Efficacy of Single Administration of Tumor Infiltrating Lymphocytes (TIL) in Heavily Pre-Treated Metastatic Melanoma Patients Following Checkpoint Therapy

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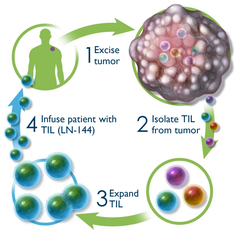
BACKGROUND

- Adoptive cell therapy (ACT) utilizing tumor infiltrating lymphocytes (TIL) has shown consistent overall response rates of >50% in metastatic melanoma patients at the National Cancer Institute (NCI) and other institutions globally.[1]
- Lion Biotechnologies aims to optimize and standardize manufacturing of TIL at central GMP facilities to provide TIL therapy as a potentially curative treatment to a broad group of patients with high unmet clinical need.
- The objective of the C-144-01 clinical study is to assess the safety and efficacy of autologous TIL (LN-144) for the treatment of patients with metastatic melanoma. The study includes three cohorts evaluating two manufacturing processes for LN-144:
  - Cohort 1 receiving fresh TIL, non-cryopreserved LN-144 product
  - Cohort 2 receiving TIL manufactured through a more streamlined and rapid (~3 week) process yielding a cryopreserved LN-144 product
  - Cohort 3 allowing retreatment of Cohort 1 or Cohort 2 patients
- These analyses present preliminary data from the first 16 patients enrolled into Cohort 1 (non-cryopreserved LN-144 product) of this ongoing, multicenter Phase 2 study of TIL for patients with metastatic melanoma.

[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.

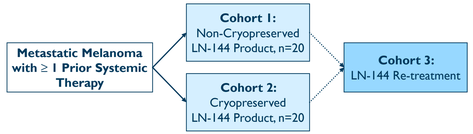
Figure 1. TIL Therapy Process

- EXTRACTION: Patient's TIL are removed from suppressive tumor microenvironment (via surgical resection of a lesion)
- EXPANSION: TIL expanded exponentially in culture with IL-2 to yield 10^9 – 10^{11} TIL, before infusing them into the patient
- PREPARATION: Patient receives NMA-LD (non-myeloablative lymphodepletion, cyclophosphamide: 60 mg/kg, IV x 2 doses and fludarabine: 25 mg/m^2 x 5 doses) to eliminate potentially suppressive tumor microenvironment and maximize engraftment and potency of TIL therapy
- INFUSION: Patient is infused with their expanded TIL (LN-144) and high-dose of IL-2 (600,000 IU/kg for up to 6 doses) to promote activation, proliferation, and anti-tumor cytolytic activity of TIL



STUDY DESIGN

Phase 2, Multicenter, 3-Cohort Study to Assess the Safety and Efficacy 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
  - At least one prior 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: Safety
  - Secondary: Efficacy defined as ORR, CRR, PFS, DOR, and OS

METHODS

- Date of data-cut: 24 Apr 2017
- All patients included in analyses were treated under Cohort 1 (non-cryopreserved LN-144 product)
- Safety Set - 16 patients as of data-cut date, who received the NMA-LD preconditioning, LN-144 infusion and at least 1 dose of IL-2
- Efficacy Set - 14 patients had at least one efficacy assessment, died or experienced clinical/unequivocal PD prior to first assessment, following the NMA-LD preconditioning, LN-144 infusion and at least one dose of IL-2*
- LN-144 product characteristics:
  - Average number of TIL cells in LN-144 products infused was 41x10^9
  - Average viability of LN-144 products was 88%
  - Average INFγ release as determined by dynabead stimulation (CD3, CD28, CD137) was 2251 (pg/10^6/24hrs)
  - Average percent of NK cells in LN-144 products was <2%

*Two of 16 patients in Safety Set had not yet reached first tumor assessment as of data-cut date.

RESULTS

Table 1. Patient Characteristics

CHARACTERISTIC	N=16, %
Gender, n (%)	
Male	7 (43.8)
Female	9 (56.3)
Age, n (%)	
Mean (SD)	54.8 (8.44)
Median	54.5
Min, Max	41, 72
Prior therapies, n (%)	
IL-2	2 (12.5)
anti-CTLA-4	14 (87.5)
anti-PD-1	16 (100.0)
Baseline ECOG score, n (%)	
0	9 (56.3)
1	7 (43.8)
BRAF Status, n (%)	
Mutated	9 (56.3)
Wild Type	7 (43.8)
Baseline LDH (U/L)	N (%)
1-2 times ULN	7 (43.8%)
> 2 times ULN	1 (6.25%)
Number of Metastatic Sites at Enrollment	
Median (range)	4 (2-11)
> 3	64.3%

The patient population was highly refractory to multiple prior lines of therapy, with significant tumor burden at Baseline, and had progressed after at least one checkpoint inhibitor:

- Median number of prior therapies: 3 (range: 1-6)
- Median Sum of Diameter for target lesions at Baseline: 10.2 cm
- 81% of patients had Stage IV disease

Table 2. Treatment Emergent Serious Adverse Events

	144-01 (N=16)		
PREFERRED TERM (PT)	ANY GRADE n (%)	GRADE ≥3 n (%)	GRADE 5 n (%)
Number of subjects reporting at least one Treatment-Emergent SAE	9 (56.3)	9 (56.3)	1 (6.3)
Febrile neutropenia	4 (25.0)	4 (25.0)	0 (0.0)
Pyrexia	1 (6.3)	1 (6.3)	0 (0.0)
Systemic inflammatory response syndrome	1 (6.3)	1 (6.3)	0 (0.0)
Parvovirus B19 infection*	1 (6.3)	1 (6.3)	1 (6.3)
Viral infection	1 (6.3)	1 (6.3)	0 (0.0)
Neutrophil count decreased	3 (18.8)	3 (18.8)	0 (0.0)
Platelet count decreased	3 (18.8)	3 (18.8)	0 (0.0)
Blood bilirubin increased	1 (6.3)	1 (6.3)	0 (0.0)
White blood cell count decreased	1 (6.3)	1 (6.3)	0 (0.0)
Dehydration	1 (6.3)	1 (6.3)	0 (0.0)
Myelodysplastic syndrome	1 (6.3)	1 (6.3)	0 (0.0)
Confusional state	1 (6.3)	0 (0.0)	0 (0.0)
Hypoxia	1 (6.3)	1 (6.3)	0 (0.0)
Hypotension	1 (6.3)	1 (6.3)	0 (0.0)

Treatment Emergent SAEs by PT.
* Not related to therapy event occurred 6 months after treatment.

Table 3. Efficacy

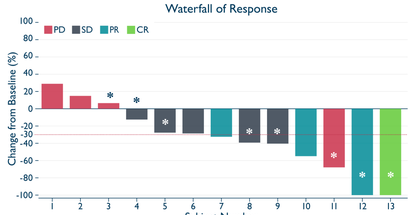
RESPONSE	PATIENTS, N=14 n (%)
Objective Response Rate	4 (29%)
Disease Control Rate	9 (64%)
Complete Response	1 (7%)
Partial Response	3 (21%)
Stable Disease	5 (36%)
Progressive Disease	4 (29%)
Non-Evaluable*	1 (7%)

- All patients entering the study had received an anti-PD-1 checkpoint inhibitor
- Median number of IL-2 administrations was 6

*In Efficacy Set 1 of 14 patients was not evaluable due to melanoma-related death prior to first tumor assessment.

Figure 2: Efficacy

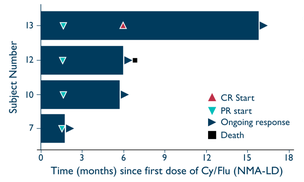
- ORR is 29%
- Tumor reduction was seen in 77% of patients representing those who had tumor reduction in the target lesions
- Responses were noted regardless of BRAF mutational status including one long lasting CR (15+ months)



* BRAF mutants
- PR for one subject yet to be confirmed.
- Of 14 patients in Efficacy Set, one patient was not evaluable due to melanoma-related death prior to first tumor assessment.

Abbreviations: CR, complete response; PD, progressive disease ; PR, partial response; SD, stable disease.
Data Cut: 24APR2017

Figure 3. Time to Best Response and Duration



- Mean time to first response: 1.6 months
- Median follow up for this data: 4.7 months

Figure 4. Percent Change in Sum of Diameters

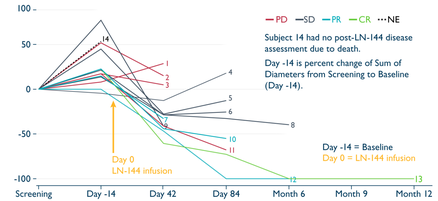
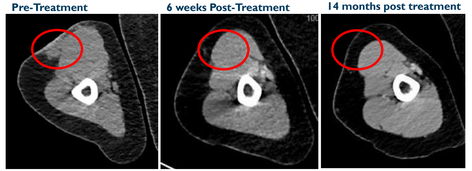


Figure 5. CT Scan for Patient with CR



Target lesion: lateral aspect of the bicep muscle on the right.

CONCLUSIONS

- This is the first time a company has manufactured TIL (LN-144) at central GMP facilities and treated patients in a multicenter clinical trial.
- Initial results indicate clinically-meaningful outcomes as assessed both by ORR and DCR in heavily pretreated patients, all with prior anti-PD-1 and >80% with prior anti-CTA-4 checkpoint inhibitors, including at least one durable complete response.
- Responses were observed in patients regardless of their BRAF mutation status.
- Initial clinical responses were rapid in the majority of patients with preliminary reduction in tumors observed at the first response assessment.
- Cohort 3 in this study will allow retreatment with a second LN-144 infusion.
- An upcoming protocol amendment to this study will increase the number of patients with unresectable or metastatic melanoma who have progressed after immune checkpoint inhibition therapy (e.g., anti-PD-1), and if BRAF mutation-positive, after BRAF targeted therapy.

DISCLOSURE & FUNDING STATEMENT
- This study and poster are sponsored by Lion Biotechnologies, Inc.
- JS, ML, BL, IG, NS, SS, LW, MM, and MF are employees of Lion Biotechnologies, Inc. and have stock options.

ACKNOWLEDGMENT
- All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.
- The authors would like to thank the participating patients and their families for participation in the study.
- The authors would also like to acknowledge Anand Veerapathran, Michelle Simpson-Abelson, and Steven Fischkoff from Lion for their contributions.
- The authors would like to acknowledge all site team members from Moffitt Cancer Center (Allison Richards & Valerie Stark), Yale Cancer Center, James Graham Brown Cancer Center, and Earle A. Chiles Research Institute, Providence Cancer Center for their contributions.