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FDA Panel: Yank Keytruda Approval in Third-Line Gastric Cancer

— As PD-1 inhibitors move upfront, third-line indication will be of little use, members argue

by Ian Ingram, Managing Editor, MedPage Today
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An advisory committee recommended that the FDA revoke the accelerated approval for pembrolizumab (Keytruda) as a third-line option in gastric or gastroesophageal junction (GEJ) cancer.

With a vote of 6-2, the Oncologic Drugs Advisory Committee (ODAC) on Thursday recommended against maintaining the PD-1 immune checkpoint inhibitor's indication for patients with metastatic or recurrent locally advanced gastric or GEJ cancers with tumors expressing PD-L1.

Committee members overwhelmingly cited the new availability of a PD-1 inhibitor, in combination with chemotherapy, in the upfront setting, as well as the fact that patients who have already received chemotherapy alone as their initial therapy could still access pembrolizumab through expanded use programs.

"I do not believe the data support continued use of single-agent pembrolizumab in the third-line setting," said Colin Weekes, MD, PhD, of Massachusetts General Hospital in Boston, explaining his vote to pull the indication.

"The landscape has changed," said Christopher Lieu, MD, of the University of Colorado in Aurora, who also voted to pull the indication. "It is highly likely that by third-line therapy, patients will have received some form of immune checkpoint therapy."

Diane Reidy-Lagunes, MD, of Memorial Sloan Kettering Cancer Center in New York City, expressed concern over access to the drug if the indication was revoked, and said the original data that led to the accelerated approval showed some patients achieve durable responses with single-agent use.

"For those of us who use these therapies, often there is a tail of the curve, and it would be terribly devastating for a patient to not receive the therapy," she said, explaining her vote to maintain the approval. "[While] recognizing there are access programs, with disparities of healthcare and differences in the way that patients are treated throughout our country, I was nervous that they may not be able to get that."

Lieu suggested "there should be strong consideration given to delaying the removal of this indication, at least for several months," to cover patients currently in second-line treatment who have yet to receive immunotherapy.

Pamela Kunz, MD, of Yale University School of Medicine in New Haven, Connecticut, agreed, recommending a delay of 6 to 12 months to ensure patients have continued access.

"We don't want to leave patients in the lurch here without a therapy," said Richard Pazdur, MD, acting director of the Office of Oncologic Diseases at the FDA's Center for Drug Evaluation and Research, explaining the agency's position.

"We firmly believe that there is a role for checkpoint inhibitors in gastric cancer here," he said. "We believe that it's in the frontline therapy where a survival [benefit] has been shown."

Thursday's session was part of a 3-day ODAC review of accelerated approvals for checkpoint inhibitors where confirmatory trials have failed to demonstrate a significant benefit.

Staff from FDA noted that revoking the third-line approval would have no impact on tumor-agnostic accelerated approvals for pembrolizumab that might cover patients whose gastric or GEJ cancers have high tumor mutational burden, high microsatellite instability (MSI), or are mismatch repair (MMR) deficient.

FDA originally granted accelerated approval to pembrolizumab as a third- or later-line option for gastric or GEJ cancers based on results of KEYNOTE-059. The trial demonstrated an overall response rate of 13.3% in 143 patients with PD-L1-positive tumors, as measured by a combined positive score (CPS) ≥1, and microsatellite stable disease or undetermined MSI or MMR status.

Complete responses were seen in 1.4% of patients, with more than half having responses beyond 6 months and a fourth having responses longer than a year.

Full approval had been contingent on two trials, neither of which demonstrated superiority over chemotherapy. In the second-line KEYNOTE-061 trial, pembrolizumab monotherapy failed to improve overall survival versus paclitaxel for gastric or GEJ tumors with CPS ≥1. In the first-line KEYNOTE-062 trial, single-agent pembrolizumab failed to demonstrate superiority with or without chemotherapy versus chemotherapy alone in PD-L1-positive tumors (CPS ≥1).

"KEYNOTE-061 and -062 are troubling in terms of their lack of positive data," said Lieu.

Sponsor Merck argued that four ongoing studies -- three combination trials in first-line, one in the neoadjuvant or adjuvant setting -- could serve as confirmatory studies for the third-line accelerated approval. But FDA staff and ODAC members pointed out that these trials would not help answer the question of whether third-line use would remain appropriate.

Concern was raised at one point that some oncologists might not hear about the recent first-line approval of nivolumab (Opdivo) for gastric or GEJ cancers, and that pembrolizumab might no longer be an option for their patients in later lines, but Pazdur shot down the notion.

"I have firm belief -- let me just tell you this -- in the marketing department of all of these large pharmaceutical companies to get the word out," he said.

Although the FDA is not required to follow its advisory committees' recommendations, it typically does.

Ian Ingram is Managing Editor at MedPage Today and helps cover oncology for the site.
