Preliminary safety and efficacy of gavocabtagene autoleucel (gavo-cel, TC-210), a T cell receptor fusion construct (TRuC™), in patients with treatment refractory mesothelin overexpressing solid tumors

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abstract 4954

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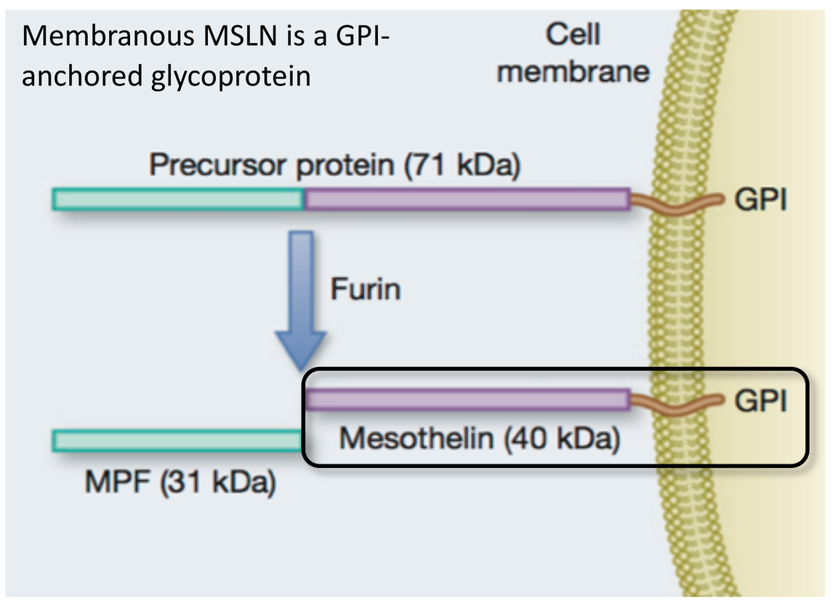
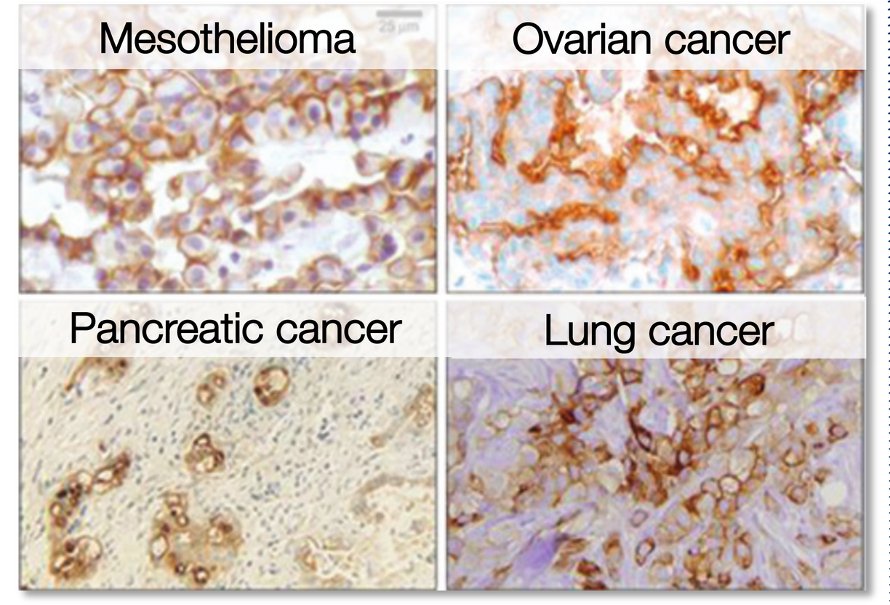
Background

- Mesothelin (MSLN) results from the cleavage of a 71-kDa GPI-anchored precursor polypeptide by the protease Furin.
- Surface MSLN expression on normal tissue is restricted to the serosal cells of the fallopian tubes, pleura, pericardium, and peritoteum.
- MSLN is highly expressed in a wide range of solid tumor types. In the U.S. alone, MSLN overexpression is present in over 80,000 patients/year with either malignant mesothelioma (MPM), ovarian cancer, cholangiocarcinoma, or non-small cell lung cancer (NSCLC).
- We are testing a novel genetically engineered anti-mesothelin TRuC™ T cell therapy called gavo-cel (TC-210) in a Phase 1 study in treatment refractory patients with any of the four aforementioned cancers (NCT03907852).

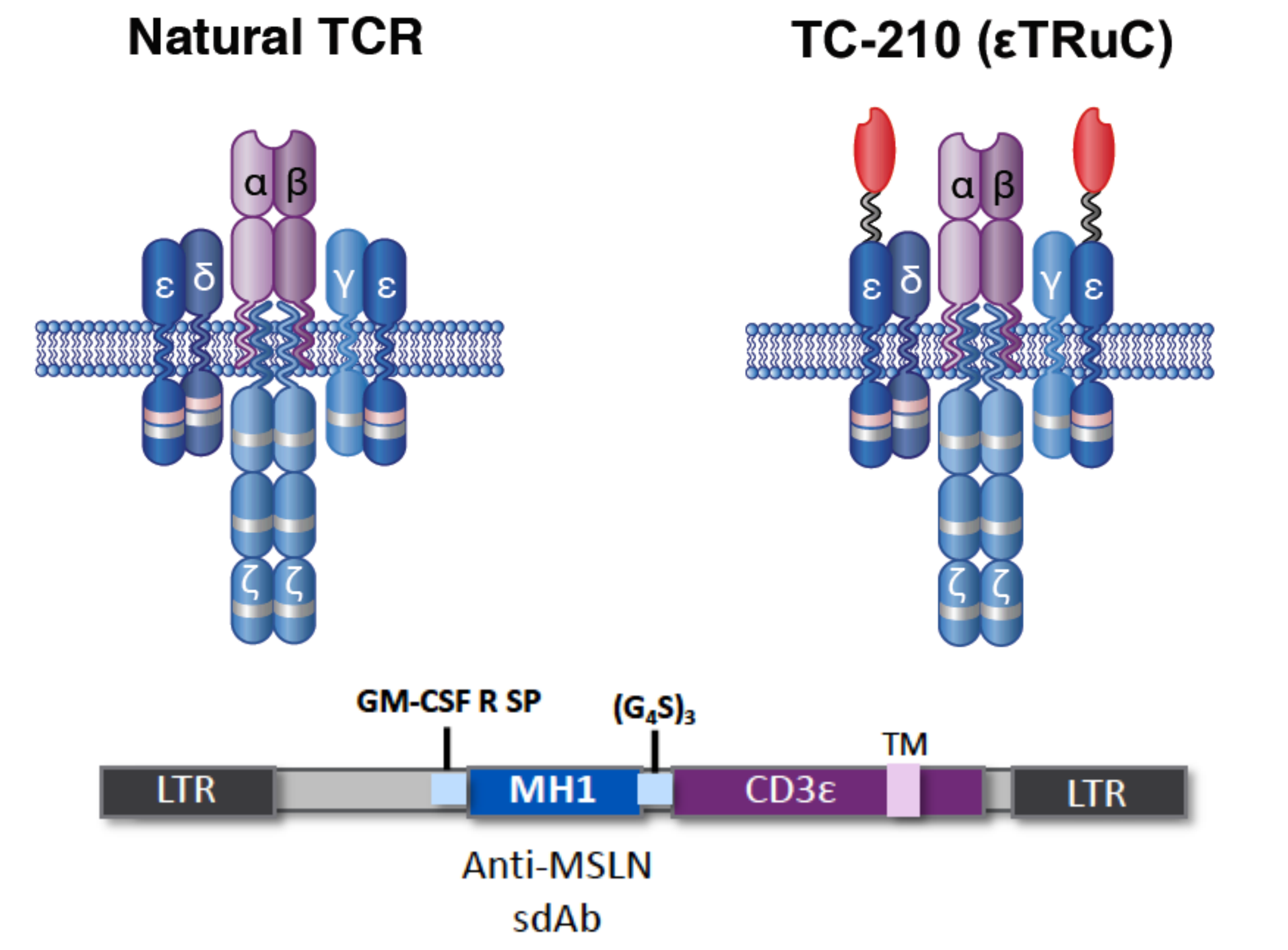




Pastan et al., Cancer Res, 2014, Morello et al., Cancer Discovery, 2016; O'Hara et al., Future Medicines, 2016; Hassan et al., JCO, 2016; Argani et al., Clinical Cancer Research. 2001; Lanitis et al., Mol Therapy, 2012

gavo-cel: anti-MSLN CD3ε TRuC

- Gavocabtagene autoleucel (gavo-cel, TC-210) is a T cell receptor fusion construct (TRuC™) engineered by transducing autologous T cells with a lentiviral vector encoding for an anti-MSLN, llama-derived, single domain antibody fused to the CD3epsilon subunit using a flexible glycine serine sequence.
- Upon translation, gavo-cel TRuCs integrate and reprogram intact TCR complexes to recognize tumor surface mesothelin in an HLA-independent manner.



Study Design

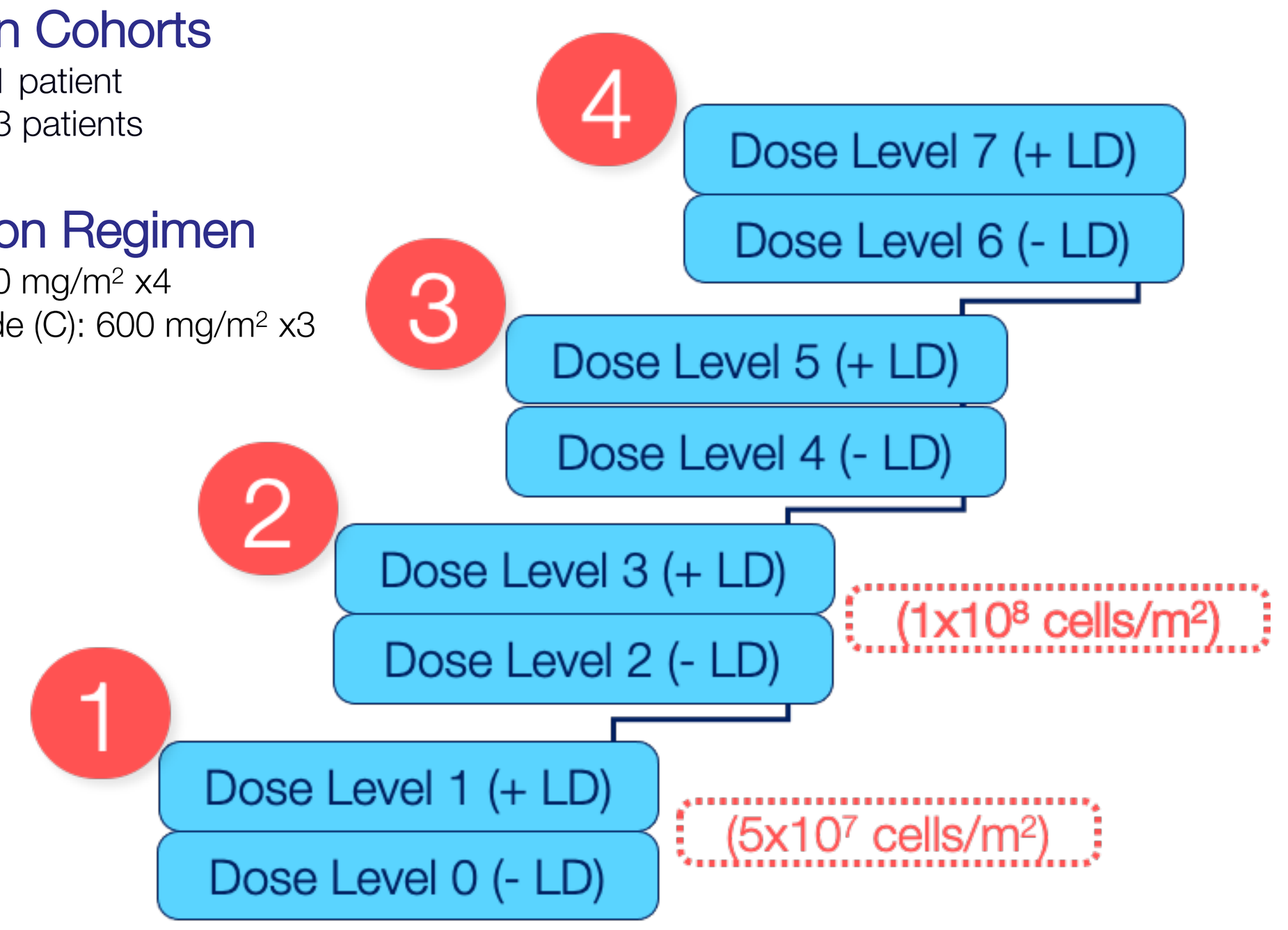
- Phase 1/2 open-label study (NCT03907852) to evaluate the safety and efficacy of gavo-cel in MSLN+ cancers.

Dose Escalation Cohorts

- (– LD) Cohorts = 1 patient
- (+ LD) Cohorts = 3 patients

Lymphodepletion Regimen

- Fludarabine (F): 30 mg/m² x4
- Cyclophosphamide (C): 600 mg/m² x3



- Dose escalation involves the testing of 4 gavo-cel doses following a 3+3 design.
- Within each dose, gavo-cel is tested at 2 dose levels (DL): first in the absence of lymphodepletion (LD) in a 1-patient cohort and then, the same dose is tested following LD in a 3-patient cohort.

Phase 1 Objectives

- Primary: determine recommended Phase 2 dose (RP2D)
- Secondary: ORR (CR+PR by RECIST v1.1), DCR (ORR+SD), duration of response, PFS, EFS, OS
- Exploratory: expansion, persistence, phenotype, functionality of T cells, cytokine levels, immunogenicity

Phase 1 Key Eligibility Criteria

- ≥ 18 years of age
- ECOG 0-1
- Adequate organ function
- Pathologically confirmed MPM, NSCLC, ovarian cancer, or cholangiocarcinoma
- Must have received at least 1 systemic standard of care therapy for metastatic and/or unresectable disease
  - Mesothelioma: platinum-based therapy
  - NSCLC: if actionable mutation must have received appropriate FDA approved agent (e.g. osimertinib); if no actionable mutation, must have received a currently approved frontline regimen
  - Ovarian cancer: post frontline therapy; post PARP inhibitor if BRCA1/2 mutated
  - Cholangiocarcinoma: post one systemic regimen (frontline if patient refuses standard frontline therapy)
- Measurable disease per RECIST v1.1
- MSLN expression by IHC (Roche Ventana): 2+/3+ in ≥ 50% viable tumor cells

Patient and Tumor Characteristics

Dose Level	0	1	1	1	1	1	1	2
Patients	1	2	3	4	5	6	7	8
Age/Sex	61/M	74/M	52/F	36/M	70/F	69/M	84/F	46/M
Diagnosis	MPM	MPM	MPM	MPM	Ovarian Ca	MPM	MPM	MPM
MSLN 2+/3+ (% of tumor cells)	90	60	73	95	55	90	100	90
No. Prior Rx	8	3	3	9	6	5	2	9
Prior ICI	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Prior anti-MSLN	Yes	No	No	No	No	Yes	No	Yes
Bridging Therapy	None	Pemetrexed + Cisplatin	Pemetrexed + Carboplatin	None	Liposomal doxorubicin	None	Rebastinib + Carboplatin	None

Summary of Grade ≥3 Treatment Emergent AEs

Adverse Event	N=8
Hematologic	
Neutropenia	6 (75)
Lymphopenia	7 (88)
Thrombocytopenia	2 (25)
Adverse Events of Special Interest	
On Target / On Tumor	
CRS	2 (25)
Neurotoxicity	0
On Target / Off Tumor	
Pericarditis / Pericardial effusion	0
Pleuritis / Pleural effusion	0
Peritonitis / Ascites	0
Infection / Inflammation	
Pneumonitis*	1 (13)
Sepsis*	1 (13)

*Occurred in same patient who experienced Grade 3 cytokine release syndrome (CRS)

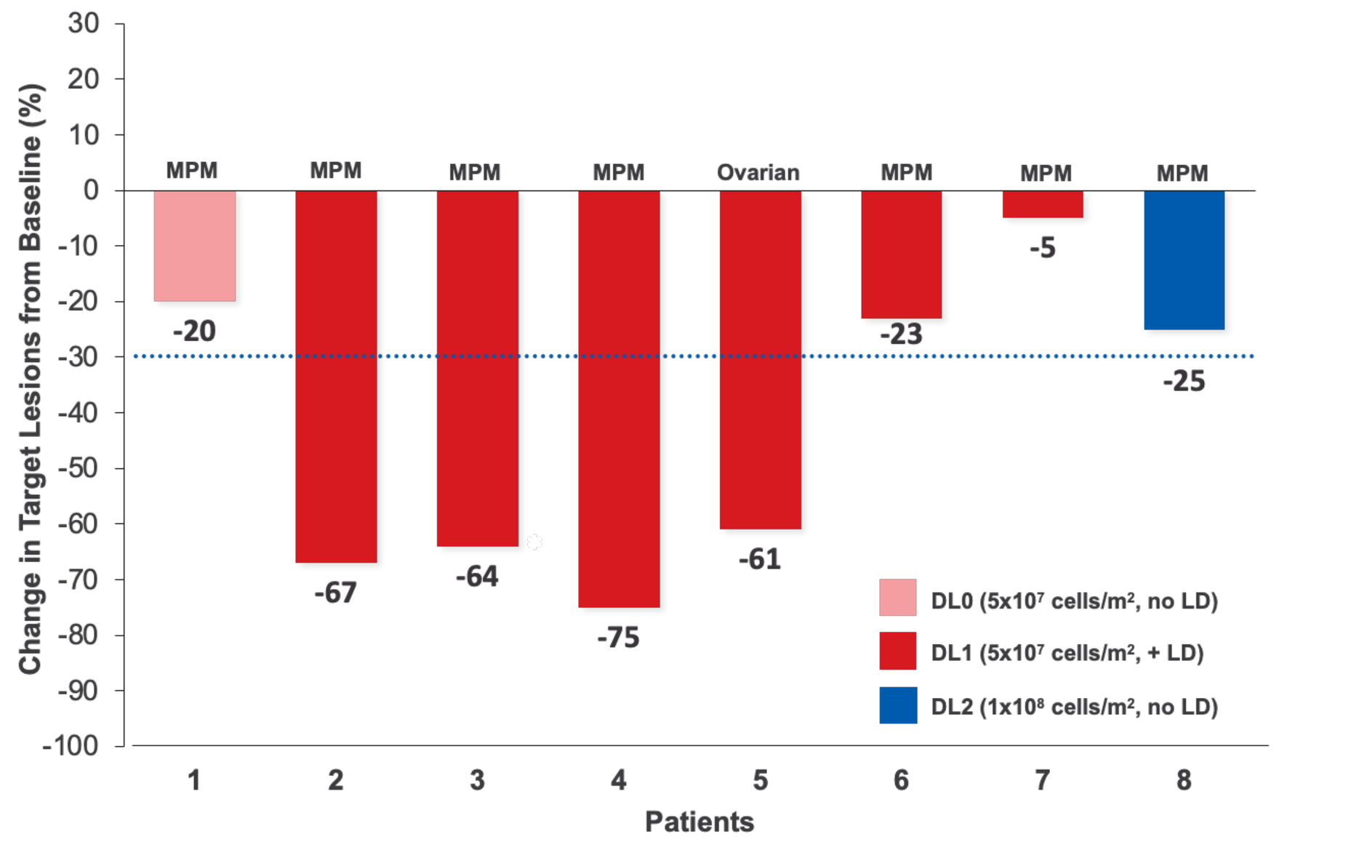
Response Assessment Summary (RECISTv1.1)

Dose Level	0	1	1	1	1	1	1	2
Patients	1	2	3	4	5	6	7	8
LD Chemo	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Gavo-cel dose	$5x10^7/m^2$	$5x10^7/m^2$	$5x10^7/m^2$	$5x10^7/m^2$	$5x10^7/m^2$	$5x10^7/m^2$	$5x10^7/m^2$	$1x10^8/m^2$
Best Target Lesion Response	SD	PR	PR	PR	PR	SD	SD	SD
Best RECIST v1.1 Response	SD	PR*	SD	PR	PR	SD	SD	SD

*Unconfirmed

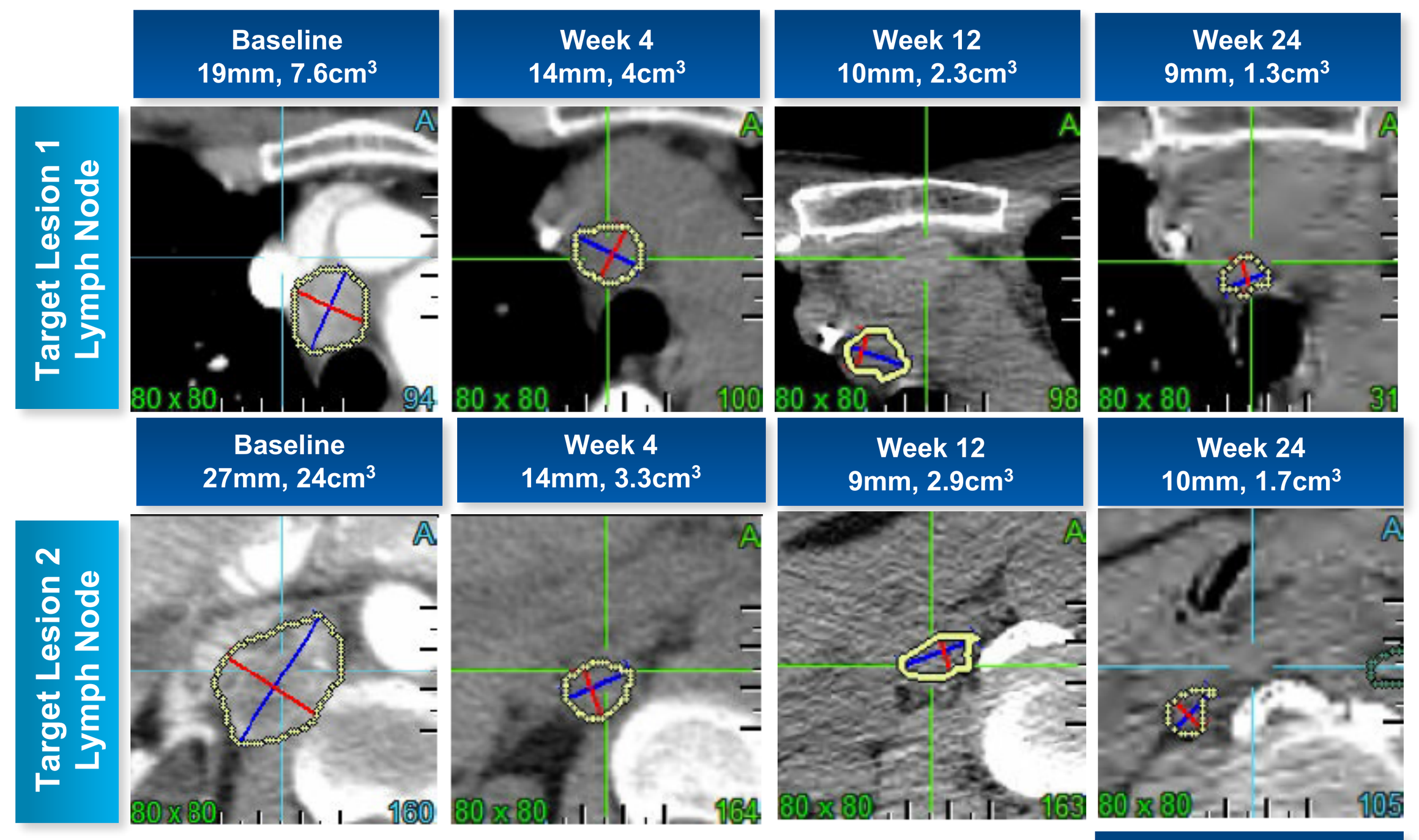
Best Tumor Regression

Patients	All	Gavo-cel + LD
Number	8	6
ORR	38%	50%
DCR	100%	100%



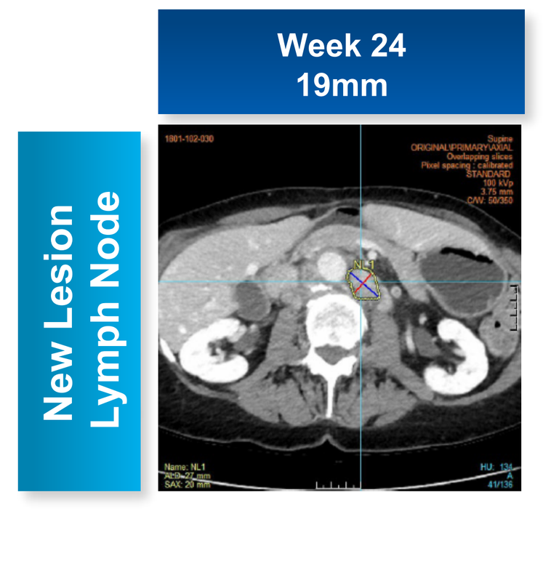
ORR: overall response rate; DCR: disease control rate (ORR + Stable Disease lasting at least 12 weeks)
DL: dose level; LD: lymphodepletion; MPM: malignant pleural/peritoneal mesothelioma

Ovarian Cancer Response (Patient #5)

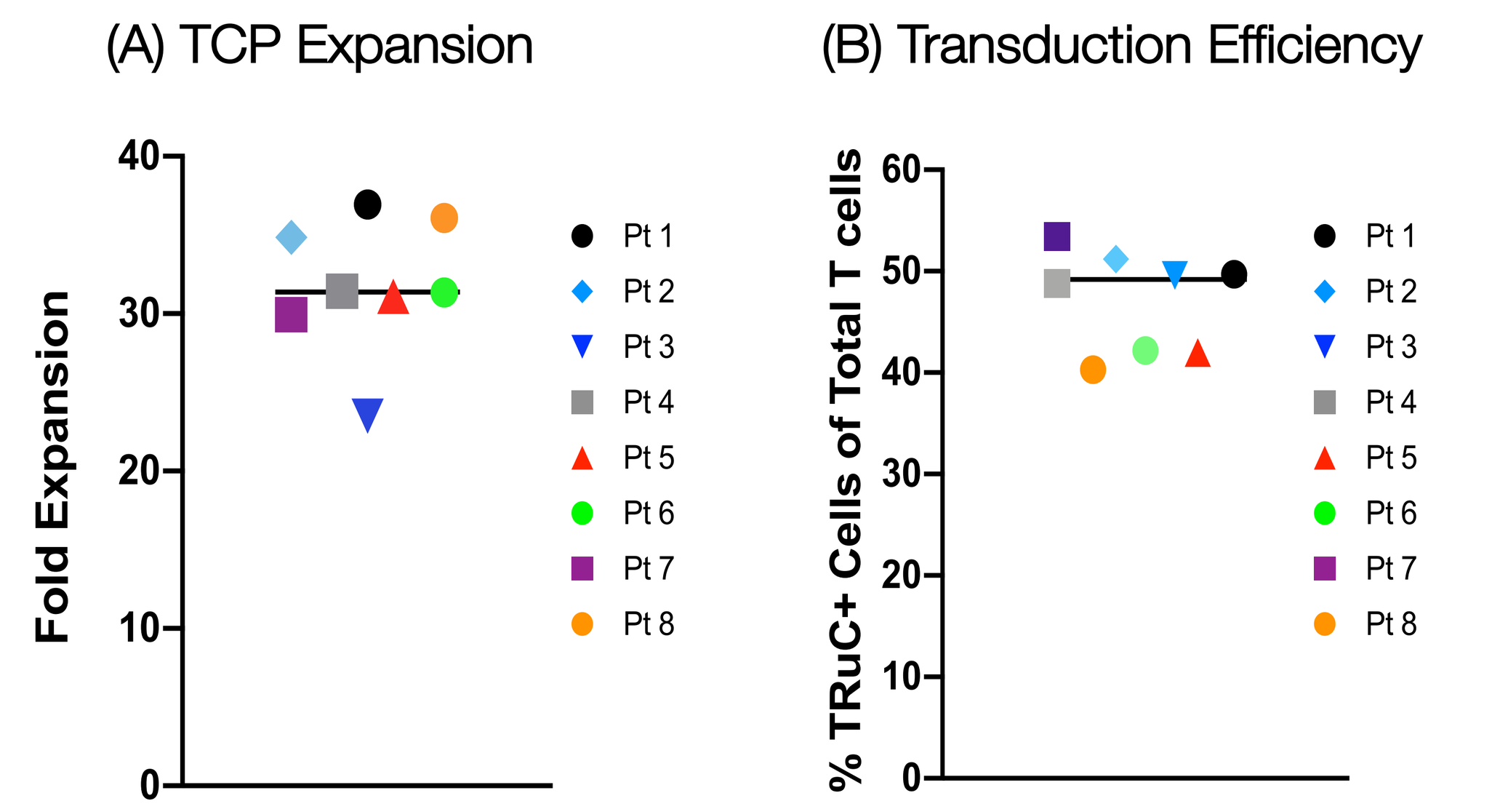


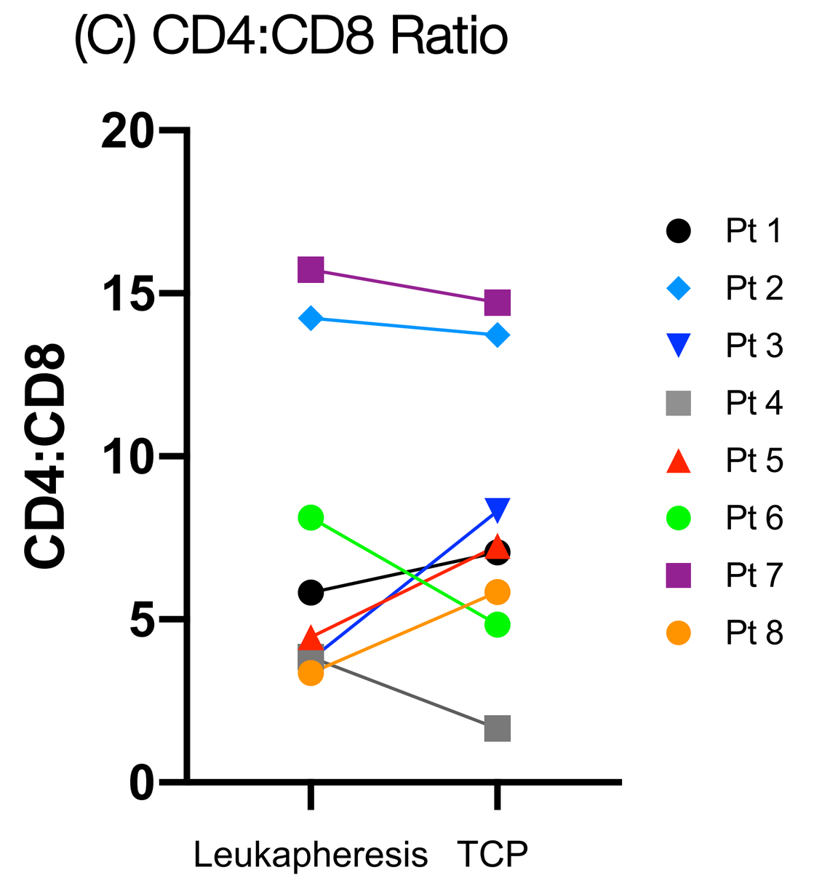
70 yo woman, high grade serous ovarian cancer

- TP53[R248Q], CCNE1 amplified, wild type BRCA1/2
- Failed all 6 prior lines of therapy, platinum resistant
- Response to gavo-cel at $5x10^7/m^2$
  - Target Lesions: PR
  - Non-target Lesions: CR
  - Best overall response: PR (progression at month 6 due to new lymph node)



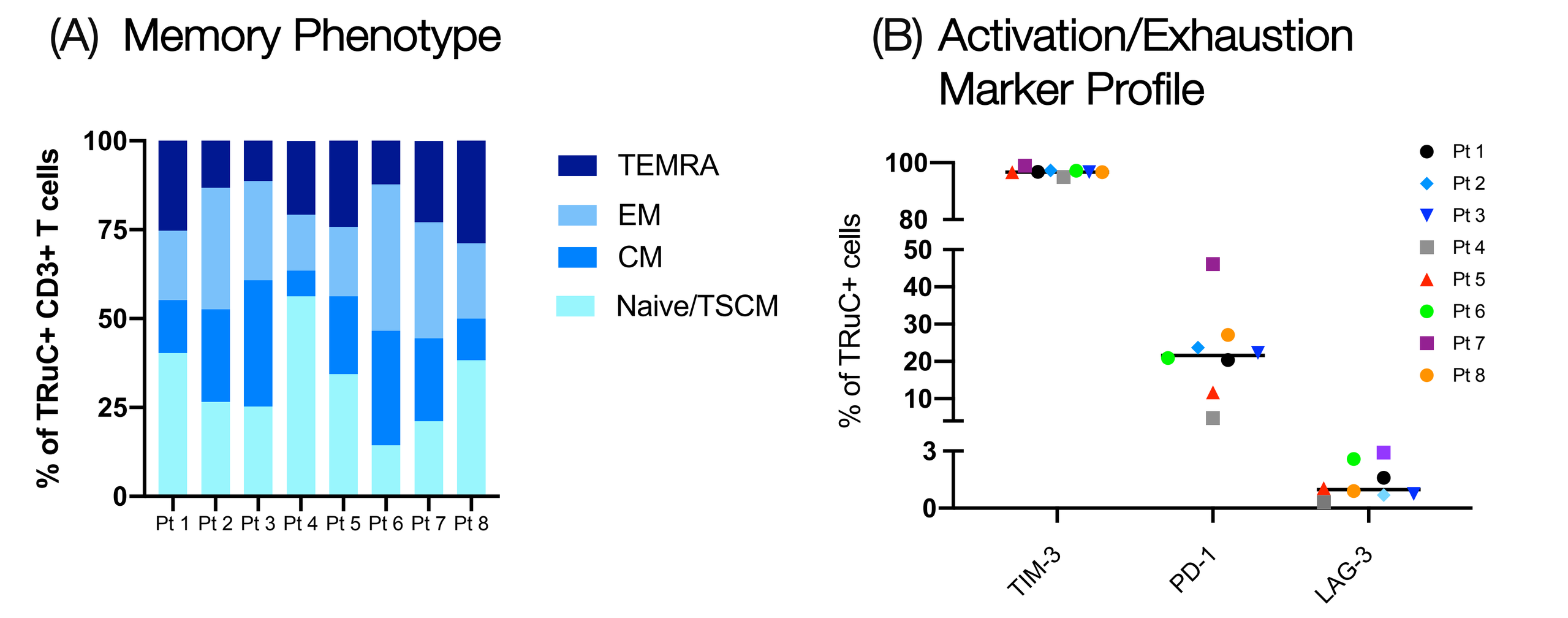
gavo-cel T Cell Product (TCP) Attributes





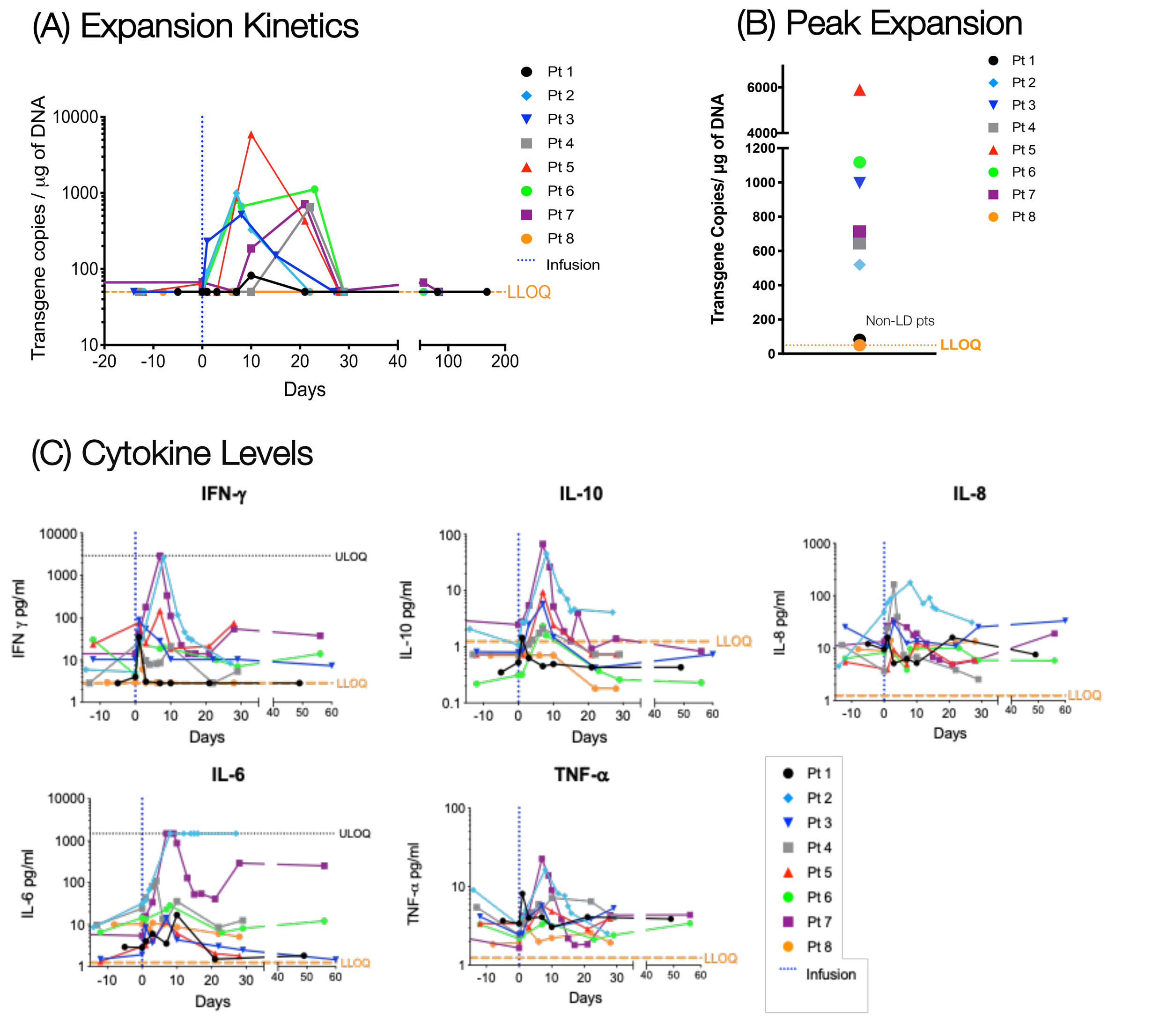
(A) Ex vivo expansion of each TCP after the 10-day manufacturing process is shown. (B) Transduction efficiency of the gavo-cel TRuC construct was determined by surface detection of the MH1 anti-mesothelin binder by flow cytometry. (C) The CD4⁺ to CD8⁺ T cell ratio in the leukapheresis starting material and final TCPs. High CD4:CD8 ratios were observed in the starting material and final TCPs of the two subjects with grade 3 CRS (2 & 7).

gavo-cel Immunophenotype



(A) T cell memory subset composition for TRuC⁺ CD3⁺ T cells in each T cell product (TCP) was assessed using the surface markers CD45RA and CCR7. The median percentage of naïve TRuCs in the TCPs was 30.45% (range, 14.1-56.2). (B) The frequency of TRuC⁺ T cells expressing the indicated activation/exhaustion markers in each TCP is shown. The final TCPs show high TIM-3 positivity, variable PD-1 positivity, and low LAG-3 positivity.

Peripheral Blood gavo-cel Kinetics and Cytokine Levels



(A & B) Post-infusion gavo-cel expansion kinetics in peripheral blood measured by a validated qPCR assay to quantify the transgene copy number per ug of genomic DNA. Median number of days for peak gavo-cel expansion was 10 (range 7-23). Significantly higher levels of expansion were observed in patients that received lymphodepleting chemotherapy prior to gavo-cel infusion. (C) Serial cytokine levels in plasma were measured using a validated multiplex assay from MescoScale Discovery. Cytokine elevations were detected in all subjects, with minor changes in non-lymphodepleted patients. The highest cytokine levels were observed in patients who experienced grade 3 CRS (2 & 7).

Conclusions

- A single gavo-cel infusion was generally safe and resulted in tumor regression in all 8 patients treated (DCR 100%) and objective responses in 3 (2 with mesothelioma and 1 with ovarian cancer)
- The addition of lymphodepletion resulted in higher gavo-cel peak expansion, which was associated with greater tumor regression and objective responses

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