PARP Inhibitor Lynparza Slows Progression of Pancreatic Cancer

Lynparza maintenance therapy after chemotherapy nearly doubled progression-free survival.

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The PARP inhibitor Lynparza (olaparib) significantly delayed the progression of metastatic pancreatic cancer in people with BRCA gene mutations, according to results from the POLO study presented at the American Society of Clinical Oncology (ASCO) annual meeting this month in Chicago and published in The New England Journal of Medicine.

Study participants who were randomly assigned to take Lynparza went about twice as long as placebo recipients before they experienced disease progression. After two years on treatment, 22% of Lynparza recipients were still alive without worsening of their disease, compared with 10% of placebo recipients.

"POLO is the first Phase III randomized study to establish a biomarker-driven approach in the treatment of metastatic pancreatic cancer, and it opens the door to a new era of personalized care for this difficult-to-treat cancer," said lead researcher Hedy Kindler, MD, of the University of Chicago.

Pancreatic cancer is often diagnosed at a late stage and is difficult to treat. Combination chemotherapy is the standard of care, but relapse is common and survival is typically short.

The POLO trial compared Lynparza versus a placebo as maintenance therapy—intended to maintain stable disease after response to chemotherapy—for pancreatic cancer patients with germline (inherited) BRCA1 or BRCA2 mutations.

Around 5% of people with pancreatic cancer have harmful BRCA mutations, which are best known for their role in raising the risk of breast and ovarian cancer. Pancreatic cancer patients with these mutations often respond to platinum-based chemotherapy drugs, such as cisplatin and oxaliplatin, but these medications have cumulative toxicities and better-tolerated therapies are needed for long-term maintenance treatment.

Lynparza and other PARP inhibitors work by blocking poly (ADP-ribose) polymerase proteins, which play a role in DNA repair. Inhibiting PARP leads to more DNA breaks in cancer cells, which can halt cell division. People with BRCA mutations do not make proteins that fix this kind of DNA damage,

so BRCA-related cancers are particularly susceptible to these drugs.

Lynparza is currently approved for the treatment of advanced ovarian and breast cancer. As previously reported, the SOLO1 trial showed that Lynparza maintenance therapy after chemotherapy slowed progression of ovarian cancer in women with harmful BRCA mutations—similar to the approach evaluated for pancreatic cancer in POLO.

POLO included 154 participants with metastatic pancreatic adenocarcinoma who had received first-line platinum-based chemotherapy for at least 16 weeks without disease progression. Just over half were men, more than 90% were white and the median age was 57. They were randomly assigned to receive twice-daily Lynparza or placebo tablets. Treatment continued until they experienced disease progression or unacceptable side effects.

The median progression-free survival, meaning patients were still alive without worsening of their disease, was 7.4 months in the Lynparza group versus 3.8 months in the placebo group. This difference was statistically significant, indicating it probably wasn't driven by chance. After a year of treatment, 34% of Lynparza recipients and 15% of placebo recipients were still alive without disease progression; after two years, the corresponding rates were 22% and 10%.

Overall survival data are not yet mature, but interim results suggest that the median duration will be similar in the two groups (18.9 months and 18.1 months, respectively).

"About a quarter of these patients responded to olaparib for a median of two years, which is truly remarkable in a disease where most patients survive for less than a year," Kindler said in a University of Chicago press release. "In a disease where almost nothing works, it is truly remarkable to finally have a drug that makes such a difference, even for a small subset of patients."

Objective response rates, meaning complete or partial tumor regression, were 23% in the Lynparza group and 12% in the placebo group. Two people taking Lynparza had complete responses, which were ongoing at the time of analysis. The median duration of response was substantially longer with Lynparza compared with the placebo: 24.9 months versus 3.7 months, respectively.

Treatment with Lynparza was generally well tolerated. The most common adverse events were fatigue, nausea, diarrhea, abdominal pain and anemia, mostly mild or moderate. Although 40% of Lynparza recipients and 23% of placebo recipients experienced severe (Grade 3 or higher) adverse events, just 6% and 2%, respectively, stopped treatment for this reason.

The researchers reported no significant differences between the two groups in health-related quality of life, and no clinically meaningful changes from baseline in either group.

These findings highlight the importance of genetic testing for people with pancreatic cancer. Although BRCA mutations are rare in this type of cancer, their presence offers additional avenues

for treatment.

“It’s encouraging to see that olaparib is consistently delaying the progression of metastatic pancreatic cancer in patients with a BRCA mutation,” Suzanne Cole, MD, of the University of Texas Southwestern Medical School said in an ASCO press release. “We’re potentially on the cusp of a new age of treatment for pancreatic cancer, where for the first time we can tailor therapy based on a biomarker and where having a BRCA mutation opens up more treatment options.”

Click here to read the ASCO study abstract.

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