Immunotherapy Combo Looks More Promising With Longer Follow-Up

NKTR-214 plus Opdivo has been granted an FDA breakthrough therapy designation for advanced melanoma.

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NKTR-214, or bempegaldesleukin, plus the checkpoint inhibitor Opdivo (nivolumab) shrank tumors in more than half of people with previously untreated advanced melanoma, including 34% with complete remission, according to research presented at the American Society of Clinical Oncology (ASCO) annual meeting in June.

This month, the Food and Drug Administration (FDA) gave this combination a breakthrough therapy designation for advanced melanoma. The combo is now in Phase III clinical trials for melanoma and kidney cancer, as well as in earlier-stage studies for several other advanced malignancies.

Checkpoint inhibitors like Opdivo block the PD-1 receptor on T cells, which can restore their activity against tumors. But they aren't effective for everyone or for all types of cancer. T cells must be present in tumors for these drugs to work, and researchers are exploring whether combining checkpoint inhibitors with other kinds of immunotherapy can improve response.

NKTR-214 is an engineered version of the naturally occurring cytokine interleukin 2 (IL-2), designed to cause fewer side effects. IL-2 is a chemical messenger that stimulates the proliferation and activity of cancer-killing T cells and natural killer cells. A version of IL-2 called aldesleukin (Proleukin) is currently approved for advanced melanoma and kidney cancer, but it requires frequent IV infusions and can cause severe side effects. NKTR-214 combines the cytokine with polyethylene glycol, leading to sustained levels in the body. The drug binds to the CD122 receptor (also known as IL-2 receptor beta subunit) on immune cells, triggering their multiplication and recruitment to tumor sites.

The PIVOT-02 trial (NCT02983045) is evaluating NKTR-214 plus Opdivo in previously untreated people with a variety of advanced or metastatic solid tumors including melanoma, kidney cancer, bladder cancer, non-small-cell lung cancer and triple-negative breast cancer.

At the 2018 ASCO meeting, researchers reported that 11 of the first 13 melanoma patients (85%) treated with the combo in the first stage of the study experienced compete or partial tumor

shrinkage, including two with full remission. What's more, it worked well in people who tested negative for PD-L1, the binding partner of PD-1. Higher PD-L1 levels in tumors are associated with better response to checkpoint inhibitors, although they don't predict individual outcomes.

But then the treatment appeared to falter, with only a handful of the next round of participants responding. At the Society for Immunotherapy of Cancer (SITC) meeting that fall, researchers reported that among the 38 melanoma patients evaluated at that point, the overall response rate (ORR) was 53%—similar to that of the approved dual checkpoint combo Opdivo plus Yervoy (ipilimumab), albeit with fewer side effects. However, the 24% complete remission rate looked promising, suggesting responses were durable and deepened over time.

Now, things are again looking up for the combo. At this year's ASCO meeting, Nikhil Khushalani, MD, of Moffitt Cancer Center in Tampa, and colleagues reported that while the overall response rate remained at 53%, the complete response rate had risen to 34%. It is quite uncommon with cancer drugs for more than half of all responses to be complete remissions. The ORR was 62% for PD-L1-positive participants versus 43% for PD-L1 negative patients.

After a year of follow-up, 16 of the 20 responders (80%) were still doing well. Because most participants were still responding, it is not yet possible to determine the median duration of response or progression-free survival.

Treatment with NKTR-214 plus Opdivo was generally safe and well tolerated. The most common side effects were fatigue, fever, chills, muscle and joint aches, other flu-like symptoms, skin rash, itching and nausea, mostly mild or moderate. About 15% of participants experienced severe side effects and 10% stopped treatment for this reason.

These results were promising enough for the FDA to grant NKTR-214 plus Opdivo a breakthrough therapy designation for inoperable or metastatic melanoma. This status is intended to speed up the development and review of treatments for serious or life-threatening diseases for which there is preliminary evidence that they may offer substantial improvement over existing therapies.

Phase III clinical trials of the NKTR-214 plus Opdivo are now enrolling people with advanced melanoma (NCT03635983) and advanced kidney cancer (NCT03729245). Phase II trials of the combo are open for people with advanced bladder cancer (NCT03785925) and various types of sarcoma (NCT03282344). A Phase I trial is evaluating NKTR-214 in combination with the checkpoint inhibitors Keytruda (pembrolizumab) or Tecentriq (atezolizumab) for advanced or metastatic solid tumors (NCT03138889). NKTR-214 is also being studied with another Nektar candidate, the toll-like receptor agonist NKTR-262, with or without Opdivo (NCT03435640).

Click here to see the ASCO study abstract.

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