065

Clinical Pharmacological Characterization of Cilta-cel, a CAR-T Therapy Directed Against BCMA in Adult Patients with Multiple Myeloma in a Multicohort CARTITUDE-2 Study

Jianmei Wu[1], Shih-Yu Chang[1], Yupeng Ren[1], Helen Varsos[2], Yogesh Jethava[2], Qingxuan Song[2], Christina Corsale[2], Nikoletta Lendvai[2], Muhammad Akram[3], Tairan Yang[3], and Indrajeet Singh[1]

[1] Janssen Research & Development LLC, Spring House, PA, United States;
[2] Janssen Research & Development, Raritan, NJ, USA;
[3] Legend Biotech, Somerset, NJ, United States

Key Takeaway

Following a single infusion of cilta-cel at a target dose of 0.75x10^6 cells/kg, CAR-T cellular expansion and persistence were observed coinciding with continued reduction of sBCMA, which reflects CAR-T cell mediated pharmacodynamic activity. Although there was evidence of treatment emergent immunogenicity (ADA positive), the impact of ADA on cellular kinetics was not apparent.

Conclusions

PK exposures assessed using transgene and cellular levels were concordant and showed similar expansion and persistence profiles. High interindividual variability of exposures was observed. The median t_{max} of cilta-cel transgene expansion in peripheral blood was approximately 2 weeks post-infusion and the median t_{bql} of cilta-cel transgene levels was approximately 4-5 months post-infusion.

Coincided with CAR-T cell expansion, continued reduction of sBCMA was observed and reached nadir level around 2 or 3 months, sBCMA levels thereafter showed a gradual increase over time, but these values remained substantially lower than baseline in most participants.

The ADA incidence was 25 to 42%, with the median onset time of 2 to 6 months post-infusion. There was no apparent impact of ADA on cilta-cel cellular kinetics.

Acknowledgments

This study was funded by Janssen Research & Development, LLC, and Legend Biotech USA Inc.

Disclosures

JMW, YR, HV, YJ, QS, CC, NL and IS are currently employed by Janssen R&D LLC, SC is not currently employed by Janssen.
JMW, YR, HV, YJ, QS, CC, NL and IS are employed by Johnson & Johnson and own Johnson & Johnson stock.
MA and TY are currently employed by Legend Biotech.

Introduction

- Ciltacabtagene autoleucel (cilta-cel) is an autologous chimeric antigen receptor T cell (CAR-T) therapy that targets B cell maturation antigen (BCMA) expressed on the surface of mature B lymphocytes and malignant plasma cells.
- Cilta-cel was approved in US and EU based on results of Phase 1b/2 CARTITUDE-1 study (NCT03548207) and Phase 3 randomized controlled trial, CARTITUDE-4 study (NCT04181827). Cilta-cel administration resulted in deep and durable responses in patients with relapsed and refractory (R/R) multiple myeloma (MM), who have received at least 1 prior line of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), and are refractory to lenalidomide.
- CARTITUDE-2 (NCT04133636) is a phase 2, multicohort, open-label study evaluating safety and efficacy of cilta-cel in various MM patient populations. Cohort A patients had received 1 to 3 prior lines of therapy and were lenalidomide-refractory, Cohort B patients received one line of prior therapy including a PI and an IMiD and had disease progression ≤12 months after ASCT, and Cohort C patients were previously treated with a PI, an IMiD, an anti-CD38 monoclonal antibody and BCMA-directed therapy (excluding cellular immunotherapy) (**Figure 1**).

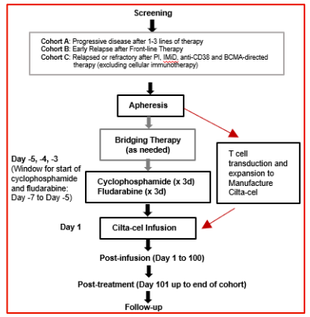
Objectives

Cellular kinetics, pharmacodynamics, and immunogenicity results of cilta-cel are presented for Cohorts A initial group [A(i)], B and C to improve our understanding of cilta-cel *in vivo* expansion and its relationships with clinical factors in various MM populations.

Methods

- Cellular kinetics was assessed for Cohorts Ai (first 20 patients who received cilta-cel using the clinical trial process), B and C by using CAR transgene copy level and CAR$^+$CD3$^+$ cell level in blood after a single infusion of 0.75 (range: 0.5-1.0) x 10^6 CAR-positive viable T cells/kg. PK parameters were estimated by NCA using Phoenix WinNonlin (version 8.0).
- Pharmacodynamics: soluble BCMA (sBCMA) level in serum was assessed using a ligand binding assay.
- Serum samples were evaluated for antibodies binding to cilta-cel (anti-drug antibodies or ADA)

Figure 1. Schematic Overview of CARTITUDE-2 Study (Cohorts A to C)



Results

1. Cellular Kinetics:

- Cilta-cel PK measurements by using transgene and cellular levels were concordant. Similar cellular kinetic profiles were exhibited across the 3 cohorts with an initial expansion phase followed by a rapid then a slower decline over months as shown in **Figure 2**. High interindividual variability was observed.
- Although higher mean C_{max} was observed in Cohort A(i) and Cohort B, and lower C_{max} in Cohort C, the $AUC_{0\text{-}28d}$ was comparable across cohorts. The median t_{max} ranged 11 to 15 days, and median t_{bql} (time to reach BQL level) were comparable ranging from 125 to 157 days among Cohorts A(i), B, and C as shown in **Table 1**.
- There was no clear dose-exposure relationship observed across 3 cohorts as shown in **Figure 3**.

Figure 2: Mean (+SD) Blood Cilta-cel CAR Transgene Levels versus Time Profile

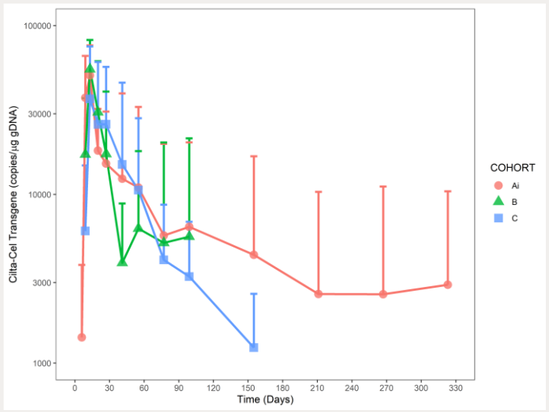
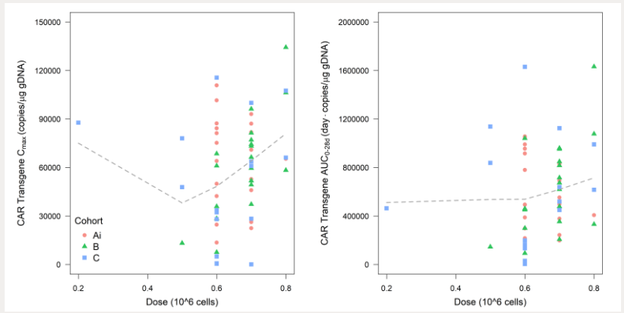


Table 1: Pharmacokinetic Parameters of Cilta-Cel Transgene Levels in Blood After a Single Infusion of Cilta-cel

Pharmacokinetics of Cilta-cel Transgene (mean [SD], t_{max}, t_{last} and t_{bql}: median [range])	Cohort Ai	Cohort B	Cohort C
n	20[a]	19[b]	18[c]
C_{max}, copies/µg genomic DNA	64039 (28184)	62097 (31062)	47809 (38948)
t_{max}, day	10.50 (8.73 - 42.88)	13.08 (8.96 – 209.88)	14.94 (8.92 – 41.02)
C_{last}, copies/µg genomic DNA	3421 (6912)	6714 (15138)	4450 (15703)
t_{last}, day	183.05 (20.97 - 331.92)	96.97 (26.90 – 330.84)	126.71 (8.92 – 323.80)
t_{bql}, day	153.47 (57.12 - 336.78)	124.81 (40.99 – 221.75)	156.97 (14.91 – 328.88)
$AUC_{0\text{-}28d}$, day×copies/µg genomic DNA	601430 (295664)	639474 (389912)	558681 (480470)
$AUC_{0\text{-}6m}$, day×copies /µg genomic DNA	1505597 (2190896)	1368431 (1799134)	1286263 (830054)
$AUC_{0\text{-}last}$, day×copies /µg genomic DNA	1712545 (3109405)	1387920 (2055365)	1202972 (1214932)
$t_{1/2}$, day	38.3 (34.8)	11.0 (5.8)	40.8 (29.9)

$AUC_{0\text{-}28}$d=area under the analyte concentration-time curve from time 0 to 28 days; $AUC_{0\text{-}6m}$=area under the analyte concentration-time curve from time 0 to 6 months; $AUC_{0\text{-}last}$=area under the analyte concentration-time curve from time 0 to the time of last measurable (non-BQL) concentration; BQL=below quantification level; C_{last}=last observed measurable (non-BQL) analyte concentration; C_{max}=maximum observed analyte concentration; SD=standard deviation; $t_{1/2}$=apparent terminal elimination half-life; t_{last}=time of first BQL concentration after reaching C_{max}; t_{last}=time of last measurable (non-BQL) analyte concentration; t_{max}=time to reach maximum observed analyte concentration.
[a] n=19 for $AUC_{0\text{-}28d}$ and $AUC_{0\text{-}6mo}$ n=11 for $t_{1/2}$ and n=10 for t_{bql}.
[b] n=17 for for t_{bql} and n=8 for $t_{1/2}$.
[c] n=16 for $AUC_{0\text{-}28d}$, n=13 for $AUC_{0\text{-}6m}$, n=9 for t_{bql}, and n=8 for $t_{1/2}$.

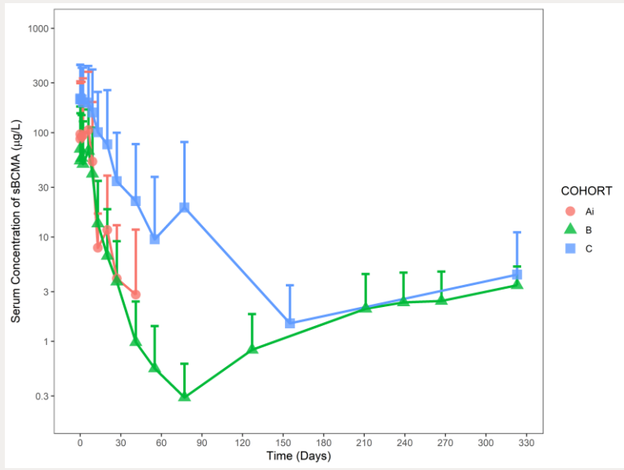
Figure 3: Correlation Between Dose and Exposures (C_{max} and $AUC_{0\text{-}28d}$)



2. Pharmacodynamics:

Following a single cilta-cel infusion, expansion and persistence of CAR-positive T cells coincided with decreases of sBCMA levels. Mean sBCMA levels reached nadir (i.e. LLOQ value <0.250 µg/L) on Day 56 for Cohort A(i) and on Day 100 for Cohorts B and C. Thereafter, sBCMA levels showed gradual increase in some patients; however, the reversed sBCMA levels (up to 1 year post cilta-cel infusion) in most patients were substantially lower than baseline sBCMA as shown in **Figure 4**.

Figure 4: Mean (+ SD) Serum sBCMA Concentration versus Time Profile

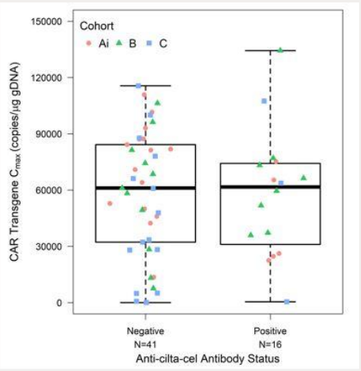


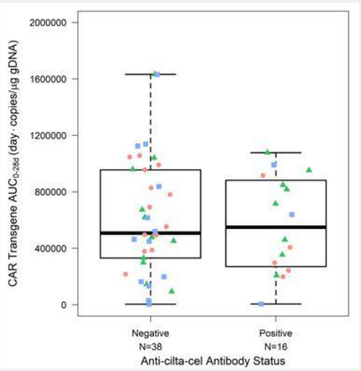
3. Immunogenicity:

The overall incidence of treatment emergent ADA to cilta-cel were 25.0% for Cohorts A(i) and C, 42% for Cohort B, with median ADA onset time ranging from 57 to 186 days across 3 cohorts.

As shown in **Figure 5**, given the high inter-individual variability and overlapping range of PK parameters, the overall cellular kinetics looks similar between ADA positive and ADA negative patients across 3 cohorts. In addition, the observed median ADA onset time for each cohort (57 to 186 days) was much later than the reported median t_{max} (around 14 days), which also suggests there was no apparent impact of ADA on the cellular kinetic parameters ((C_{max} and $AUC_{0\text{-}28d}$) of cilta-cel.

Figure 5: Correlation Between ADA Status and Exposures (C_{max} and $AUC_{0\text{-}28d}$)





References

- Clinical Protocol, A Phase 2, Multicohort Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Multiple Myeloma. Dated Oct. 23, 2023.
- 2023 ACCP: Pharmacokinetics, Pharmacodynamics, and Exposure- Response for Neurotoxicity Adverse Events in a Phase Ib/II CARTITUDE-1 Open-Label Study. Shih-Yu Chang[1], Jianmei Wu[1], Yupeng Ren[1], Dong Geng[2], Tairan Yang[2], Deepu Madduri[1], Carolyn Jackson[1], Jordan Schecter[1], and Xuewen Ma[1]

Multiple Myeloma

Presented by JM Wu at American College of Clinical Pharmacology (ACCP); September 8-10, 2024; Bethesda Maryland, US