

TUMOR-REACTIVE TIL WITH AN EXHAUSTED PHENOTYPE CAN BE EXPANDED AND REGRESS HUMAN TUMORS

Session Title: Late-Breaking Research: Immunology 1
Session Date and Time: Sunday Apr 7, 2024 1:30 PM - 5:00 PM
Location: Poster Section 54
Poster Board Number: 3
Abstract Presentation Number: LB067

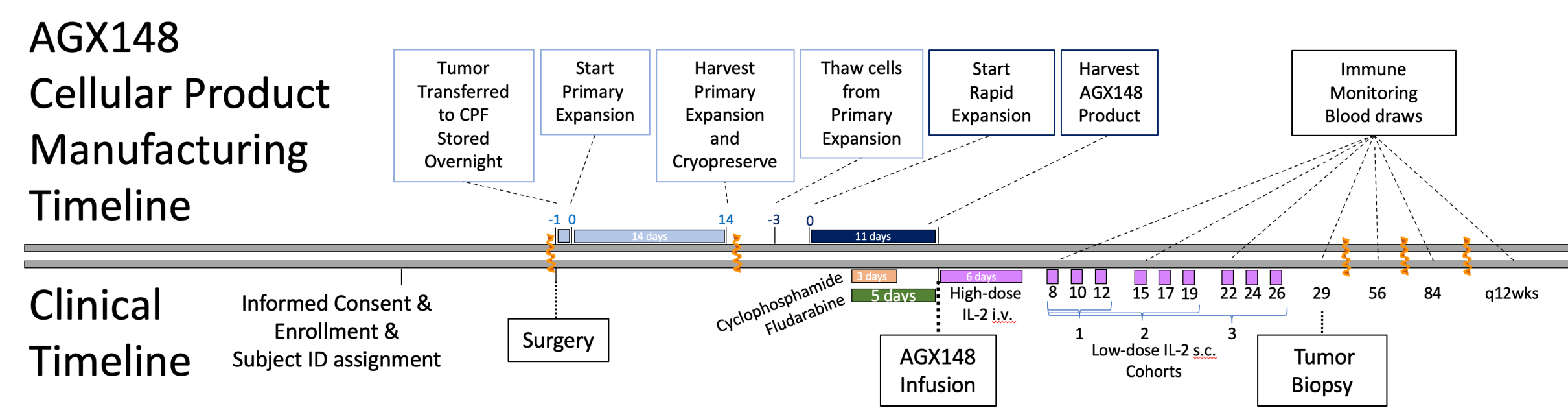
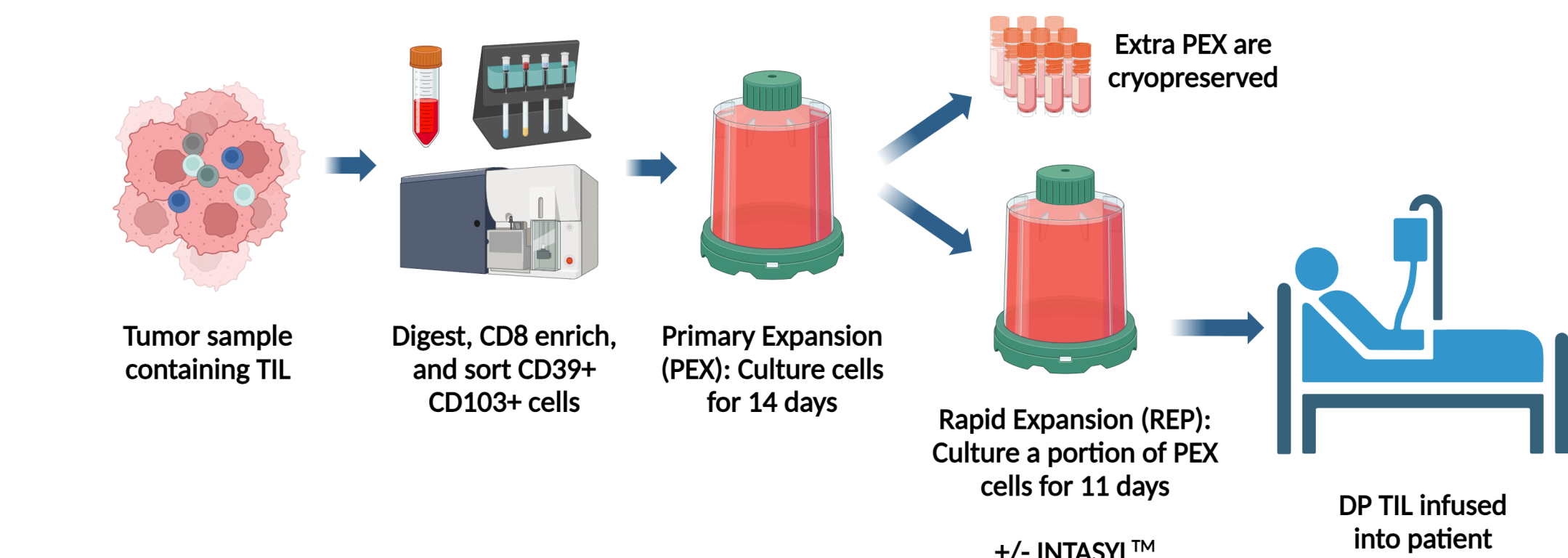
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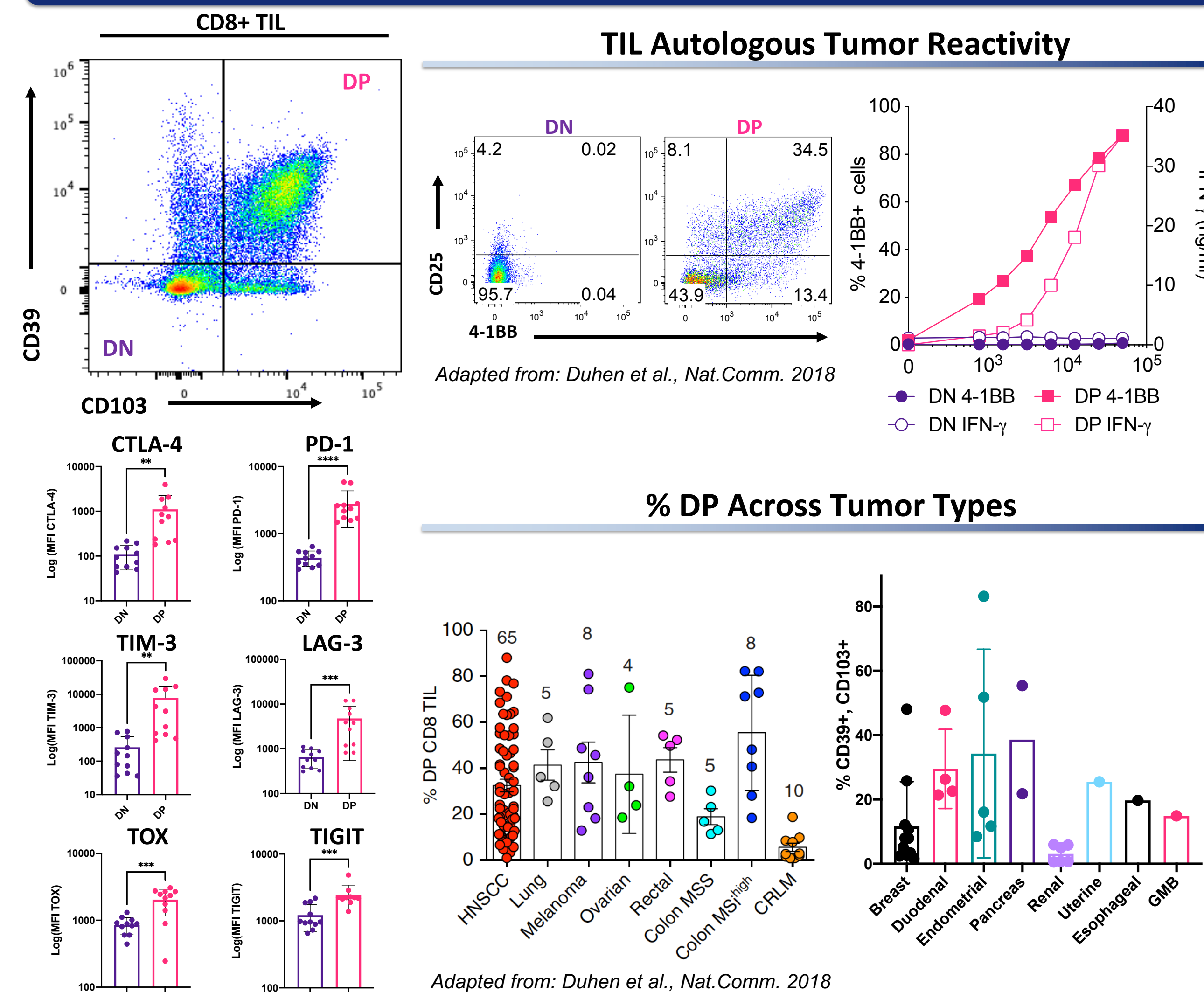


SUMMARY

Tumor-reactive human CD8⁺ CD39⁺ CD103⁺ (Double Positive, DP) T cells are predominantly found in the tumor microenvironment with an exhausted phenotype (significantly high levels of CD39, PD-1, CTLA-4, and TIM-3). Our unique expansion method allows these DP cells to grow from thousands into billions, traffic to the tumor site, recognize autologous tumor, and facilitate tumor regression. We tested the CD8 DP TIL *in vivo* using a xenograft model with immune-compromised mice that constitutively secrete human IL-2 (NOG-hIL-2), which was necessary for the long-term survival of TIL in the periphery and for tumor regression. These preclinical data were the basis for our Phase 1 human clinical trial design for the adoptive transfer of CD8 DP TIL (AGX148). The trial is a first-in-human protocol for adults with solid tumors (NCT05902520) consisting of three cohorts: 2 weeks, 3 weeks, or 4 weeks of IL-2 administration after adoptive TIL transfer. Each cohort contains six patients; 3 receiving DP TIL alone and 3 receiving DP TIL with PD-1 siRNA knockdown using INTASYLTM compound PH-762. The first 3 patients have been treated; all previously failed standard therapy, including checkpoint blockade. No serious adverse events were observed. Two of the three patients had partial responses and the third patient had stable disease.



BACKGROUND



CD8⁺ CD39⁺ CD103⁺ (DP) cells are found in a variety of tumor types and have a distinct exhausted phenotype compared to the DN. DP cells upregulate 4-1BB, CD25, and IFN- γ in tumor coculture; DN cells do not.

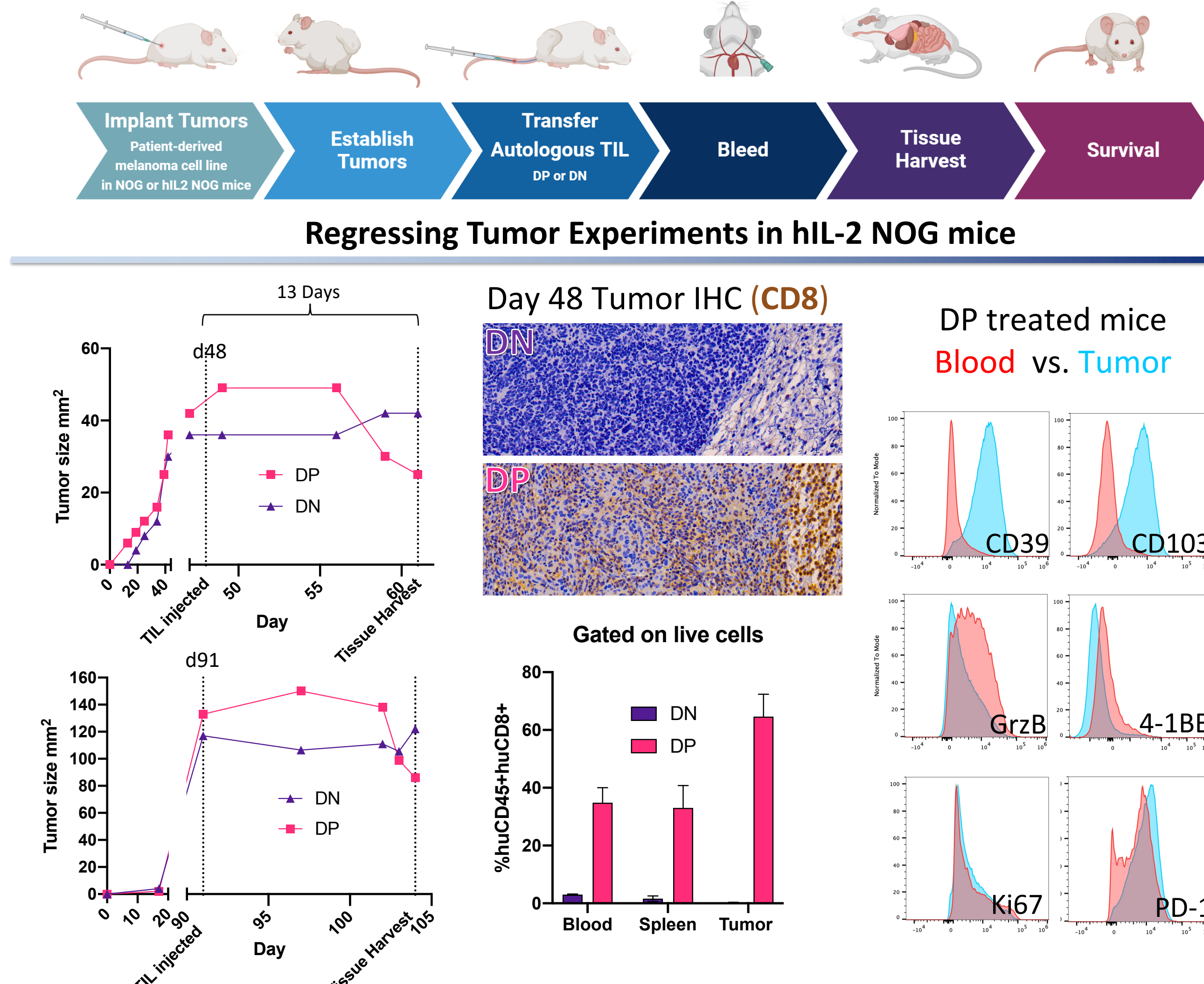
ACKNOWLEDGEMENTS



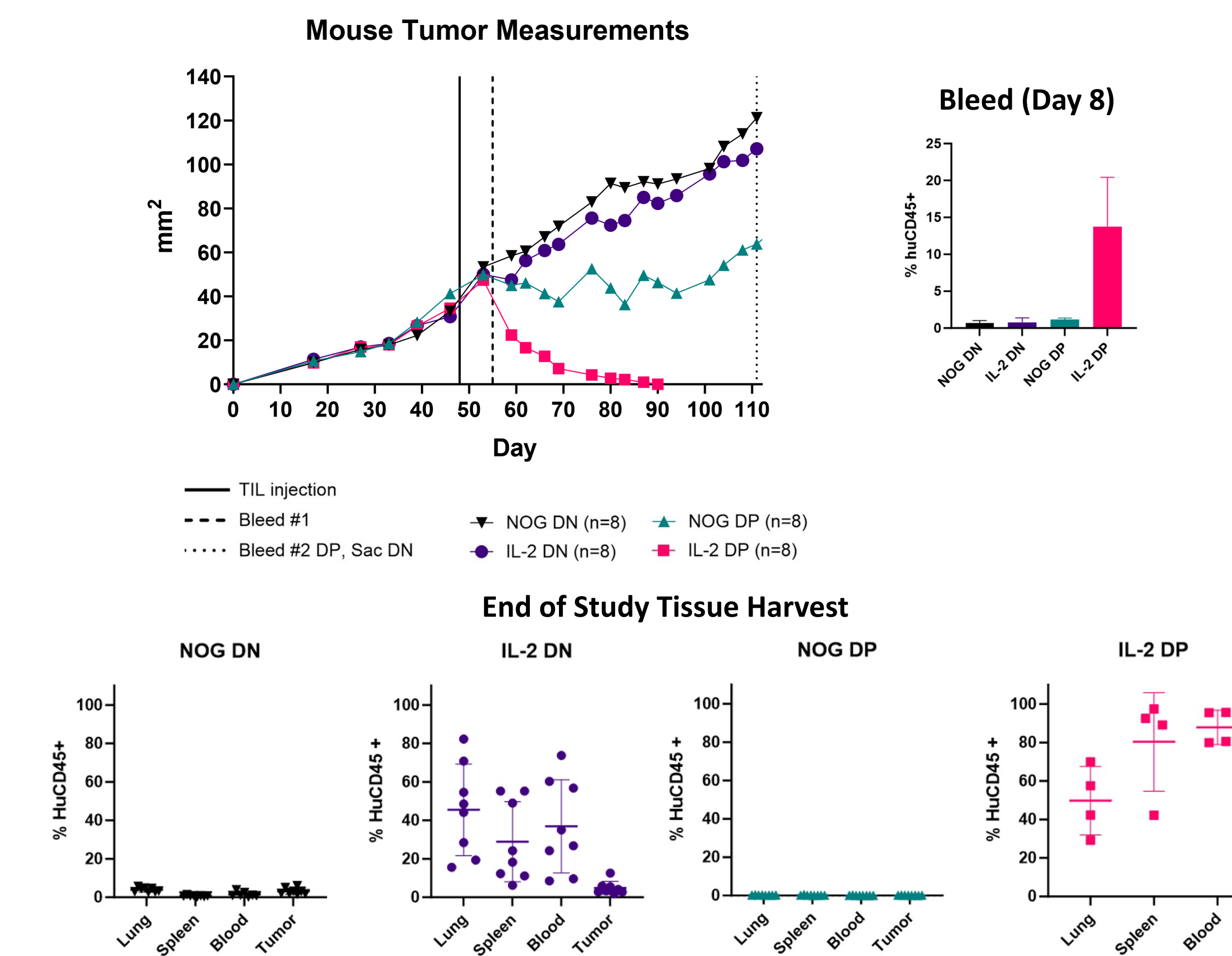
- Clinical Trials- Tracy Kelly, Shannon Erickson, Aaron Enciso
- CRAD- Amanda Lyon, Traci Brotherton
- CPF- Jessica Huang
- Computational Immuno-oncology and Bioinformatics- Venkatesh Rajamanickam
- IML- Iliana Gonzalez, Tanisha Christie, Yoshinobu Koguchi
- Molecular Pathology Core
- IHC- Zhaoyu Sun



PRECLINICAL PDX DATA

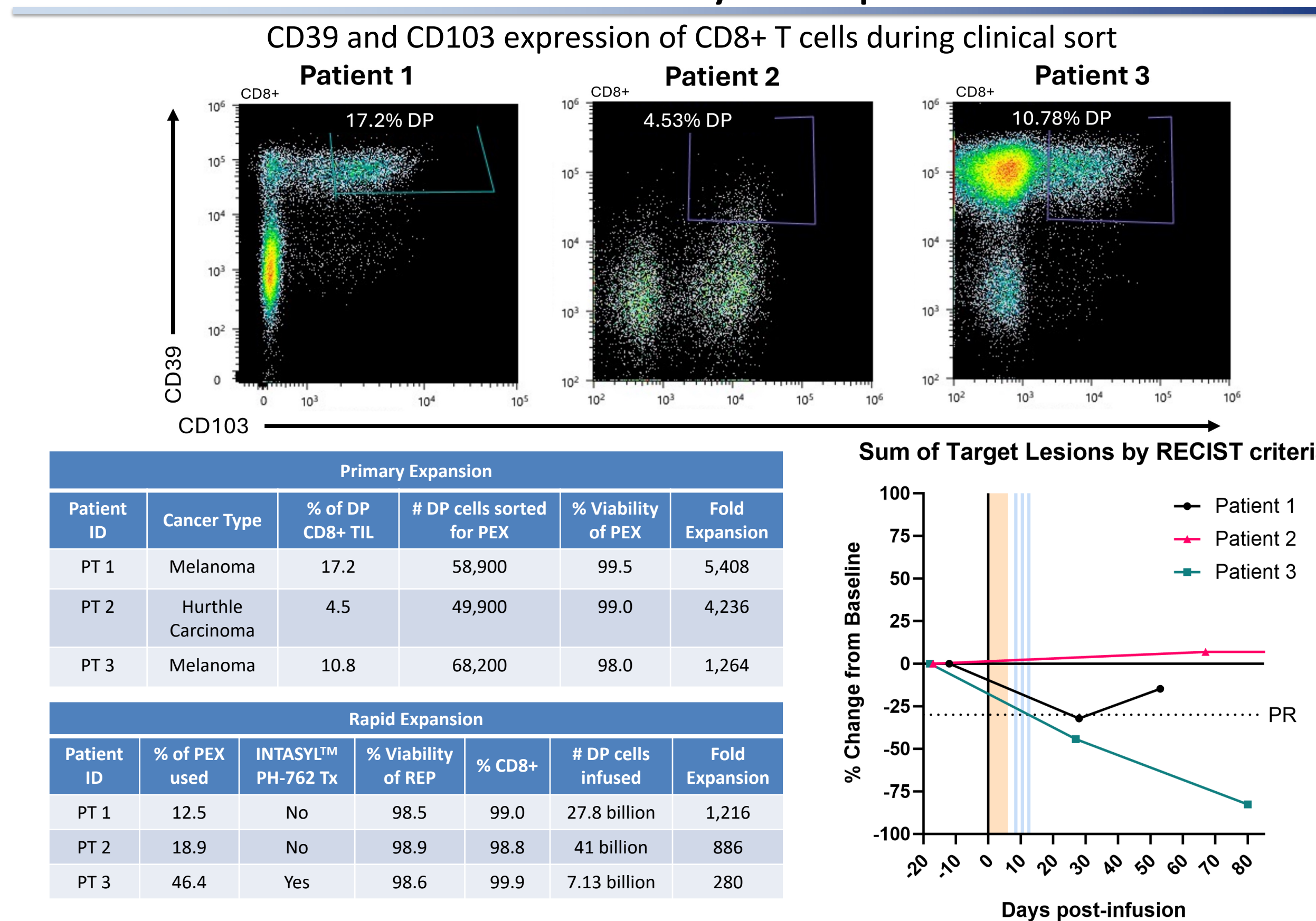


Survival Experiment in NOG or hIL-2 NOG mice

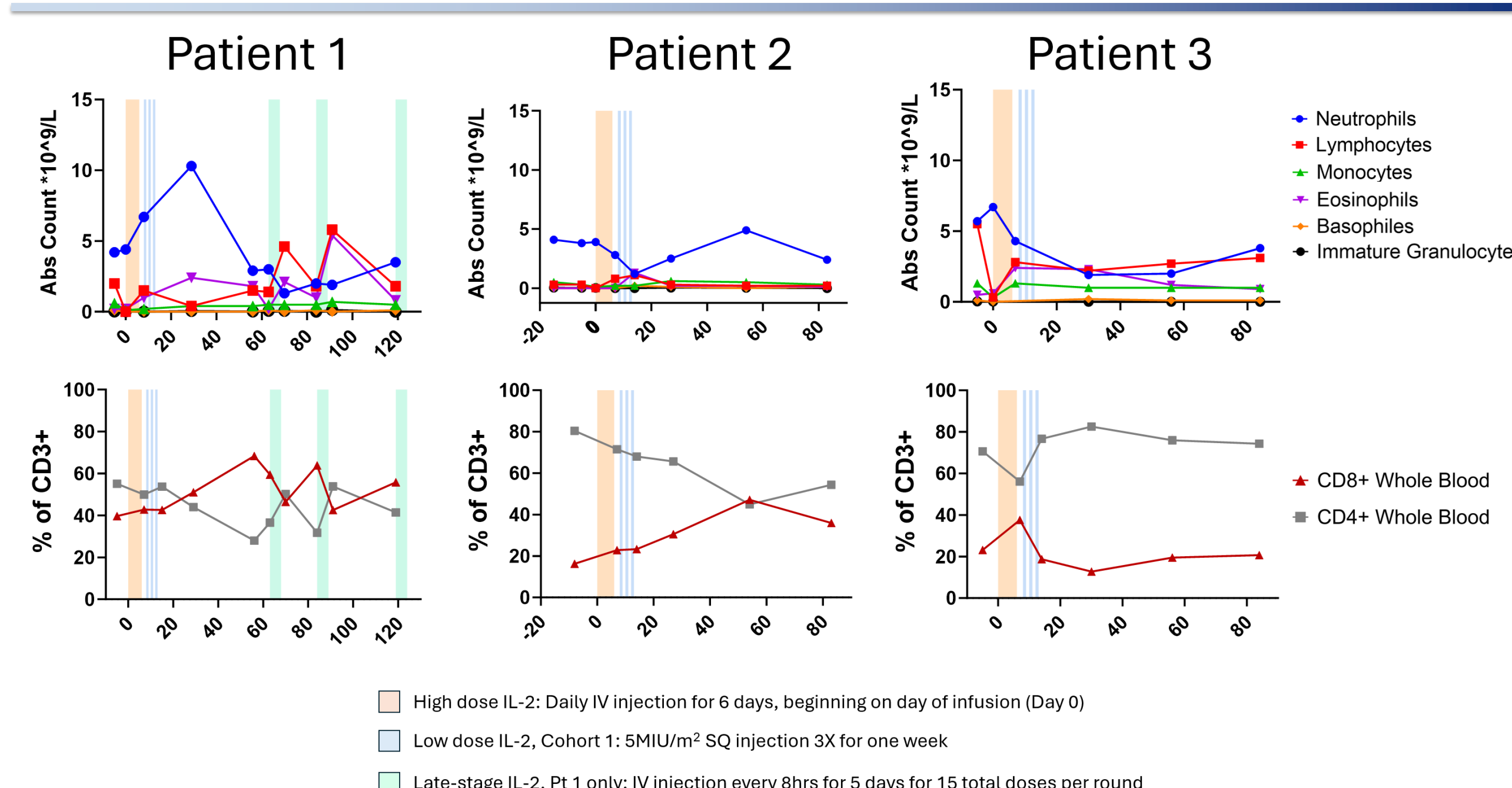


PRELIMINARY CLINICAL TRIAL RESULTS

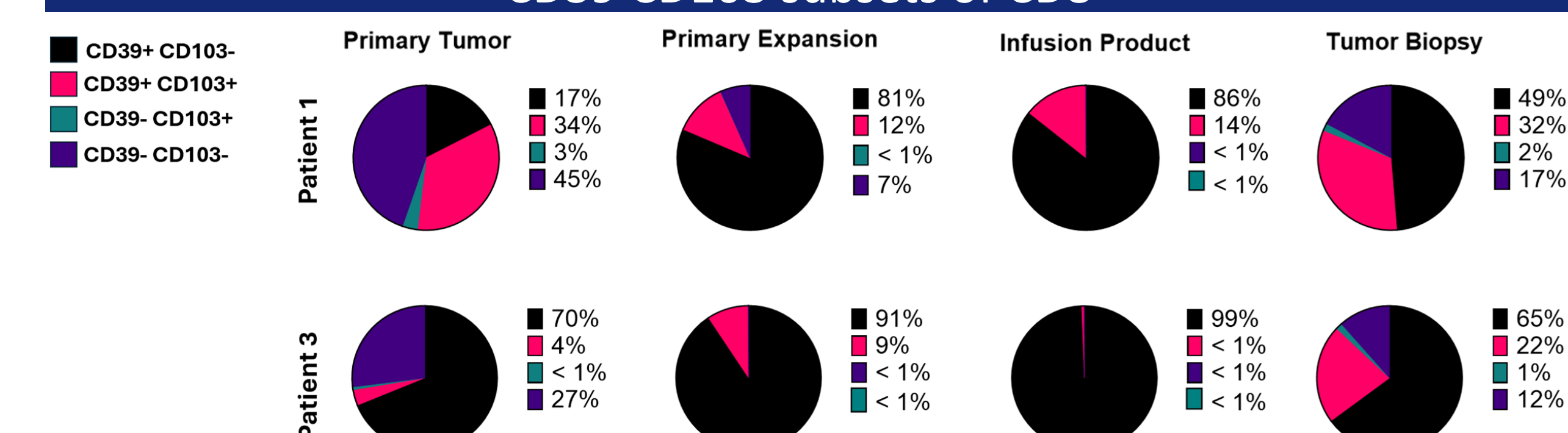
Product summary: First 3 patients



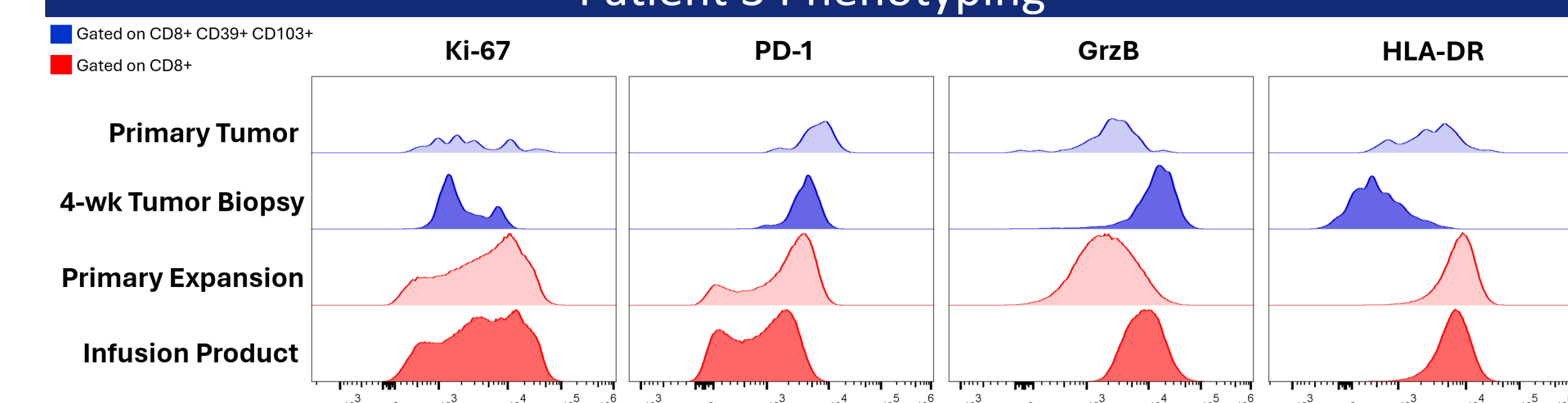
Immune Monitoring: Blood and TIL Product Phenotypes



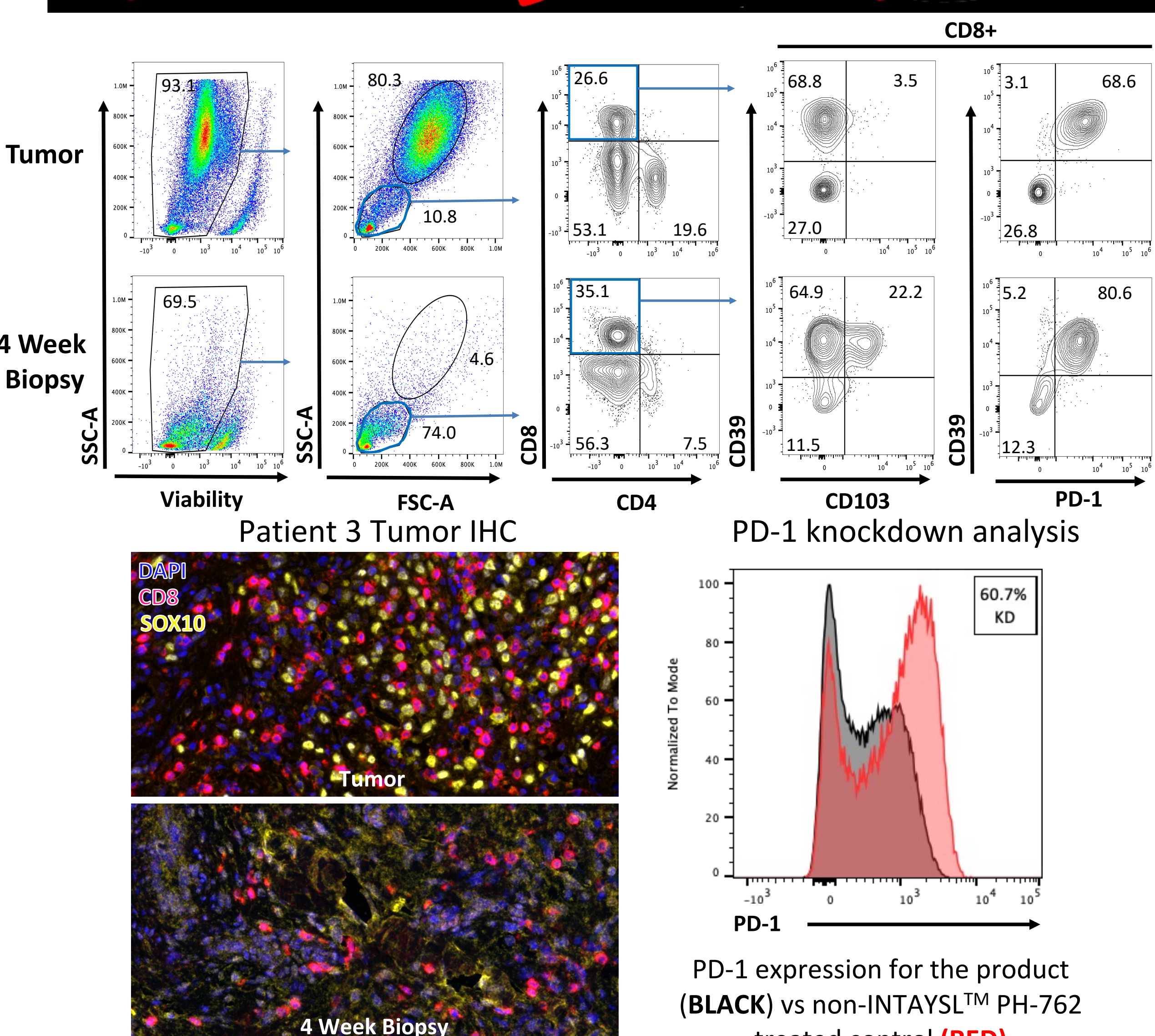
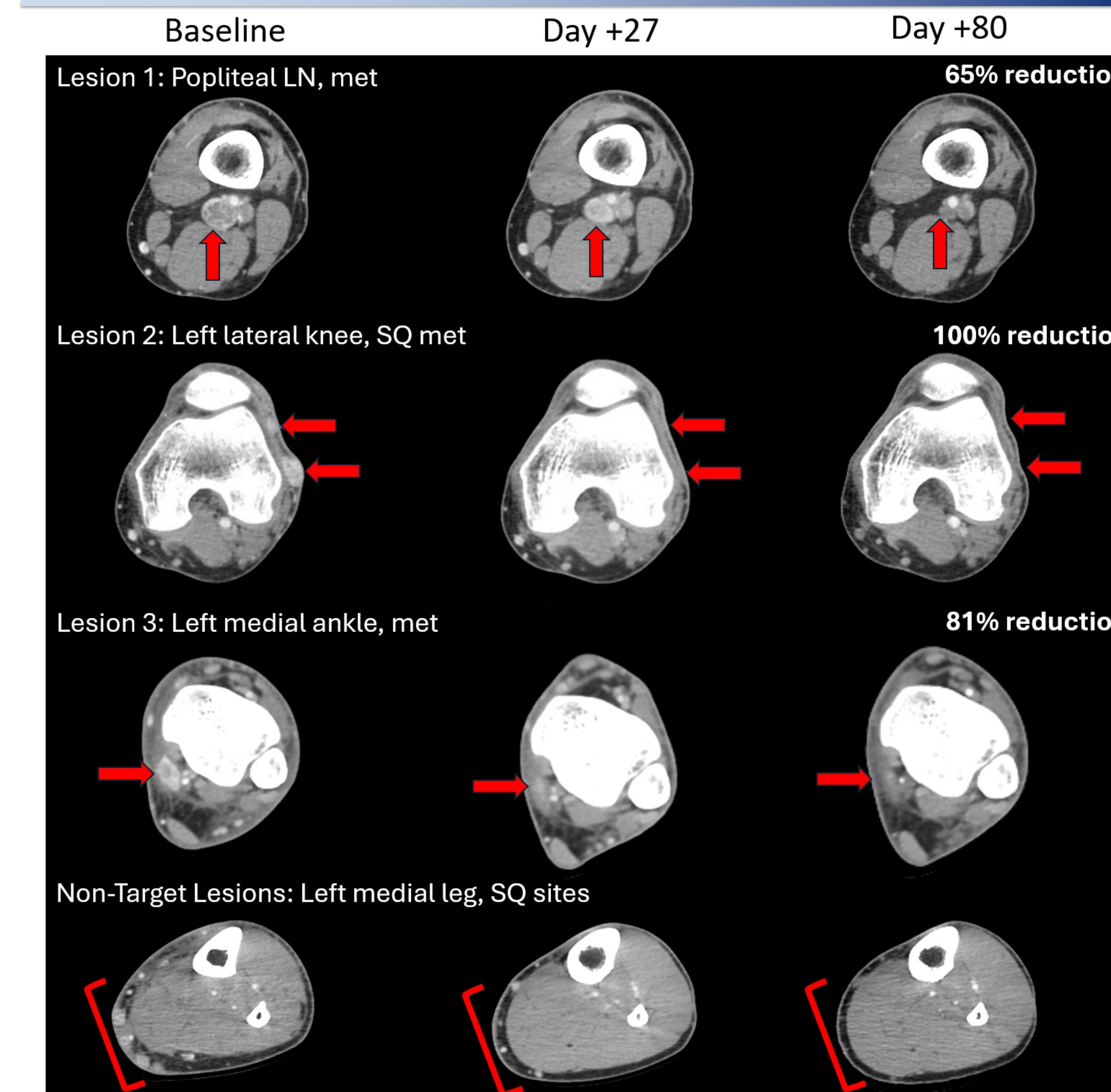
CD39 CD103 subsets of CD8+



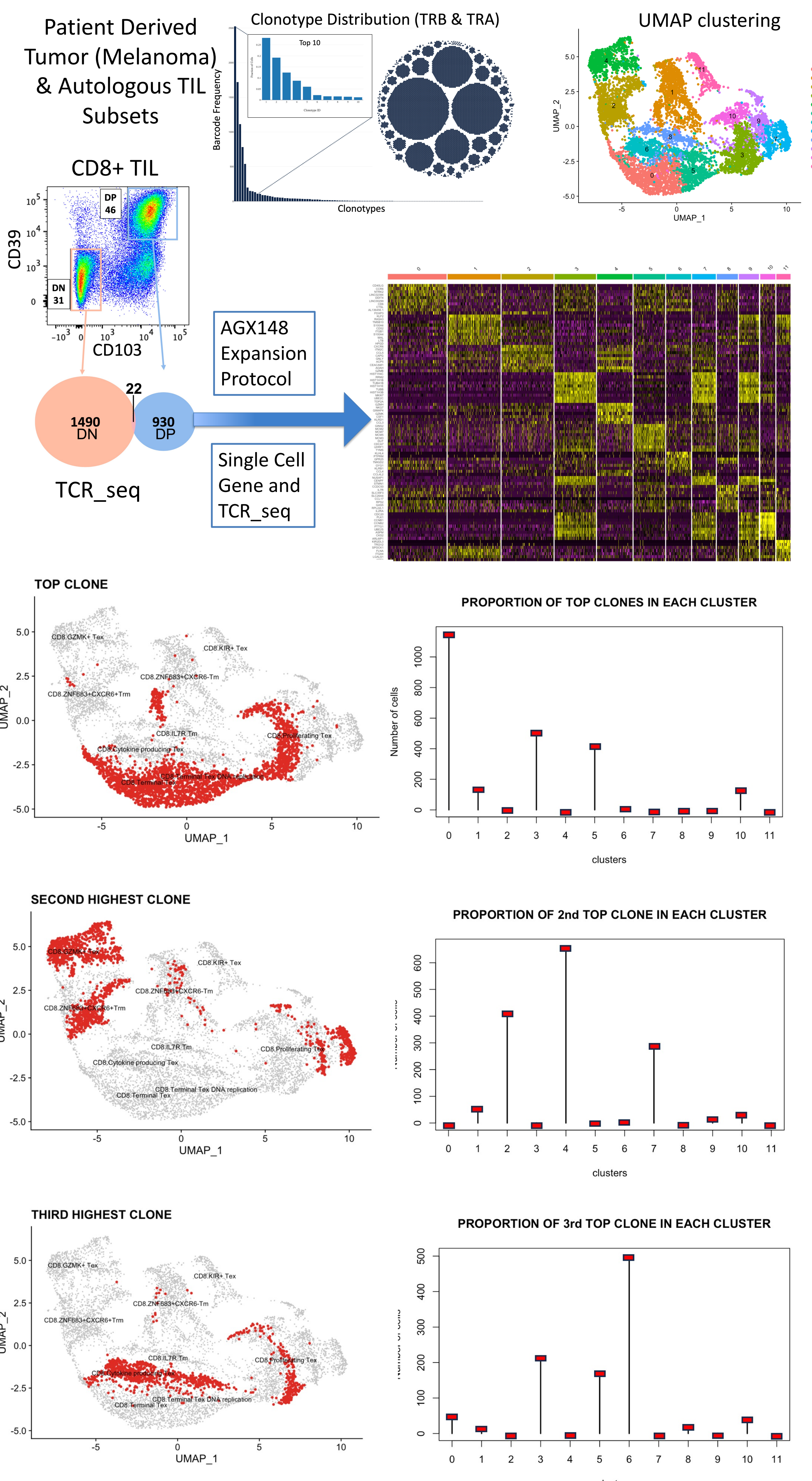
Patient 3 Phenotyping



Patient 3: INTASYLTM PH-762 treated



DP SINGLE CELL GENE AND TCR-SEQ



CONCLUSIONS

- CD8⁺ CD39⁺ CD103⁺ DP tumor-reactive TIL are found in a variety of solid tumor types at varying frequencies and have a significant "exhausted" phenotype.
- In pre-clinical PDX models, adoptively transferred DP TIL persisted long-term, trafficked to and cleared autologous tumors in the presence of IL-2.
- TCR-seq showed distinct TCR repertoire in the DP vs DN TIL.
- Single-cell TCR-seq and gene-seq demonstrated diversity of phenotypes within the DP TIL product.
- Using AgonOx's AGX148 selection and expansion method, DP TIL can be grown *in vitro* to billions of highly functional cells.
- AgonOx's AGX148 selected-TIL product minimizes bystander expansion and is highly enriched with tumor-reactive T cells.
- INTASYLTM PH-762 treatment reduced PD-1 protein expression on AGX148 TIL Product.
- Phenotype of blood and tumor biopsies revealed distinct phenotypic changes after TIL treatment in both humans and mice.
- Preliminary clinical trial results from 3 patients showed evidence of tumor regression on day +29 (2 PR (melanoma) and 1 SD (thyroid cancer) with 1 PR and 1 SD ongoing > 80 days).