Persistence of cryopreserved tumor-infiltrating lymphocyte product lifileucel (LN-144) in C-144-01 study of advanced metastatic melanoma

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BACKGROUND & INTRODUCTION

- Adoptive cell transfer utilizing tumor-infiltrating lymphocytes (TILs) is recognized as an effective treatment in metastatic melanomas and other solid tumors existing durable and complete responses, in heavily pretreated patients, presumably by targeting somatic mutations specific to each tumor.

- C-144-01 (NCT0360579) is an ongoing Phase 2 multicenter study:
  - Investigational agent: autologous TIL (lifileucel; LN-144)
  - Patient population: unresectable metastatic melanoma

- Since TIL products are preparations of polyclonal autologous T cells, each T cell clone expresses a unique T cell receptor (TCR) that can be identified by its complementary determining region 3 (CDR3).

RESULTS

- Analysis of diversity of CDR3 products:
  - Post-processing, the unique CDR3 sequence (CDR3) and, therefore, the individual T cell clones are identified for each Iovance TIL product. The CDR3 groups are based on the frequency distribution criteria in Table 2 and frequency patterns for each CDR3 group are summarized in Table 3.
  - The most frequent CDR3 clones in the TIL product correspond to the clones present in the initial TIL infusion.

- Evaluation of shared clones between TIL products and D42 PBMC:
  - Numbers of shared CDR3s were determined by measuring the number of CDR3s clonally distributed in clonal D42 that were present in the corresponding TIL products. Shared CDR3s were identified in D42 PBMC sequences and were expanded in vitro using autologous lymphodepleted feeder cells, yielding a polyclonal mixture of TILs. These clones represent an entire high or low frequencies in the TIL product would persist for at least 6 months post-infusion.

- Anti-tumor T cells are present in the TIL infusion products of low and high diversity, consistent with both purifiers can recover relevant TIL, without prior knowledge of tumor antigens.

- Persistence of cryopreserved tumor infiltrating lymphocyte product lifileucel (LN-144) in C-144-01 study of advanced metastatic melanoma

MATERIALS & METHODS

- TIL products corresponding to 27 patients who underwent resection for the purpose of TIL generation and their matching D42 PBMC samples were analyzed.
- Total RNA was extracted, using Qiagen’s RNeasy® Mini Kit protocol (Germantown, MD).
- CDR3 were amplified and sequenced by Next Generation Sequencing using iRepertoire technology (Huntsville, AL).
- Custom python scripts were used to identify CDR3 clones of interest and perform statistical analyses and generate figures.

CONCLUSION

- 100% of Iovance TIL infusion products demonstrate substantial level of in vivo persistence 6 weeks post-infusion.
- The TIL product is highly polyclonal and number of unique clones or diversity index are not related to clinical response.
- In vivo fate of individual TIL clones is irrespective of their frequency in the infusion product, reflecting their specific antigen reactivities.
- The patient TIL products are comprised of unique TCR repertoires, which are highly specific to each patient.

Overall, the data support using a polyclonal product such as bulk TIL to treat solid tumors with their associated unique, patient-specific, mutational and neoantigen spectra.