Novel Cryopreserved Tumor Infiltrating Lymphocytes (LN-144) Administered to Patients with Metastatic Melanoma Demonstrates Efficacy and Tolerability in a Multicenter Phase 2 Clinical Trial

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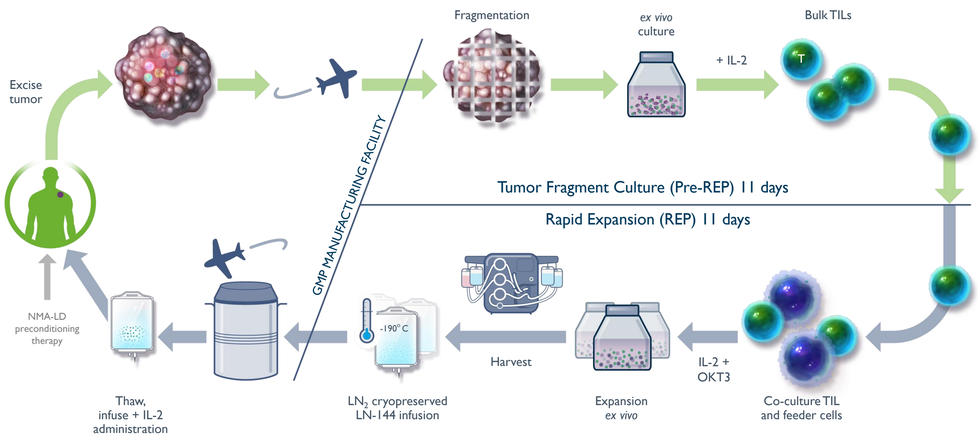
BACKGROUND

- The safety and efficacy of adoptive cell therapy (ACT) utilizing tumor infiltrating lymphocytes (TIL) has been studied in hundreds of patients with metastatic melanoma, and has demonstrated meaningful and durable objective response rates (ORR).[1]
- Iovance Biotherapeutics is conducting an ongoing Phase 2 trial, C-144-01, utilizing centralized GMP manufacturing of TIL, assessing both non-cryopreserved generation-1 (Gen-1) and cryopreserved generation-2 (Gen-2) TIL manufacturing processes.
- Gen-1 is approximately 5-6 weeks in duration of manufacturing (administered in Cohort 1 of C-144-01 study), while Gen-2 is 22 days in duration of manufacturing (administered in Cohort 2 of C-144-01 study).
- Preliminary data from Cohort 1 patients infused with the Gen-1 LN-144 manufactured product, was encouraging in treating post-PD-1 metastatic melanoma patients as the TIL therapy produced responses.[2]
- Benefits of Gen-2 include:
  - Reduction in the time patients wait to receive their TIL
  - Cryopreservation permits flexibility in scheduling, distribution, and delivery
  - Reduction of manufacturing costs
- Preliminary data from Cohort 2 is presented herein.

[1]Goff, et al. Randomized, Prospective Evaluation Comparing Intensity of Lymphodepletion Before Adoptive Transfer of Tumor-Infiltrating Lymphocytes for Patients With Metastatic Melanoma. *J Clin Oncol*. 2016 Jul 10;34(20):2389-97.

[2]Sarnaik A, Kluger H, Chesney J, et al. Efficacy of single administration of tumor-infiltrating lymphocytes (TIL) in heavily pretreated patients with metastatic melanoma following checkpoint therapy. *J Clin Oncol.* 2017; 35 [suppl; abstr 3045].

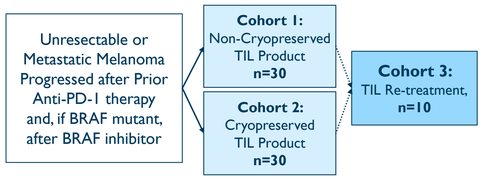
Gen-2 Cryopreserved LN-144 Manufacturing Process



STUDY DESIGN

Iovance C-144-01 Phase 2 Trial in Metastatic Melanoma *(Current Amendment)*

Phase 2, Multicenter, 3-Cohort Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144) for Treatment of Patients with Metastatic Melanoma



- **Key Inclusion Criteria:**
  - Measurable metastatic melanoma and ≥ 1 lesion resectable for TIL generation
  - Progression on at least one prior line of systemic therapy
  - Age ≥ 18
  - ECOG PS 0-1
- **Treatment Cohorts:**
  1. Non-Cryopreserved LN-144 product
  2. Cryopreserved LN-144 product
  3. Retreatment with LN-144 for patients without response or who progress after initial response
- **Endpoints:**
  - Primary: Efficacy defined as ORR
  - Secondary: Safety and Efficacy

METHODS

- Data cut-off date: 10 October 2017 for Cohort 2
- Cohort 2 Safety Set: 13 patients who underwent resection for the purpose of TIL generation and received any component of the study treatment.
- Cohort 2 Efficacy Set: 9 patients who received the NMA-LD preconditioning, LN-144 infusion and at least one dose of IL-2, and had at least one efficacy assessment:
  - 4 patients did not have an efficacy assessment at the time of the data cut.
- Biomarker data has been shown for all available data read by the date of the data cut.

RESULTS

Table 1. Comparison Patient Characteristics from Cohort 1(*ASCO 2017*) vs Cohort 2

CHARACTERISTIC	Historical Cohort 1* N=16, (%)	Cohort 2 N=13, (%)
Gender, n (%)		
Male	7 (44)	5 (39)
Female	9 (56)	8 (62)
Age		
Median	55	54
Min, Max	41, 72	35, 66
Prior therapies, n (%)		
Mean # prior systemic therapies	3	4
Anti-CTLA-4	14 (88)	13 (100)
Anti-PD-1	16 (100)	13 (100)
Target Lesion Sum of Diameter (mm)		
Mean (SD)	104 (68)	141 (102)
Min, Max	15, 225	38, 342
Baseline ECOG score, n (%)		
0	9 (56)	8 (62)
1	7 (44)	5 (39)
BRAF Status, n (%)		
Mutated	9 (56)	6 (46)
Wild Type	7 (44)	7 (54)
Baseline LDH (U/L [SD])		
1-2 times ULN	7 (44)	7 (54)
> 2 times ULN	1 (6)	2 (15)
Number of Target & Non-Target Lesions (at Base Line)		
>3	12 (75)	10 (77)
Mean	5.6	5.5

* Database cut off of 24 Apr 2017

Cohort 2 has:
- 4 median prior therapies; all patients have received prior anti-PD-1 and anti-CTLA-4
- Had higher tumor burden reflected by greater SoD for target lesions and higher mean LDH at Baseline.

Table 2. Treatment Emergent Adverse Events (≥ 30%)

PREFERRED TERM	Historical Cohort 1 (N=16) Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Cohort 2 (N=13) Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Number of patients reporting at least one Treatment-Emergent AE	14 (87.5)	14 (87.5)	1[1]	12 (92.3)	11 (84.6)	0
Nausea	14 (87.5)	0	0	7 (53.8)	0	0
Platelet count decreased	12 (75.0)	12 (75.0)	0	7 (53.8)	6 (46.2)	0
Anaemia	11 (68.8)	8 (50.0)	0	8 (61.5)	7 (53.8)	0
Neutrophil count decreased	11 (68.8)	11 (68.8)	0	6 (46.2)	6 (46.2)	0
Febrile neutropenia	10 (62.5)	10 (62.5)	0	7 (53.8)	6 (46.2)	0
White blood cell count decreased	10 (62.5)	10 (62.5)	0	6 (46.2)	6 (46.2)	0
Chills	9 (56.3)	0	0	6 (46.2)	1 (7.7)	0
Diarrhoea	8 (50.0)	1 (6.3)	0	4 (30.8)	0	0
Fatigue	7 (43.8)	0	0	7 (53.8)	0	0
Vomiting	7 (43.8)	0	0	2 (15.4)	0	0
Constipation	6 (37.5)	0	0	3 (23.1)	0	0
Decreased appetite	5 (31.3)	0	0	4 (30.8)	0	0
Headache	5 (31.3)	0	0	3 (23.1)	0	0
Hypocalcaemia	5 (31.3)	0	0	1 (7.7)	0	0
Hypokalaemia	5 (31.3)	0	0	3 (23.1)	1 (7.7)	0
Hypophosphataemia	5 (31.3)	5 (31.3)	0	4 (30.8)	3 (23.1)	0
Hypotension	5 (31.3)	2 (12.5)	0	3 (23.1)	1 (7.7)	0
Lymphocyte count decreased	5 (31.3)	5 (31.3)	0	3 (23.1)	3 (23.1)	0
Nasal Congestion	5 (31.3)	0	0	0	0	0
Pyrexia	5 (31.3)	0	0	9 (69.2)	1 (7.7)	0
Cough	4 (25.0)	0	0	4 (30.8)	0	0
Oedema peripheral	4 (25.0)	0	0	4 (30.8)	0	0
Pruritus	4 (25.0)	0	0	4 (30.8)	0	0

Notes: Adverse events are coded by MedDRA version 18.1.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
Events are sorted by decreasing frequency of preferred term.
Treatment-Emergent Adverse Events refer to all AEs starting on or after the first dose date of pre-treatment chemotherapy (Fludarabine and Cyclophosphamide) up to the last dose of IL-2 + 30 days.
[1] Death due to metastatic melanoma

Cohort 2 (cryopreserved LN-144): Infusion Product and TIL Therapy Characteristics

- Mean number of TIL cells infused: 37 x 10^9
- Median number of IL-2 doses administered was 4.5

- PR for Patient 6 is unconfirmed as the patient has not reached the second efficacy assessment yet.
- One patient (Patient 9) had passed away prior to the first assessment (still considered in the efficacy set).

Abbreviations: PR, partial response; SD, stable disease, PD, progressive disease

Figure 1. Efficacy

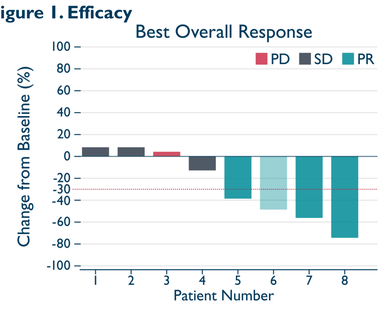


Figure 2. Clinical Status of Response Evaluable Patients with SD or a Better Response

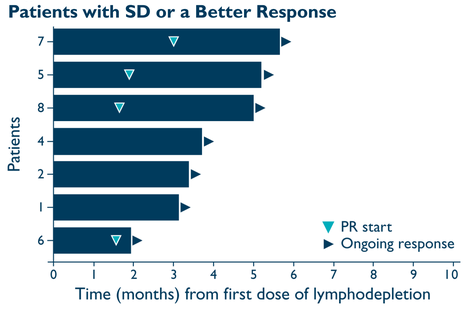


Figure 2. Of 9 patients in Efficacy Set, one patient (Patient 9) is not evaluable (NE) due to melanoma-related death prior to first tumor assessment not represented on figure.
- Responses are seen in patients treated with Gen-2
- DCR is: 78%
- Time to response is similar to Cohort 1
- One patient (Patient 3) with PD as best response is not included in the swim lane plot.

Figure 3. Percent Change in Sum of Diameters

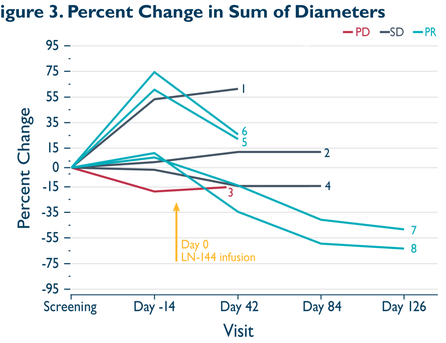


Figure 3. Patient 9 had no post-LN-144 disease assessment due to melanoma-related death prior to Day 42.
- Day -14: % change of Sum of Diameters from Screening to Baseline (Day -14)
- Day -14 to Day 126: % change of SOD from Baseline
- Day -14 = Baseline
- Day 0 = LN-144 infusion

Figure 4: Increase of HMGB1 Upon TIL Treatment

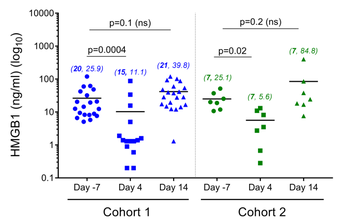


Figure 4. Plasma HMGB1 levels were measured using HMGB1 ELISA kit (Tecan US, Inc). Data shown represents fold change in HMGB1 levels pre (Day -7) and post (Day 4 and Day 14) LN-144 infusion in Cohort 1 and Cohort 2 patients (p values were calculated using two-tailed paired t-test based on log-transformed data). Sample size (***bold and italicized***) and mean (*italicized*) values are shown in parentheses for each time point. HMGB1 is secreted by activated immune cells and released by damaged tumor cells. The increased HMGB1 levels observed after treatment with LN-144 are therefore suggestive of an immune-mediated mechanism of anti-tumor activity.

Figure 5. Biomarker of Interest: IP-10

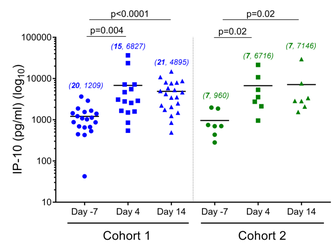


Figure 5. Plasma IP-10 levels were measured using Luminex assay. Data shown represents fold change in IP-10 levels pre (Day -7) and post (Day 4 and Day 14) LN-144 infusion in Cohort 1 and Cohort 2 patients (p values were calculated using two-tailed paired t-test based on log-transformed data). Sample size (***bold and italicized***) and mean (*italicized*) values are shown in parentheses for each time point. The post-LN-144 infusion increase in IP-10 is being monitored to understand possible correlation with TIL persistence.

CONCLUSIONS

- Preliminary results from the existing data demonstrate comparable safety between Gen-1 and Gen-2 LN-144 TIL products.
- Administration of Gen-2 LN-144 leads to clinical responses seen in advanced disease metastatic melanoma patients; all had progressed on anti-PD-1 and anti-CTLA-4 prior therapies.
- Disease Control rate for Cohort 2 was 78%.
- Preliminary biomarker data is supportive of the cytolytic mechanism of action proposed for TIL therapy.
- The Gen-2 manufacturing takes 22 days. This process significantly shortens the duration of time a patient has to wait to receive their TIL, offers flexibility in the timing of dosing the patients, and leads to a reduction of cost of manufacturing.

DISCLOSURE
- This study and poster are sponsored by Iovance Biotherapeutics, Inc.
- MF, IG, SS, BL, and NS are employees of Iovance Biotherapeutics, Inc. and have stock options.

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