

FDA Approves Nivolumab Plus Ipilimumab for Previously Untreated Unresectable Malignant Pleural Mesothelioma

Kevin Wright

The FDA approved nivolumab (Opdivo) in combination with ipilimumab (Yervoy) for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM), according to Bristol Myers Squibb.

The approval was based on efficacy results from a pre-specified interim analysis from the open-label, multi-center, randomized phase 3 CHECKMATE 743 (NCT02899299) trial, designed to evaluate nivolumab plus ipilimumab compared with chemotherapy (pemetrexed and cisplatin or carboplatin) in patients with histologically confirmed unresectable MPM and no prior systemic therapy or palliative radiotherapy within 14 days of initiation of therapy.¹

With a minimum of 22.1 months of follow-up, the immunotherapy combination demonstrated superior overall survival (OS), compared with the standard chemotherapy arm (HR, 0.74; 95% CI, 0.61-0.89; $P = .002$), with a median OS of 18.1 months (95% CI, 16.8-21.5) versus 14.1 months (95% CI, 12.5-16.2), respectively. Two-year OS was 41% with nivolumab plus ipilimumab, compared with 27% with chemotherapy.^{1,2}

A total of 303 patients were randomized to receive 3 mg/kg nivolumab every 2 weeks and 1 mg/kg ipilimumab every 6

weeks, while 302 patients were randomized to receive 75 mg/m² cisplatin or 500 mg/m² carboplatin area under the curve 5 plus pemetrexed in 3-week cycles for 6 cycles until disease progression or unacceptable toxicity or, in the combination arm, up to 24 months.

The primary end point was OS in all randomized patients. Secondary end points included progression-free survival (PFS), objective response rate (ORR) and duration of response (DOR).

Median PFS for the immunotherapy arm, per blinded independent central review (BICR), was 6.8 months (95% CI, 5.6-7.4) and 7.2 months (95% CI, 6.9-8.1) in the standard chemotherapy arm (HR 1.0; 95% CI, 0.82-1.21). Confirmed ORR per BICR was 40% (95% CI, 34%-45%) and 43% (95% CI, 37%-49%) in the nivolumab plus ipilimumab and chemotherapy arms, respectively. Median DOR was 11.0 months for patients receiving the immunotherapy combination compared with just 6.7 months in the chemotherapy arm.

Although the interim analysis from CHECKMATE 743 showed improvements in survival rates in both nonepithelioid and epithelioid malignant pleural mesothelioma, patients with a nonepithelioid histology derived the larger benefit.

Median OS for this subgroup was 18.1 months (HR, 0.46; 95% CI, 0.31-0.68) with the dual immunotherapy combination compared with 8.8 months for those patients receiving standard chemotherapy. At 24 months, OS was 38% for those patients with nonepithelioid histology who received the immunotherapy combo, versus 8% for those receiving the standard chemotherapy treatment.³

In the immunotherapy arm, 23% of patients discontinued treatment due to adverse events (AEs) and 52% had at least 1 dose withheld for an AE. Moreover, 4.7% of patients permanently discontinued ipilimumab alone due to AEs. The most frequent grade 3/4 AEs included pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism.²

This approval represents the first and only immunotherapy treatment approved for this patient population and comes 6 weeks after the submission of a new supplemental biologics license application.² ■

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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COMMENTARY

Marjorie G. Zauderer, MD*Co-Director, Mesothelioma Program, Memorial Sloan Kettering Cancer Center*

There has not been new treatment regimen approved for mesothelioma in over 15 years. This was desperately needed for so many patients. To have another option, particularly up front, when patients are at their healthiest and best able to tolerate treatment is great. We've seen immunotherapy really come into primetime for lots of other malignancies, and it's nice to see it come forward for a less common disease like mesothelioma.

With these types of treatments, the devil is always in the details. For certain subtypes of mesothelioma—sarcomatoid and biphasic—the data show that the combination of ipilimumab (Yervoy) and nivolumab (Opdivo) seemed to lead to better outcomes than cisplatin and pemetrexed.

That difference is much smaller in patients with epithelioid mesothelioma, however.

Often, and particularly in the United States, we'll give 3 chemotherapy agents for epithelioid disease, and the trial only compared nivolumab and ipilimumab with 2 chemotherapy agents. When you factor that in as well, again, the difference is smaller. So, in terms of how we implement this in our practice, there are still some questions. But certainly, using immunotherapy is a highly effective way of treating patients, and it spares them the toxicities of chemotherapy. Many toxicities like fatigue and nausea, can be so difficult for people going through traditional chemotherapy.

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Q: Do you see a common clinical development theme across all hematologic malignancies, like some trend that's coming to the forefront no matter which cancer type you're talking about?

LONIAL: There are 2 developing trends that I think are important. While I think many of us in the field would argue that immunotherapy was first invented in hematologic malignancies, with allogeneic transplant for instance, we have learned to refine that a little, particularly by using cellular therapies such as CAR T cells and other ways to augment cellular therapy in all hematological malignancies. I think the second trend is taking the explosion of precision medicine in solid tumor oncology and beginning to apply some of those lessons to hematological malignancies as well. We know that in acute leukemia, for instance, we're beginning to look at certain mutations and treat them differently. We know that in myeloma, we're starting to test precision medicine-based approaches as well. We're also using genetics and genomics to identify lymphoma subsets. That's getting us into

both an immune era and a precision medicine era. And as I said at SOHO [the Society of Hematology Oncology annual meeting], the challenge now for us is marrying the 2 concepts. How do you take both precision medicine and immune therapy and make it a 1-treatment approach for a patient?

Q: You're a co-chair of the 25th Annual International Congress on Hematologic Malignancies®, which is devoting a full afternoon session to advances in CAR T-cell therapy. What can we expect from that session?

LONIAL: What you will see there is the current state of the art as well as the future state of the art. The current state of the art is really important, because while CAR T-cell therapies are not given in the community oncology practice, knowing when to refer from the community practice for a CAR T-cell treatment, and what that treatment can offer patients, is critically important. That's why it's important to know where we are today. The future, to me, is really exciting, because I think it suggests we can take

diseases that are treatable and potentially cure a larger fraction of them.

Q: Do you see CAR T-cell therapy becoming more accessible to the community practice over time?

LONIAL: A lot of that depends on the regulations that go along with administering treatment. Right now, you have to be FACT (Foundation for the Accreditation of Cellular Therapy)-accredited to get CAR T cells, which means [that treatment locations] are going to be limited to transplant centers. There probably are going to be opportunities for large community practices at some point to [become accredited] and be able to [administer treatment]. But at least for now, I think that it's not quite ready for prime time. The advantage [of CAR T-cell therapy] from my perspective is it is a one-and-done therapy. And if that one-and-done really is done, then it's a true victory. I think that opportunity for patients is one that we don't want to limit just to people who are seen in academic centers. ■

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