First Phase 2 Results of Autologous Tumor-Infiltrating Lymphocyte (LN-145) Monotherapy in Patients with Advanced, Immune Checkpoint Inhibitor-Treated, Non-Small Cell Lung Cancer (NSCLC)

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Introduction

Background

- A majority of patients with advanced NSCLC develop disease progression with first-line ICI ± chemotherapy[1]
- In the setting of ICI resistance, effective strategies to provide deep and durable responses are urgently needed
- Lifileucel (LN-144) and LN-145 are centrally manufactured autologous TIL cell products that have demonstrated activity in advanced melanoma, cervical cancer, and head and neck carcinoma[2–5]
- TIL + nivolumab has demonstrated safety and efficacy in ICI-naïve patients with advanced NSCLC in a phase 1 trial[6]
- Here, we report the first safety and efficacy data for single-agent LN-145 TIL cell therapy in patients with advanced NSCLC from a multicenter phase 2 study

Methods

Study Design

- IOV-COM-202 (NCT03645928) is a prospective, phase 2, multicenter, multicohort, open-label study evaluating autologous TIL cell therapy in multiple settings and indications
- We report data from Cohort 3B, investigating LN-145 monotherapy in patients with advanced or metastatic NSCLC

Cohort 3B Patients

- Eligibility required age ≥18 years, 1–3 prior lines of systemic therapy including either ICI or oncogene-directed therapy, ECOG performance status 0–1, ≥1resectable lesion (~1.5 cm in diameter) for LN-145 manufacturing, and ≥1 measurable lesion post-resection for response assessment

Endpoints

- Primary
  - Efficacy, defined as investigator-assessed ORR per RECIST v1.1
  - Safety, as measured by incidence of Grade ≥3 TEAEs (defined as AEs that occur from the time of TIL infusion, up to 30 days after TIL infusion or start of a new anticancer therapy)
- Exploratory
  - Biomarker analyses, including TCR repertoire of the TIL product using RNA sequencing (HTBIvc assay, iRepertoire, Inc., Huntsville, AL); clones present above the limits of detection in each individual patient TIL product lot were counted and their proportion estimated to assess TIL clonality and diversity

Data cutoff: 24 August 2021

Figure 1. Patient Journey and Central Gen 2 GMP Manufacturing

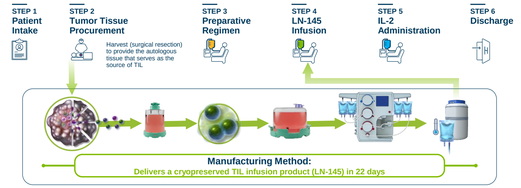
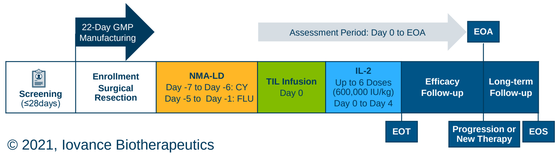
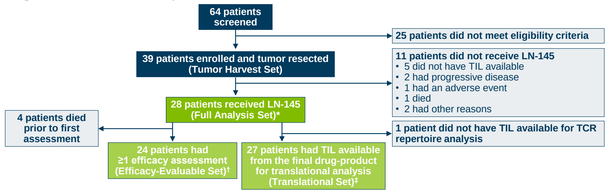


Figure 2. Cohort 3B Patient Treatment Schema



Results

Figure 3. Patient Disposition



*Full analysis set includes all patients who received LN-145 infusion within specifications.
†Efficacy-evaluable set includes all patients who received LN-145 within specifications and had ≥1 efficacy evaluation.
‡Translational set includes all patients who received LN-145 infusion and had TIL available from the final drug-product for translational analysis.

Table 1. Baseline Patient Characteristics (FAS)

Characteristic	COM-202 Cohort 3B (N=28)
Sex, n (%)	
Male	14 (50.0)
Female	14 (50.0)
Median (min, max) age, y	61.0 (40, 74)
Smoker (current or former), n (%)	24 (85.7)
Histologic cell type, n (%)	
Adenocarcinoma	22 (78.6)
Squamous	5 (17.9)
Other	1 (3.6)
Tumor PD-L1 expression, n (%)*	
TPS <1%	4 (14.3)
TPS 1%–49%	10 (35.7)
TPS ≥50%	8 (28.6)
Median (min, max) number of target and non-target lesions	4.5 (2, 11)
Median (min, max) target lesion sum of diameters, mm	79.0 (22, 179)

Characteristic	COM-202 Cohort 3B (N=28)
Prior brain metastases, n (%)	10 (35.7)
Median (min, max) number of prior systemic therapies	2.0 (1, 6)
Prior systemic therapies, n (%)	
Anti–PD-1 and/or anti–PD-L1	28 (100)
Chemotherapy	27 (96.4)
Anti–PD-1	23 (82.1)
Anti–PD-L1	7 (25.0)
Anti–VEGF	6 (21.4)
Anti–CTLA-4	6 (21.4)
EGFR inhibitor	1 (3.6)
Tyrosine kinase inhibitor	1 (3.6)
Other	3 (10.7)

*Per central laboratory from tumor harvest specimen; tumor PD-L1 expression data were missing for 6 patients.

- All patients received prior ICI
- TIL were most commonly harvested from lung metastases (60.7%)

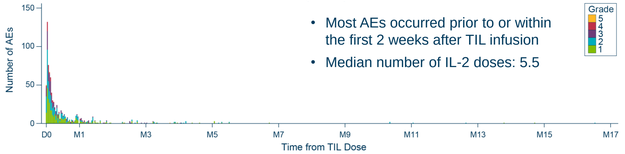
Table 2. Treatment-Emergent Adverse Events* (≥30%, FAS)

TEAE, n (%)	COM-202 Cohort 3B (N=28) Any Grade	Grade 3/4	Grade 5
Any event	28 (100)	27 (96.4)	2 (7.1)‡
Thrombocytopenia	20 (71.4)	19 (67.9)	0
Anemia	19 (67.9)	14 (50.0)	0
Hypotension	17 (60.7)	7 (25.0)	0
Chills	16 (57.1)	1 (3.6)	0
Pyrexia	16 (57.1)	1 (3.6)	0
Hypoxia	13 (46.4)	5 (17.9)	0
Diarrhea	10 (35.7)	3 (10.7)	0
Neutropenia†	10 (35.7)	6 (21.4)	0
Peripheral edema	10 (35.7)	0	0
Alopecia	9 (32.1)	0	0
Decreased appetite	9 (32.1)	3 (10.7)	0
Dyspnea	9 (32.1)	3 (10.7)	0
Fatigue	9 (32.1)	4 (14.3)	0

- Safety was consistent with the underlying advanced disease and known safety profiles of NMA-LD and IL-2
- Any-grade tumor harvest-related AEs were reported for 16 (41.0%) patients, most commonly:
  - Procedural pain, n=7 (17.9%)
  - Hypoxia, n=4 (10.3%)
- Majority of tumor harvest-related AEs were Grade 1 or 2

*TEAEs include AEs that occur from the time of TIL infusion, up to 30 days after TIL infusion or start of a new anticancer therapy.
†Only laboratory abnormalities considered clinically significant by the investigator were reported as AEs.
‡One Grade 5 event each was reported for chronic cardiac failure (not related to TIL) and multiple organ dysfunction syndrome (possibly related to TIL).

Figure 4. Adverse Events Over Time (FAS)



- Most AEs occurred prior to or within the first 2 weeks after TIL infusion
- Median number of IL-2 doses: 5.5

Table 3. Efficacy

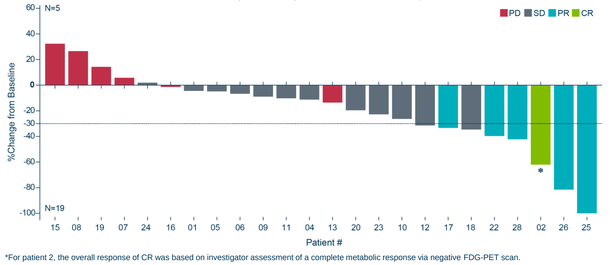
Response	COM-202 Cohort 3B (N=28) n/N	% (95% CI)
Full-Analysis Set (FAS)		
ORR	6/28	21.4 (8.3, 41.0)
CR	1/28	3.6
PR	5/28	17.9
SD	12/28	42.9
PD	6/28	21.4
DCR	18/28	64.3 (44.1, 81.4)
NE*	4/28	14.3
Efficacy-Evaluable Set		
ORR	6/24	25.0 (9.8, 46.7)
DCR	18/24	75.0 (53.3, 90.2)

Duration, months	Median (95% CI)	Min, Max
Study follow-up (FAS)	9.8 (5.8, 14.5)	0.1+, 22.1

*Excluded from efficacy-evaluable set due to death prior to first assessment.

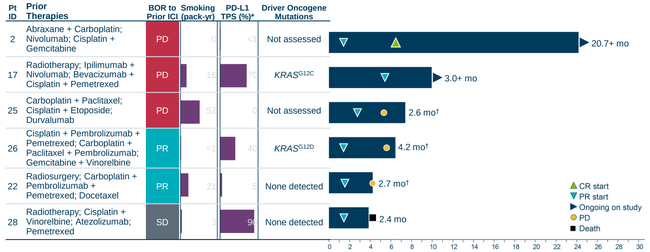
- ORR:
  - 21.4% in the FAS
  - 25.0% in the efficacy-evaluable set
- All responders received ≥2 prior lines of systemic therapy
- Median number of TIL infused was 20.9×10^9
  - Median time from resection to infusion was 35.0 days
  - Median time from infusion to BOR was 2.2 months

Figure 5. Best Percentage Change from Baseline in Target Lesion Sum of Diameters (Efficacy-Evaluable Set)



*For patient 2, the overall response of CR was based on investigator assessment of a complete metabolic response via negative FDG-PET scan.

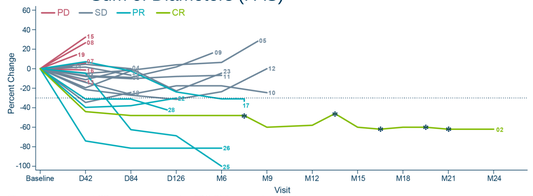
Figure 6. Time to First Response, Duration of Response, and Time on Efficacy Assessment for Confirmed Responders Who Achieved PR or Better



*Per central laboratory from tumor harvest specimen, except for patient 2, who had TPS assessed locally using archival tumor sample.
†Patient 25 had PD due to new lesion; patients 26 and 22 had unequivocal PD of non-target disease.

- One patient had a complete metabolic response, ongoing at 20.7 months
- 2 responses, including the CR, occurred in patients with TPS <1%

Figure 7. Percentage Change from Baseline in Target Lesion Sum of Diameters (FAS)



*The overall response of CR is based on a negative FDG-PET scan by Investigator.

Table 4. TIL TCR Repertoire Analyses

TIL Product Parameter	COM-202 Cohort 3B, Translational Set (N=27) Median*	Min, Max
Unique TCR clones	4396	865, 17,317
Shannon Entropy Index (TCR clone diversity)†	7.18	3.55, 11.66
Simpson Clonality Index (TCR clonality)‡	0.20	0.02, 0.60

*Comparison with prior published datasets[7,8] using the limit of detection applied to this dataset:
- Unique TCR clones: 5596 for melanoma and 6874 for cervical.
- Shannon Entropy Index: 7.60 for melanoma and 7.11 for cervical.
- Simpson Clonality Index: 0.18 for melanoma and 0.20 for cervical.

†A larger Shannon Entropy Index indicates a more diverse CDR3 population. Values can range from 0 (monoclonal sample) to $\log_2(R)$ (evenly distributed, polyclonal sample with R unique clones).
‡Simpson Clonality Index reflects mono- or poly-clonality of a sample and is inversely related to diversity (Shannon Entropy Index). Values can range from 0 (evenly distributed, polyclonal sample) to 1 (monoclonal sample).

- 27 patients had TIL available from the final drug-product for TCR repertoire analysis; analyses of correlation with clinical outcome are ongoing

Conclusions

- This signal-finding study demonstrated the feasibility of tumor harvest, TIL manufacturing, and TIL treatment in patients with advanced NSCLC
  - Patients tolerated surgical resection, including pulmonary lesions
  - TIL manufacturing was feasible for most patients
  - One-time LN-145 treatment with conditioning regimen was well-tolerated
- The TCR repertoire of LN-145 generated from NSCLC tumors demonstrated a similar number of unique TCR clones, as well as measures of diversity and clonality, as previously published for lifileucel for melanoma[7] and LN-145 for cervical cancer[8]
- Despite multiple prior lines of therapy, 6 patients experienced responses, including 2 with durable responses, consistent with published experience including durable CRs extending beyond 1 year[6]

Learnings from this study:

- TIL cell therapy is a potentially viable treatment option for patients with advanced NSCLC
- Study IOV-LUN-202 (NCT04614103) was designed to enroll patients with NSCLC with an unmet medical need but with fewer prior lines of therapy to maximize the potential for more sustained responses

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Abbreviations

AE, adverse event; BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T lymphocyte antigen-4; CY, cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EOA, end of assessment; EOS, end of study; EOT, end of treatment; FAS, full-analysis set; FDG-PET, fluorodeoxyglucose-positron emission tomography; FLU, fludarabine; GMP, good manufacturing practices; ICI, immune checkpoint inhibitors; IL-2, interleukin-2; NA, not assessed; ND, none detected; NMA-LD, nonmyeloablative lymphodepletion; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; Pt, patient; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TCR, T-cell receptor; TEAEs, treatment-emergent adverse events; TIL, tumor-infiltrating lymphocytes; TPS, tumor proportion score.

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Disclosures

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- FGF, MJ, RF, GS, GC, and VG are employees of Iovance Biotherapeutics, Inc., and have stock options.