Adjusted comparison of outcomes between patients from CARTITUDE-1 versus multiple myeloma patients with prior exposure to PI, IMiD and anti-CD-38 from a German registry

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INTRODUCTION

- Patients with relapsed and refractory multiple myeloma (rrMM) who are triple-class exposed to immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and anti-CD38 monoclonal antibodies (MoABs) have few treatment options available and poor outcomes[1,2].
- Ciltacabtagene autoleucel (cilta-cel), a chimeric antigen receptor T-cell (CAR-T) therapy, was studied in CARTITUDE-1, an open-label, single arm phase 1b/2 clinical trial assessing safety and efficacy of cilta-cel in adult patients with triple-class exposed rrMM.
- In the absence of a comparator arm in CARTITUDE-1, comparison of trial outcomes vs. an external cohort of similar patients allows quantification of clinical benefits relative to treatments used in clinical practice.

OBJECTIVE

To compare overall survival (OS) and time to next treatment (TTNT) in triple-class exposed patients with rrMM treated with cilta-cel vs. therapies used in real-world clinical practice (RWCP).

METHODS

Data Source

- Individual patient data (IPD) for baseline risk factors and outcomes were available for cilta-cel patients from CARTITUDE-1 (clinical cutoff February 2021) and for RWCP patients from a German Registry maintained by OncologyInformationService (OIs).
- Cilta-cel patients from the CARTITUDE-1 study[3] fulfilled the following key eligibility criteria:
  - Received ≥3 prior MM treatment lines of therapy (LOT) (rrMM per IMWG consensus criteria)
  - Received as part of previous therapy a PI, an IMiD, and an anti-CD38 antibody
  - ECOG performance status (PS) 0 or 1
- OIs includes longitudinal follow-up data from ~4,000 patients with rrMM followed since diagnosis from a representative sample of 108 German centers from January 1, 2016 to December 31, 2020. Data collection is ongoing.
- Measures of progression-free survival (PFS) and response rate are not gathered in the OIs registry. Time to next treatment (TTNT) was used as a proxy measure for PFS.
- RWCP patients were selected from the OIs registry to match CARTITUDE-1 patients by applying the following criteria:
  - Received ≥ 3 LOTs
  - Received as part of previous therapy a PI, an IMiD, and an anti-CD38 antibody
  - ECOG PS 0 or 1
  - Received ≥ 1 active therapies after meeting above criteria
- All treatment lines within the same patients fulfilling these criteria were included in the analysis.

Statistical Methods:

- Time-to-event analyses were performed for OS and TTNT for both intention-to-treat (ITT) and modified intention-to-treat (mITT) populations.
- Populations and index dates were defined as follows:

Population	Description
CARTITUDE-1 ITT	All enrolled patients; Index date: date of apheresis
CARTITUDE-1 mITT	All infused patients; Index date: date of infusion
RWCP ITT	All LOTs; Index date: date of treatment initiation of LOT
RWCP mITT	All LOTs, excluding patients with an event or follow-up <52 days since treatment initiation (mean time from apheresis to infusion); Index date: date of treatment initiation plus 52 days

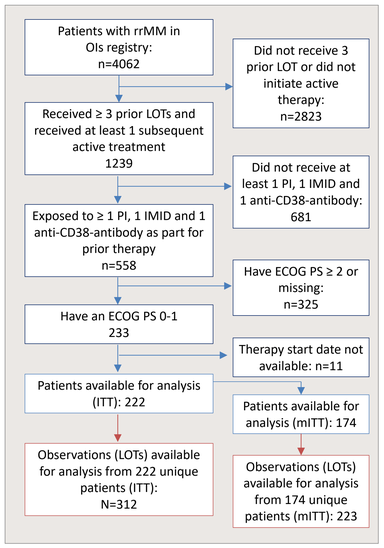
- TTNT was defined as time from index date to initiation of the next LOT or death (whichever occurred first). Patients who were still alive and did not initiate a next LOT at time of data-cut were censored at last date known to be alive.
- Univariate Cox proportional hazards (PH) models were fit to explore the prognostic value of available baseline characteristics, including refractoriness status, R-ISS stage, time to progression on prior LOT, number of prior LOTs, ECOG PS, age, gender, average duration of prior LOT, years since diagnosis.
- Hazard ratios (HR) with 95% confidence intervals (CI) for cilta-cel vs. RWCP were estimated for OS and TTNT using inverse probability weighting (IPW) (average treatment effect in the treated population (ATT) and the average treatment effect in the overlap population (ATO)) and multivariable Cox proportional hazards regression models, adjusting for differences in commonly available baseline characteristics (Table 1).[5,6] These baseline characteristics also represent the most clinically important confounders.
- A robust variance estimator was used to account for clustering of observations within the same patient.

RESULTS

Study Population

- A total of 113 patients were enrolled in CARTITUDE-1 and 97 patients were dosed with cilta-cel.
- Among 4,062 patients in the OIs registry, 312 LOT from 222 patients were available for analysis for ITT comparisons and 223 LOT from 174 patients for mITT analyses (see Figure 1).
- A total of 33 different treatment regimens were observed, the most common ones being: IxaRd (18%), Pd (15%), MP (11%), EloRd (8%) and Vd (7%).
- Patient characteristics prior to IPW analyses are shown in Table 1. Prior to IPW being applied, differences between the cilta-cel and RWCP groups existed in terms of all characteristics considered.
- Following IPW ATT weighting, differences between groups were greatly reduced. After IPW ATO weighting, there were no longer differences between groups.
- Observed outcomes (naïve comparison) showed separation of KM curves for both OS (Figure 2, Panel A) and TTNT (Figure 2, Panel B) and demonstrated strong advantages favoring cilta-cel compared to RWCP, corresponding to HRs of 0.25 (95% CI 0.16-0.40) and 0.17 (95% CI 0.11-0.26) for OS and TTNT.

Figure 1. Patient Selection, OIs Registry



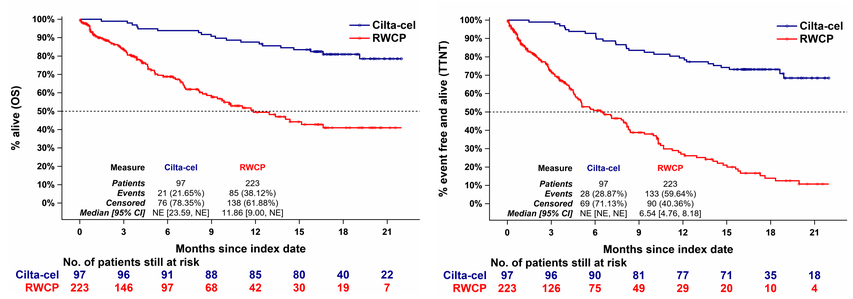
ECOG PS = Eastern Cooperative Oncology Group performance status; IMID = immunomodulatory drug; LOT = line of therapy; PI=protease inhibitor.

Table 1. Patient and Disease Characteristics

Patient/disease characteristic	Subgroup	Cilta-cel (N=97)	RWCP (N=223)
Refractory status	≤ Double	12 (12.4%)	181 (81.2%)
	Triple	8 (8.2%)	26 (11.7%)
	Quadruple	36 (37.1%)	15 (6.7%)
	Penta	41 (37.1%)	1 (0.4%)
R-ISS Stage*	I	33 (34.0%)	3 (1.3%)
	II	57 (58.8%)	95 (42.6%)
	III	7 (7.2%)	125 (56.1%)
TTP, prior line (months)	<4	48 (49.5%)	47 (21.1%)
	≥4	49 (50.5%)	176 (78.9%)
# of prior LOTs	≤4	33 (34.0%)	193 (86.5%)
	5+	64 (66.0%)	30 (13.5%)
ECOG PS	0	50 (51.5%)	25 (11.2%)
	1	47 (48.5%)	198 (88.8%)
Age (years)	<65	62 (63.9%)	32 (14.3%)
	65 to <75	24 (24.7%)	111 (49.8%)
	75+	11 (11.3%)	80 (35.9%)
Sex	Male	57 (58.8%)	138 (61.9%)
	Female	40 (41.2%)	85 (38.1%)
Average duration of prior lines of trt (months)	<8.14	20 (20.6%)	34 (15.2%)
	8.14 to <11.76	22 (22.7%)	74 (33.2%)
	11.76 to <17.61	27 (27.8%)	77 (34.5%)
	17.61+	28 (28.9%)	38 (17.0%)
Years since diagnosis	<6	49 (50.5%)	191 (85.7%)
	≥6	48 (49.5%)	32 (14.3%)

ECOG PS = Eastern Cooperative Oncology Group performance status; LOT = line of therapy; R-ISS = Revised International Staging System; RWCP = real-world clinical practice; TTP = time to progression.
* R-ISS was derived for CARTITUDE-1 and OIs

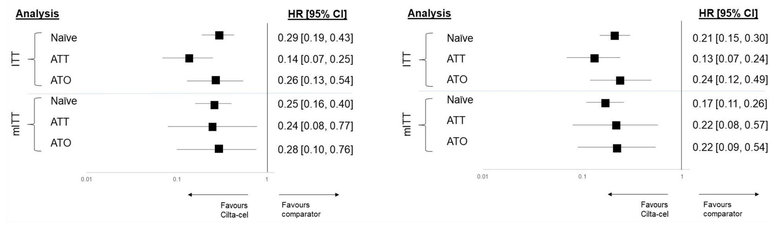
Figure 2. OS (A) and TTNT (B) by Intervention Group – Observed outcomes (mITT)



Adjusted Comparisons of OS and TTNT

- Following adjustments with IPW, comparisons of cilta-cel vs. RWCP showed consistently better outcomes for cilta-cel, for both endpoints (OS, TTNT), both analysis methods (ATT, ATO), and both compared populations (ITT, mITT).
- HRs for ITT comparisons were 0.14 and 0.26 for ATT and ATO for OS (Figure 3, Panel A) and 0.13 and 0.24 for ATT and ATO for TTNT (Figure 3, Panel B). HRs for mITT comparisons were 0.24 and 0.28 for ATT and ATO for OS (Figure 3, Panel A) and 0.22 and 0.22 for ATT and ATO for TTNT (Figure 3, Panel B).
- Similar findings were reached from multivariable regression analysis, with HRs for OS being 0.29 for ITT and 0.16 for mITT, and for TTNT being 0.20 for ITT and 0.13 for mITT (not shown).

Figure 3. Findings, OS (A) and TTNT (B) by Intervention Group



ATT = average treatment effect in the treated population; ATO = average treatment effect in the overlap population; CI= confidence interval; HR = hazard ratio; ITT = intention to treat; mITT = modified intention to treat.

CONCLUSIONS

- Outcomes for patients treated with RWCP are sub-optimal.
- Using different approaches to analysis, findings consistently identified clinically and statistically important advantages with cilta-cel vs. RWCP interventions corresponding to a reduction in risk of death by up to 86% and a reduction in time to next treatment or death (a proxy for progression-free survival) by up to 87%.
- Imbalances on a wide range of prognostic factors between patient cohorts were accounted for, however, as in every non-randomized study, residual confounding cannot be excluded.
- These results highlight cilta-cel's potential as a novel and effective treatment option to address unmet treatment needs in triple-class exposed patients with rrMM based on comparisons with a European cohort.

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