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Efficacy of CARVYKTI in CARTITUDE-4 versus Other Conventional Treatment Regimens for Lenalidomide-Refractory Multiple Myeloma Patients Using Inverse Probability of Treatment Weighting

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Key Takeaway

Based on this updated analysis, cilta-cel demonstrates significantly greater benefit across all efficacy outcomes including overall survival, compared to other conventional treatments (DVd, DKd, Kd, and Pd) for patients with lenalidomide-refractory multiple myeloma as early as second line

Conclusions

Cilta-cel showed superior efficacy across response and survival outcomes compared to other common treatments for patients with lenalidomide-refractory RRMM who received 1-3 prior lines of therapy, including a PI and IMiD

This analysis with longer follow-up strengthens the previously published results comparing cilta-cel to these treatments, and the new OS results highlight the added value of cilta-cel in this population

These findings further confirm that cilta-cel is an effective treatment for lenalidomide-refractory RRMM patients who received 1-3 prior lines of therapy, including a PI and IMiD

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Poster

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Introduction

- CARVYKTI (ciltacabtagene autoleucel; cilta-cel), has demonstrated superior progression-free survival (PFS), overall survival (OS), and response rates over daratumumab, pomalidomide and dexamethasone (DPd), or pomalidomide, bortezomib and dexamethasone (PVd), in patients with relapsed and refractory multiple myeloma (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), in the phase 3 randomized CARTITUDE-4 trial.[1]
- The comparative efficacy of cilta-cel (median follow-up: 16 months) was previously evaluated against other frequently used treatment regimens in this setting: daratumumab with bortezomib and dexamethasone (DVd), daratumumab with carfilzomib and dexamethasone (DKd), carfilzomib with dexamethasone (Kd), and pomalidomide with dexamethasone (Pd) using the available patient level data.[2]
- Data from a later prespecified data-cut of CARTITUDE-4 with median follow-up of 34 months became available,1 allowing for an updated assessment of the comparative efficacy, including OS, between cilta-cel and these treatment regimens.

Objective

To assess the comparative efficacy of cilta-cel versus DVd, DKd, Kd, and Pd for patients with lenalidomide-refractory RRMM who received 1-3 prior lines of therapy, including a PI and IMiD.

Methods

Data Sources and Population

- Individual patient data (IPD) were obtained from the CARTITUDE-4, CASTOR, CANDOR, and APOLLO. All were randomized, multi-center, open-label phase III trials.
- CARTITUDE-4 (cilta-cel):
  - Median follow-up was 34 months.
  - Patients randomized to receive cilta-cel and underwent apheresis were included in the cilta-cel cohort.
  - As no patients in the comparative trials had prior treatment with anti-CD38*, patients with prior exposure to anti-CD38 therapies in the cilta-cel cohort were excluded.
- CASTOR (DVd), CANDOR (DKd and Kd), and APOLLO (Pd):
  - Median follow-up was 73 months for CASTOR, 50 months for CANDOR, and 40 months for APOLLO.
  - Patients who met CARTITUDE-4 eligibility criteria were identified at enrollment (lenalidomide-refractory RRMM, 1-3 prior LOTs including an IMiD and a PI, have ECOG scores of <2).

*The CANDOR trial allowed pre-exposure to anti-CD38 therapies, but only had one patient in the DKd arm pre-exposed to anti-CD38.

Outcomes

- Response rates (overall response rate [ORR], very good partial response or better [≥VGPR], and complete response or better [≥CR])
- PFS and OS

Statistical Analysis

- Baseline characteristics in the comparator cohorts were adjusted for using inverse probability of treatment weighting (IPTW) to make them comparable to the cilta-cel cohort, approximating a head-to-head trial.
  - Patients in the comparator cohorts were reweighted using average treatment effect in the treated (ATT) weighting. Extreme weights were truncated.
- Key prognostic baseline covariates for adjustment included refractory status, ISS stage, time to progression on prior line, and presence of plasmacytomas/ extramedullary disease (EMD).
- Population differences were assessed using standardized mean differences (SMDs) with an SMD of ≥0.25 indicating the covariate is imbalanced between cohorts.[3]
- Response endpoints were analyzed using weighted logistic regression estimating response rate ratios (RRs) and 95% confidence intervals (CIs).
- For PFS and OS, a weighted Cox proportional hazards regression was used to derive hazard ratios (HRs) and 95% CIs.
- Sensitivity analyses using alternative statistical approaches and including additional covariates were explored.

Results

Population Adjustment

- After the exclusion of 53 patients with prior exposure to an anti-CD38 therapy, 155 patients in the cilta-cel arm remained.
- The comparator cohorts consisted of 44 patients treated with DVd, 98 patients treated with DKd, 46 patients treated with Kd, and 92 patients treated with Pd who met the CARTITUDE-4 inclusion criteria.
- Baseline patient characteristics prior to and following IPTW analysis are presented in **Table 1**. The majority of covariates were well balanced across the cohorts after adjustment.
  - Imbalances remained between cohorts for proportion of patients with plasmacytomas/EMD (SMD ≥0.25) after IPTW due to few patients in the comparator cohorts with EMD, suggesting that results are conservative for cilta-cel.

Table 1: Key Prognostic Baseline Characteristics Before and After Adjustment with IPTW

Variable	Categories	Cilta-cel	DVd			DKd			Kd			Pd		
		N = 155 N (%)	Unadjusted N = 44 N (%)	IPTW N = 36 N (%)	SMD*	Unadjusted N = 98 N (%)	IPTW N = 85 N (%)	SMD*	Unadjusted N = 46 N (%)	IPTW N = 42 N (%)	SMD*	Unadjusted N = 92 N (%)	IPTW N = 71 N (%)	SMD*
Refractory status	< Double refractory ≥ Double refractory	82 (52.9) 73 (47.1)	18 (40.9) 26 (59.1)	18 (49.5) 18 (50.5)	-0.068	54 (55.1) 44 (44.9)	46 (53.4) 40 (46.6)	0.009	26 (56.5) 20 (43.5)	23 (53.9) 19 (46.1)	0.021	45 (48.9) 47 (51.1)	37 (52.1) 34 (47.9)	-0.015
ISS stage	I II III	103 (66.5) 44 (28.4) 8 (5.2)	19 (43.2) 15 (34.1) 10 (22.7)	24 (66.7) 10 (28.7) 2 (4.6)	0.026	51 (52.0) 28 (28.6) 19 (19.4)	57 (67.2) 23 (27.2) 5 (5.6)	0.030	23 (50.0) 15 (32.6) 8 (17.4)	28 (65.5) 12 (29.3) 2 (5.1)	0.021	41 (44.6) 33 (35.9) 18 (19.6)	48 (68.1) 19 (26.8) 4 (5.1)	0.037
Time to progression on prior line	< 6 months ≥ 6 months	22 (14.2) 133 (85.8)	7 (15.9) 37 (84.1)	4 (11.0) 32 (89.0)	-0.095	20 (20.4) 78 (79.6)	12 (14.6) 73 (85.4)	0.010	14 (30.4) 32 (69.6)	5 (12.2) 37 (87.8)	-0.059	19 (20.7) 73 (79.3)	10 (14.3) 61 (85.7)	0.002
EMD	Yes No	29 (18.7) 126 (81.3)	1 (2.3) 43 (97.7)	2 (4.5) 34 (95.5)	-0.455	5 (5.1) 93 (94.9)	7 (7.7) 79 (92.3)	-0.329	3 (6.5) 43 (93.5)	4 (9.2) 38 (90.8)	-0.277	3 (3.3) 89 (96.7)	4 (5.5) 67 (94.5)	-0.415

* SMD between the cilta-cel cohort and the comparator cohort following adjustment
EMD = presence of plasmacytomas/ extramedullary disease; DKd = carfilzomib in combination with daratumumab and dexamethasone; DVd = daratumumab in combination with bortezomib and dexamethasone; IPTW = inverse probability of treatment weighting; ISS = International staging system; Kd = carfilzomib and dexamethasone; Pd = pomalidomide in combination with dexamethasone; SMD = standardized mean difference

Comparative Efficacy for Cilta-cel vs. DVd, DKd, Kd, Pd

Overall Response Rate

- Following adjustment, cilta-cel demonstrated an increased chance of patients achieving an overall response, by 1.1-fold vs. DKd, 1.1-fold vs. DVd, 1.2-fold vs, Kd, and a significant 2.0-fold vs. Pd (**Figure 1**).
- Consistent results were obtained in all sensitivity analyses.

Very Good Partial Response or Better

- Following adjustment, cilta-cel demonstrated a significant increased chance of patients achieving VGPR or better, by 1.3- fold vs. DKd, 1.7-fold vs Kd, 2.0-fold vs DVd, and 5.6-fold vs. Pd (**Figure 2**).
- Consistent results were obtained in all sensitivity analyses.

Complete Response or Better

- Following adjustment, cilta-cel demonstrated a significant increased chance of patients achieving CR or better, by 2.7-fold vs. DKd, 6.2-fold vs Kd, 7.9-fold vs. DVd, and 31.5-fold vs. Pd (**Figure 3**).
- Consistent results were obtained in all sensitivity analyses.

Progression-free survival

- Following adjustment, cilta-cel was associated with a significant reduction in the risk of disease progression or death, by 42% vs. DKd, 68% vs. Kd, 77% vs. Pd, and 79% vs. DVd (**Figure 4**).
- Consistent results were obtained in all sensitivity analyses.

Overall survival

- Following adjustment, cilta-cel was associated with a significant reduction in the risk of death, by 45% vs. DKd, 56% vs. Kd, 64% vs. DVd, and 69% vs. Pd (**Figure 5**).
- Consistent results were obtained in all sensitivity analyses.

Figure 1: ORR

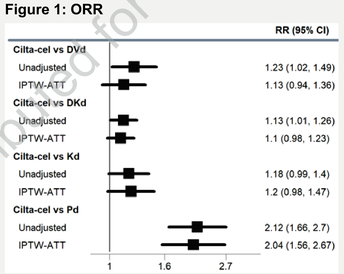


Figure 2: ≥VGPR

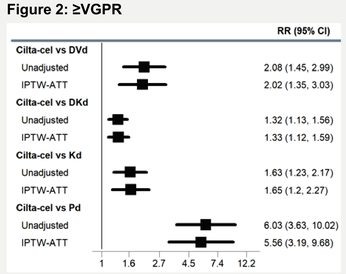


Figure 3: ≥CR

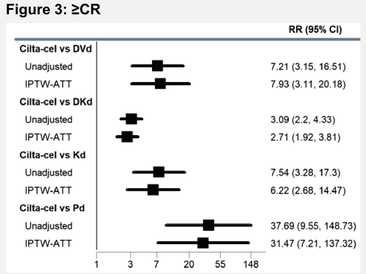


Figure 4: PFS

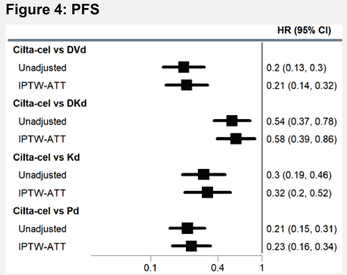
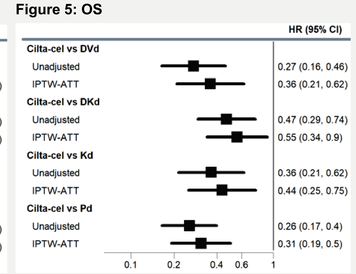


Figure 5: OS



RR>1 and HR<1 indicates favorable treatment effect for cila-cel.
ATT = average treatment effect in the treated; CI = confidence interval; ≥CR = complete response or better; DKd = carfilzomib in combination with daratumumab and dexamethasone; DVd = daratumumab in combination with bortezomib and dexamethasone; HR = hazard ratio; IPTW = inverse probability of treatment weighting; Kd = carfilzomib and dexamethasone; ORR = overall response rate; OS = overall survival; Pd = pomalidomide in combination with dexamethasone; PFS = progression-free survival; RR = rate ratio; ≥VGPR = very good partial response or better

References

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Multiple Myeloma

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