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Comparative Effectiveness of Ciltacabtagene Autoleucel From the CARTITUDE-4 Trial vs Real-World Physician's Choice of Therapy From the Flatiron Registry in Lenalidomide-Refractory Multiple Myeloma

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Key Takeaway

In this analysis, cilta-cel demonstrated superior clinical benefit over RWPC for earlier-line patients with PI- and IMiD-exposed, relapsed, lenalidomide-refractory MM

Conclusions

Cilta-cel reduced the risk of progression or death by 71% vs RWPC and the risk of moving to next treatment by 64%

Results of the full model and sensitivity analyses were consistent with the base case

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Poster

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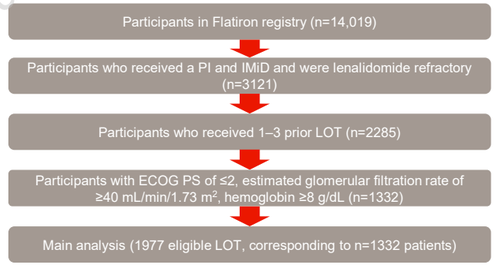
Introduction

- CARTITUDE-4 demonstrated superior efficacy of ciltacabtagene autoleucel (cilta-cel, a BCMA-directed CAR-T therapy) vs pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd) in patients with lenalidomide-refractory multiple myeloma (MM) after 1–3 prior lines of therapy (LOT)[1]
  - DPd and PVd are National Comprehensive Cancer Network (NCCN)-preferred regimens for treatment of lenalidomide-refractory MM after 1–3 prior LOT
- In general, little is known about the comparative efficacy of cilta-cel vs standard of care regimens in real-world settings
- Here, we compare the relative efficacy of cilta-cel in CARTITUDE-4 vs real-world physician's choice (RWPC) using an external control arm from the Flatiron Health MM cohort registry

Methods

- Data from February 2016 to December 2022 were extracted from the Flatiron Health US cohort registry of deidentified patient-level electronic health records for patients who matched key eligibility criteria for CARTITUDE-4 (**Figure 1**)
- The CARTITUDE-4 study data cut-off was November 2022
- Data analyzed in the Flatiron cohort were real-world progression-free survival (PFS), which included progression, next treatment, and deaths as events
- As the base case, the inverse probability of treatment weighting was used to adjust for unbalanced baseline covariates: proteasome inhibitor (PI)-refractory status, anti-CD38–refractory status, cytogenetic profile, International Staging System (ISS) stage, time to progression on last LOT, number of prior LOT, years since diagnosis, age, and hemoglobin level
  - Prior transplant, Eastern Cooperative Oncology Group performance status (ECOG PS), race, sex, and MM type were also included in the fully adjusted sensitivity analyses
- Comparative effectiveness was estimated for PFS and time to next treatment (TTNT). Overall survival (OS) data in CARTITUDE-4 were immature at the time of the analysis
  - Time 0 for cilta-cel is apheresis (with PFS measured from randomization)
  - Time 0 for RWPC is when patients met inclusion criteria
- Sensitivity analyses conducted were the multivariate regression and doubly robust methods[2]
- The estimand was the average treatment effects on the treated, ensuring that RWPC patients resembled patients in CARTITUDE-4

Figure 1: Selection of comparator cohorts



IMiD, immunomodulatory drug.

Results

- The CARTITUDE-4 cohort consisted of 208 patients in the cilta-cel arm (median follow-up, 15.9 months); of these, 176 patients received a cilta-cel infusion as study treatment
- The Flatiron cohort consisted of 1332 patients, corresponding to 1977 eligible LOT (external control arm; median follow-up, 34 months) (**Table 1**)
  - Prior to adjustment, baseline characteristics for cilta-cel vs the Flatiron cohort showed imbalances: ISS stage III, 5.8% vs 26.2%; high-risk cytogenetics, 59.1% vs 20.3%; prior transplant, 82.2% vs 44.4%, respectively
  - Baseline characteristics were similar between the 2 cohorts after adjustment

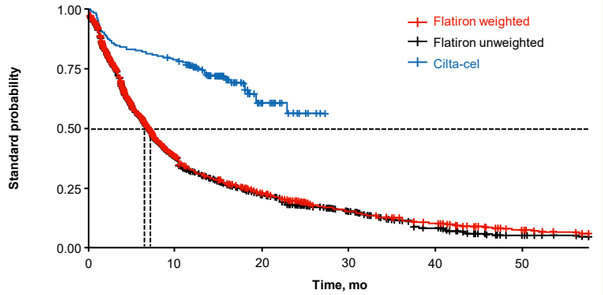
Table 1: Baseline characteristics prior to adjustment

Variables, n (%)	Flatiron (N=1977)	Cilta-cel (N=208)
Refractory to PI	1323 (66.9)	103 (49.5)
Refractory to anti-CD38	207 (10.5)	50 (24.0)
Cytogenetic risk categories		
High risk	401 (20.3)[a]	123 (59.1)[b]
Standard risk	1072 (54.2)	69 (33.2)
Unknown	504 (25.5)	16 (7.7)
ISS categories		
I	755 (38.2)	136 (65.4)
II	704 (35.6)	60 (28.8)
III	518 (26.2)	12 (5.8)
Progression on last LOT, mo		
≤16	1564 (79.1)	102 (49.0)
>16	413 (20.9)	106 (51.0)
Prior LOT		
1	545 (27.6)	68 (32.7)
2	752 (38.0)	83 (39.9)
3	680 (34.4)	57 (27.4)
Duration from diagnosis to index, y		
<3	1409 (71.3)	104 (50.0)
≥3	568 (28.7)	104 (50.0)
Age, y		
<65	783 (39.6)	126 (60.6)
≥65	1194 (60.4)	82 (39.4)
Hemoglobin, g/dL		
<12	1118 (56.6)	130 (62.5)
≥12	859 (43.4)	78 (37.5)
Prior transplant	878 (44.4)	171 (82.2)
ECOG PS		
0	791 (40.0)	114 (54.8)
1	1186 (60.0)	94 (45.2)
Race		
White	1302 (65.9)	157 (75.5)
Black	308 (15.6)	6 (2.9)
Not reported/other	367 (18.6)	45 (21.6)
Sex, male	1093 (55.3)	116 (55.8)
Type of MM		
IgG	1204 (60.9)	113 (54.3)
Light chain	290 (14.7)	47 (22.6)
Other	483 (24.4)	48 (23.1)

[a]Includes any of the following: del17p, t(4;14), or t(14;16). [b]Includes any of the following: del17p, t(4;14), t(14;16), or gain/amp(1q).

- The most commonly used RWPC regimens in the Flatiron cohort were:
  - DPd (12.7%)
  - Pomalidomide and dexamethasone (8.5%)
  - Daratumumab (with or without dexamethasone; 7.0%) and other MM combinations (which included all MM drugs not recommended as regimens by NCCN, which may include any PI, IMiD, anti-CD38 monoclonal antibody, melphalan, cyclophosphamide, or selinexor; 16.6%)
- Cilta-cel PFS was numerically prolonged compared with RWPC PFS: median PFS for cilta-cel was not reached (NR; 95% CI, 22.8–not estimable [NE]) vs 6.7 (95% CI, 5.6–7.9) months for weighted RWPC (adjusted base model) (**Figure 2**)
- Median TTNT for cilta-cel was NR (95% CI, 21.4–NE) and 9.1 (95% CI, 7.4–11.6) months for weighted RWPC (adjusted base model) (**Figure 3**)
- The unadjusted hazard ratio (HR), base model with adjusted HR, and full model with adjusted HR all favored cilta-cel over RWPC for PFS and TTNT (**Table 2**)

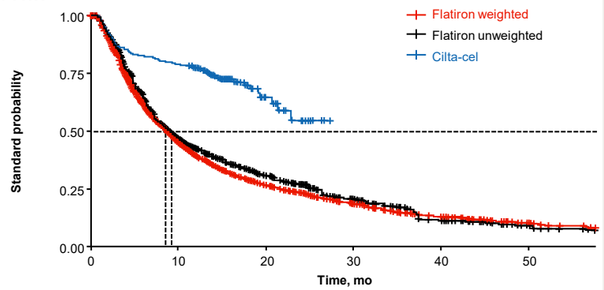
Figure 2: PFS



Flatiron weighted[a]	1977	619	292	159	87	44
Flatiron unweighted[a]	1977	614	261	151	64	30
Cilta-cel	208	163	25	0	0	0

[a]Number at risk in the Flatiron cohort are rescaled to match the unadjusted number of eligible LOT in Flatiron.

Figure 3: TTNT



Flatiron weighted[a]	1977	743	350	196	113	60
Flatiron unweighted[a]	1977	727	302	174	71	48
Cilta-cel	208	164	27	0	0	0

[a]Number at risk in the Flatiron cohort are rescaled to match the unadjusted number of eligible LOT in Flatiron.

Table 2: HR for cilta-cel vs RWPC

Cilta-cel vs RWPC, HR (CI)		PFS	TTNT
Inverse probability of treatment weighting	Unadjusted	0.29 (0.22–0.37)	0.32 (0.25–0.42)
	Base model, adjusted	0.29 (0.22–0.38)	0.36 (0.26–0.48)
	Full model, adjusted	0.27 (0.20–0.37)	0.33 (0.24–0.46)
Doubly robust (sensitivity analysis)	Unadjusted	0.29 (0.22–0.37)	0.32 (0.25–0.42)
	Base model, adjusted	0.28 (0.21–0.37)	0.36 (0.27–0.48)
	Full model, adjusted	0.27 (0.20–0.37)	0.33 (0.24–0.45)
Multivariable regression (sensitivity analysis)	Unadjusted	0.29 (0.22–0.37)	0.32 (0.25–0.42)
	Base model, adjusted	0.28 (0.21–0.36)	0.32 (0.24–0.42)
	Full model, adjusted	0.29 (0.22–0.38)	0.32 (0.24–0.42)

- OS data for CARTITUDE-4 were immature at the time of this analysis; OS benefit of cilta-cel vs RWPC will be analyzed when OS data matures in CARTITUDE-4
- Limitations of this analysis include:
  - As with any nonrandomized study, the potential for residual confounding cannot be excluded
  - The Flatiron cohort did not have data available for response outcomes, comorbidities, and plasmacytomas
  - Missing outcomes, such as progression data, may have biased the comparison results against cilta-cel

References

1. San-Miguel J, et al. *N Engl J Med* 2023;389:335-47. 2. Funk MJ, et al. *Am J Epidemiol* 2011;173:761-67.

Multiple Myeloma

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