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New US FDA Adcomm Trend: Approved Cancer Meds Get Another Look When Competitors Coming

by Sarah Karlin-Smith

Recent ODAC meetings suggest the FDA will expand focus beyond applications with pending approval decisions to refining trial designs and drug labels for competitors.

For the second time in recent months, the US Food and Drug Administration's Oncologic Drugs Advisory Committee is using the presence of a pending application to debate potential changes to the broader field of drugs in the same class and indication.

The move should put sponsors on notice that their medications may unexpectedly catch the FDA's advisory committee spotlight, particularly if competitors are in development.

The timing of what may be a new advisory committee trend at the agency is notable since the FDA has been formally considering reforms to optimize use of the panels. FDA Commissioner Robert Califf has stressed his interest in having committees spend more time debating topics that apply to multiple products. (Also see "*US FDA Advisory Committees' Future: Drug-Agnostic Panels, More Debate Time*" - Pink Sheet, 22 Feb, 2023.)

Key Takeaways

- For the second time in recent months, the FDA is using a cancer drug advisory committee to weigh broader class-wide changes, not just a pending application.
- These unusual meetings may become more common, as they are consistent with Commissioner Robert Califf's vision for advisory committee reform.
- Sponsors now may need to prepare for a competitor product's pending approval to

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Recent advisory committee formats suggest the agency is slowly making some adjustments even as the reform process remains ongoing. (Also see "*Advisory Committees: US FDA Should Explain Divergent Decisions But Keep The Vote*" - Pink Sheet, 19 Jun, 2024.)

call them back to an advisory committee meeting for labeling refinement.

Vote To Remove PD-L1 Agnostic Label

On 26 September the ODAC will vote on whether two immune checkpoint inhibitor indications for unresectable or metastatic gastric and gastroesophageal junction adenocarcinoma should be permitted in patients with PD-L1 expression <1.

BeiGene, Ltd. has a pending biologics license application for Tevimbra (tislelizumab) for the indications with a 28 December user fee goal date.

The current labels for the approved treatments, *Merck & Co., Inc.*'s Keytruda (pembrolizumab) and *Bristol Myers Squibb Company*'s Opdivo (nivolumab), is agnostic of PD-L1 expression, but the agency's advisory committee preview documents indicate it is leaning towards restricting the label to those with PD-L1 expression ⩾1. (*See sidebar.*)

The advisory committee will not take a vote or even be explicitly asked to formally discuss BeiGene's BLA.

Instead, the focus is entirely on the role of PD-L1 expression as a predictive biomarker for selecting patients for treatment with the drugs and adjusting the new and old labels.

US FDA Revisits PD-L1 Biomarker In Gastric, Esophageal Cancers

By Bridget Silverman

24 Sep 2024 The Oncologic Drugs Advisory Committee will discuss restrictions for patients expressing PD-L1 in first-line labeling for Merck's Keytruda, Bristol Myers Squibb's Opdivo, and a pending NDA for BeiGene's Tevimbra. *Read the full article here*

This meeting follows in the footsteps of a July session where the agency asked the committee to consider *AstraZeneca PLC*'s supplemental perioperative indication for Imfinzi (durvalumab) in resectable non-small cell lung cancer and the trial designs that should be used for pivotal studies in perioperative regimens in NSCLC. (Also see "*US FDA Sending AZ, Other Cancer Sponsors Trial Design Message With Imfinzi AdComm*" - Pink Sheet, 23 Jul, 2024.)

In an unusual move, the July meeting did not include a committee vote on the AstraZeneca application, although the FDA did ask for a discussion that helped elucidate the committee's

thoughts.

Instead, the key ODAC voting moment focused on the future trial designs for perioperative applications. The FDA was concerned that the trial designs being used cannot detect whether pre- and post-surgery treatment is needed, potentially leading patients to receive unnecessary medicine. The vote formally recognized perioperative lung cancer indications, but the agency indicated the design requirements were relevant to all solid tumors. (Also see "*AstraZeneca's Imfinzi Gets Pass From FDA Advisors But Future Perioperative Drugs Don't*" - Pink Sheet, 25 Jul, 2024.)

The meeting also put a target on two other applications.

BMS's sBLA for Opdivo for perioperative treatment of NSCLC remains pending FDA approval and contains the same trial design problem that lead to FDA questions about whether to clear Imfinzi. (Also see "*BMS's Opdivo May Be Next Casualty Of US FDA's Perioperative Trial Redesign Push*" - Pink Sheet, 29 Jul, 2024.)

Merck's Keytruda also came up because the company obtained approval for its perioperative NSCLC regimen with similar missing data on the contribution of each treatment phase. At the meeting, the FDA noted that since the Keytruda indication approval, more data from studies has emerged that raised questions about the need for the drug in both treatment phases.

Ultimately Imfinzi received its perioperative NSCLC indication, but Keytruda's label remains unchanged pending an outcome for Opdivo. (Also see "*AstraZeneca's Imfinzi Squeezes Through: Is FDA Reversing Course Or In A Transition Period?*" - Pink Sheet, 19 Aug, 2024.)

Consistency Of Subgroup Effects Across Trials

The 26 September ODAC seems likely to result in changes to the PD-L1 drug indications under discussion. Unlike the July ODAC, this time FDA has very explicitly brought all the impacted sponsors to the meeting.

Notably, the FDA also appears prepared to act based on exploratory analyses of the treatment effects in the PD-L1 negative (or low) populations from the three drugs' pivotal trials for the indications. Multiple studies with similar results seemed to make the agency more confident in relying on exploratory analyses.

"Based on a single trial it can be difficult to assess whether a result in a subgroup is based on chance alone or a real finding," the FDA's *preview documents for the meeting* said. "However, consistency of subgroup effects over multiple trials, as well as biological plausibility can increase confidence in the subgroup results."

The agency briefing also cites a 2022 meta-analysis of randomized clinical trials in gastroesophageal cancers that was conducted to evaluate the overall survival benefits of immune checkpoint inhibitors based on high vs. absent or low-PD-L1 expression. The analysis found improved efficacy outcomes in patients with high PD-L1 expression.

The FDA seems to be leaning towards standardizing the labeling approach so if PD-L1 cutoffs for the indication are implemented they are consistent across approved drugs. Ideally, the move could facilitate consistency and improved outcomes in treatment and positively impact the design of future trials, FDA said. However, the agency acknowledged that each of the pivotal studies for the three drugs used separate PD-L1 immunohistochemistry assays and scoring algorithms and specified different cutoffs for patient stratification.