

Phase 1 trial of gavocabtagene autoleucel (gavo-cel, TC-210) in patients with treatment refractory mesothelioma and other mesothelin-expressing solid tumors

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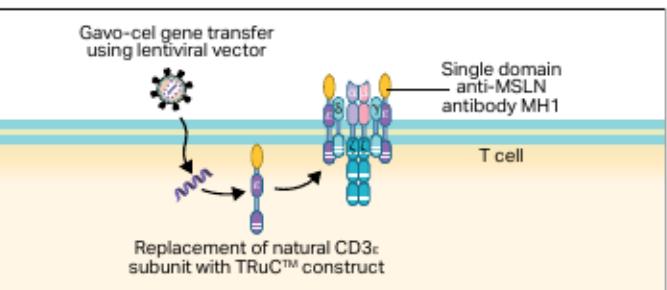
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Introduction

- We describe results of a Phase 1 clinical trial of gavo-cel, an autologous genetically engineered anti-MSLN T cell receptor fusion construct (TRuC™) cell therapy [Figure 1].
- In adult patients with MPM, OVA, CHO, or non-small cell lung cancer (NCT03907852).

Figure 1. Schematic of gavo-cel



Objectives

- To evaluate safety and determine the RP2D of gavo-cel.

Secondary

- To evaluate efficacy of gavo-cel.

Exploratory

- To correlate response with gavo-cel expansion, persistence, phenotype and functionality, and with changes in immune cell markers.
- To study the tumor microenvironment and gavo-cel tumor infiltration.

Conclusions

- A single gavo-cel infusion at the RP2D was associated with a manageable toxicity profile and favorable disease control in patients with refractory MPM and OVA.
- A Phase 2 trial to test the safety and efficacy of gavo-cel in combination with checkpoint inhibitors in patients with MSLN-expressing solid tumors is underway.

References

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Abbreviations

- AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CD3, cluster of differentiation; CHO, cholangiocarcinoma; CI, confidence interval; CML, chronic myeloid leukemia; CRS, cytokine release syndrome; CTCAE, NCI Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; ECOG performance status; IL, interleukin; ICI, immune checkpoint inhibitor; IFN, interferon; IHC, immunohistochemistry; IL, interleukin; LD, lymphoproliferative; MPM, malignant pleural/pleuroperitoneal mesothelioma; MSLN, mesothelin; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; OVA, ovarian cancer; panCK, pan-cytokeratin; PB, peripheral blood; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; Pt, patient; RECIST, Response Evaluation Criteria In Solid Tumors; RP2D, recommended phase 2 dose; SD, stable disease; TEAE, treatment-emergent adverse event.

Acknowledgments

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Disclosure of interests

TCR² Therapeutics has received institutional funding for conduct of clinical trials via a cooperative research and development agreement between NCI, Bayer AG and TCR² Therapeutics.

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Methods

- Autologous T cells were transduced with a lentiviral vector expressing a single domain antibody fused to the CD3ε subunit that targets MSLN in an HLA-independent manner (Figure 1).¹
- Eligible patients had central laboratory-confirmed IHC-assessed MSLN expression of 2+ or 3+ intensity in ≥50% of tumor cells, and ECOG performance status 0 or 1.
- Dose escalation followed a modified 3+3 design (Figure 2).
- Response was assessed per RECIST v1.1² by blinded independent central review.

Figure 2. Dose levels and determining RP2D



LD therapy before gavo-cel administration comprised ifosfamide 30 mg/m² on Days -7, -6, -5, and -4 and cyclophosphamide 600 mg/m² on Days -6, -5 and -4. *Required enrollment of three patients to proceed to dose escalation. **Required enrollment of one patient to proceed to dose escalation.

Results

Baseline characteristics

- 32 patients (23 MPM, 8 OVA, 1 CHO) received gavo-cel [Table 1].
- Prior therapies included ICI in 66% of all patients (87% of MPM patients).
- Bridging therapy was employed in 75% of all patients.

Table 1. Patient tumor characteristics^a

Characteristic	RP2D						Overall n=32
	DL0 (-LD) 5x10 ⁶ /m ² n=1	DL1 (+LD) 5x10 ⁶ /m ² n=8	DL2 (-LD) 1x10 ⁶ /m ² n=1	DL3 (+LD) 3x10 ⁶ /m ² n=13	DL3.5 (+LD) 3x10 ⁶ /m ² n=5	DL4 (-LD) 5x10 ⁶ /m ² n=1	
Age, median (range)	61 (28-84)	46	59 (28-70)	63 (43-69)	67	52 (37-66)	63 (28-84)
Diagnosis	1 MPM 7 MPM; 1 OVA	1 MPM	6 MPM; 6 OVA; 1 CHO	4 MPM; 1 OVA	1 MPM	3 MPM	23 MPM; 8 OVA; 1 CHO
MSLN 2+/3+, median (range) % tumor positivity	90 (55-100)	90	72 (55-100)	70 (50-95)	75 (50-92)	60	65 (55-73)
No. prior therapies, median (range)	8	5	9	5	7	7	4
ICI, n (%)	1 (100)	6 (75)	1 (100)	6 (46)	4 (80)	1 (100)	2 (66)
Anti-MSLN therapy, n (%)	1 (100)	1 (13)	1 (100)	1 (8)	2 (40)	0	1 (33)

^aData cut-off: September 8th 2022.

Safety

- Two DLT events were reported: Grade 3 pneumonitis at DL1 and Grade 5 bronchoalveolar hemorrhage at DL5 [Table 2].
- Reversible grade ≥3 CRS occurred in 15% of patients at RP2D.
- The RP2D was determined to be DL3: 1 × 10⁶ cells/m² with LD [Figure 2].

Efficacy

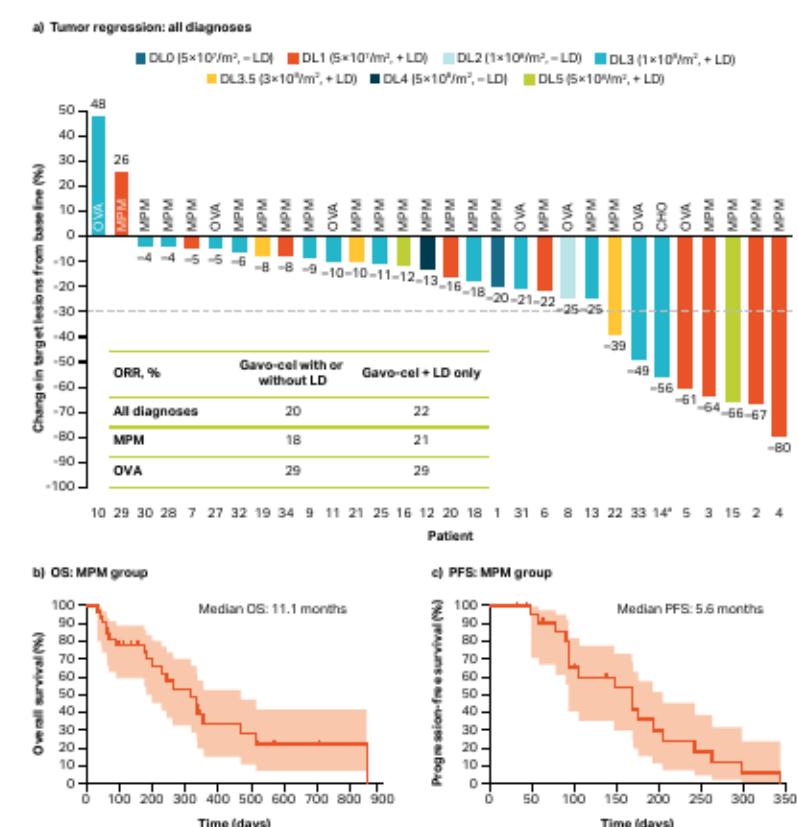
- Tumor regression was observed in 93% of patients [Figure 3A], with a DCR of 77%.
- Median (95% CI) OS and PFS, in months, for the MPM group were 11.1 (5.9, 15.1) and 5.6 (3.3, 6.1; Figure 3B and C), and for OVA were 9.4 and 5.8, respectively.
- When considering all diagnoses, the 6-month OS rate was 70.2%.

Table 2. Grade ≥3 TEAEs

AE, n (%)	DL0 5x10 ⁶ /m ² n=1	DL1 5x10 ⁶ /m ² n=8	DL2 1x10 ⁶ /m ² n=1	RP2D 3x10 ⁶ /m ² n=13	DL3.5 3x10 ⁶ /m ² n=5	DL4 5x10 ⁶ /m ² n=1	DL5 5x10 ⁶ /m ² n=3	Overall n=32
Hematologic								
Lymphopenia	1 (100)	8 (100)	0	13 (100)	5 (100)	1 (100)	3 (100)	31 (97)
Neutropenia	0	8 (100)	0	13 (100)	5 (100)	0	3 (100)	29 (91)
Thrombocytopenia	0	2 (25)	0	2 (15)	1 (20)	0	2 (67)	7 (22)
On target/on tumor								
CRS	0	2 (25)	0	2 (15)	1 (20)	0	3 (100)	8 (25)
On target/off tumor								
Pericarditis/ pericardial effusion	0	0	0	0	1 (20)	0	0	1 (3)
Pleuritis/pleural effusion	0	0	0	1 (8)	1 (20)	0	0	2 (6)
Peritonitis/ascites	0	0	0	1 (8)	0	0	0	1 (3)
Other								
Pneumonitis	0	1 (13)*	0	0	3* (60)	0	1 (33)	5 (16)
Sepsis	0	1 (13)**	0	0	0	0	0	1 (3)
Hemorrhage	0	0	0	0	0	0	1 (33)†	1 (3)
Respiratory failure	0	0	0	0	0	1 (33)†	0	1 (3)

AEs were graded according to the NCI CTCAE, version 5.0. CRS and neutropenia were evaluated using the ASTCT Consensus Grading for CRS and Neutropenia/Toxicity Associated with Immune Effector Cells.¹ *Grade 3 AE. †Patient developed fungal sepsis unrelated to gavo-cel. ‡One patient developed Grade 5 pneumonitis and respiratory failure related to gavo-cel. §Patient had bronchial/bronchioalveolar hemorrhage following CRS-related disseminated intravascular coagulation. Respiratory failure in patient with concurrent CMV pulmonary infection and pneumothorax.

Figure 3. Efficacy outcomes



Gavo-cel expansion and persistence

- Gavo-cel expansion in the periphery increased following LD. Gavo-cel was also detected within serosal effusions (Figure 4).
- Gavo-cel administration was associated with:
 - Elevation in IL-6 and IFN-γ levels
 - Increased CD3+CD8+ T cell tumor infiltration (Figure 5)
 - Upregulation of immuno-inhibitory ligands CD155 and PD-L1 in non-responders, indicating potential resistance mechanisms (Figure 6).

Figure 4. Gavo-cel expansion and persistence

