Cell therapy improves progression-free survival in advanced melanoma, first phase 3 study shows

September 11 2022

Lead author Professor John Haanen. Credit: European Society for Medical Oncology

A novel treatment strategy with personalized cell therapy significantly improves progression-free survival compared to standard

immunotherapy in patients with advanced melanoma, according to ground-breaking results reported at the ESMO Congress 2022 from the phase 3 M14TIL trial.

"This study shows for the first time in a randomized, controlled trial that cell therapy can be efficacious and beneficial for patients with solid cancers," said lead author John Haanen, Netherlands Cancer Institute, Amsterdam, Netherlands. "For patients with melanoma, we see a 50% reduction in the chance of progression of the disease or dying from the disease, which is absolutely practice changing. This is the first time that a TIL-based approach has been compared directly to standard-of-care treatment, in this case ipilimumab. So we are now able to position TIL treatment much better in the management landscape for patients with metastatic melanoma."

"TIL therapy is an extraordinary therapy," commented George Coukos, Lausanne University Hospital and the Ludwig Institute for Cancer Research, Lausanne, Switzerland, who was not involved in the study. "TIL is a new paradigm for treating cancers and, as these results clearly demonstrate, it's efficacious and feasible at large scale. The findings raise hopes for the management and potential cure of metastatic solid tumors."

The treatment essentially involves taking a small sample from a patient's resected tumor, growing immune T cells from the tumor in the laboratory and then infusing the personalized TIL therapy back into the patient following chemotherapy. TILs recognize tumor cells as abnormal, penetrate them and then work to kill them.

The phase 3 M14TIL trial randomized 168 patients with unresectable stage IIIC-IV melanoma to immunotherapy with the anti-CTLA-4 antibody ipilimumab or to TIL treatment; most patients had failed prior anti-PD-1 treatment. Results reported for the first time at the ESMO

Congress 2022 showed that patients treated with TIL therapy had significantly longer median progression-free survival of 7.2 months compared to 3.1 months in those receiving ipilimumab; the overall response rate to TILs was 49% versus 21% for ipilimumab; median overall survival was 25.8 months versus 18.9 months. Patients are still being followed up for overall survival.

Treatment options for patients with metastatic melanoma have changed considerably over the last 10 years with the development of checkpoint inhibitors, including the PD-1 inhibitors nivolumab and pembrolizumab and the CTLA-4 inhibitor ipilimumab. These drugs release a natural brake on the immune system so that the body's own immune cells can recognize and attack tumor cells. "They have a very good safety profile and quite high efficacy and are now often given as first-line therapy. But if patients fail first-line treatments then the options become very scarce, particularly for patients failing anti-PD-1 drugs so there is a real unmet need," explained Haanen. He added: "In our study, 89% of patients had failed anti-PD-1 treatment." The remaining patients joined the trial before anti-PD-1 therapies were licensed.

Exploring the possible mechanism by which TIL therapy is effective in patients who have failed anti-PD-1 treatment, Haanen suggested: "We think that the mechanism of resistance to anti-PD-1 treatment is mostly delivered by the tumor microenvironment. So when we take these cells out of their natural environment, reactivate them in the laboratory, grow them up to very large numbers and give them back to the patients we can overcome some of the escape mechanisms. And that's what we are seeing—otherwise TILs wouldn't work in this setting."

Even though grade 3 or higher adverse events occurred in all patients treated with TIL therapy and 57% of those randomized to ipilimumab, Haanen specified: "The side-effects are well manageable and most resolve by the time patients leave the hospital after their TIL therapy".

He also added that most side-effects are related to the other therapies, including chemotherapy and interleukin-2, that patients receive as part of the TIL regimen. About the impact of TIL therapy, Haanen concluded: "TIL has the potential to benefit patients with a wide range of solid tumors and trials are currently underway in many cancer types, including lung, cervical and head and neck cancers."

Haanen explained that the trial was run by academics in the Netherlands and Denmark, with no industry involvement. The researchers are now working to obtain EMA approval for their TIL therapy to try to ensure that it remains affordable, free from commercial pressures.

"The results from this phase 3 study could potentially lead to regulatory approval that would be practice changing," said Coukos. "It would enable countries that would consider this path to establish centers that can deliver TIL therapy for patients and establish this a potential second-line treatment in advanced melanoma."

More information: LBA3 'Treatment with tumor infiltrating lymphocytes (TIL) versus ipilimumab (IPI) for advanced melanoma: results from a multicenter, randomized phase 3 trial' will be presented by John Haanen during Presidential Symposium 1 on Saturday, 10 September, 16:30 to 18:00 CEST in Paris Auditorium. *Annals of Oncology*, Volume 33 Supplement 7, September 2022. www.esmo.org/meetings/esmo-congress-2022

Provided by European Society for Medical Oncology