P-016

Comparative Efficacy of CARVYKTI in CARTITUDE-4 versus Alternative Treatments from Daratumumab Clinical Trials for the Treatment of Patients with Lenalidomide-Refractory Multiple Myeloma

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Key Takeaway

Based on this analysis, cilta-cel demonstrates significantly greater clinical benefit compared to alternative continuously administered treatments for patients with lenalidomide-refractory multiple myeloma.

Conclusions

Cilta-cel showed superior efficacy compared to alternative treatments from the daratumumab clinical trials, across all outcomes (ORR, ≥VGPR, ≥CR, PFS, RW-PFS, TTNT).

The comparator cohort included over 175 different treatment regimens for patients with lenalidomide-refractory RRMM and was balanced with the cilta-cel cohort across key clinically important prognostic factors following adjustment.

These findings highlight the potential for cilta-cel to be considered a new standard of care option for lenalidomide-refractory RRMM patients, who have received 1-3 prior LOTs, including an IMiD and a PI.

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Poster

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Disclosures

Michel Delforge reports consultancy with Bristol Myers Squibb, Janssen, GSK, Roche, and Sanofi.

Introduction

- CARVYKTI (ciltacabtagene autoleucel; cilta-cel), has demonstrated superior progression-free survival (PFS) 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 open-label CARTITUDE-4 trial.[1]
- However, a number of therapies are available for this patient population,[2,3] and it is important to understand how cilta-cel compares to other treatments used in clinical practice.

Objective

- To evaluate the comparative efficacy of cilta-cel versus a combined group of alternative treatments for RRMM patients refractory to lenalidomide from daratumumab clinical trials.

Methods

Data Sources and Population

- *CARTITUDE-4*
  - Patients randomized to receive cilta-cel and underwent apheresis in CARTITUDE-4 were included in the cilta-cel cohort.
- *9 Daratumumab Clinical Trials*
  - CASTOR, CANDOR, APOLLO, MAIA, ALCYONE, GRIFFIN, CASSIOPEIA, POLLUX and EQUULEUS trials.
  - All trials were open label. Patients had either RRMM or newly diagnosed MM at enrollment. Trial phases ranged from 1b to 3.
  - Combined comparator cohort included:
    - Patients who received active or subsequent treatments with/without daratumumab, constituting a mixed cohort of regimens.
    - Patients who met the key eligibility criteria of CARTITUDE-4 (lenalidomide-refractory RRMM, with 1-3 prior LOTs, including an IMiD and a PI) at enrollment or at a subsequent LOT.
    - Patients could contribute multiple LOTs (as independent observations), if they remained eligible at the start of each LOT.

Outcomes

- Overall response rate (ORR; defined as ≥ partial response)
- Very good partial response or better rate (≥VGPR)
- Complete response or better rate (≥CR)
- Progression free survival (PFS)
- Real-world PFS (RW-PFS; defined as time to next treatment, progression, or death, whichever comes first)
- Time to next treatment (TTNT)

Statistical Analysis

- Inverse probability of treatment weighting (IPTW) was used to adjust for imbalances between the cohorts on key patient characteristics, emulating a head-to-head trial.
  - Average treatment effect in the treated (ATT) weighting was used, with propensity scores estimated with a logistic regression.
- Prognostic factors for adjustment were identified *a priori* in consultation with clinical experts: refractory status, cytogenetic risk profile, International Staging System (ISS) stage, baseline plasmacytoma, time to progression on last regimen, number of prior LOTs, years since MM diagnosis, age, and hemoglobin.
- Odds ratios (OR) / hazard ratios (HR) and 95% confidence intervals (CI) were derived using weighted logistics regression / Cox proportional hazards model.
- Separate sensitivity analyses including only the first eligible LOT and adjusting for additional characteristics (prior stem cell transplant, Eastern Cooperative Oncology Group status, race, sex, type of MM), were also performed.

Results

Study Population

- The cilta-cel cohort consisted of 208 patients from CARTITUDE-4.
- The comparator cohort consisted of 800 patients from the daratumumab trials, contributing 1045 eligible LOTs.
- After adjustment, baseline patient characteristics were similar between the cilta-cel and comparator cohort (**Table 1**).
- In the comparator cohort, over 175 unique treatment regimens were received across all eligible LOTs. The most frequently used (>5% of LOTs) are listed in **Table 2**.

Comparative Efficacy

- *Response Outcomes*
  - Cilta-cel substantially improved response versus the comparator cohort with **3.51**, **7.25**, and **16.45** increased odds of achieving ORR, ≥VGPR, and ≥CR, respectively (**Table 3**).
- *Time to Event Outcomes*
  - Cilta-cel was found to reduce the risk of progression or death by **63%** (PFS), reduce the risk of progression, next treatment, or death by **73%** (RW-PFS), and reduce the risk of next treatment or death by **72%** (TTNT) (**Figure 1**).
  - Cilta-cel exceeded the Kaplan–Meier estimated median PFS, RW-PFS, and OS of the comparator cohort (**Figure 1**).
- All results were statistically significant (P<0.0001). Results across sensitivity analyses were consistent with the main findings.

Table 1: Patient Characteristics Before and After IPTW Adjustment

Characteristic	Categories	Unadjusted		Adjusted
		Cilta-cel N (%) 208 (100%)	Comparators N (%) 1045 (100%)	Comparators N[a] (%) 190 (100%)
Refractory status[b]	Refractory to a PI Refractory to an anti-CD38 Antibody	103 (49.5%) 50 (24.0%)	692 (66.2%) 255 (24.4%)	118 (62.5%) 52 (27.4%)
Cytogenetic risk profile	High risk[c] Standard Risk Unknown	123 (59.1%) 69 (33.2%) 16 (7.7%)	144 (13.8%) 391 (37.4%) 510 (48.8%)	100 (52.7%) 74 (39.0%) 16 (8.3%)
ISS stage	I II III	136 (65.4%) 60 (28.8%) 12 (5.8%)	571 (54.6%) 330 (31.6%) 144 (13.8%)	133 (70.1%) 46 (24.0%) 11 (5.9%)
Baseline plasmacytoma[d]	No Yes	164 (78.8%) 44 (21.2%)	985 (94.3%) 60 (5.7%)	150 (79.3%) 39 (20.7%)
Time to progression on last regimen	≤ 16 months > 16 months	102 (49.0%) 106 (51.0%)	706 (67.6%) 339 (32.4%)	102 (53.7%) 88 (46.3%)
Number of prior LOTs	1 2 3	68 (32.7%) 83 (39.9%) 57 (27.4%)	86 (8.2%) 433 (41.4%) 526 (50.3%)	56 (29.5%) 80 (42.3%) 54 (28.3%)
Years since MM diagnosis	< 3 years ≥ 3 years	104 (50.0%) 104 (50.0%)	410 (39.2%) 635 (60.8%)	85 (44.6%) 105 (55.4%)
Age	< 65 years ≥ 65 years	126 (60.6%) 82 (39.4%)	496 (47.5%) 549 (52.5%)	112 (59.2%) 77 (40.8%)
Hemoglobin	< 12 g/dL ≥ 12 g/dL	130 (62.5%) 78 (37.5%)	654 (62.6%) 391 (37.4%)	115 (60.4%) 75 (39.6%)

[a] Number for the adjusted comparator cohort represents the sum of the propensity score weights. [b] Refractory was defined as progressive disease while on treatment, discontinuation of drug within 60 days, or progressive disease within 60 days after the end of previous treatment. [c] High risk in the cilta-cel cohort was defined as at least one of del17p, t(4, 14), t(14, 16), or gain/amp(1q). High risk in the comparator cohort was defined as at least one of del17p, t(4, 14), or t(14, 16). [d] Refers to soft-tissue mass that is not in contact with bone; does not include bone-based plasmacytomas. ISS, International Staging System; LOTs, lines of therapy; MM, multiple myeloma; PI, proteasome inhibitor.

Table 2: Treatments Most Frequently* Used in the Comparator Cohort

Treatments	N (%) 1045 (100%)
DKd	147 (14.1%)
DPd	147 (14.1%)
Pd	124 (11.9%)
Kd	92 (8.8%)
D	54 (5.2%)

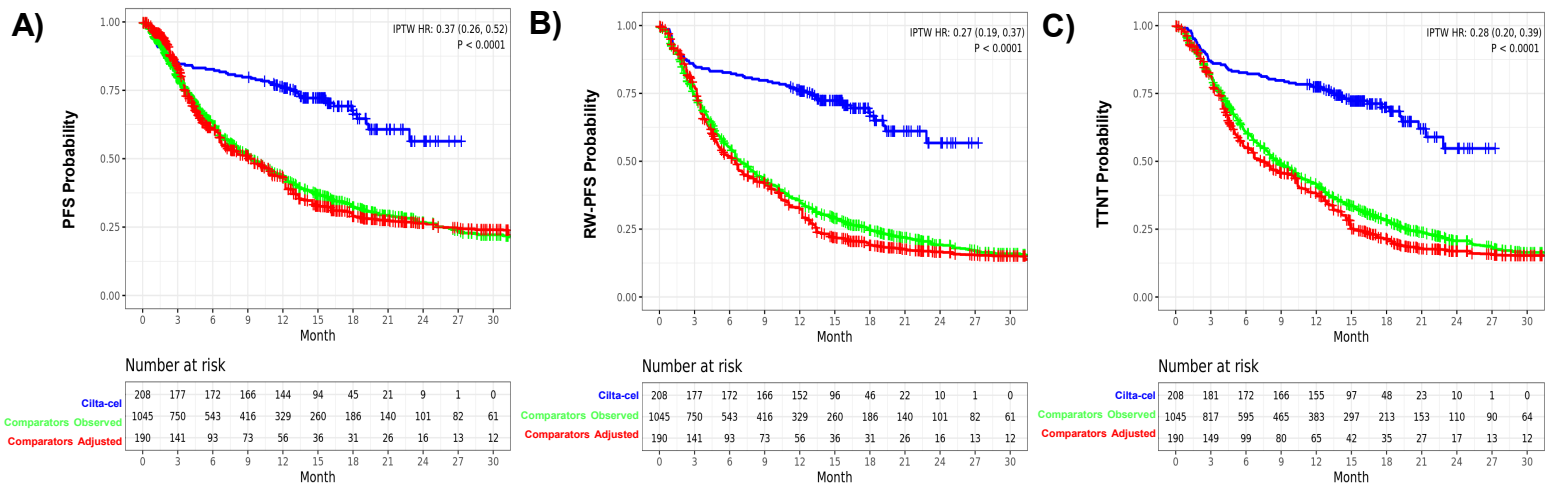
* Used in >5% of patients. D, daratumumab; DKd, daratumumab, carfilzomib and dexamethasone; DPd, daratumumab, pomalidomide and dexamethasone; Kd, carfilzomib and dexamethasone; Pd, pomalidomide and dexamethasone.

Table 3: Results for Response Outcomes

	Response			Cilta-cel vs. Comparators Odds Ratio[a] (95% CI)	
	Cilta-cel	Comparators			
	Unadjusted	Unadjusted	Adjusted[b]	Unadjusted*	Adjusted[b]*
ORR	83.70%	51.90%	59.30%	4.75 (3.27, 7.10)	3.51 (2.21, 5.65)
≥VGPR	79.80%	29.10%	35.30%	9.63 (6.76, 14.01)	7.25 (4.66, 11.49)
≥CR	72.10%	11.90%	13.60%	19.21 (13.53, 27.61)	16.45 (9.99, 28.00)

* P< 0.0001 for all analyses
[a] OR>1 indicates favorable treatment effect for cilta-cel. [b] Adjusted for refractory status, cytogenetic risk profile, International Staging System stage, baseline plasmacytoma, time to progression on last regimen, number of prior lines of therapy, years since multiple myeloma diagnosis, age, and hemoglobin. CI, confidence interval; ≥CR, complete response or better rate; OR, odds ratio; ORR, overall response rate; ≥VGPR, very good partial response or better rate.

Figure 1: Comparative Efficacy for A) PFS, B) RW -PFS, and C) TTNT



Median, months (95% CI)			Cilta-cel vs. Comparators Hazard Ratio[a] (95% CI)	
Cilta-cel	Comparators			
Unadjusted	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
NR (22.83, NR)	9.26 (8.31, 10.55)	9.26 (6.47, 12.22)	0.37 (0.28, 0.48)*	0.37 (0.26, 0.52)*

Median, months (95% CI)			Cilta-cel vs. Comparators Hazard Ratio[a] (95% CI)	
Cilta-cel	Comparators			
Unadjusted	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
NR (22.83, NR)	6.93 (6.47, 7.82)	6.47 (4.67, 9.03)	0.29 (0.23, 0.38)*	0.27 (0.19, 0.37)*

Median, months (95% CI)			Cilta-cel vs. Comparators Hazard Ratio[a] (95% CI)	
Cilta-cel	Comparators			
Unadjusted	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
NR (21.36, NR)	8.74 (7.92, 9.92)	7.43 (5.32, 10.41)	0.32 (0.24, 0.41)*	0.28 (0.20, 0.39)*

Number at risk for Comparator Cohort Adjusted represents the sum of the propensity score weights.
* P< 0.0001 for all analyses
[a] HR<1 indicates favorable treatment effect for cilta-cel. [b] Adjusted for refractory status, cytogenetic risk profile, International Staging System stage, baseline plasmacytoma, time to progression on last regimen, number of prior lines of therapy, years since multiple myeloma diagnosis, age, and hemoglobin. CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival; RW-PFS, real-world progression-free survival; TTNT, time to next treatment.

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Multiple Myeloma

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