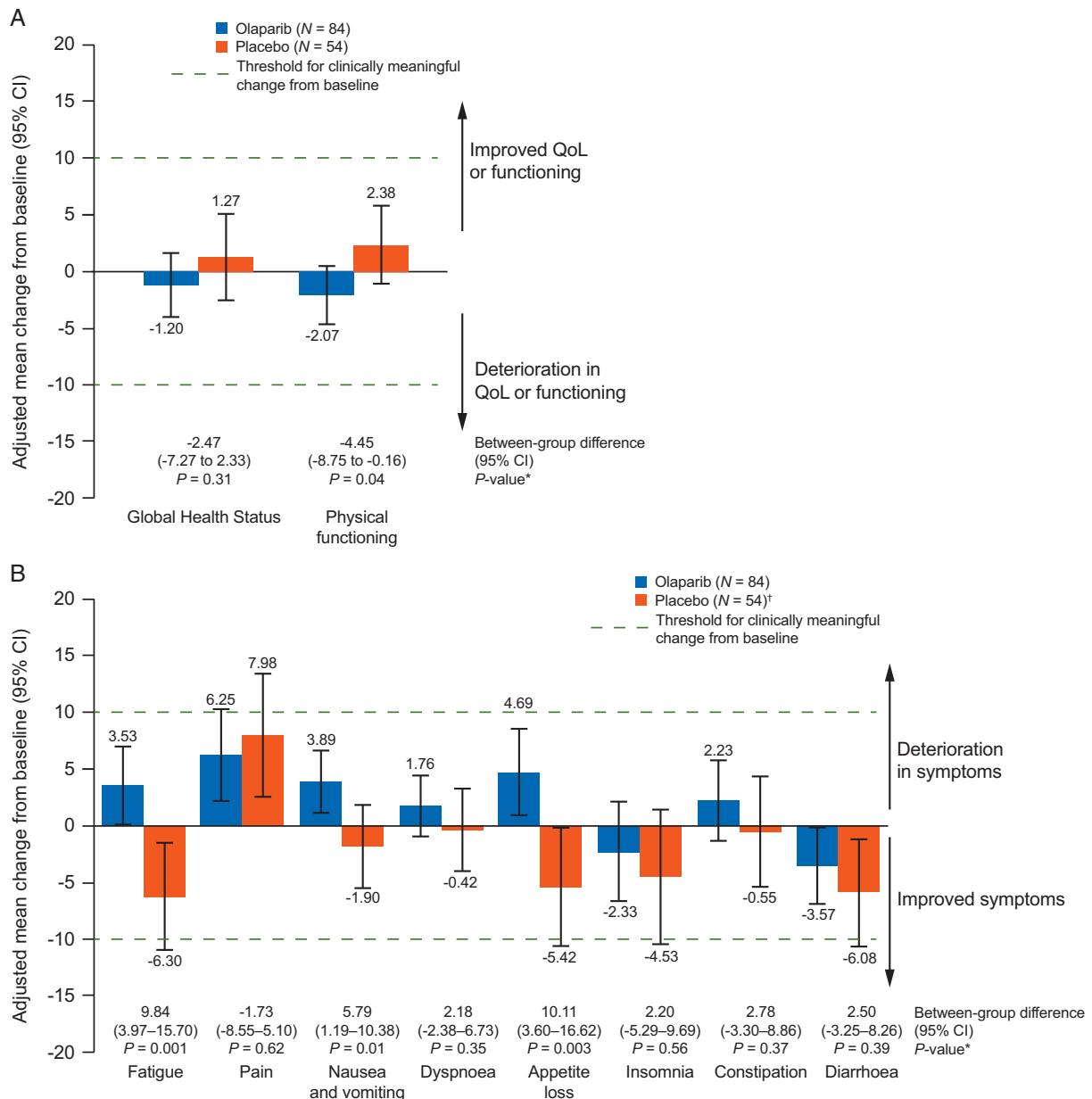


Figure 2. Overall adjusted mean change from baseline in EORTC QLQ-C30 scores over the first 6 months of treatment (A) Global Health Status and physical functioning and (B) symptom scales. An adjusted mean change from baseline or between-group difference of ≥ 10 points was considered to be clinically meaningful. For each subscale, only visits with at least 25% non-missing values in each treatment arm were included, therefore analyses cover only the first 6 months of treatment. Error bars denote 95% confidence intervals. *Between-group differences were considered statistically significant if $P < 0.05$. †For diarrhoea, $N = 53$. CI, confidence interval; QoL, quality of life.

Furthermore, standard-of-care chemotherapy agents are often associated with cumulative treatment-emergent toxicities that further affect HRQoL and a potential decrease in GHS has been observed when FOLFIRINOX treatment is continued beyond 6 months [10, 13].

High baseline GHS scores in the POLO study were preserved with olaparib maintenance treatment and the primary HRQoL end point (adjusted mean change from baseline) showed no statistically significant or clinically meaningful difference between the olaparib and placebo groups. Furthermore, median TSCMD was longer in the olaparib (21.2 months) than the placebo group

(6.0 months), although this difference was not statistically significant. This result may be influenced by a higher degree of censoring and smaller number of assessable patients (reflective of earlier disease progression) in the placebo arm compared with the olaparib arm. In addition, the proportion of patients with improved GHS score was similar in the olaparib (29.2%) and placebo groups (22.4%).

Evaluation of the physical functioning subscale indicated a significant between-group difference in adjusted mean change from baseline, favouring placebo; however, this difference was not considered to be clinically meaningful based on the 10-point change

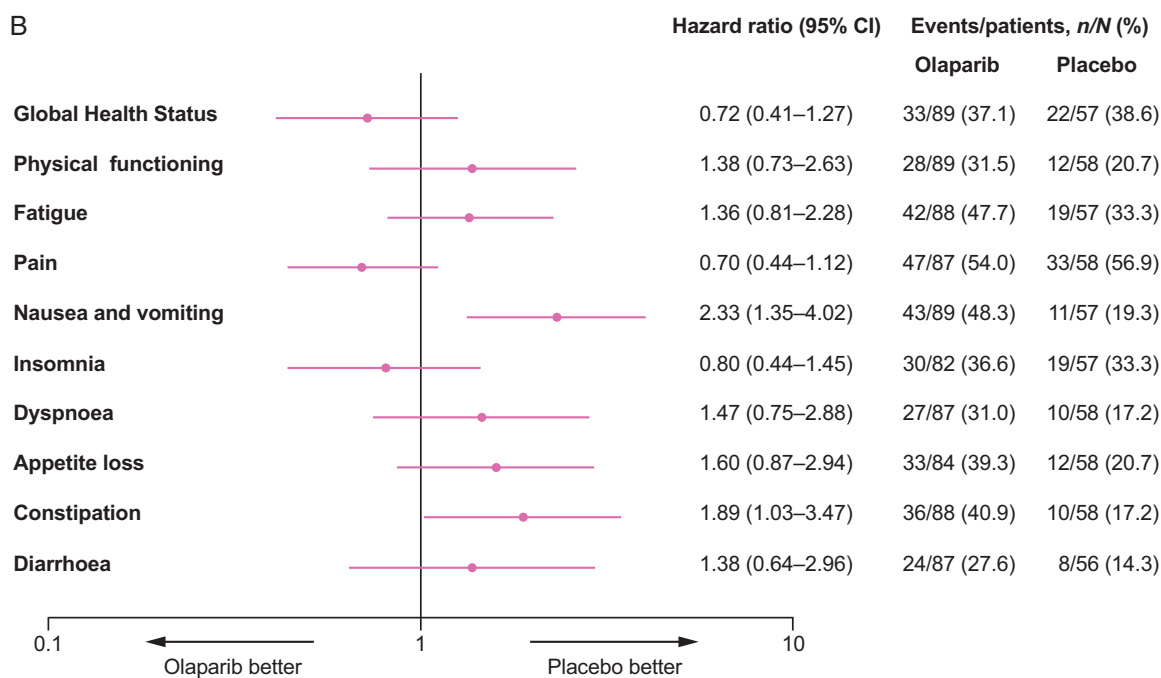
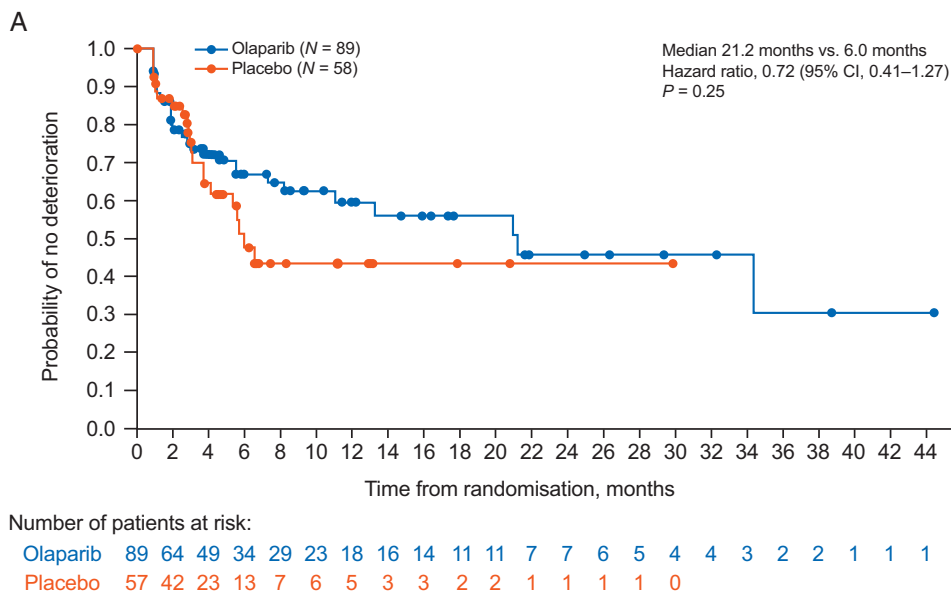


Figure 3. Time to sustained clinically meaningful deterioration (A) Kaplan–Meier plot for EORTC QLQ-C30 Global Health Status and (B) Forest plot for EORTC QLQ-C30 Global Health Status, physical functioning and symptom scales. Patients with baseline scores ≥ 10 were included in analyses of Global Health Status and physical functioning scores; patients with baseline scores ≤ 90 were included in analyses of symptom scores. Patients who had not had a TSCMD event or who had a TSCMD event after two or more missed HRQoL assessment visits were censored at the time of their last HRQoL assessment where the respective score could be evaluated; however, patients were not censored if they had two missing visits between two evaluable HRQoL assessments (and the outcome of the second assessment was not deterioration) and subsequently went on to show sustained clinically meaningful deterioration. CI, confidence interval.

threshold [17–19] and high baseline scores were preserved with olaparib treatment. In addition, there were no clinically meaningful between-group differences in change from baseline for symptom scales, with the exception of appetite loss, which showed a clinically meaningful difference favouring placebo. The notable findings in appetite loss scores appear to be driven by an improvement of these symptoms in the placebo group, since appetite loss scores remained low and stable over time in the olaparib

group. Furthermore, appetite loss is a recognised treatment-related symptom of olaparib [22]. Lower symptom scores indicate reduced symptom burden and all other symptom scores remained low during maintenance olaparib treatment.

A ≥ 10 -point change from baseline in EORTC QLQ-C30 score was predefined as clinically meaningful, based on the published literature. A study designed to determine the significance to patients of HRQoL scores showed that a ≥ 10 -point change from

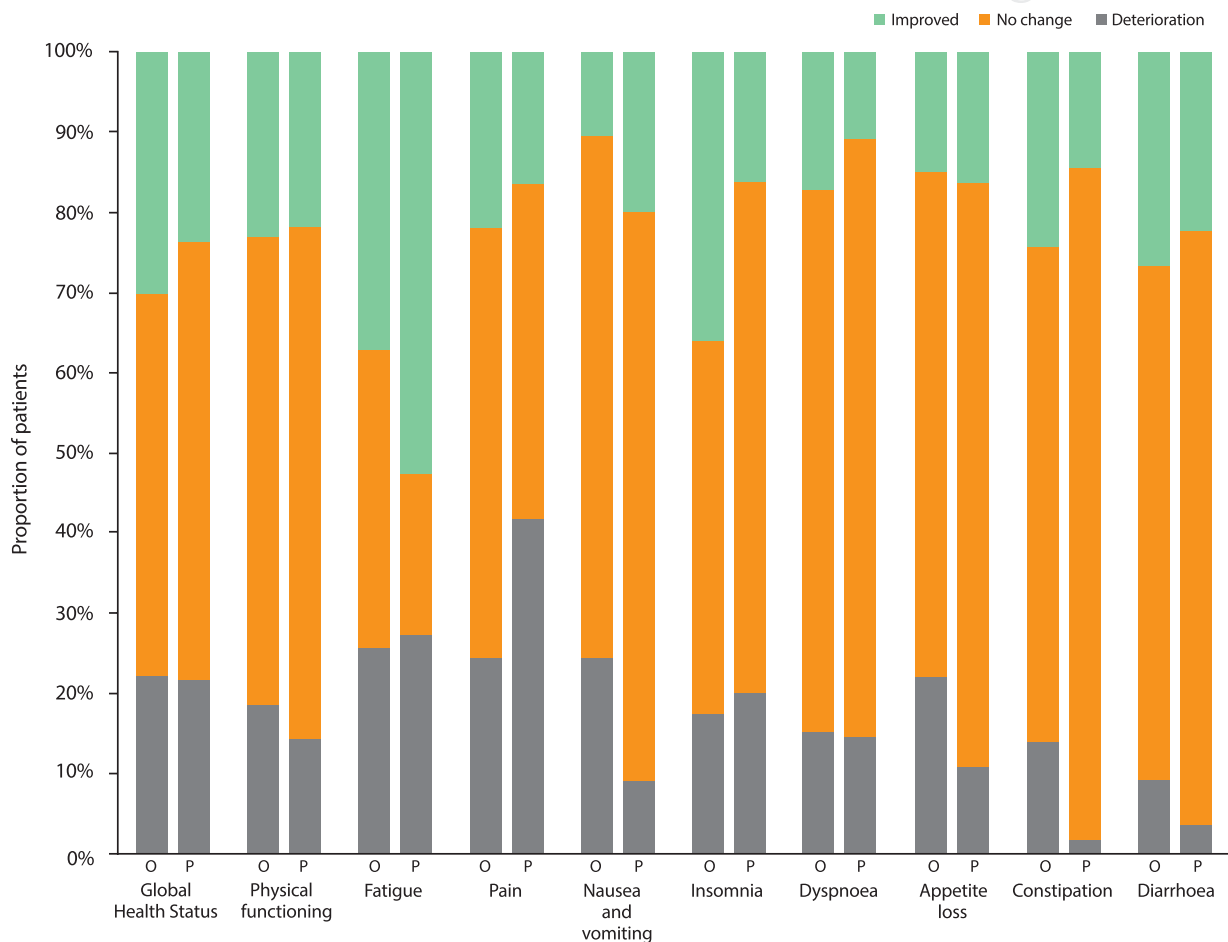


Figure 4. Best overall quality of life response for EORTC QLQ-C30 Global Health Status, physical functioning and symptom scales. Percentages are calculated based on the 86 olaparib-arm patients and 55 placebo-arm patients (54 for the diarrhoea subscale) with available results. Three patients in each arm (4 placebo arm patients for the diarrhoea subscale) were included in the PRO analysis set, but had no evaluable baseline or post-baseline results and are excluded from this figure. O, olaparib; P, placebo.

baseline in EORTC QLQ-C30 score generally reflected a change in quality of life that was 'moderately' or 'very much' better or worse [17] and was consistent with results from a systematic review of randomized controlled trials in various cancer settings, which demonstrated that a mean difference of 10–15 points in GHS score represented a medium effect size that was likely to be clinically relevant [18]. This 10-point threshold has been adopted for other studies based on EORTC QLQ-C30 data, including those in the pancreatic cancer setting, suggesting that it is an appropriate and generally accepted definition [19, 23, 24]; however, it is worth noting that at the time the POLO study was designed, there was no precedent for defining a clinically meaningful change in the maintenance setting.

In the POLO study, patients in the olaparib arm derived a statistically significant and clinically meaningful PFS benefit compared with placebo and a trend towards increased time to second progression was observed, suggesting the treatment benefit may be maintained through subsequent lines of therapy [12]. In addition, time to first subsequent therapy was significantly delayed in the olaparib arm [25]. Patients discontinued study treatment at disease progression and were only followed for HRQoL for 1 month after this point, therefore follow-up for HRQoL was considerably shorter in the placebo arm and the impact of disease

progression, or any subsequent treatments, on HRQoL was not taken into account. Adjusted mean change from baseline analyses only included visits at which $\geq 25\%$ of patients in each treatment arm had evaluable questionnaires; for the GHS analysis this equated to the first 6 months of treatment. This may mean that these analyses underestimate the overall impact of olaparib treatment in comparison with placebo, since disease progression and associated subsequent therapies would be expected to result in decreased HRQoL. Additional data assessing the psychological impact of having prolonged disease control (e.g. Brief Illness Perception Questionnaire or depression scale data) were not collected; however, the possibility of a positive benefit for this population of patients who had significantly improved PFS with maintenance olaparib may be considered.

Conclusions

HRQoL was preserved with olaparib maintenance therapy in patients with metastatic pancreatic cancer and a gBRCAm whose disease had not progressed during first-line platinum-based chemotherapy, with no meaningful difference observed compared with placebo. Results of prespecified end points from the POLO trial show that maintenance olaparib significantly

improved PFS without compromising quality of life, an important result for patients particularly when considering the cumulative toxicities of standard-of-care chemotherapies.

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Appendix

POLO Investigators

The table lists the principal investigator for each site who participated in the study.

Country	Principal investigator
Australia	Lorraine Chantrill, ^a David Goldstein, Warren Joubert, Nick Pavlakis, Annette Tognela
Belgium	Eric Van Cutsem, Frank Van Fraeyenhove, Jean-Luc Van Laethem, Marc Peeters
Canada	Neesha Dhani, Petr Kavan, Frederic Lemay
France	Antoine Adenis, ^a Pascal Artru, Nabil Baba-Hamed, Christine Belletier, Meher Ben Abdelghani, ^a Jean-Frederic Blanc, Christophe Borg, Romain Coriat, Gael Deplanque, ^a Roger Faroux, Philippe Follana, Rosine Guimbaud, Farid el Hajbi, Pascal Hammel, Vincent Hautefeuille, David Malka, Jean-Philippe Metges, David Tougeron, Thomas Walter
Germany	Hana Algül, Thomas Ettrich, Ulrich Thorsten Hacker, Elke Hennes, Lutz Jacobasch, Stephan Kanzler, Ursula Pession, Anke Reinacher-Schick, Christian Scholz, Marianne Sinn, Alexander Stein, Christian Strassburg, Arndt Vogel
Israel	Menachem Ben-Shahar, ^a Ronen Brenner, Ron Epelbaum, ^a Ravit Geva, Alexander Gluzman, Talia Golan, Efraim Idelevich, Maya Kolin, ^a Valeriya Semenisty, Ayelet Shai, Salomon Stemmer, Nirit Yarom
Italy	Luigi Celio, Pierfranco Conte, Carlo Garufi, Luca Gianni, Francesco Leonardi, Evaristo Maiello, Mariacristina Di Marco, Michele Milella, Carmine Pinto, ^a Daniele Santini, Mario Scartozzi, Giampaolo Tortora, ^a Vanja Vaccaro, Enrico Vasile
Republic of Korea	Ji-Won Kim, Jin-Won Kim, ^a Do-Youn Oh, Joon Oh Park
The Netherlands	Hanneke Wilmink
Spain	Rafael Alvarez Gallego, Gema Duran Ogalla, Adelaida Garcia Velasco, Elena Garralda Cabanas, ^a Carlos Gomez Martin, Carmen Guillén Ponce, Berta Laquente Saez, Rafael Lopez, Teresa Macarulla, Andres Munoz Martin, Roberto Pazo, Carles Pericay Pijaume, Javier Rodriguez, Ricardo Yaya-Tur
UK	Arvind Arora, David Alan Anthoney, T.R. Jeffrey Evans, Mark Harrison, Daniel Hochhauser, Daniel Palmer, Debashis Sarker, Naureen Starling, Juan Valle, Lucy Wall
USA	Richy Agajanian, James Bearden, Tanios Bekaii-Saab, ^a Corey Carter, Deirdre Cohen, Alfred DiStefano, Tomislav Dragovich, Samuel Ejadi, James Ford, Stephen Grabelsky, Michael Hall, Howard Hochster, ^a Peter Hosein, Milind Javle, Hedy Kindler, Jill Lacy, Daniel Laheru, Stephen Leong, Maeve Lowery, ^a Robert Marsh, Anne Noonan, Paul Oberstein, Allyson Ocean, Eileen O'Reilly, David Ryan, Tara Seery, Somasundaram Subramaniam, David Van Echo, ^a Andrea Wang-Gillam, Colin Weekes, ^a Stephen Welch

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