Trial in progress: A phase 1/2 open-label study (IOV-GM1-201) of TALEN-mediated PD-1–inactivated autologous tumor-infiltrating lymphocytes (TIL; IOV-4001) in patients with advanced melanoma and NSCLC

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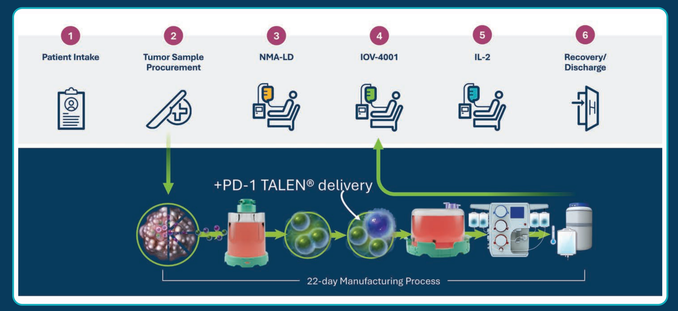
Background

- Adoptive cell therapy using autologous tumor-infiltrating lymphocytes (TIL; lifileucel, LN-145) has demonstrated encouraging efficacy in patients with advanced solid tumors, including melanoma and non-small cell lung cancer (NSCLC)[1,2]
  - One-time lifileucel TIL cell therapy achieved durable responses in the post-immune checkpoint inhibitor (ICI) setting in patients with advanced (unresectable or metastatic) melanoma,[1,3] with an investigator-assessed objective response rate (ORR) of 36.4% and median duration of response (DOR) not reached after 33.1 months of follow-up[3]
  - In ICI-naive patients with advanced melanoma, combination of lifileucel plus pembrolizumab resulted in a 60% investigator-assessed ORR, with a 30% complete response (CR) rate[4]
  - Among patients with advanced or metastatic NSCLC, LN-145 monotherapy resulted in a 21.4% ORR after a median of 2 prior lines of therapy, including ICI and chemotherapy (in most patients)[2]
- IOV-4001 is a programmed cell death protein-1 (PD-1)–inactivated autologous TIL cell therapy product genetically modified with transcription activator-like effector endonucleases (TALEN®) technology to knock out (KO) the *PDCD-1* gene. *PDCD-1* KO may enhance the efficacy of TIL cell therapy and abrogate the need for systemic anti–PD-1 therapy, while avoiding short- and long-term systemic adverse events (AEs) associated with ICI
  - TALEN® are hybrid molecules composed of a DNA-binding domain and the FokI nuclease.[5] Combination of 2 TALEN® arms directed at the *PDCD-1* gene encoding PD-1 mediates DNA double-strand breaks, leading to gene disruption and PD-1 inactivation[5-7]
  - A process has been established for the generation of TALEN®-mediated *PDCD-1* KO TIL and their expansion to therapeutically relevant numbers with robust effector function and phenotypic markers indicative of functional TIL (TALEN® gene-editing technology is licensed from Cellectis)[8]
  - No statistically significant differences in TIL differentiation markers or memory phenotype were observed between *PDCD-1* KO and non-edited TIL[9]
  - *PDCD-1* KO efficiency by flow cytometry was approximately 63%[9]
  - No genotoxicity was observed following TALEN®-mediated genome editing at *PDCD-1*[9]
  - Preclinical studies suggest that PD-1 inactivation by *PDCD-1* gene KO may enhance TIL cell therapy efficacy[9]
- The clinical efficacy observed for lifileucel/LN-145[1-4] provides a benchmark for the anticipated efficacy of genetically modified TIL cell therapies, such as IOV-4001, where this technology may allow for additional optimization of the treatment regimen and subsequently broaden investigation of TIL cell therapy to additional tumor types and/or therapeutic settings

Figure 1. IOV-4001 Manufacturing and Patient Journey



Objective

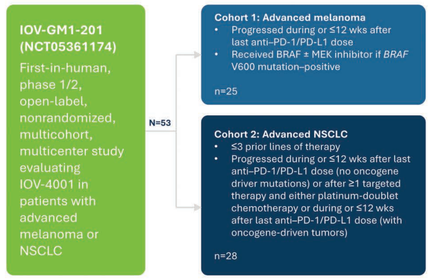
- To assess the safety and efficacy of IOV-4001 for treatment of patients with advanced melanoma and NSCLC

IOV-GM1-201 Study Overview

- IOV-GM1-201 (NCT05361174) is a first-in-human, phase 1/2, open-label, nonrandomized, multicohort, multicenter study with a safety run-in evaluating IOV-4001 in patients with advanced melanoma or NSCLC
- The FDA allowed an Investigational New Drug (IND) Application to proceed in March 2022

Study Design and Treatment Regimen

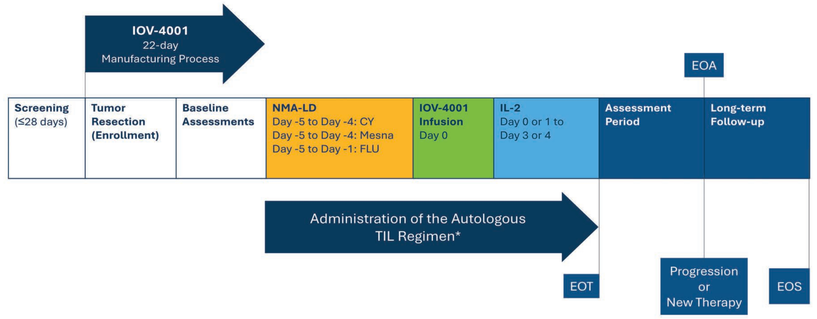
Figure 2. IOV-GM1-201 Study Design



Objectives

- **Phase 1**
  - Confirm safety of IOV-4001 during safety run-in and determine recommended phase 2 dose (RP2D) of IOV-4001
- **Phase 2**
  - Assessment of efficacy of IOV-4001 (per RECIST v1.1 as assessed by the investigator) using RP2D determined in phase 1

Figure 3. Treatment Schema for Phase 2



*During the safety run-in, patients across either cohort will be treated in a staggered fashion (after completion of 28-day dose-limiting toxicity [DLT] period, the next patient may proceed with NMA-LD). Additional patients will be entered upon evaluation of emerging IOV-4001 safety and tolerability data in a standard 3 + 3 de-escalation design.

Abbreviations

AE, adverse event; CR, complete response; CY, cyclophosphamide; DCR, disease control rate; DLT, dose-limiting toxicity; DNA, deoxyribonucleic acid; DOR, duration of response; FDA, Food and Drug Administration; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOA, end of assessment; EOS, end of study; EOT, end of treatment; FLU, fludarabine; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; IND, Investigational New Drug; KO, knockout; NMA-LD, nonmyeloablative lymphodepletion; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; *PDCD-1*, programmed cell death protein 1 gene; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; TALEN®, transcription activator-like effector endonucleases; TIL, tumor-infiltrating lymphocytes; wks, weeks.

Study Endpoints

Primary Endpoints

- Phase 1: Safety as assessed by DLTs and AEs
- Phase 2: Investigator-assessed ORR per RECIST v1.1

Secondary Endpoints

- CR rate, DOR, DCR, PFS, OS, safety, tolerability, feasibility

Exploratory Endpoints

- IOV-4001 persistence, relationship between IOV-4001 persistence and efficacy, relationship between IOV-4001 PD-1 KO efficiency and efficacy and correlative immune biomarkers

Key Inclusion and Exclusion Criteria

Inclusion Criteria

- **Cohort 1:** Confirmed histologic or pathologic stage IIIC, IIID, or IV unresectable or metastatic melanoma that has progressed during or ≤12 weeks after last anti–PD-1/PD-L1 dose
  - Patients must have also received a BRAF ± MEK inhibitor if *BRAF* V600 mutation–positive
- **Cohort 2:** Stage III or IV NSCLC with ≤3 prior lines of therapy and disease progression either:
  - During or ≤12 weeks after last anti–PD-1/PD-L1 dose (patients without oncogene-driven tumors) or
  - During or after ≥1 targeted therapy and either platinum-doublet chemotherapy or during or ≤12 weeks after last anti–PD-1/PD-L1 dose (patients with oncogene-driven tumors)
- Age ≥18 years
- ECOG PS 0-1 and an estimated life expectancy >6 months
- ≥1 resectable lesion(s) for IOV-4001 generation (≥1.5 cm diameter) and ≥1 remaining RECIST-measurable lesion(s)
- Cardiac function test required
- Pulmonary function test may be required

Exclusion Criteria

- Uveal/ocular melanoma
- Symptomatic untreated brain metastases
- Organ allograft or prior cell transfer within the past 20 years
- Systemic steroid therapy ≥10 mg/day of prednisone or another steroid equivalent
- Any form of primary immunodeficiency
- No other primary malignancy within prior 3 years
- Live or attenuated vaccination within 28 days prior to the start of NMA-LD

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Ethics Approval

The study was approved by the institutional review board at each site and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonization.

Consent

All patients provided written informed consent.

For more information, please contact Allison Betof Warner (betofa@mskcc.org) and/or Madan Jagasia (madan.jagasia@iovance.com)

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