Updated Comparative Efficacy of Ciltacabtagene Autoleucel versus Idecabtagene Vicleucel in Patients with Relapsed or Refractory Multiple Myeloma Previously Treated with 2-4 Prior Lines of Therapy Using a Matching-Adjusted Indirect Comparison

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Key Takeaway

Based on this updated analysis, cilta-cel demonstrates a significant overall survival, compared to ide-cel for patients with triple-class exposed RRMM treated with 2-4 prior LOTs

Conclusions

- Cilta-cel showed significant improvements in OS, response outcomes, and PFS compared to ide-cel in triple-class exposed RRMM patients treated with 2-4 prior LOTs
- Comparative results were confirmed for cilta-cel vs. ide-cel with longer follow-up, and the new OS results highlight the added value of cilta-cel in this population
- This analysis further demonstrated the superior clinical benefits of cilta-cel compared to ide-cel for triple-class exposed RRMM patients treated with 2-4 prior LOTs

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Introduction

- CARVYKTI (ciltacabtagene autoleucel; cilta-cel) and Abecma (idecabtagene vicleucel; ide-cel) are novel B-cell maturation antigen targeting chimeric antigen receptor T-cell (CAR-T) therapies initially approved for heavily pretreated relapsed and refractory multiple myeloma (RRMM).[1,2]
  - In CARTITUDE-4, cilta-cel showed superior overall survival (OS) compared to standard of care (SoC) in patients with RRMM who are refractory to lenalidomide and have received 1-3 prior line(s) of therapy (LOTs) including an immuno-modulatory agent (IMiD) and a proteasome inhibitor (PI) (HR, 0.55; 95% CI, 0.39–0.79).[3]
  - In KarMMa-3, a statistically significant improvement in OS has yet to be demonstrated for ide-cel versus SoC in the intention-to-treat population for triple-class-exposed RRMM with 2-4 prior LOTs (HR, 1.01; 95% CI, 0.73-1.40).[4]
- A previous matching-adjusted indirect comparison (MAIC) of cilta-cel versus ide-cel showed clinical benefit for cilta-cel over ide-cel across response outcomes and progression-free survival (PFS) for patients with triple-class exposed RRMM treated with 2-4 prior LOTs.[5] Results for OS were not available.
- The objective of this analysis was to assess cilta-cel versus ide-cel using longer follow-up data from CARTITUDE-4 and KarMMa-3, including OS.[3,4]

Methods

- Given the availability of individual patient-level data (IPD) for cilta-cel and only published aggregate data for ide-cel from KarMMa-3, the cilta-cel cohort could be adjusted to align with the KarMMa-3 population using MAIC. Due to the absence of a common comparator, an unanchored MAIC was performed.
- Given the differences in the number of prior LOTs received in CARTITUDE-4 (1-3 LOT) and KarMMa-3 trials (2-4 LOT), cilta-cel patients were supplemented with patients from CARTITUDE-1 with 3-4 prior LOTs.
- Cilta-cel patients who fulfilled the inclusion criteria from KarMMa-3 were selected (patients with 1 prior LOT and no prior daratumumab were excluded, and patients with 3-4 prior LOT were included) (**Table 1**).

Table 1: Analysis Sets for KarMMa-3 and CARTITUDE-4/CARTITUDE-1

Ide-cel	Cilta-cel	
KarMMa-3 (N=254)	CARTITUDE-4 (N=208)	CARTITUDE-1 patients with 3-4 prior LOTs (N=37)
	CARTITUDE-1 + CARTITUDE-4 (N=245)	
	KarMMa-3 eligibility criteria applied: Patients with only 1 prior LOT or no prior daratumumab were excluded, leaving N=85 included in the cilta-cel cohort (CARTITUDE-1, 36; CARTITUDE-4, 49)	

- Additional imbalances in patient characteristics were adjusted for by weighting the cilta-cel IPD to match the reported baseline characteristics of KarMMa-3 (**Table 2**).
  - Prognostic factors to be adjusted for in the analyses were identified *a priori* based on input from independent clinical experts.
  - The factors in the base-case analysis were selected based on ability to match factors ranked most important while maintaining a sufficient effective sample size (ESS).
- Reconstructed IPD were derived from reported results for ide-cel by replicating IPD for each response outcome, and by simulating IPD for PFS and OS from published Kaplan-Meier curves.
- Comparative efficacy was estimated for response outcomes from a weighted logistic regression analysis, with corresponding response rate ratios (RRs) and 95% confidence intervals (CIs). For PFS and OS, hazard ratios (HRs) with 95% CIs were estimated from a weighted Cox proportional hazards model.
- A sensitivity analysis that adjusted for additional prognostic factors was also conducted (**Table 2**).

Results

Population Adjustment

- 85 patients were included in the cilta-cel cohort after applying the KarMMa-3 inclusion and exclusion criteria to the CARTITUDE-1 and CARTITUDE-4 IPD.
- The ide-cel cohort consisted of the 254 patients randomized to receive ide-cel in KarMMa-3.
- After population adjustment, the baseline characteristics of the cilta-cel cohort matched the reported average baseline characteristics of the ide-cel population from KarMMa-3 and the ESS was 39 (**Table 2**).

Table 2: Baseline Characteristics Matched for Pooled CARTITUDE-4/ CARTITUDE-1 and KarMMa-3 Analysis Sets

Baseline characteristics matched		Cilta-cel observed N=245	Ide-cel observed N=254	Cilta-cel adjusted (N=79[a], ESS=39[b])
Refractory status	Refractory to lenalidomide	97%	73%	73%
	Non-triple refractory	76%	35%	35%
	Triple-/quadruple-refractory	19%	59%	59%
	Penta-refractory	5%	6%	6%
	Refractory to PI	55%	74%	74%
	Refractory to CD38	36%	95%	95%
Cytogenetic risk	High risk	54%	42%	42%
R-ISS stage	I	24%	22%	22%
	II	71%	65%	65%
	III	5%	13%	13%
Time to progression	Medium TTP on last treatment (months)	13.8	7.1	7.3
EMD	Yes	20%	24%	24%
Tumor burden	High	27%	28%	28%
Prior lines*	Median number	2	3	3
Time from diagnosis to screening*	Medium time from diagnosis to screening (years)	3.2	4.1	4.4
Age*	<65	61%	59%	50%
	65 to 75	36%	36%	48%
	≥75	3%	5%	2%
Prior transplant*	Yes	83%	84%	88%
ECOG PS*	1+	48%	53%	53%
Race*	White	84%	86%	85%
	Black	6%	9%	9%
	Other	10%	5%	6%
Sex*	Male	57%	61%	56%

[a] An additional 6 patients in the cilta-cel cohort were excluded due to missing values in baseline characteristics for adjustment.
[b] ESS is reflective of the weighted population.
*Additional factors adjusted for in a sensitivity analysis, resulting in an ESS of 32.
EMD = extramedullary disease; ECOG = Eastern Cooperative Oncology Group Performance Status Score; ESS = effective sample size; PI = proteasome inhibitor; R-ISS = Revised International Staging System; TTP = time to progression.

Response

- As shown in **Figure 1**, cilta-cel patients were:
  - 1.2 times more likely to achieve an overall response (ORR) versus ide-cel,
  - 1.4 times more likely to achieve a very good partial response or better (≥VGPR) versus ide-cel,
  - 1.8 times more likely to achieve a complete response or better (≥CR) versus ide-cel.

Progression-free Survival

- Cilta-cel was associated with a significant 58% reduction in the risk of disease progression or death versus ide-cel (**Figure 2**).

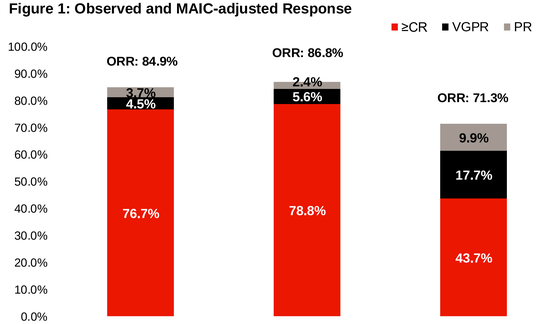
Overall Survival

- Cilta-cel was associated with a significant 42% reduction in the risk of death versus ide-cel (**Figure 3**).

Sensitivity Analyses

- Sensitivity analyses results that matched on additional prognostic factors (ESS=32) were generally consistent with the base-case estimates.

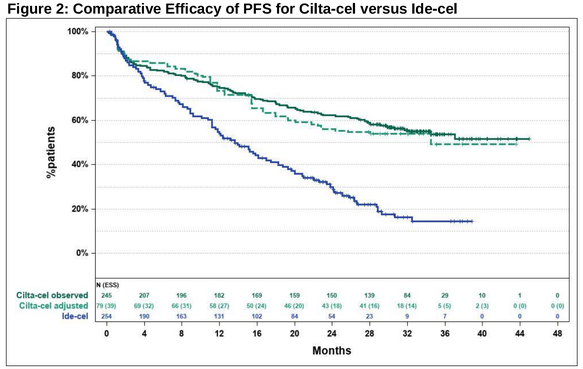
Figure 1: Observed and MAIC-adjusted Response



	Response			Comparative Efficacy of Response Cilta-cel vs. Ide-cel RR (95% CI)	
	Cilta-cel		Ide-cel		
	Observed	Adjusted	Observed	Adjusted	P-value
ORR	84.9%	86.8%	71.3%	1.22 (1.08, 1.38)	0.0126
≥VGPR	81.2%	84.4%	61.4%	1.37 (1.19, 1.59)	0.0009
≥CR	76.7%	78.8%	43.7%	1.80 (1.49, 2.18)	<0.0001

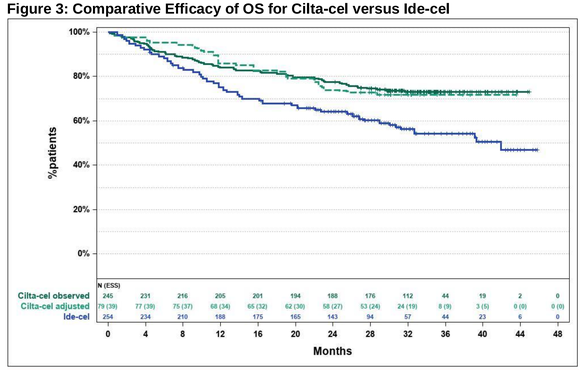
RR>1 indicates favorable treatment effect for cilta-cel.
CI = confidence interval; CR = complete response; ORR = objective response rate; RR = response rate ratio; VGPR = very good partial response

Figure 2: Comparative Efficacy of PFS for Cilta-cel versus Ide-cel



Median, months (95% CI)			Cilta-cel vs. Ide-cel HR (95% CI)		
Cilta-cel		Ide-cel			
Observed	Adjusted	Observed	Observed	Adjusted	P-value
NE	34.5 (15.5, NE)	13.7 (11.6, 16.1)	0.39 (0.30, 0.49)	0.42 (0.26, 0.68)	0.0004

Figure 3: Comparative Efficacy of OS for Cilta-cel versus Ide-cel



Median, months (95% CI)			Cilta-cel vs. Ide-cel HR (95% CI)		
Cilta-cel		Ide-cel			
Observed	Adjusted	Observed	Observed	Adjusted	P-value
NE	NE	41.9 (31.2, NE)	0.54 (0.40, 0.74)	0.58 (0.34,0.99)	0.0452

HR<1 indicates favorable treatment effect for cilta-cel. CI = confidence interval; HR = hazard ratio; NE, not estimable; OS = overall survival; PFS = progression-free survival.

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Multiple Myeloma

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