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The uniqueness and persistence of clonal profiles associated with response in study C-144-01 following treatment with lifileucel (LN-144) supports using a polyclonal product to treat solid tumors

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Background & Introduction

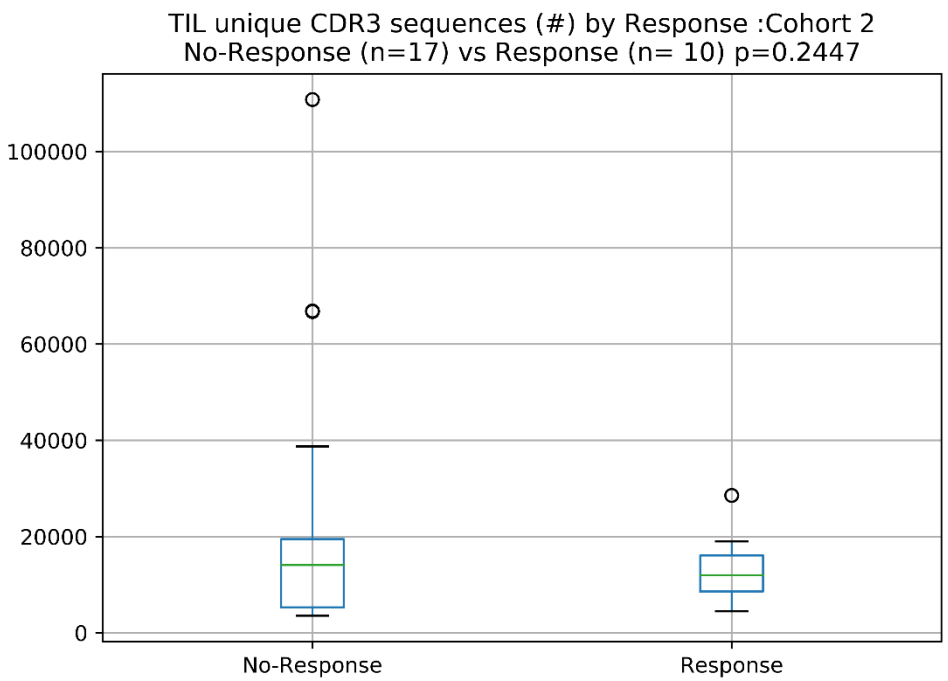
- Adoptive cell transfer utilizing tumor-infiltrating lymphocytes (TIL) is recognized as an effective treatment in metastatic melanoma and other solid tumors eliciting durable and complete responses in heavily pretreated patients, presumably by targeting somatic mutations specific to each tumor.[1]
- C-144-01 (NCT02360579) is an ongoing Phase 2 multicenter study of lifileucel, a centrally manufactured, autologous, cryopreserved TIL.
- An objective response rate of 38% (n=66) has been reported.[2]
- We analyzed the composition of the initial TIL products and the T cells circulating 42 days post-infusion (D42) to uncover a potential link between clonal diversity, TIL *in vivo* persistence, and anti-tumor activity.

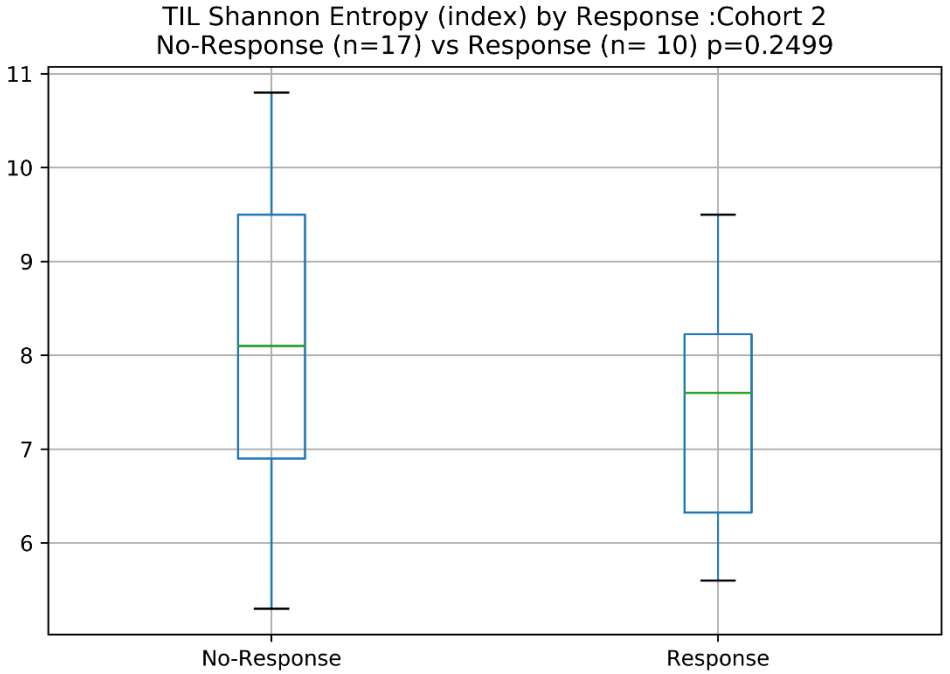
1. Rosenberg et al. CCR 2011
2. ASCO June 2019

Materials & Methods

- TIL products corresponding to 27 patients who underwent resection for the purpose of TIL generation and their matching Day 42 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 CD3 clones of interest and perform statistical analyses and generate figures.

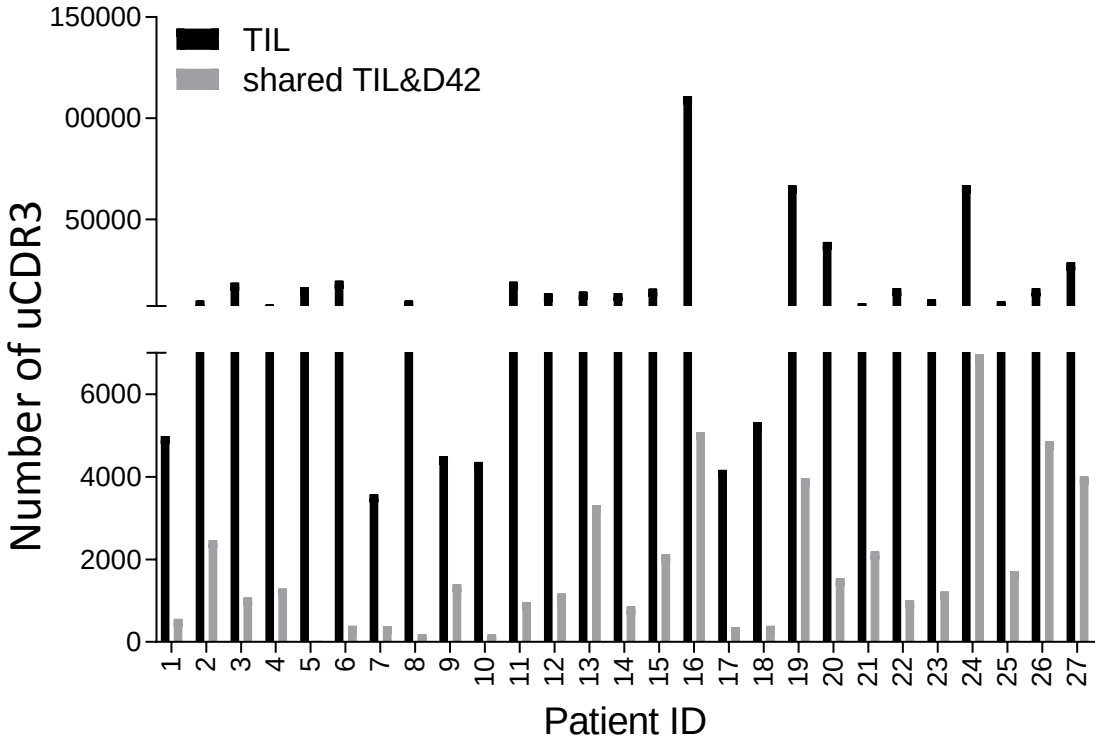
Assessment of TIL product diversity and clinical response

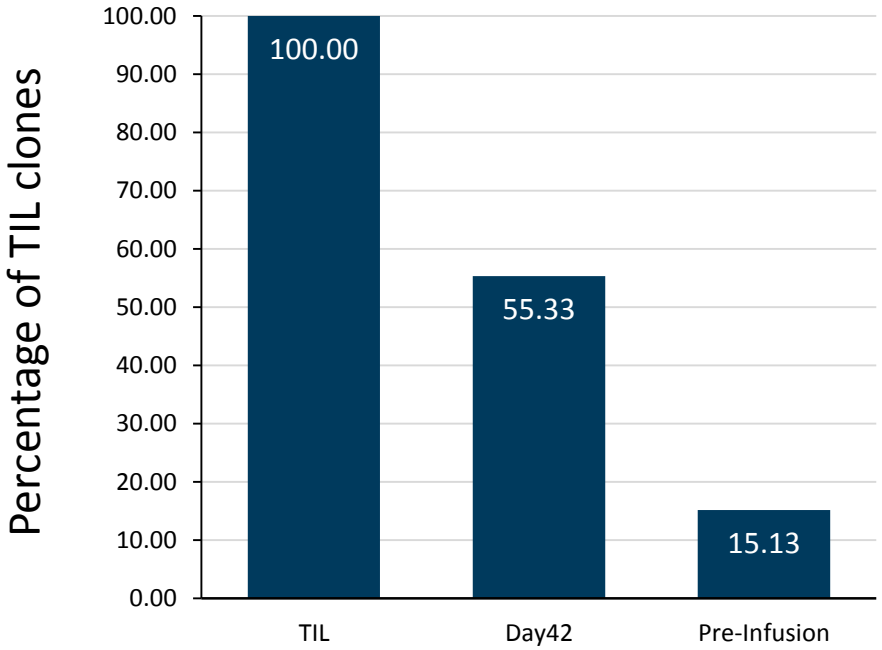




- No association between the number or diversity score of TCR clonotypes and clinical response.
- Anti-tumor T cells are present in the TIL infusion products of low and high diversity

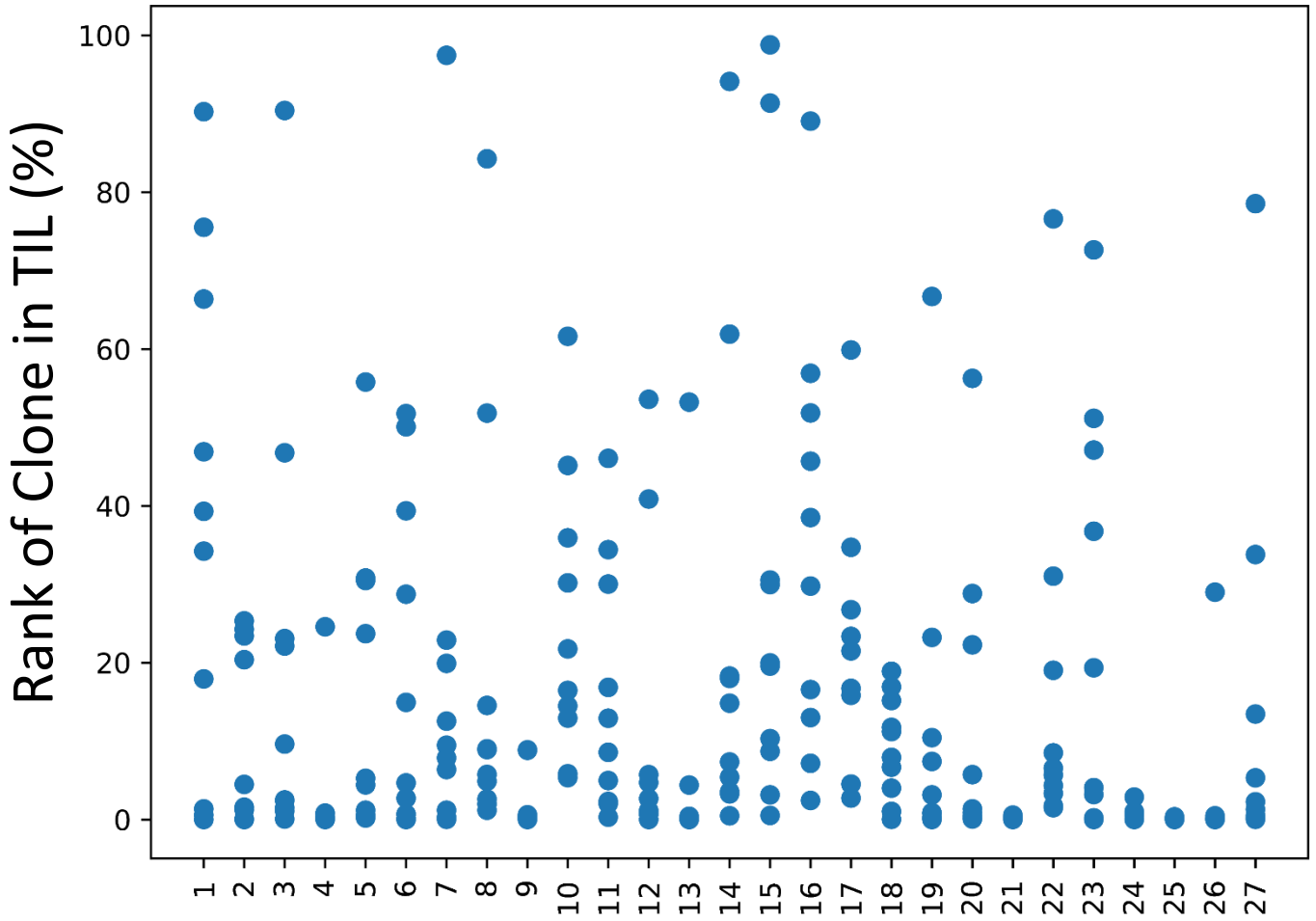
Assessment of persistence of clones post infusion





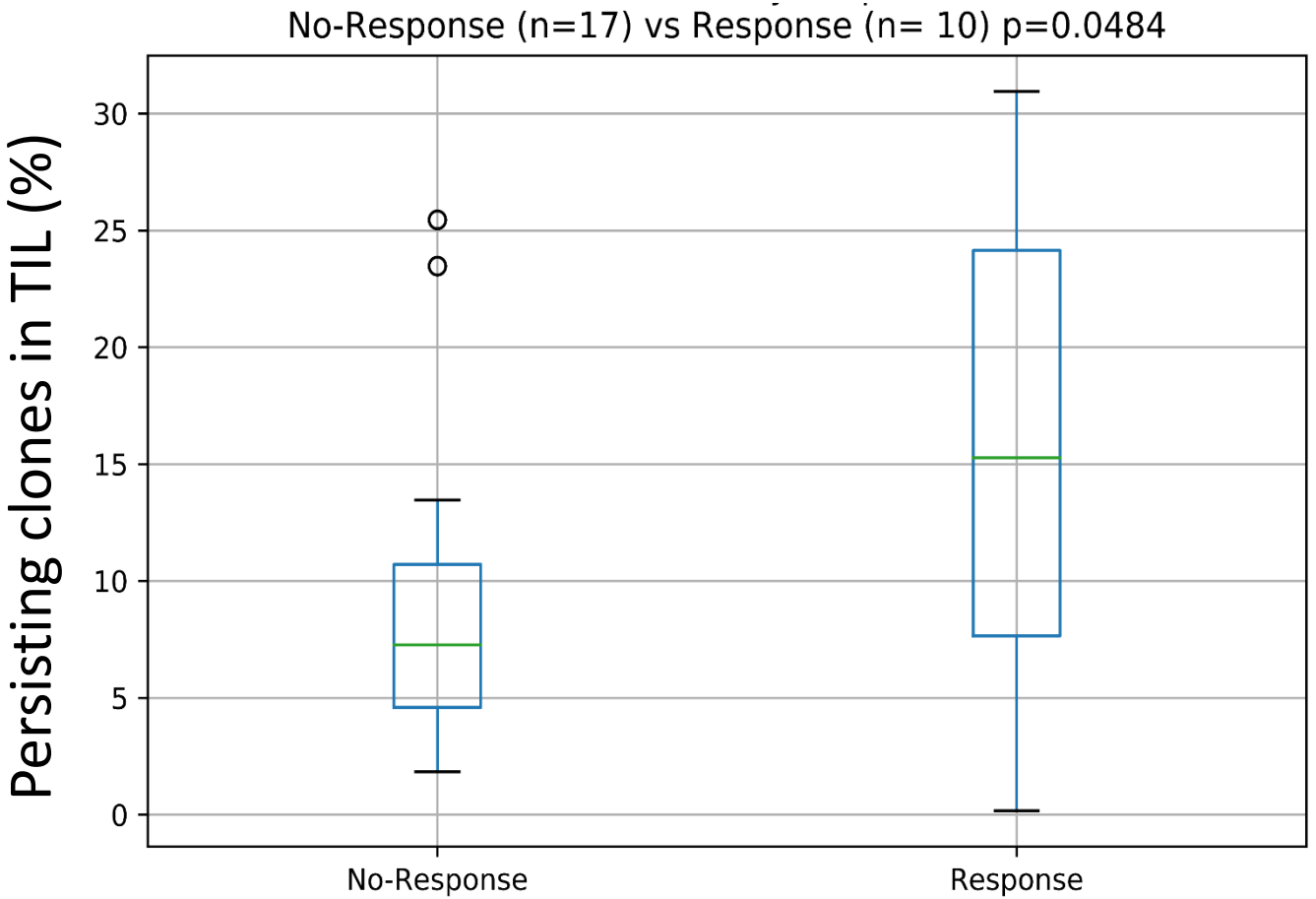
- Persisting TIL found in 100% of Patients at D42
- *In vivo* persisting TIL clones are present at much lower frequency in the blood pre-TIL infusion.

Assessment of prevalence of persisting clones



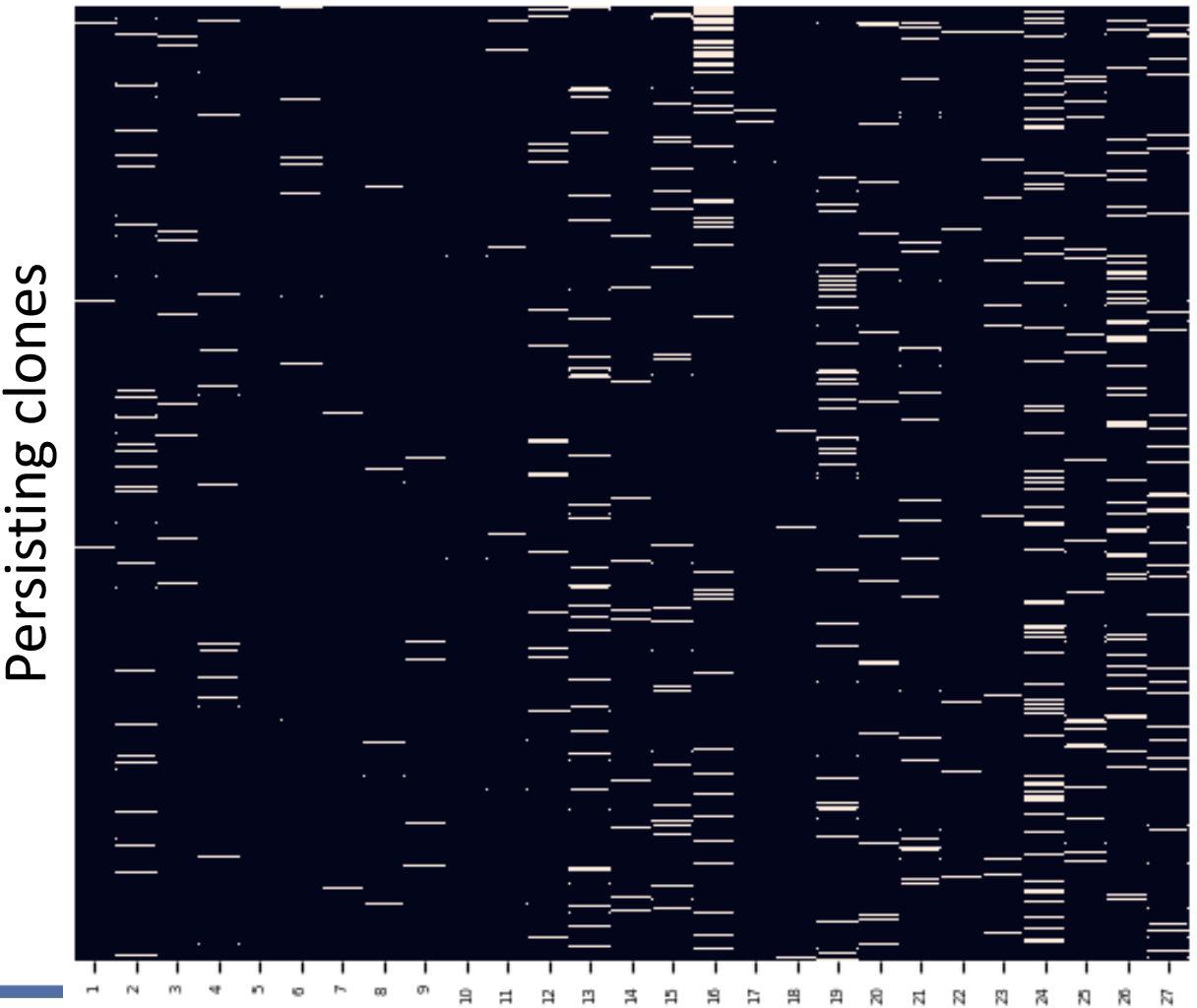
- The incidence of the most abundant clones post-infusion was determined in the TIL product of each of the 27 patients.
- The frequency of each clone in the initial TIL product did not predict prevalence at D42.

Correlation analysis of persisting T cell clones and clinical response



- Percentage of persisting clones provide a measure of overlap between the composition of the infusion product and T cells circulating *in vivo*.
- Clinical response may be associated with *in vivo* TIL persistence.

The T cell repertoire, including potentially tumor-specific clones, is unique in each Iovance TIL preparation



- 47,508 persisting clones were identified among the 27 subjects
  - 45,944 (96.7%) sequences found in only 1 subject.
  - 45 sequences were found in more than 4 subjects.
    - 17 (37.8%) corresponded to CDR3s previously identified to recognize non-tumor-related epitopes.

# OF SUBJECTS WITH COMMON CLONE(S)	# OF CLONES IN GROUP	# OF NON-TUMOR RELATED CLONES*
8	1	1
7	5	2
6	9	5
5	30	9
Sum	**45**	**17**

*CMV, EBV, flu, etc. per VDJdb [https://vdjdb.cdr3.net/]

- No association between any common clone and clinical response was observed.

Conclusions

- 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 lifileucel bulk TIL to treat solid tumors with their associated unique, patient-specific, mutational and neoantigen spectra.

Acknowledgements

- Sam Suzuki, Michelle Abelson, Michelle Blaskovich, Cécile Chartier
- Iovance team
- Physicians and patients

Disclosures

- Bioinformatics Consultant with Iovance Biotherapeutics