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

Jason Chesney,[1] Trisha Wise-Draper,[2] Amod Sarnaik,[3] Friedrich Graf Finckenstein,[4] Parameswaran Hari,[4] Madan Jagasia,[4] Anjali Desai,[4] Akiko Suzuki,[4] Xiao Wu,[4] Allison Betof Warner[5,a]

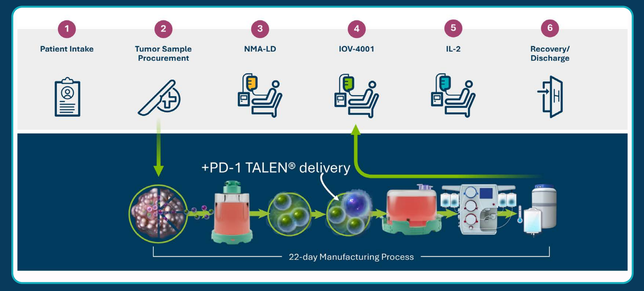
[a]Presenting author.

[1]Univeristy of Louisville Health – Brown Cancer Center, University of Louisville, Louisville, KY, USA; [2]University of Cincinnati Cancer Center (UCCC), Vontz Center for Molecular Studies, Cincinnati, OH, USA; [3]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [4]Iovance Biotherapeutics, Inc., San Carlos, CA, USA; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA

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

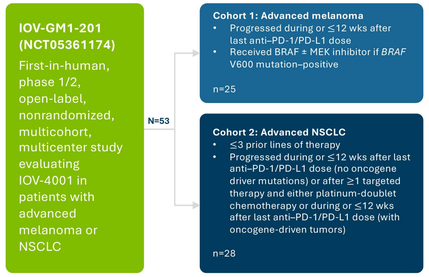
- Here, we describe the IOV-GM1-201 study investigating IOV-4001 for treatment of patients with advanced melanoma and NSCLC

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

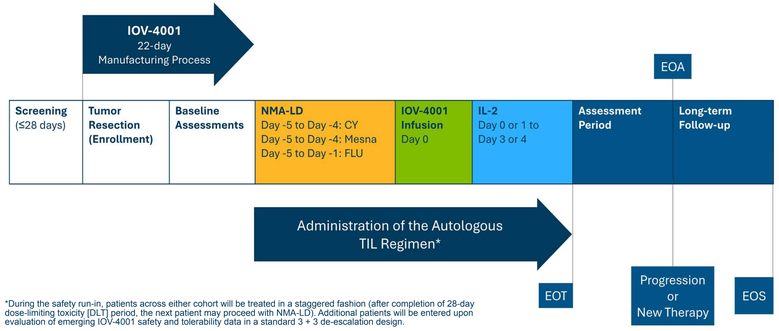
Figure 2. IOV-GM1-201 Study Design



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