Editorial Commentary

Pancreatic cancer patients with germline BRCA mutations can benefit from olaparib treatment

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Pancreatic cancer, which is one of the leading causes of cancer death in the United States, can be initiated by many factors, including mutations in BRCA1 and BRCA2. The majority of familial pancreatic cancers are caused by these mutations. For individuals with a BRCA2 mutation, the lifetime risk of developing pancreatic cancer is 5–10% (1-3).

It has long been known that, because of deficiencies in homologous recombination repair, patients with BRCA mutations respond well to chemotherapeutic agents that bind to DNA directly and induce double-strand breaks to cause their cytotoxic effect (4). The BRCA mutation prevents tumor cells from repairing the double-strand damage caused by these chemotherapeutic agents. Accumulated DNA damage in the tumor cells ultimately eliminates the tumor. PARP inhibitors are a group of drugs that inhibit cells from repairing double strand breaks (5), and they are used in platinum therapy for cancer. Olaparib (AZD2281) is a powerful oral PARP inhibitor that induces toxicity for BRCA1/2-deficient tumor cells (6).

In a recent paper, "Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer," Golan *et al.* (2019) screened 3,315 patients with pancreatic cancer and found that 247 of them had a germline *BRCA* mutation. All 3,315 patients received platinum-based chemotherapy before this study was conducted. Out of the 247 patients with a germline *BRCA* mutation, 154 were selected for randomized study. Ninety patients were given 300 mg olaparib orally twice a day, and 61 patients were given placebo (7). The authors found no difference in overall median survival between the olaparib (18.9 months) and placebo (18.1 months) groups at a data maturity of 46% (*Figure 1*). However, at this interim data analysis stage, the median disease-free progression time was longer in the olaparib group (13.2 months) than in the placebo group (9.2 months). Importantly, the median progression-free survival was significantly longer (P=0.004) in the olaparib group (7.4 months) than in the placebo group (3.8 months) at a data maturity of 69%. At the closing of this study (January 15, 2019), 30 patients in the olaparib group and 8 from the placebo group were still on the treatment regime. Moreover, two patients in the olaparib group had a complete response. The authors reported that the duration of median response for the olaparib group was 24.5 months. By contrast, Kaufman *et al.* (2015) found that, when patients with pancreatic cancer were given 400 mg olaparib orally twice a day, the duration of median response was 134 days (8). Significantly, olaparib was most effective in increasing the progression-free survival of metastatic pancreatic cancer patients with a germline *BRCA* mutation.

Conclusions

Unhindered, pancreatic cancer will soon be the second leading cause of cancer-related death. Despite the recent advances in surgery, chemotherapy, radiotherapy, and targeted therapies, pancreatic cancer continues to have a 5-year survival rate of less than 10%. Immunotherapy has demonstrated efficacy in treating several types of solid

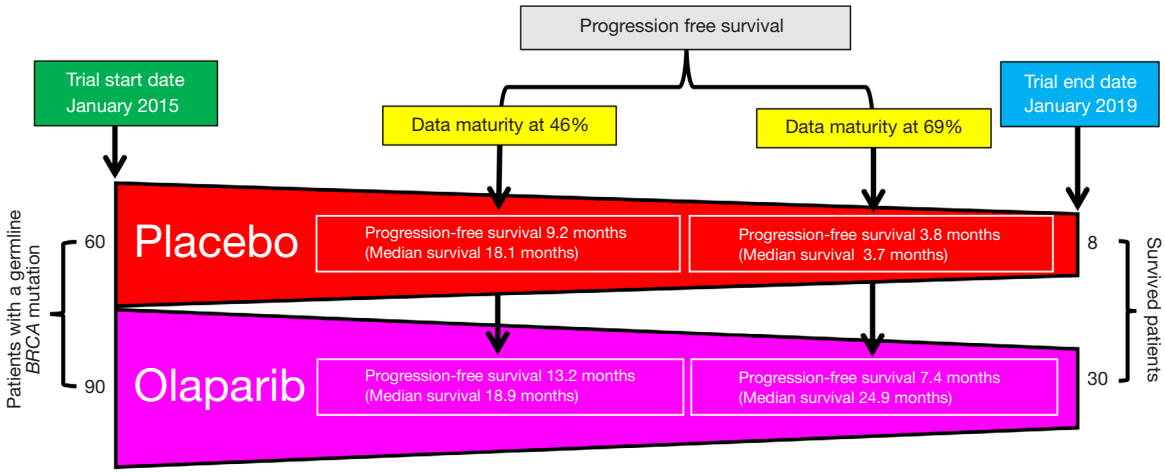

Figure 1 Schematics show the overall outcome of the randomized clinical trial with Placebo and Olaparib reported in Golan et al. (2019).

tumors; accordingly, there has been great interest in the role of immune cells in pancreatic cancer and applying various immunotherapeutic approaches, but most trials currently remain negative. Although pancreatic cancer is distinguished by prominent desmoplasia (fibrosis), its microenvironment is enriched with immune cells. Despite the presence of many immune cells in pancreatic cancer, immune dysfunction is observed in patients with pancreatic cancer where the tumor microenvironment is immunosuppressive, which thus inhibits the activation or function of immune effectors. Therefore, identifying novel combinational approaches that can overcome immune signaling suppression in response to genotoxic cancer therapeutic agents is required. In order to develop effective combination therapies, it is imperative to understand multi-modal interactions between therapeutic agents. Golan *et al.* (2019) show that a population of pancreatic cancer patients with germline *BRCA* mutations can achieve longer progression-free survival with olaparib treatment. It would be important in the future to understand the roles of olaparib in overcoming the immune signaling suppression microenvironment of germline *BRCA*-mutant pancreatic cancer.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.03.07). The authors have no conflicts of interest to declare.

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