Iovance Generation-2 Tumor-infiltrating Lymphocyte (TIL) Product is Reinvigorated During the Manufacturing Process

Michelle R. Simpson-Abelson, Angel Cedano-Hilton, Kenneth D’Arigo, Maria Fardis and Cécile Chartier

Introduction

Background

- Adoptive cell transfer (ACT) is a therapeutic strategy that has emerged as a powerful and potentially curative therapy for several cancers.
- The presence of TILs in the tumor microenvironment can drive a robust anti-tumor response.
- To determine whether Iovance’s second generation (Gen2) TIL product, when compared to the prior generation (Gen1) TIL product, would deliver a more potent therapeutic benefit when reinvigorated back in the patient, in high numbers, can drive a robust anti-tumor response.

Methods

- Gen2 T-cells (D0), isolated from resected primary tumor, melanoma, or melanoma cell lines, were expanded and reinvigorated using a digestion cocktail to reconstitute tumor-reactive TILs.
- Gen1 T-cells were isolated from the tumor (D0 cells) for phenotype, function, and tumor reactivity.

Results

Figure 2. TIL expansion enriched the product for CD8+ T cells, while excluding Treg

- CD8+ T cells increased from 3% to 4% (D0 cells) and from 7% to 8% (D22 cells). T regulatory cells (Tregs) decreased from 9% to 7% (D0 cells) and from 6% to 3% (D22 cells).
- Gen2 T-cells displayed higher CD8+ T-cell content and lower Treg content than Gen1 T-cells.

Figure 3. Both CD4+ and CD8+ T-cell lineages became mostly of the effector memory phenotype during the ex vivo expansion

- CD4+ T cells showed an increase in memory phenotype cells, including TEMRA (Tumor Infiltrating Memory Regulator Activated), TCM (Tumor Infiltrating Central Memory), and TEM (Tumor Infiltrating Effector Memory) cells.
- CD8+ T cells also demonstrated a shift towards effector memory phenotype, including TEMRA, TCM, and TEM cells.

Figure 4. Ex vivo expansion induced the expression of multiple activation/exhaustion markers, while downregulating PD-1 levels

- Expression of PD-1 decreased from 100% to 50% (D0 cells) and from 100% to 50% (D22 cells).
- The expression of other activation markers, such as CD27 and CD28, also increased, indicating a more activated phenotype.

Figure 5. Ex vivo expansion did not push the T cells toward a terminal state of differentiation and preserved T cell youth

- The TIL product contains both helper and cytotoxic T cells with rapid effector capabilities.
- CD3% and CD8% were maintained, indicating the preservation of T-cell youth.

Figure 6. Most phenotypic changes occurred during the initial phase of the culture

- The short duration of the Gen2 process maintained the T-cells in a low state of differentiation, compatible with long-term in vivo persistence.

Figure 7. Ex vivo expansion restored the TIL ability to secrete multiple cytokines in response to TCR engagement

- Culture in the presence of IL-2 is sufficient to induce many but not all the TILs, indicating that the TILs produced in this process retain their functional potential.

Figure 8. Tumor reactivity was increased upon ex vivo culturing of the TIL

- The high functionality of the T cells as well as their enhanced tumor reactivity represents a measure of TILs in vivo activation potential.

Discussion and Funding Statement

- Iovance Generation-2 TIL product provided enhanced functional and cytolytic potential compared to the Gen1 product.
- Enhanced functionality in response to pan and tumor specific stimulation.
- Reinvigorated TILs can enhance tumor reactivity by improving their cytolytic, functional, and tumor reactive profiles.

Conclusion

- Enhanced functionality of TILs using Iovance’s Gen2 process, reverses the dysfunctional state of the T-cells back to the tumor microenvironment by improving their cytolytic, functional, and tumor reactive profiles.
- Gen2 T-cells can be used to treat patients with advanced melanoma, bladder cancer, and other cancers.

*The TIL product contains both helper and cytotoxic T cells with rapid effector capabilities.*

Summary

- Enhanced functionality in response to pan and tumor specific stimulation.
- Reinvigorated TILs can enhance tumor reactivity by improving their cytolytic, functional, and tumor reactive profiles.

Disclosure and Funding Statement

- Iovance Biotherapeutics, Inc., and its wholly owned subsidiary, Iovance Therapeutics, Inc., are committed to the advancement of immunotherapy for the treatment of cancer.
- The TIL product is composed of highly activated T-cells. This is due to down-regulation of PD-1.
- The differential expression of TIM3 and Lag3 in Gen2 HNSCC is an indicator of actively stimulated and reinvigorated T cells, rather than markers of exhaustion.