It's About Time!

Compared with other malignancies, the treatment landscape for pancreatic cancer is pretty sparse. The last 2 drug approvals occurred several years ago and both drugs (albumin-bound paclitaxel and liposomal irinotecan) were formulated for better delivery, rather than addressing new therapeutic targets. So, the FDA announcement of a new drug approval for olaparib for pancreatic cancer on the last day of 2019 provided an additional cause to celebrate on New Year's Eve.

Of course, this isn't a new drug. Olaparib has been on our shelf for a few years. This PARP inhibitor was originally approved in 2014; it is commonly used to treat *BRCA*-mutated ovarian and breast cancers. Surprisingly, *BRCA* carriers, especially patients with *BRCA2*, have an increased risk of pancreatic cancer as well. Depending on the series, researchers have noted that up to 18% of patients with pancreatic cancer carry a germline mutation that probably drove the development of their cancer, and the most common mutations are *BRCA*.

Approval of olaparib was based on results of the POLO trial, a randomized placebo-controlled trial of maintenance therapy in patients whose cancer did not initially progress on platinum-based first-line treatment.[1] This was a difficult trial to conduct and required global effort. More than 3,300 patients were screened over 4.5 years to find 154 patients both eligible for and willing to participate in randomization. The primary endpoint was progression-free survival, which was nearly doubled. Some patients on the treatment arm showed exceptional responses that were unusually durable.

Normally, these results would seem like a slam dunk for approval, but there was no difference in overall survival, not even a clear trend. Of course, the trial could not have been powered for overall survival; to reach that endpoint, >30,000 patients would need to be screened. Given the length of time required for this screening, it just would not have been feasible. So, the FDA convened the Oncologic Drugs Advisory Committee to weigh in on whether the benefit of treatment outweighed the risk.

I was privileged to hear the discussion that day and felt that both the FDA and the committee did just what the public should expect: they considered the pros and cons. In the end, the majority vote supported approval. I was most impressed by very candid remarks from Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence. He noted that the agency is struggling with how to handle approvals for drugs that target very small subsets of patients. For these drugs, large trials that show improvement in survival just aren't practical or economical, and surrogate endpoints must be used. Recently, we've seen approvals across many disease types based on objective response data alone. Pembrolizumab for microsatellite instability–high cancers and larotrectinib for cancers with *NTRK* gene fusions are cases in point.

So, this past New Year's Eve, I was happy for my patients with *BRCA* mutations because they now had another treatment option. And I was very proud of our colleagues at the FDA who clearly put our patients first.

Reference

1. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 2019;381:317–327.

WHAT DO YOU THINK? To submit a Letter to the Editor, email JNCCN@nccn.org or log into www.editorialmanager.com/JNCCN.

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