ELSEVIER

Blood 142 (2023) 3501–3503

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

Clinical Experience with Cranial Nerve Impairment in the CARTITUDE-1, CARTITUDE-2 Cohorts A, B, and C, and Cartitude-4 Studies of Ciltacabtagene Autoleucel (Cilta-cel)

Niels W.C.J. Van De Donk[1], Surbhi Sidana, MD[2], Jordan M. Schecter[3], Carolyn Chang Jackson[3], Nikoletta Lendvai[3], Kevin C De Braganca[3], Ana Slaughter[4], Carolina Lonardi[5], Philip Vlummens[6], Helen Varsos[3], Christina Corsale[3], Deepu Madduri[3], Shirin Jadidi[3], Junchen Gu[7], Hao Zhao[7], Katherine Li[7], Erin Lee[8], Loreta Marquez[3], Man Zhao[9], Tzu-min Yeh[3], Diana Chen[10], Erika Florendo[11], Nitin Patel[11], Muhammad Akram[11], Jaime Gellego Perez-Larraya[12], Paula Rodriguez Otero, MD PhD[13]

[1] Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands
[2] Stanford University School of Medicine, Stanford, CA
[3] Janssen Research & Development, Raritan, NJ
[4] Cilag GmbH International, Zug, Switzerland
[5] Janssen, Buenos Aires, ARG
[6] Janssen Research & Development, Beerse, Belgium
[7] Janssen Research & Development, Spring House, PA
[8] Janssen Research & Development, Titusville, NJ
[9] IQVIA, Shanghai, China
[10] Janssen Research & Development, Shanghai, China
[11] Legend Biotech USA Inc., Somerset, NJ
[12] Clínica Universidad de Navarra, IDISNA, Pamplona, Spain
[13] Clínica Universidad de Navarra, Pamplona, Spain

Introduction: Cilta-cel is a dual-binding, BCMA-targeting CAR-T cell therapy that has shown high rates of deep and durable response in patients (pts) with relapsed/refractory multiple myeloma (RRMM), and significantly prolonged PFS vs SOC in pts with lenalidomide-refractory MM after 1-3 prior lines of therapy (LOT; HR, 0.26) in the phase 3 CARTITUDE-4 trial. CAR-T therapies are associated with AEs related to immune activation, including neurologic toxicities (Gonzalez Castro. *Neuro-Oncol Pract.* 2020). Here, we describe the clinical experience with presentation and management of cranial neuropathy (CNP) in pts treated with cilta-cel in the CARTITUDE-1, CARTITUDE-2 Cohorts A, B, and C, and CARTITUDE-4 studies.

Methods: CARTITUDE-1 and CARTITUDE-2 Cohort C pts had ≥3 prior LOT, incl PIs, IMiDs, and anti-CD38 mAbs, or were double-refractory to PI and IMiD; CARTITUDE-2 Cohort C pts also had non-cellular anti-BCMA therapy. CARTITUDE-2 Cohort B pts relapsed within 12 months of initial therapy. CARTITUDE-2 Cohort A and CARTITUDE-4 pts had 1-3 prior LOT, incl PI and IMiD, and were lenalidomide-refractory. After apheresis, pts received bridging therapy, then 1 cilta-cel infusion (target dose 0.75×10^{6} CAR+ viable T cells/kg) 5-7 days (d) after lymphodepletion. Pts presenting with signs/symptoms of cranial nerve impairment commonly underwent a diagnostic workup that included CSF analysis and brain MRI at investigator discretion. Correlative data were available for pts in CARTITUDE-4: cilta-cel levels and T cell memory phenotypes in peripheral blood were assessed by flow cytometry, and serum cytokines were measured using multiplex sandwich immunoassays on the Meso Scale Discovery platform.

Results: Of the 332 pts infused with cilta-cel as study treatment in CARTITUDE-1, CARTITUDE-2 (Cohorts A, B, and C), and CARTITUDE-4, 21 (6.3%) developed CNP (TABLE); most cases were grade (gr) 2 (n=3 gr 3). 6 pts had CNP that affected both sides; most unilateral impairments were left-sided. Median time to onset was 22 d (range 17-101; 81% had onset on d 22 +/- 5). Cranial nerve (CN) VII was involved in all pts; 2 pts had additional CNs involved (1 CN III [gr 3], 2 CN V [gr 3]). Twelve pts had concurrent neurologic symptoms/neurotoxicities (headache, n=7; n=1 each for dysgeusia, parosmia, restlessness, peripheral sensory neuropathy, polyneuropathy, amnesia, aphasia, agitation, depressed level of consciousness).

Clinical characteristics of pts with or without CNP were comparable. In the 21 pts with CNP, median age was 64 years; 81% were male; at baseline, 1 pt had high disease burden (BM 95% plasma cells), 4 had plasmacytomas (1 bone-based); 1 pt had ISS stage III. Most pts responded to bridging therapy. Six pts had an infection after cilta-cel infusion and prior to CNP onset

(bacterial, n=5; CMV, n=2; both, n=1). CRS rate was comparable between pts with vs without CNP. 90% of pts with CNP had preceding CRS (all gr 1/2; median onset, d 7; median duration, 3 d); 13 received tocilizumab for CRS. One pt had preceding gr 2 ICANS; no pts had movement/neurocognitive TEAEs (MNT) at any time.

CSF analysis and brain MRI were performed in 14 and 17 pts, respectively. No evidence of infectious or malignant etiology was identified in any of these cases; MRI showed facial nerve enhancement in 7 pts, in whom there were no other significant findings. Most CNP cases were treated with corticosteroids for median 13 d. CNP resolved in 19/21 pts within median 66 d, including the 3 pts with gr 3 CNP.

In CARTITUDE-4, pts with CNP had significantly higher levels of CAR+ T cell expansion (C_{max}) and greater exposure to CAR+ T cells ($AUC_{0\text{-}CNP\ onset}$) than those without CNP (FIGURE). Pts with CNP had a trend toward higher peak concentration and exposure level ($AUC_{0\text{-}CNP\ onset}$) of IL-6, IL-10, and IL-2Rα, but not in IFNγ. The differentiation pattern of memory T cells from apheresis to the time of peak CAR+ T expansion (T_{max}) was comparable in pts with vs without CNP; CAR+ T cells at T_{max} were dominant with central memory T cells in both groups.

Conclusions: Ptstreated with CAR-T cells, including cilta-cel, may experience CNP.The pathogenesis of the events in these 3 studies was unknown/idiopathic, but it is important to rule out etiology of infection or MM progression. Most cases were low-grade and resolved with a limited course of corticosteroids. CNP in CARTITUDE-4 was associated with higher exposure to CAR-T cells before onset, but no predictive clinical factors have been established.

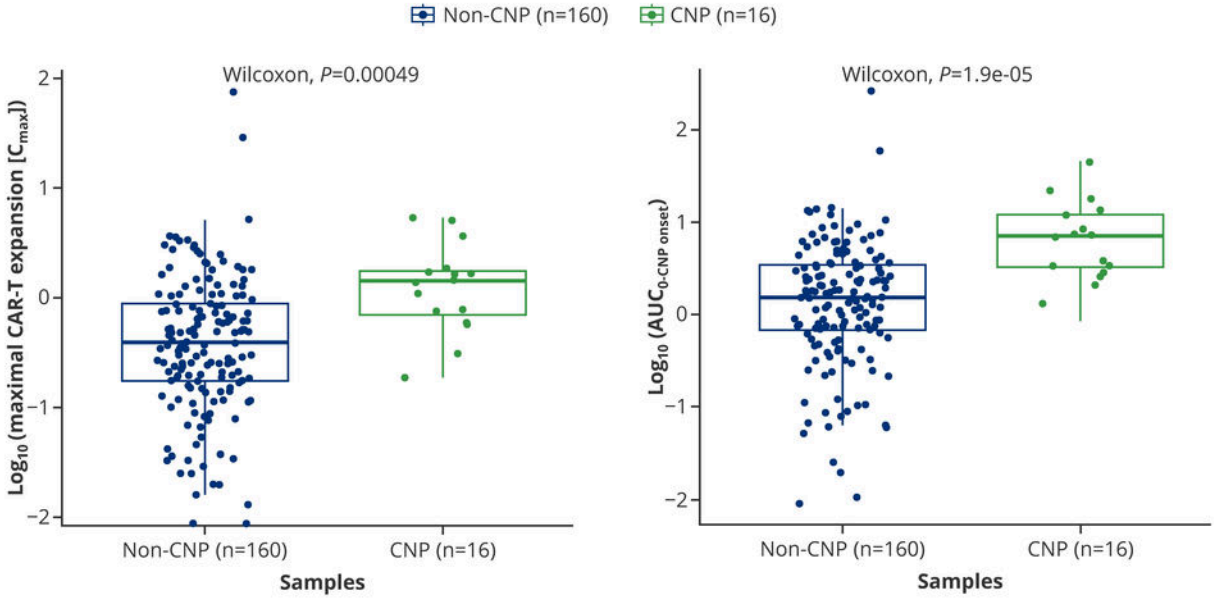
Disclosures Van De Donk: *Janssen Pharmaceuticals, Amgen, Celgene, Novartis, Cellectis, BMS:* Research Funding; *Janssen, Amgen, Celgene, BMS, Takeda, Roche, Novartis, Bayer, Adaptive, Servier:* Consultancy. **Sidana:** *Magenta Therapeutics, BMS, Allogene, Janssen, Novartis:* Research Funding; *Magenta Therapeutics, BMS, Janssen, Sanofi, Oncopeptides, Takeda, Pfizer:* Consultancy. **Schecter:** *Janssen:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties: Janssen. **Jackson:** *Janssen R&D:* Current Employment, Current equity holder in publicly-traded company. **Lendvai:** *Janssen R&D:* Current Employment, Current holder of *stock options* in a privately-held company. **De Braganca:** *Janssen:* Current Employment. **Slaughter:** *Janssen:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Lonardi:** *Janssen R&D:* Current Employment. **Vlummens:** *Janssen Oncology/JnJ:* Current Employment. **Varsos:** *Janssen R&D:* Current Employment, Current equity holder in private company. **Corsale:** *Janssen:* Current Employment, Current equity holder in publicly-traded company. **Madduri:** *Janssen R&D:* Current Employment. **Jadidi:** *Janssen:* Current Employment. **Gu:** *Johnson & Johnson:* Current Employment, Current equity holder in private company. **Li:** *Janssen R&D:* Current Employment, Current equity holder in publicly-traded company. **Lee:** *Johnson & Johnson:* Current Employment, Current equity holder in private company. **Marquez:** *Janssen R&D:* Current Employment, Current holder of *stock options* in a privately-held company, Divested equity in a private or publicly-traded company in the past 24 months. **Yeh:** *Janssen R&D:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Florendo:** *Legend Biotech:* Current Employment, Current equity holder in publicly-traded company. **Patel:** *Legend Biotech, GSK, Freeline, BMS (spouse), AbbVie (spouse):* Current Employment, Current equity holder in publicly-traded company, Divested equity in a private or publicly-traded company in the past 24 months, Ended employment in the past 24 months. **Akram:** *Legend Biotech:* Current Employment, Current equity holder in publicly-traded company. **Gellego Perez-Larraya:** *Janssen & GSK:* Consultancy, Honoraria. **Rodriguez Otero:** *AbbVie:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Honoraria for lectures; *Sanofi:* Membership on an entity's Board of Directors or advisory committees, Other: Honoraria for lectures; *GlaxoSmithKline:* Membership on an entity's Board of Directors or advisory committees, Other: Honoraria for lectures; *Amgen:* Other: Honoraria for lectures; *Regeneron:* Other: Honoraria for lectures; *Bristol Myers Squibb:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Honoraria for lectures; *Oncopeptides:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel grants; *Roche:* Consultancy.

TABLE: CNP cases and CN involvement by CARTITUDE study

	Patients in trial, n	Patients with CNP,[a] n (%)	Maximum CN VII Impairment Grade, n		CN involvement in addition to CN VII, n
			Grade 2	Grade 3	
CARTITUDE-1	97	3 (3.1)	2	1	1 (CN V, gr 3)
CARTITUDE-2					
Cohort A	20	1 (5.0)	1	0	0
Cohort B	19	1 (5.3)	1	0	0
Cohort C	20	0	-	-	-
CARTITUDE-4	176	16 (9.1)	15	1	2 (CN III, gr 3; CN V; gr 3)
Total	**332**	**21 (6.3)**	**19**	**2**	**3**

[a]CNP defined as facial nerve (VII) palsy (n=21), oculomotor (III) nerve palsy (n=1), trigeminal (V) nerve palsy (n=2)
CN, cranial nerve; CNP, cranial neuropathy.

FIGURE: Maximal expansion (C_{max}) and exposure ($AUC_{0\text{-CNP onset}}$) of CAR+ T cells in patients with and without CNP[a] in CARTITUDE-4



[a]CNP onset defined as day 21 for both groups. CNP, cranial neuropathy.

Figure 1

https://doi.org/10.1182/blood-2023-178743