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 with TIL has demonstrated efficacy in patients (pts) with advanced solid tumors, including melanoma (Sarnaik JCO 2021) and NSCLC (Schoenfeld SITC 2021). IOV-4001 is a TALEN®-mediated PDCD-1 knockout autologous TIL cell therapy product. Preclinical studies suggest that PD-1 inactivation by PDCD-1 gene knockout may enhance TIL cell therapy efficacy, with similar quality attributes and phenotypes to those of non-edited TIL (Natarajan AACR 2022).

Methods: This first-in-human phase 1/2, open-label, nonrandomized, multicenter study (NCT05361174; open to enrollment) will enroll ~53 adult pts. During the phase 1 portion, enrollment and dose level decisions will be based on emerging safety and tolerability data in a 28-day dose-limiting toxicity (DLT) observation period. Cohort 1 will include pts with unresectable/metastatic melanoma that has progressed during/within 12 wks of last anti–PD-1/PD-L1 dose (pts must have also received a BRAF ± MEK inhibitor if BRAF V600 mutation-positive). Cohort 2 will include pts with advanced NSCLC who have received ≤3 prior therapies and whose disease progressed either: (1) during/within 12 wks after last anti–PD-1/PD-L1 dose (pts without oncogene-driven mutations) or (2) during/after ≥1 targeted therapy and either platinum doublet chemotherapy or during/within 12 wks after last anti–PD-1/PD-L1 dose (pts with oncogene-driven tumors). Pts must have ECOG PS ≤1, ≥1 resectable lesion(s) (≥1.5 cm), ≥1 remaining RECIST-measurable lesion(s) and recovered from prior surgery/anticancer treatment-related AEs (grade ≤1). IOV-4001 is generated from resected tumor in a centralized GMP process. The regimen includes nonmyeloablative lymphodepletion, IOV-4001 infusion, and a short course of high-dose IL-2.

The primary endpoints of phases 1 and 2 are safety (DLTs and AEs) and objective response rate per RECIST v1.1, respectively. Secondary endpoints include complete response rate, duration of response, disease control rate, progression-free survival, overall survival, feasibility, and additional safety.