ASH 2024 | December 7-10; San Diego, California

Abstract #4824

First Phase 1 Clinical Results of IMPT-314, an Autologous Dual-Targeting CD19/CD20 CAR T-cell Product Candidate Enriched for Naïve and Central Memory T Cells, for the Treatment of Large B-cell Lymphoma

Sarah M Larson[1], Umar Farooq[2], Boyu Hu[3], Tahir Latif[4], Felix Mensah[5], Deepthi Kolli[6], Giulia Parisi[6], Greg Kaufman[6], Jonathan Benjamin[6], Akil Merchant[7]

[1]Department of Medicine, Division of Hematology-Oncology, David Geffen School of Medicine at University of California Los Angeles (UCLA), Los Angeles, CA; [2]University of Iowa, Iowa City, IA; [3]Division of Hematology/Hematologic Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [4]Division of Hematology-Oncology, University of Cincinnati, Cincinnati, OH; [5]Indiana Blood and Marrow Transplantation, Franciscan Health, Indianapolis, IN; [6]ImmPACT Bio, a Lyell company; [7]Cedars-Sinai, Samuel Oschin Cancer Center, Cedars Sinai Medical Center, Los Angeles, CA

For more information contact:
Sarah M. Larson, MD, slarson@mednet.ucla.edu
Greg Kaufman, MD, gkaufman@lyell.com

Introduction

- CD19-directed CAR T-cell therapies have revolutionized the treatment of B-cell lymphomas, though many patients do not respond or relapse.
  - More than 40% of patients never obtain a complete response (CR)[1, 2]
  - Approximately 50 to 60% of patients do not experience durable responses[3] and the median PFS rates in 3rd line+ LBCL remain only 6 to 7 months. Key reasons may include:
    - Heterogeneous and potentially suboptimal antigen density[4]
    - CAR T-cell exhaustion which is associated with an effector-rich product[5]
    - Antigen escape due to single antigen targeting[6]
- IMPT-314 is an autologous, dual-targeting CD19/CD20 CAR T-cell product candidate manufactured using enriched CD62L+ cells to yield a final drug product comprising predominantly naïve and central memory T cells (**Figure 1**).
- IMPT-314 was designed to overcome variable CD19 antigen density, enhance cell persistence, and reduce CAR T cell exhaustion to maximize durable CRs.
- IMPT-314 incorporates the same CAR construct as CART19/20, with durable responses in a Phase 1 trial of 13 patients with NHL at UCLA (NCT04007029).[7, 8]
  - The ORR was 92% with a CR rate of 77%[9], the median PFS was 50.1 months, and the median overall survival was not reached (95% CI: 5.7 – NE) with a median follow-up time of 32 months.
  - No ≥ Grade 3 CRS or ICANS was reported.
  - Of note, two patients who achieved CR and relapsed (one after 18 months and one after 4 years of CR) were successfully retreated with CART19/CD20 and achieved CR.

Figure 1: IMPT-314 is Designed for Enhanced CR Rates and Durable Responses

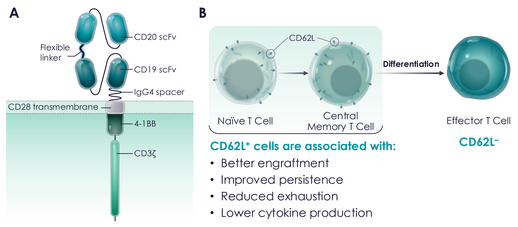

Figure 1. (A) Schematic of IMPT-314, dual-targeting CD19/CD20 CAR. **(B)** IMPT-314 is manufactured using a linear process starting with CD62L+ isolation from Leukopaks™, followed by activation, lentiviral transduction, cell expansion and harvest. CD62L is expressed on naïve and central memory T-cells and not expressed on T-effector cells.

Methods

- MPCT-012L (NCT05826535) is an open-label, dose-escalation (modified 3+3) and expansion Phase 1-2 trial of IMPT-314 for patients with LBCL, including DLBCL, HGBCL, tFL and PMBCL. Dosing was initiated with 100 x 10^6 CAR T cells.
  - Cohorts include CAR T-naïve patients in the 3rd line+ setting, CAR T-naïve patients in the 2nd line setting, and CAR-T experienced patients. Data from the 3rd line+ CAR T-naïve cohort are presented here.
- Eligibility for the 3rd line+ CAR T-naïve cohort required 2 or more prior lines of therapy including exposure to an anti-CD20 monoclonal antibody and an anthracycline, and no prior treatment with an approved or investigational CAR T-cell product.
- Patients received a standard lymphodepletion regimen (fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2) and, after two rest days, a single flat dose (based on CAR+ cells) of IMPT-314 at the target dose level, given in either the inpatient or outpatient setting.
- The data cutoff date for this presentation is October 22, 2024.

Clinical Results

Demographics and Baseline Characteristics

- The Safety Analysis set comprises 23 patients with LBCL dosed with IMPT-314 in the CAR T-naïve cohort.
- Twenty-one patients were dosed with 100 x 10^6 CAR T cells, and two at 300 x 10^6 CAR T cells.

Table 1: Demographics & Baseline Characteristics of the CAR T-naïve Cohort in the 3rd Line+ Setting

Characteristics	N = 23
Median (range) age, years	65 (21 – 87)
LBCL histology n (%)	
DLBCL	14 (61%)
HGBCL	4 (17%)
tFL	3 (13%)
Other	2 (9%)
Male n (%)	16 (70%)
Hispanic or Latino n (%)	4 (17%)
Race n (%)	
Asian	1 (4%)
Black or African American	1 (4%)
Caucasian	18 (78%)
Not Reported	1 (4%)
Other	2 (9%)
ECOG Performance Status: n (%)	
0	7 (30%)
1	16 (70%)
IPI score[3] 3 at study entry	9 (39%)
Stage ≥ 3 at diagnosis	13 (57%)
Median lines of prior therapy (range)	3 (2 – 6)
Elevated (above normal) LDH %	11 (48%)
Received bridging therapy n (%)	12 (53%)

Key Safety Outcomes

- No cases of Grade 3 CRS were reported. Grade 1 and 2 CRS were reported in 70% (16/23) of patients and 50% (8/16) with CRS received tocilizumab.
- Grade 3 ICANS was reported in 13% (3/23) of patients with a median time to complete ICANS resolution of 5 days, and rapid improvement to ≤ Grade 2 with standard therapy.
- Four patients had Grade 3 infection (bacteremia NOS, tooth, UTI, zoster), all of which responded to treatment and resolved.

Table 2: Key Safety Outcomes

Adverse Event, n (%)	N = 23
CRS	
Grade 1 or 2	16 (70%)
Grade 3+	0
Median time to onset, days (range)	1.5 (0 – 13)
Median time to resolution days (range)	4 (2 – 8)
ICANS	
Grade 1 or 2	3 (13%)
Grade 3	3 (13%)
Median time to onset, days (range)	6 (3 – 10)
Median time to resolution, days (range)	5 (3 – 12)
Prolonged Cytopenias	
Neutropenia	3 (13%)
Thrombocytopenia	1 (4%)
Infections	
Grade 3	4 (17%)

Clinical Responses

- The efficacy evaluable population included 17 patients with LBCL, including DLBCL (n = 10), HGBCL (n = 4), and tFL (n = 3).
  - Two patients with T-cell histiocyte-rich LBCL were not included in the analysis (1 PR, 1 PD) and this histology will not be enrolled moving forward
- Patients were evaluable for a response assessment at Day 84 or later, or if they had a prior CR or PD.
- The ORR is 94%, with most (71%) patients achieving a CR by three months (**Table 3, Figure 2**).
- 71% of patients were in response at last follow-up, with a median follow-up of 6.3 months (range, 1.2–12.5). No deaths occurred during the study treatment period (prior to disease progression or subsequent anti-cancer therapy).

Table 3: Response Rates

Best Overall Response	N = 17
Objective Responses, n (%)	16 (94%)
Complete Responses, n (%)	12 (71%)
Partial Responses, n (%)	4 (24%)
Stable Disease, n (%)	1 (6%)
Median Follow Up, months (range)	6.3 (1.2 – 12.5)
Median Duration of Response	Not reached

Figure 2: Swimmer Plot of Individual Patient Trajectories over Time

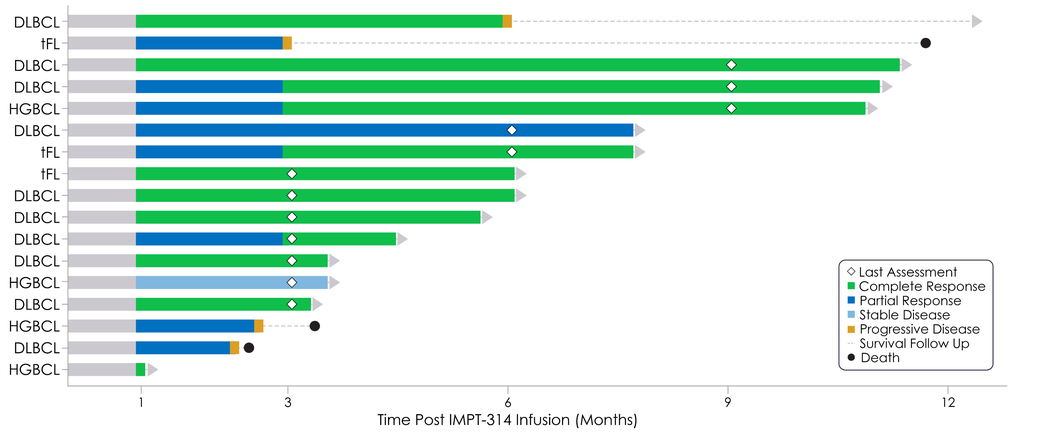

Figure 2. Individual patient trajectories demonstrate a 94% ORR and a 71% CR rate with 71% of patients in response at last follow-up with median follow up of 6.3 months of (range, 1.2 – 12.5 months).

Pharmacokinetics & Drug Product Characteristics

- In the Efficacy Evaluable set, 16 patients were evaluable for PK.
- IMPT-314 showed robust expansion for pharmacokinetic analysis. Peak cell expansion occurred between Days 7-28 post IMPT-314 infusion (median T_{max} = 10 days).
- Median peak of expansion (C_{max}) was 93,723 copies/µg gDNA (range 2,338 – 555,284). IMPT-314 cells persisted multiple weeks post infusion across multiple patients with median expansion at Day 28 of 11,766 copies/µg gDNA (range 56 – 555,284).
- Median $AUC_{(0\text{-}28\ Days)}$ was 1,335,253 days x copies/µg gDNA (range 20,164 – 6,848,015).
- The CD3 component of the final drug product is a CD62L-rich product comprising naïve and central memory populations (median, 91%; range, 82 – 99%).

Figure 4: IMPT-314 Final Drug Product Characteristics

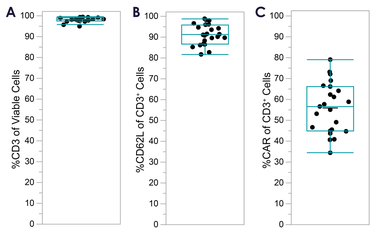

Figure 4. The final drug product from clinical lots (N = 23) is: **(A)** predominantly a CD3-rich product (median, 98%; range, 95 – 98%); **(B)** comprising naïve and central memory populations (median, 91%; range, 82 – 99%), and **(C)** Median percent CAR positive of CD3+ cells was 57% (range, 35 – 80%).

Figure 3: Robust CAR T-cell Expansion in IMPT-314-Treated CAR-T-Naïve Patients

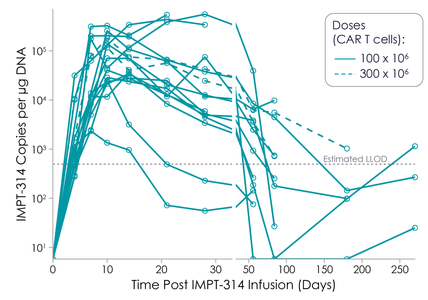

Figure 3. Time plots of individual IMPT-314 PK concentration by droplet digital PCR (ddPCR) on DNA extracted from isolated peripheral blood mononuclear cells from 16 patients. Samples were analyzed in a duplex reaction at a DNA input of 50 ng per reaction using probes targeting FMC-63 and normalized using housekeeping gene SDC4. Intended timepoints of blood collection shown, actual timepoints vary by +/- 2 days.

Conclusions

- IMPT-314 is an autologous, dual-targeting CD19/CD20 CAR T-cell product candidate enriched for naïve and central memory T cells via a differentiated manufacturing process using CD62L+ selection.
- IMPT-314 has a manageable safety profile with no high-grade CRS and low rates of Grade 3 ICANS. Adverse events were resolved with standard management algorithms.
- An objective response rate of 94% and a complete response rate of 71% were achieved after IMPT-314 treatment in CAR T-naïve patients with LBCL who had received at least 2 prior lines of therapy.

Summary

Data evaluating IMPT-314, a novel dual-targeting CD19/CD20 CAR T-cell product candidate enriched for naïve and central memory T cells, support the potential for a high rate of durable clinical responses with a favorable safety profile in CAR T-naïve patients with LBCL in the 3rd-line+ setting.

Abbreviations:
AACR, American College of Clinical Research; CAR, chimeric antigen receptor; CD, cluster of differentiation; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DNA, deoxyribonucleic acid; ECOG, Eastern Cooperative Oncology Group; HGBCL, high-grade B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; IFNγ, interferon gamma; IPI, international prognostic index for DLBCL; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; LLOD, lower limit of detection; M, million; NE, not estimable; NOS, not otherwise specified; ORR, objective response rate; PCR, polymerase chain reaction; PFS, progression-free survival; PK, pharmacokinetics; PMBCL, primary mediastinal B-cell lymphoma; tFL, transformed follicular lymphoma to DLBCL; UTI, urinary tract infection.

References
1. Neelapu SS, et al. Axicabtagene Ciloleucel CAR T -Cell Therapy in Refractory Large B-Cell Lymphoma. *NEJM* 2017.
2. Abramson JS, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet* 2020.
3. Neelapu SS, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood* 2023.
4. Majzner RG, et al. Tuning the Antigen Density Requirement for CAR T-cell Activity. *Cancer Discovery* 2020.
5. Westin JR, et al. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. *NEJM* 2023.
6. Spiegel JY, et al. Outcomes of patients with large B-cell lymphoma progressing after axicabtagene ciloleucel therapy. *Blood* 2021.
7. Larson SM, et al. CD19/CD20 Bispecific Chimeric Antigen Receptor (CAR) in Naïve/Memory T Cells for the Treatment of Relapsed or Refractory Non-Hodgkin Lymphoma. *Cancer Discovery* 2023.
8. Puliafito BR, et al. *Blood* 2023; 142(Supplement 1):3490.
9. Chen YY. AACR Special Conference in Cancer Research, Tumor Immunology and Immunotherapy. October 2024.

Acknowledgments
Editorial support and figure schematics for this poster were provided by Cognition Studio, Inc.