Recent approvals and the pipeline

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Karen Lusky

December 2016—Pembrolizumab (Keytruda) is now FDA approved as monotherapy for patients with untreated metastatic NSCLC, both squamous and nonsquamous histologies, that express PD-L1 at a high level of 50 percent or more, says Dr. Roger Dansey, who headed up Keytruda development at Merck Research Laboratories. "We do not have data at this point that would say whether a cutpoint lower than 50 percent in the first-line setting would be of equal value in terms of response to Keytruda," he says.

The FDA also approved Keytruda monotherapy for second-line patients whose cancer expresses PD-L1 positivity of one percent or more. "With our assay, that's about two-thirds of the lung cancer population," Dr. Dansey says. "Approximately 30 percent of the population are high [≥ 50 percent] expressors. In both of those populations, Keytruda beat standard of care chemotherapy and improved overall survival."

Also now available for clinical use is Roche's PD-L1 inhibitor, atezolizumab (Tecentriq) as second-line therapy for metastatic NSCLC. Rod Cotton, senior vice president at Roche Diagnostics, says he believes the FDA approved Tecentriq along with its complementary PD-L1 test "because patients responded to the drug regardless of their PD-L1 status. The OAK and POPLAR studies showed favorable outcomes which informed the FDA's drug approval."

The KEYNOTE-024 trial for front-line metastatic cancer did not include patients with an EGFR mutation or ALK translocation. That's because there is effective although not curative therapy for them, Dr. Dansey says. "In the second-line setting, we required the patients with those abnormalities to receive the specific targeted therapy for those abnormalities before enrolling in the trial." KEYNOTE-024 showed improved overall responses, progression-free survival, and overall survival with Keytruda monotherapy compared with platinum doublet-based standard chemotherapy.

The FDA says in an online document that patients who have "EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab." The same is true for nivolumab (Opdivo).

Regarding Opdivo's potential for front-line therapy, Fouad Namouni, MD, head of development for oncology at Bristol-Myers Squibb, said in an email that BMS "set the bar high" in its CheckMate-026 trial to address all patients who express PD-L1. "Opdivo did not show superiority to chemotherapy in this broad population of patients where there remains a high unmet need," he said.

He wrote, "The trial results along with the evidence from CheckMate-012, presented at ASCO, strengthen our belief that the majority of previously untreated NSCLC patients may benefit from combination therapy. And we look forward to assessing our Opdivo and Yervoy combination in the CheckMate-227 trial." That trial, Dr. Namouni noted, is described at clinicaltrials.gov.

As for using PD-1 and PD-L1 inhibitors to head off metastatic disease, Dr. Dansey says Merck has two ongoing adjuvant trials, one in Europe and one in the U.S., for patients with resected melanoma who don’t have evidence of disease but are at high risk for recurrence.

Bristol-Myers Squibb has studies underway of Opdivo in adjuvant bladder cancer, melanoma, and esophageal/gastroesophageal junction cancer, Dr. Namouni said.[hr]

Karen Lusky is a writer in Brentwood, Tenn.