Exciting End of Year Melanoma Clinical Trial Results

Researchers at the annual Society for the Immunotherapy for Cancer reported on melanoma clinical trial results from this year.

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The annual Society for the Immunotherapy for Cancer (SITC) meeting did not disappoint, despite its virtual format and inability to see colleagues from across the globe in person, when it came to new clinical advances for melanoma. Researchers presented data from several important clinical trials and highlighted several novel agents that may boost responses to checkpoint immunotherapy as well as exciting therapeutic approaches for patients with earlier stages of melanoma. Beyond results presented at SITC, results in a uveal melanoma trial suggest progress for this difficult-to-treat and rare subtype may soon be on the horizon.

PIVOT-02 Study: Bempegaldesleukin (BEMPEG) + nivolumab (nivo) (NCT02983045)

This Phase 1/2 trial aims to test the combination of PD-1-targeting nivolumab, which is already FDA- approved for treating melanoma, with BEMPEG (NKTR-214), an IL-2 pathway agonist. IL-2, otherwise known as interleukin 2, is a protein that expands the number of tumor-fighting T cells and natural killer cells and promotes their tumor-killing abilities. IL-2 was approved in 1998 as a single agent to treat melanoma, but its clinical use has been eclipsed by checkpoint immunotherapies that have proven effective in a greater number of patients with fewer side effects. BEMPEG was engineered to stimulate the same pathway as IL-2, but in a way that limits its often severe side effects.

MRA Young Investigator Dr. Adi Diab of MD Anderson Cancer Center presented updated results from the PIVOT-02 trial, which evaluated BEMPEG + nivolumab in 41 patients with metastatic melanoma who had not received any previous therapy. At a median follow-up time of 29 months, the research team observed an overall response rate (ORR) of 53%, with a complete response rate (CR) of 34%. The median progression-free survival (PFS) was 30.9 months, suggesting responses to the treatment combination are quite long-lasting. The treatment was relatively well-tolerated. These encouraging results have led to the initiation of a Phase 3 trial comparing BEMPEG + nivolumab to nivolumab alone in untreated inoperable or metastatic melanoma patients (NCT03635983) and in patients with surgically resected melanoma who are at high risk for recurrence (NCT04410445).

KEYNOTE-695 Trial: TAVO + pembrolizumab (NCT03132675)

This Phase 2 trial is testing the combination of TAVO (tavokinogene telseplasmid) with the FDA-approved PD1-targeting drug, pembrolizumab, in patients with metastatic melanoma who have progressed on pembrolizumab or nivolumab alone. TAVO is a DNA plasmid – that is, a small, circular piece of DNA, that encodes interleukin 12 (IL-12), a protein that boosts anti-tumor T cell responses and helps turn immunologically 'cold' tumors 'hot'. TAVO is administered directly to the tumor, rather than systemically, by a device that delivers a series of short energy pulses that help TAVO enter cells. This delivery method helps reduce toxicities associated with giving IL-12 systemically through an infusion.

Dr. Adil Daud of University of California, San Francisco presented interim results of the KEYNOTE-695 trial, which achieved an ORR of 30% in the 54 patients analyzed thus far and a CR of 6%. The median duration of response was just over 12 months. The overall safety profile was very encouraging, with only 5.4% of patients experiencing grade 3 ((significant but not life threatening) treatment-related adverse events and no grade 4-5 (life threatening or potentially fatal) treatment-related adverse events. Importantly, tumors not treated with TAVO also shrank, suggesting this combination can lead to durable, systemic responses in patients resistant to PD1 therapy. (NCT03132675)

Neoadjuvant T-VEC (NCT02211131)

The oncolytic (cancer-killing) virus T-VEC is currently FDA approved to treat Stage IIIb-IVM1c melanoma patients for whom surgical intervention is not appropriate, and who have tumors accessible for direct injection. Given the relatively minor side effects of T-VEC, and the need for more options for patients who are at high risk for having their melanomas recur after surgery, investigators are testing whether giving T-VEC to stage IIIB-IVM1a melanoma patients ahead of surgery – what researchers call neoadjuvant therapy – will lead to better outcomes compared to patients who receive surgery alone.

Reinhard Drummer of University Hospital Zurich presented an interim analysis of this Phase 2 trial. At a median follow-up of 41.3 months, and correcting for treatments received after surgery, the researchers found that the 3-year recurrence-free survival rate was 49.1% for patients who received T-VEC before surgery and 22.9% for those that did not. Overall survival estimates also favored receiving T-VEC ahead of surgery: 83.2% of patients who received T-VEC were alive at 3 years compared to 71.6% of those who did not. The final analysis of this trial will occur at five years. (NCT02211131)

Neoadjuvant Nivolumab + CMP-001 (NCT03618641)

While many novel immunotherapy combinations are being tested in patients with advanced melanoma, combinations are now being tested in patients with earlier stages of melanoma, too, and at times with promising results. One such study, that enrolled 30 people, is a Phase 2 trial testing nivolumab, the FDA-approved PD1-targeting therapy, with the novel agent CMP-001, to stage III melanoma patients both before and following surgery. Like T-VEC, CMP-001 is injected

directly into tumors but has a different mechanism of action. Where T-VEC utilizes a live virus, CMP-001 is composed of short fragments of DNA packaged into virus-like particles and activates an inflammatory response that boosts anti-tumor immunity.

Dr. Diwakar Davar of the Hillman Cancer Center, University of Pittsburgh, who presented the results, reported radiographic responses (shrinkage of tumors as determined by PET scan) in 43% of patients and stable disease in 30% of patients. Major pathological responses (evaluated by looking at slides of surgically removed tumor samples, and thought to be indicative of response to treatment), were observed in 60% of patients. Grade 3/4 (significant or life threatening) immune-related adverse events were seen in 11% of patients, a rate similar to what is observed in other trials testing nivolumab alone. Overall, these data suggest nivolumab + CMP-001 is a promising combination therapy for patients with stage 3 surgically removable melanoma. (NCT03618641)

Tebentafusp for Uveal melanoma (NCT03070392)

This Phase 3 trial is testing tebentafusp (IMCgp100) versus standard of care (which was left to the treating doctor's discretion, and included the choice of pembrolizumab, ipilimumab, or dacarbazine), in patients with metastatic uveal melanoma. Uveal melanoma, also known as ocular melanoma, is a rare form of melanoma that occurs in the eye. Patients with metastatic uveal melanoma tend to have poorer outcomes and very few treatment options. In fact, no new therapies have been approved for uveal melanoma in over 30 years.

Tebentafusp is a novel class of immunotherapy – and works by binding to both melanoma cells and T cells, bringing these two cell types into proximity to facilitate tumor killing. Interim analysis of the Phase 3 trial testing tebentafusp estimated a one-year overall survival rate of 73% for patients taking tebentafusp versus 58% for patients who received standard of care. Although data analysis for all patients enrolled in this trial is not yet complete, this survival benefit signal is a promising step towards a potential new treatment for patients with uveal melanoma. (NCT03070392)

Together, these trials highlight several promising new therapies that may help increase the number of patients who benefit from already FDA-approved immune checkpoint inhibitors without significant increases in toxicity. They also highlight the progress being made in rare melanomas, and in expanding the reach of both novel and already approved therapies to earlier stage patients who are at a high risk of relapse. While additional studies and analyses are needed to determine whether these treatments warrant FDA approval, they provide an excellent snapshot of what is likely to be another decade of major therapeutic advances for patients with melanoma.

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