Iovance Biotherapeutics
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IOVANCE BIOTHERAPEUTICS

Iovance unleashes natural-born killers: tumor-infiltrating lymphocytes

Applying its TIL-based therapy, Iovance Biotherapeutics is expanding TIL numbers in patients to target solid tumors.

Lymphocytes, notably T cells, are capable of killing cancer cells with exquisite specificity and power. However, few clinically detectable solid tumors simply vanish, despite the presence of tumor-infiltrating lymphocytes (TIL). The potentially lethal TIL are instead held at bay by immunosuppressive signals in the tumor microenvironment. Steven A. Rosenberg and colleagues at the US National Cancer Institute (NCI) have shown that extracting and expanding TIL populations *ex vivo* can assist them in overcoming this immunosuppression, which allows them to express potent antitumor activity that can be effective even in relapsed/refractory cancer. In a phase 2 NCI study in metastatic melanoma patients, for example, the objective response rate (ORR) to TIL therapy was 56%, with a complete response rate (CRR) of 24%.

Iovance Biotherapeutics (formerly Lion Biotechnologies) has developed extensive TIL-manufacturing capabilities and is charting a path to gain approval for TIL therapy in a wide range of solid tumor indications. "TIL are the immune system's natural defenses against tumors. We are expanding each patient's TIL to generate therapeutic quantities of cells to attack and destroy tumors," explained Maria Fardis, Iovance's president and CEO. "TIL do not require genetic manipulation and are not restricted to a single tumor antigen," continued Fardis. "Patients respond to TIL therapy despite failing prior chemotherapy or immune checkpoint inhibitors." She also noted that a patient's response to TIL therapy can be exceptionally durable. "We have data from TIL therapy from NCI that span over a decade, and in some cases the response is complete and lasting." In an NCI study in pretreated melanoma patients, 19 of 20 complete responders had ongoing complete responses beyond three years after a one-time TIL treatment[1].

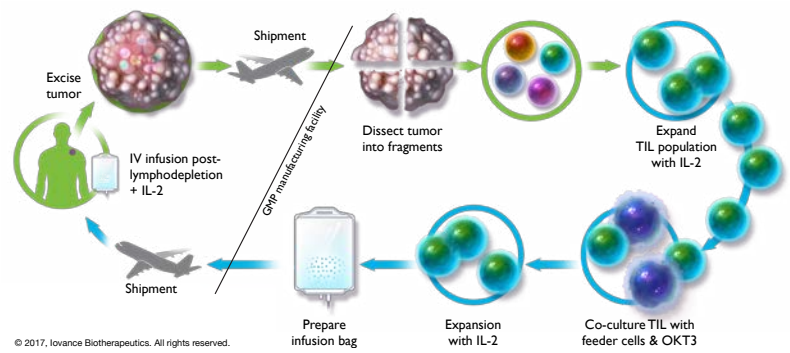

Figure 1: Manufacturing and delivery of TIL therapy. GMP, good manufacturing practice.

The company's first TIL-based treatment candidate, LN-144, was designated an orphan drug in metastatic melanoma by the US Food and Drug Administration. Patients in the first cohort of Iovance's phase 2 trial of LN-144 were heavily pretreated: at the start of the study, all patients had failed a PD-1 checkpoint inhibitor and, on average, two additional prior therapies, and had a median of four metastatic sites. After a single TIL treatment (see **Box 1** for details), cohort 1 had an ORR of 29% (14 efficacy-evaluable patients) and a CR rate of 7% (1 patient)[2]. A reduction in tumor volume was observed in 77% of patients and appeared to be independent of *BRAF* mutational status. Safety findings were similar to those in prior NCI studies: the most common serious adverse events were febrile neutropenia and lowered neutrophil and platelet counts. No serious adverse events led to discontinuation of the TIL regimen. It is worth noting that the total amount of IL-2 delivered in this study was significantly lower than that used in treatment of melanoma with IL-2 alone.

Iovance's phase 2 metastatic melanoma study is being expanded from the initial cohort to include an additional cohort of 30 patients who will be treated with a second-generation TIL product. Generation 2 TIL can be manufactured in just over 3 weeks, versus 5–6 weeks for generation 1, and allow the use of cryopreserved product, which provides flexibility in the timing of patient treatment.

Iovance is also currently enrolling phase 2 TIL trials in cervical cancer and squamous cell carcinomas of the head and neck. In addition, the company, in partnerships with the NCI and the Moffitt Cancer Center, is testing TIL therapy in combination with other treatments, including PD-1 checkpoint inhibitors, in melanoma and lung cancer. Through a clinical partnership with MD Anderson Cancer Center, Iovance is also exploring the potential of TIL therapy in sarcomas, ovarian, and pancreatic cancer.

In addition to its extensive clinical program, Iovance is working to further improve TIL expansion and activity. In partnership with the Karolinska University Hospital, Iovance will have access to data from phase 1 studies of TIL therapy in pancreatic cancer and glioblastoma where different cytokines will be used to expand TIL populations. The MD Anderson collaboration is also using an alternative TIL-expansion method. "We are building our pipeline through both Iovance-sponsored trials and in collaboration with research institution partners," noted Fardis. "Ultimately, as TIL therapy is applied in earlier lines of treatment and in additional oncology indications, we hope to offer more patients, even patients with no other approved available therapy, the potential for a deep, long-lasting response."

1. Rosenberg, S.A. *et al. Clin. Cancer Res.* **17**, 4550–4557 (2011).
2. Sarnaik A. *et al.* Efficacy of single administration of tumor-infiltrating lymphocytes (TIL) in heavily pretreated patients with metastatic melanoma following checkpoint therapy. *J. Clin. Oncol.* **35**, (suppl; abstr 3045) (2017).

Box 1: TIL therapy

Iovance's TIL therapy products are made at centralized manufacturing facilities in the United States, and similar manufacturing capabilities are set to come on line in Europe in the near future. The 'first generation' method is a modification of a protocol developed at the NCI and follows the four steps outlined below and in the figure.

1. Extraction
Tumor-associated cells are isolated from patient tumor tissue after surgical excision.

2. Expansion
Recovered cells are cultured *ex vivo* with IL-2, causing rapid expansion of TIL populations to 10^9–10^{11} cells.

3. Preparation
To counteract the immunosuppressive tumor microenvironment and support engraftment, patients undergo lymphodepletion the week before TIL infusion.

4. Administration
A single infusion of TILs is delivered intravenously, along with up to six doses of IL-2, which enhances TIL antitumor activity.

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