

The Role of Olaparib in Metastatic Pancreatic Cancer

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EDITORIAL

Olaparib, a PARP inhibitor, was approved in 2019 for use as a first-line maintenance treatment of germline BRCA-mutated metastatic pancreatic ductal adenocarcinoma (mPDAC), based on findings from the pivotal POLO trial [1]. This phase III randomized, double-blind controlled trial included 154 metastatic PDAC patients with mutation in germline *BRCA1* or *BRCA2* who received at least 16 weeks of first line platinum-based chemotherapy, mainly FOLFIRINOX. As maintenance therapy within 4 weeks - 8 weeks of completion of chemotherapy, 92 patients were randomized to olaparib 300 mg twice daily while 62 patients were assigned to placebo. The primary endpoint of the study was progression free survival (PFS) which was nearly doubled in olaparib group compared to placebo group (7.4 months and 3.8 months respectively; HR 0.53; P = 0.004). Secondary endpoints were overall survival (OS), second PFS (PFS2), objective response rate (ORR) and the change in scores of global health-related quality of life (QoL). Although the study met its primary endpoint, median OS was not statistically significant (18.9 months in Olaparib arm versus 18.1 months in placebo arm, HR 0.91, 95% CI, 0.56 - 1.46, p = 0.68). Interestingly, two patients from olaparib group had a complete response at the time of interim analysis and data maturity of 46% [1].

At the annual gastrointestinal cancers meeting in January 2021, the investigators reported an update on the study outcomes. The median OS was 19.2 months for olaparib

group and 19.0 months for placebo group (HR 0.83, 95% CI 0.56 - 1.22; p = 0.3487), but it was not statistically significant [2]. The patients in the placebo group received multiple subsequent lines of therapies upon progression of disease (PoD) and after stopping the study medication which could bias the OS. Additionally, even though crossover was not allowed, 26% of patients in the placebo arm received Olaparib after disease progression. Another point to consider is that POLO study was inadequately powered to detect difference in OS between the 2 groups. However, there is a larger proportion of patients on olaparib survived longer than placebo group at after 2 years. Three-year overall survival was 33.9% for olaparib group and 17.8% for placebo group [2]. Another key secondary endpoint time to first subsequent treatment (TFST) was significantly longer in olaparib group (9.0 months vs 5.4 months, HR 0.44, 95% CI 0.30-0.67, p<0.0001). Time to second subsequent treatment (TSST) was also longer in olaparib group (14.9 months vs 9.6 months, HR 0.61, 95% CI 0.42-0.89; p=0.0111).

Despite the lack of statistically significant OS benefit in POLO study, olaparib offers significantly prolonged PFS which in theory should translate to better health-related quality of life (HRQoL). A recent large German registry study suggested that in PDAC patients, disease progression is associated with almost uniformly worse HRQoL measures [3]. Previously, PRODIGE 4/ACCORD 11

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showed patients who received FOFIRINOX compared to single agent gemcitabine enjoyed significantly prolonged time to definitive deterioration, longer physical, cognitive, and social functioning. These benefits are in large part attributable to longer PFS [4]. HRQoL in POLO study did not show statistically significant difference between the two groups which is an important goal for maintenance therapy. The QoL outcome was measured at baseline, every 4 weeks until PoD, at the study treatment discontinuation and 30 days after the last dose [1].

The lack of improvement in HRQoL could be 2 folds. First, the baseline physical functioning scores in the POLO study were higher (83.3 and 84.9 for olaparib and placebo arms, respectively) than those in the PRODIGE 4/ACCORD 11 study due to the requirement that all post-chemotherapy adverse effects in patients other than alopecia needed to resolve to grade 1 or better. The high baseline HRQoL scores in patients on the POLO study likely limited room for further improvement while patients received maintenance therapy. Secondly, patients in the placebo arm of the POLO trial were censored from the HRQoL assessment at PoD (median 3.8 months). The exclusion of patients after PoD meant earlier censoring of patients on placebo, and this may have also obscured relative benefit of olaparib at later timepoints. An alternative approach that could more optimally assess differences between the two arms would be measuring and comparing HRQoL outcomes at 3 months or 4 months, rather than censoring patients at time of progression.

Olaparib's benefit on delaying disease progression led investigators to study its economic impact. The incremental cost-utility ratios were calculated for patients taking maintenance olaparib versus those taking a placebo. Medical costs included drug acquisition, costs attributed to health states, managing adverse effects, and end-of-life care. All were calculated and considered based on 2018 U.S. dollar values. The study model suggested that

maintenance olaparib can be potentially cost-effective in certain scenarios, using a threshold of \$200,000 per quality-adjusted life year (QALY) gained [5]. However, if a threshold of <\$100,000 per additional QALY gained is used, it becomes not cost-effective. The investigators acknowledged that the benefit of overall survival is not conclusive as a major driver of economic evaluation.

In a disease such as mPDAC where OS is poor and effective treatment options are limited, a new targeted therapy is certainly a welcome addition to the treatment armamentarium. Olaparib showed a statistically significant increase in PFS with tolerable adverse events. Despite the lack of improved OS and HrQoL in the POLO trial, the positive primary PFS, and multiple key secondary endpoints, TTFS and TTSS, support a meaningful clinical benefit of maintenance olaparib in gBRCA mutated mPDAC patients.

FUTURE IMPLICATIONS

It is important to note that the patient population eligible for olaparib maintenance therapy is small due to the relatively low frequency (0.5%-2%) of germline BRCA mutations in the PDAC [6]. In addition to BRCA mutation, olaparib has also been shown to have activities in other germline and somatic DNA damage repair (DDR) gene mutations such as PALB2, ATM, CDK12 [7]. This calls for clinical trials to include other DDR gene mutations so that a larger population of PDAC patients can benefit from olaparib.

In addition to olaparib, there are three PARP inhibitors, rucaparib, niraparib, and talazoparib, currently approved for use in the treatment of several types of cancer including ovarian, fallopian tube, primary peritoneal, breast and castration-resistant prostate cancer [8-10]. In mPDAC, these PARP inhibitors are currently in early phase I/II trials as monotherapy or in combinations with chemotherapies, immunotherapies or targeted therapies [11]. Olaparib is the

first PARP inhibitor approved by FDA for maintenance therapy in mPDAC and the field of PARP inhibition continues to evolve rapidly. With many ongoing clinical trials, it is hopeful that the management of PDAC in the future would include other PAPP inhibitors and novel

combinations and eventually lead to better patient outcomes.

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