The POLO study presented a novel approach to targeting germline BRCA-mutant pancreatic adenocarcinoma while also adding insight into the role of maintenance therapy in the treatment of this devastating disease (1). Study investigators successfully recruited a subset of patients with metastatic pancreatic adenocarcinoma who harbored germline BRCA1 or BRCA2 mutations (a rare mutational profile comprising 4–7% of all cases), screening 3,315 patients and ultimately randomizing 154 of them. Eligible patients had received a minimum of 16 weeks of platinum-based therapy (84% had received FOLFIRINOX) without disease progression prior to being randomized in a 3:2 fashion to olaparib maintenance (300 mg twice daily) or placebo. Upon discontinuation of the trial intervention due to disease progression or unacceptable toxicity, patients could pursue subsequent therapy, but crossover to olaparib was not permitted within the scope of the trial. The olaparib cohort demonstrated prolonged progression-free survival (PFS) compared to placebo-treated patients but did not demonstrate improved overall survival (OS). At the time of study publication, only 46% of OS outcomes had been reached, so it is possible, though unlikely, that an OS benefit may yet emerge. The limitations of the study have been well-chronicled; however, the study findings ultimately led to the FDA approval of olaparib in the maintenance setting for germline BRCA-mutant pancreatic adenocarcinoma patients.

Health-related quality of life (HRQoL) assessment was a prespecified secondary objective of the study, and the results were published in a recent article by Hammel et al. (2). The quality of life (QoL) outcomes were measured through the EORTC QLQ-C30 questionnaire. Assessments were performed at baseline, every 4 weeks until disease progression, at study treatment discontinuation, and 30 days after the last dose. The primary HRQoL endpoint was adjusted mean change from baseline in Global Health Status (GHS). There were two secondary HRQoL endpoints: best HRQoL response (i.e., improvement, no change, or worsening), the proportion of patients with a ≥10-point change from baseline, and time to sustained clinically meaningful deterioration (TSCMD, defined as the time until either a ≥10-point decrease in GHS or functioning subscales or a ≥10-point increase in symptom scores is reached). All patients in the POLO trial were included in the HRQoL assessment with the exception of seven patients who had missing data. Adherence was excellent, with 100% of patients filling out surveys at baseline, and more than 95% of patients in each arm filling out surveys subsequently. The results from the HRQoL analysis from the POLO study demonstrated that there was no statistically significant difference between groups in adjusted mean change from baseline for GHS scores across the first 6 months of treatment, nor any clinically significant deterioration in GHS in either group. Further, there was no statistically significant difference between groups with regards to TSCMD for GHS or physical functioning. The
only statistically significant between-group differences in TSCMD by symptom score were for nausea, vomiting, and constipation, which all favored the placebo arm. In this commentary, we will address four major areas of discussion regarding this HRQoL analysis: (I) whether absence of meaningful deterioration of QoL, as opposed to outright improvement, is a reasonable standard for maintenance therapy, (II) the timepoints at which HRQoL was assessed and whether they influenced the study findings, (III) the impact of olaparib treatment on QoL from the standpoint of specific symptoms of key relevance for pancreatic cancer patients, and (IV) whether a placebo control remains a fair comparator for maintenance therapy in metastatic pancreatic adenocarcinoma.

To put the present study in context, it is important to review the QoL impact of FOLFIRINOX, the antecedent treatment for the majority of patients in the POLO study. In the QoL analysis of the PRODIGE 4/ACCORD 11 study (FOLFIRINOX versus gemcitabine for first-line treatment of metastatic pancreatic cancer), mean GHS scores for the FOLFIRINOX group improved from 53.8 to 68.3 and physical functioning scores remained stable from 79.0 to 80.1 after 6 months of treatment (all scores reported on a 0 to 100 scale) (3). The time until definitive deterioration was significantly prolonged with FOLFIRINOX compared to gemcitabine for GHS, physical functioning, cognitive functioning, social functioning, and multiple other symptom categories. In the POLO trial, the baseline GHS scores of 70.4 in the olaparib group and 74.3 in the placebo group were reflective of the fact that by design, this trial picks up at the therapeutic juncture where PRODIGE 4/ACCORD 11 concluded—at the transition from first-line to maintenance therapy. Baseline physical functioning scores in the POLO study were even higher (83.3 and 84.9 for olaparib and placebo arms, respectively) than in the PRODIGE 4/ACCORD 11 study. The high QoL baselines in the present study reflect the study inclusion criteria, which stipulated that beyond not developing disease progression while on platinum-based chemotherapy, all adverse effects in patients aside from alopecia needed to resolve to grade 1 or better. The high baseline QoL scores in patients on the POLO study likely limited room for further improvement while patients received maintenance therapy. For example, in order to achieve a clinically significant ≥10-point change in physical functioning, study patients would need to be at a value near 95, which would require the average study patient to respond “not at all” to every question posed about different scenarios measuring possible physical impairment.

The larger question is whether it is reasonable to anticipate that maintenance therapies such as PARP inhibitors would improve QoL metrics after de-escalating from a highly efficacious first-line therapy. In other instances where olaparib has been compared to placebo in the maintenance setting, such as following first-line platinum chemotherapy in ovarian cancer, no difference in QoL measures was observed despite a significant benefit in PFS (4). Perhaps, another component of this pertains to the toxicity profile of PARP inhibitors, which carry a side-effect profile that includes fatigue (from myelosuppression), nausea, vomiting, and anorexia (5). These adverse events may make it difficult for patients treated with PARP inhibitor maintenance therapy to demonstrate QoL improvements compared to placebo-treated patients, even in instances when the PARP inhibitor successfully slows disease progression, which in itself would be expected to have a net positive impact on QoL. Regardless of whether the absence of observed improvements in QoL measures over the course of the trial was due to high baselines or adverse effect profiles, it is important to ask what impact the statistically significant differences in PFS for olaparib compared to placebo had on the HRQoL results, and how methodology surrounding the timing of HRQoL assessments included in the analysis may have affected whether such differences could be detected.

Thus, the timing of HRQoL assessments in the POLO study needs to be discussed in the context of disease progression. A recent large German registry study suggested that in pancreatic adenocarcinoma patients, disease progression is associated with almost uniformly worse HRQoL measures (6). In this analysis, at initial disease progression, patients experienced statistically significant worsening of GHS, physical functioning, pain, appetite loss, and fatigue. Several other QoL measures also deteriorated (constipation, nausea, insomnia, and dyspnea) but did not meet statistical significance. Of patients included in the analysis, 43.2% received gemcitabine plus nab-paclitaxel in the first-line setting while 29.9% received FOLFIRINOX. Because patients in the placebo arm of the POLO trial progressed at a shorter time interval (median 3.8 months), an alternative approach that could more optimally assess differences between the two arms would be measuring and comparing HRQoL outcomes at 3 or 4 months, rather than censoring patients at time of progression and measuring GHS over a 6-month period. By extending the assessment to a 6-month period, the authors were comparing HRQoL...
measures between a much smaller proportion of patients in the placebo arm compared to the treatment arm. For example, at 6 months, GHS measures were being compared between 41 patients in the olaparib arm and 13 patients in the placebo arm. Such few patients in the placebo arm at this time point could skew the QoL average higher, since these were the minority of patients who could sustain long term stable disease without any further treatment.

Another important dimension of the HRQoL analysis concerns the symptom-specific survey questions. When considering the adverse event profile of olaparib in the context of common disease-associated symptoms associated with pancreatic adenocarcinoma, which overlap considerably, several points merit consideration. First, if the POLO study had employed a crossover design, the QoL impact of the olaparib could have been compared between patients with responding disease and those with progressive disease. This would have enabled investigators to assess whether olaparib could improve QoL after disease progression in patients. Next, the investigators maintain that the PFS benefit in patients who received the drug, without clinically significant compromise of overall GHS or physical functioning, supports the use of maintenance olaparib. The risk-benefit discussion surrounding this treatment, however, does need to acknowledge the fact that there was an increase in specific symptoms in patients treated with olaparib, with statistically significant worsening of fatigue, nausea/vomiting, and anorexia. The absolute between-group difference in mean change of these symptom scores over the course of treatment was around 10 points on the 100-point scale. Worsening symptoms, even on a small absolute scale, may be unacceptable to certain patients, particularly when the therapy did not demonstrate a corresponding OS benefit. Pancreatic cancer-associated pain carries a major QoL impact for patients; however, no between-group difference in change in pain score were noted. Ultimately, patients in both study arms demonstrated increases in pain scores over the course of the study. Perhaps as with GHS and physical functioning, the low baseline pain scores (17.6 in the olaparib group and 14.9 in the placebo group) post-FOLFIRINOX, may have left little room for improvement.

Beyond the specific results of the HRQoL analysis, an important limitation of the POLO study was the choice of placebo as the control arm in the study. In the PRODIGE4/ACCORD11 study, patients received a maximum of 6 months of FOLFIRINOX per the study protocol. Durations beyond this period are difficult to sustain for most patients due to neuropathy, myelosuppression, or other regimen-related toxicity. In current clinical practice, several maintenance approaches post-FOLFIRINOX are utilized, such as LV5FU2 or FOLFIRI. The use of maintenance LV5FU2 has been suggested based on interim findings from the phase II PRODIGE 35-PANOPTIMOX trial (7). In this study, metastatic pancreatic adenocarcinoma patients were randomized to 6 months of FOLFIRINOX (Arm A), 4 months of FOLFIRINOX followed by LV5FU2 maintenance with treatment re-introduction at disease progression (Arm B), or sequential treatment alternating gemcitabine and FOLFIRI (Arm C). Median PFS in Arm A and Arm B were 6.3 and 5.7 months, respectively, while median OS in Arm A and Arm B were 10.1 and 11.2 months, respectively. No statistically significant differences in PFS or OS were observed between the arms. A smaller single-institution retrospective study assessed FOLFIRI maintenance in pancreatic adenocarcinoma patients who were without disease progression after a median of 4 months of FOLFIRINOX (8). In this study, the median PFS with FOLFIRI was 8 months. The patient population who entered the POLO trial would have been eligible for either approach to maintenance therapy, and future studies may therefore benefit from comparing olaparib to maintenance fluorouracil or FOLFIRI.

In sum, the HRQoL analysis from the POLO study revealed important insights about maintenance therapy in pancreatic cancer; here, we have explored several nuances of these QoL results. The first issue pertains to the question of preservation of QoL versus improvement in QoL. While active therapies in pancreatic cancer traditionally improve HRQoL by increasing the time to disease progression, in this instance, because of the stellar baseline QoL measures of study patients, improvements beyond these values was likely not possible. Further, the exclusion of patients after progression of disease meant earlier censoring of patients on placebo, and this may have also obscured relative benefit of olaparib at later timepoints. However, even with no statistically significant differences between the two groups in terms of GHS, the results from the study do not pronounce that olaparib is truly equivalent to placebo in the maintenance setting with regards to QoL, since study patients in the treatment arm experienced increases in several key symptoms and no improvement in pain. Moreover, maintenance treatment for pancreatic cancer is an evolving area of study and the comparison to placebo may no longer reflect current clinical practice as patients are often maintained on active fluorouracil-based therapy.
A future study comparing LV5FU2 and olaparib may be warranted to determine the optimal maintenance strategy in germline BRCA mutant pancreatic cancer patients with response to platinum-based chemotherapy. For now, such a decision about maintenance treatment rests upon a nuanced risk-benefit discussion including the considerations detailed above. Fortunately, in-depth HRQoL analyses, like this one presented by Hammel and colleagues, can serve as important companions to primary efficacy outcomes for novel therapeutics in order to comprehend the global impact of a treatment for patients and equip clinicians with necessary context for framing discussions with patients about optimal available treatments.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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