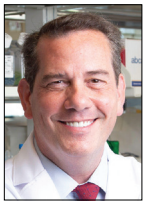
MELANOMA IN FOCUS

Current Developments in Melanoma

Section Editor: Sanjiv S. Agarwala, MD

Tumor-Infiltrating Lymphocyte Therapy in Metastatic Melanoma



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H&O What options are available for patients with metastatic melanoma that does not respond or has stopped responding to checkpoint inhibition and BRAF/MEK-targeted agents?

JC No US Food and Drug Administration (FDA)-approved options have been shown to improve overall survival in patients with metastatic melanoma that has progressed after immune checkpoint inhibition and—if a *BRAF* mutation is present—BRAF and MEK inhibition. As a result, the only options for these patients right now are either the off-label use of medication or enrollment in a clinical trial.

Among the off-label options, a valid option for patients who have not received an anti–cytotoxic T-lymphocyte–associated protein 4 (anti–CTLA-4) agent is the anti–CTLA-4 agent ipilimumab (Yervoy, Bristol Myers Squibb) plus the anti–programmed death 1 (anti–PD-1) agent nivolumab (Opdivo, Bristol Myers Squibb). Several nonrandomized studies, most of them retrospective analyses, have demonstrated the efficacy of this combination in patients with melanoma that is refractory to anti–PD-1 agents, with objective response rates (ORRs) ranging from 15% to 30%.

Another off-label option is talimogene laherparepvec, also known as T-VEC (Imlygic, Amgen), plus pembrolizumab (Keytruda, Merck). T-VEC, which is an injectable form of an oncolytic herpes simplex virus that has been genetically engineered to induce immunity, has been approved for use in patients with unresectable advanced melanoma. At the most recent American Society of Clinical Oncology (ASCO) annual meeting, Dr Brian Gastman presented data from our study showing that although the addition of T-VEC to pembrolizumab did not improve progression-free survival or overall survival, it did improve the ORR from 41.3% to 48.6% in patients with melanoma whose disease had progressed with immune checkpoint inhibitors in the adjuvant setting. As a result, we consider T-VEC plus pembrolizumab to be a reasonable option for patients with refractory disease. The ORRs were much lower in patients with metastatic disease.

H&O What is the rationale behind the use of tumor-infiltrating lymphocyte (TIL) products in metastatic melanoma?

JC The problem we need to solve is that the patient's own melanoma antigen–specific CD8-positive T cells, which are supposed to be killing the melanoma cells, just sit in the tumor instead of doing their job. Many hypotheses have been suggested for why this might occur, but nothing has been proven. What we do is extract these cells from the patient's tumor and propagate them in vitro so that we get a marked increase in the number of cells—from a few million to maybe 20 to 50 billion. We then reintroduce the cells into the patient after lymphodepletion. The idea is to overcome the natural resistance to T cells that has occurred within the tumor microenvironment.

H&O Could you talk more about the manufacture of lifileucel?

JC The manufacturing of lifileucel is straightforward. Candidates for treatment with this product must have at least 2 tumors so that we can harvest tissue from one tumor and still have another tumor to follow. The tissue is shipped to a central Good Manufacturing Practice Facility, where the T cells are extracted from the tumor and then induced to proliferate in vitro, which takes anywhere from 2 to 6 weeks. After we see that the cells are proliferating, we arrange for the patient to enter the hospital and start a nonmyeloablative transplant regimen of cyclophosphamide and fludarabine for 5 to 7 days to deplete the patient's own lymphoid cells. This regimen is generally well tolerated. The patient's facility then receives the purified cells for administration.

Because the TIL product is autologous, we have not seen significant numbers of reactions. We are not even seeing cytokine release syndrome, which is a common problem in chimeric antigen receptor T-cell therapy. We do administer up to 6 doses of high-dose interleukin 2 (IL-2) starting the day after the TIL product has been infused. We then wait for hematopoietic recovery before sending the patient home. The typical patient is in the hospital for approximately 3 weeks.

H&O Could you please describe your 2021 study with Sarnaik and colleagues, in which the TIL product lifileucel was used?

JC This was an open-label, single-arm, multicenter phase 2 study that enrolled 66 patients with advanced melanoma who had been previously treated with checkpoint inhibition and targeted agents if appropriate. All patients had received an anti–PD-1 agent and 80% had received an anti–CTLA-4 agent, so these were patients whose disease was refractory to immune checkpoint inhibition. Most of the patients who were BRAF-positive had received BRAF inhibitors. The patients had received a mean of 3.3 prior therapies. The tumor burden was high, with a mean diameter of 10.6 cm for the target lesion.

Patients experienced the typical side effects of chemotherapy after receiving the requisite nonmyeloablative lymphodepletion regimen before TIL therapy. These included lymphopenia, which is the goal of this regimen, along with neutropenia and anemia. Blood cell counts started to recover as soon as the chemotherapy was stopped. Patients also experienced the expected side effects of high-dose IL-2, such as fever, tachycardia, and arrhythmias. Most of the adverse events dissipated within 2 weeks. Patients did not appear to experience any additional side effects from the lifileucel. So, as we reported, patients come in for a one-time treatment, spend 3 weeks in the hospital, experience anticipated adverse events from FDA-approved drugs, and go home with essentially no long-term side effects.

> Based on these findings, I hope to see lifileucel receive FDA approval for this use in the first half of 2023.

The ORR with lifileucel was 36%, which did not include tumor regression that fell short of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria of 30% reduction in maximum diameter. The reductions proved to be quite durable, with the median duration of response not reached after a median of 18.7 months. The disease control rate was 80%. The waterfall plot showed that tumor regression occurred in most patients in this trial, and in most cases the regression lasted throughout follow-up. These were remarkable findings for patients whose disease had progressed on all FDA-approved options. On the basis of the findings, I hope to see lifileucel receive FDA approval for this use in the first half of 2023. We are also very excited about the possibility of using lifileucel in other cancer types, and in combination with other agents for patients with melanoma.

H&O What follow-up is planned for this trial?

JC Every patient is being monitored with scans every 3 months to determine the rates of overall survival and long-term side effects; this was part of the FDA registration agreement. In addition, we presented results with the Iovance Biotherapeutics TIL product in November at the 2022 annual meeting of the Society for Immunotherapy of Cancer, in which we combined data from the 66-person cohort with data from an 87-person cohort, for a total of 153 patients. In these results, the ORR after 27.6 months of follow-up was 31%, and the median duration of response was not reached.

H&O How much of a concern is morbidity associated with tumor biopsy?

JC Melanoma tissue is relatively easy to harvest when the tumors are superficial or lymphatic in nature, but

more difficult—with more morbidity—when we need to harvest tumors that have metastasized to the liver or lung. Cohort 3 of an ongoing phase 2 study from Iovance, called IOV-LUN-202, is looking at the use of image-guided core biopsy to harvest cells for TIL expansion in patients with non–small cell lung cancer who have just one tumor (NCT04614103). If this approach proves to be effective in lung cancer, it might have the potential to permit less-invasive harvesting in melanoma as well as in other cancer types.

H&O What other future studies of TILs are planned?

JC Iovance is currently working to modify the TILs genetically to make them better at inducing cytotoxicity and tumor regression. For example, in an ongoing phase 1 study sponsored by Iovance, we are deleting the PD-1 gene (*PDCD1*) in the TILs to see if we can improve efficacy. So far, 3 patients at the University of Louisville have received these genetically modified TILs. If we do not observe any safety issues, we should be able to enroll more patients in this trial. I consider this to be the most cutting-edge approach to TILs to date. We are also working closely with our partners at Moffitt Cancer Center to take TILs to the next level. We hope to find ways to modify and manufacture TILs so that we get better outcomes, meaning that we would like to boost our ORRs from 30% to 40%.

H&O What other TILs are being investigated in melanoma?

JC Our institution is participating in a multicenter study of an agent called ITIL-168 in the phase 2 DELTA-1 trial, which is being sponsored by Instil Bio (NCT05050006). This agent, which is not as far along in development as lifileucel, is being tested in non–small cell lung cancer as well as in melanoma.

H&O What role do you see TILs playing in melanoma?

JC I think that TILs hold the greatest promise of any of the agents for patients with melanoma that does not respond to immune checkpoint inhibitors. The fact that we are already getting remarkable results in clinical trials by using unmodified TILs as monotherapy means that we should be able to get even better ORRs with modified TILs or TILs in combination with other agents. The big challenge will be ramping up our expertise and our facilities to make TIL products available to all the patients who can benefit from them.

Disclosures

Dr Chesney has received research support from Amgen, Iovance Biotherapeutics, Fate Therapeutics, Bristol Myers Squibb, Replimune, and Instil Bio.

Suggested Readings

Chesney JA, Ribas A, Long GV, et al. Randomized, double-blind, placebo-controlled, global phase III trial of talimogene laherparepvec combined with pembrolizumab for advanced melanoma [published online August 23, 2022]. *J Clin Oncol*. doi:10.1200/JCO.22.00343.

Gastman B, Robert C, Gogas H, et al. Primary analysis of a phase 2, open-label, multicenter trial of talimogene laherparepvec (T-VEC) plus pembrolizumab (pembro) for the treatment (Tx) of patients (pts) with advanced melanoma (MEL) who progressed on prior anti–PD-1 therapy: MASTERKEY-115 [ASCO abstract 9518]. *J Clin Oncol*. 2022;40(16)(suppl).

Sarnaik A, Lewis K, Kluger H, et al. Lifileucel TIL cell monotherapy in patients with advanced melanoma after progression on immune checkpoint inhibitors (ICI) and targeted therapy: pooled analysis of consecutive cohorts (C-144–01 study) [SITC abstract 789]. *J Immunother Cancer.* 2022;10(suppl 2).

Sarnaik AA, Hamid O, Khushalani NI, et al. Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma. *J Clin Oncol*. 2021;39(24):2656-2666.