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# Survival Benefit of Ciltacabtagene Autoleucel in Second-Line Compared With Later-Line Treatment of Lenalidomide-Refractory Multiple Myeloma: Updated Treatment Positioning Model Analysis

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## Key Takeaway

This simulation model using longer follow-up data from CARTITUDE-4 confirmed the survival benefit with cilta-cel when used earlier in the disease course and reinforces the results from the previous analysis[3]

## Conclusions

This simulation model using IA2 data shows that using a single cilta-cel infusion earlier in the treatment pathway results in improved survival outcomes for len-refractory patients with RRMM

These results further support the survival benefit associated with cilta-cel in earlier LOT

Continued investigation with additional real-world data would be beneficial to further support the results of this model

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**Disclosures**

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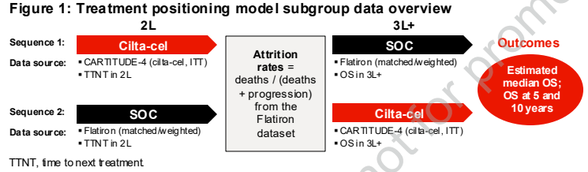
## Introduction

- Ciltacabtagene autoleucel (cilta-cel) was approved for lenalidomide (len)-refractory patients with relapsed/refractory multiple myeloma (RRMM) who received ≥1 prior lines of therapy (LOT), including a proteasome inhibitor and an immunomodulatory agent[1]
  - This approval was based on the ongoing CARTITUDE-4 trial (NCT04181827), which demonstrated significantly improved progression-free survival, overall response rate, and depth of response in len-refractory patients with RRMM with 1–3 prior LOT compared with daratumumab, pomalidomide, and dexamethasone (DPd) and pomalidomide, bortezomib, and dexamethasone (PVd)[1,2]
- Following a prior simulation model using the CARTITUDE-4 first interim analysis (IA1),[3] a second interim analysis (IA2) was used to assess the survival benefit of using cilta-cel vs standard of care (SOC) earlier in the treatment pathway

## Methods

- A Markov model was used to compare the survival outcomes of 2 treatment sequences: (1) using cilta-cel in second line (2L) followed by SOC in third line or later (3L+) vs (2) using SOC in 2L followed by cilta-cel in 3L+
- Data from CARTITUDE-4 (cilta-cel) and deidentified, US nationwide Flatiron Health multiple myeloma (MM) electronic health record databases (SOC) were used to assess the efficacy of cilta-cel and SOC (**Figure 1**)

**Figure 1: Treatment positioning model subgroup data overview**




TTNT, time to next treatment

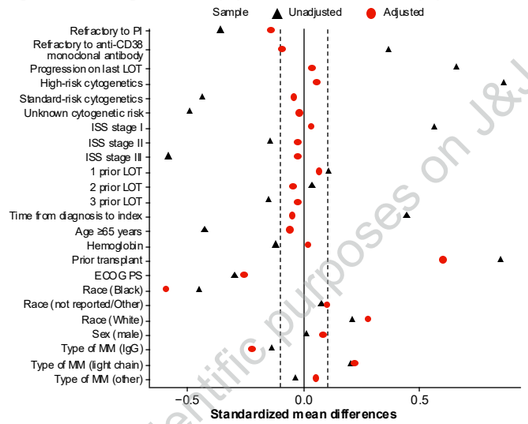
- CARTITUDE-4 inclusion/exclusion criteria were applied to the Flatiron SOC cohort, and patients were weighted on key prognostic factors and treatment effect modifiers
- SOC was defined based on the treatment regimens received by patients with len-refractory MM previously treated with 2L and 3L+ in the Flatiron database, with different distributions of treatments between 2L and 3L+
- Time spent in 2L with cilta-cel and SOC was obtained from TTNT data from CARTITUDE-4 2L and Flatiron 2L subgroups, respectively; time spent in 3L+, starting with SOC and with cilta-cel, was derived from OS data from CARTITUDE-4 and Flatiron 3L+ subgroups
- Transition probabilities over time were derived from parametric survival models, and attrition rates were assumed to be the same in both arms; the base case was tested by scenario analyses

## Results

### Databases

- In total, there were 208 patients in the cilta-cel arm of the CARTITUDE-4 ITT cohort; data cut-off was May 2024, and median follow-up was 33.6 months
- The adjusted Flatiron (SOC) cohort comprised 1445 observations that fulfilled inclusion criteria similar to CARTITUDE-4 between January 2020 and May 2024; median follow-up was 23.6 months
- Key prognostic factors and treatment effect modifiers from the CARTITUDE-4 (cilta-cel) and Flatiron (SOC) cohorts were matched (**Figure 2**)
- The base case settings in the model are presented in **Table 1**

**Figure 2: Matching of Flatiron population to CARTITUDE-4 population**




ECOG PS, Eastern Cooperative Oncology Group performance status; Ig, immunoglobulin; ISS, International Staging System; PI, proteasome inhibitor.

**Table 1: Base case settings**

| Patient characteristics | |
|---|---|
| Starting age, years | 60.1 |
| Female, % | 42.7 |
| **Model settings** | |
| General population mortality adjustment | Yes |
| Flatiron population adjustment | Adjusted |
| Attrition rate,[a] % | 15.8 (applied to both arms) |

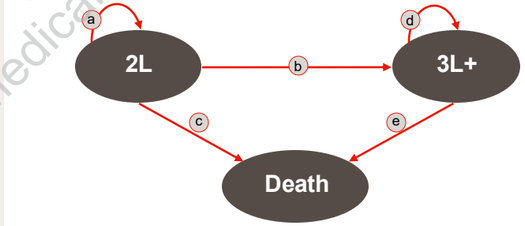
[a]The base case attrition rate was defined as number of deaths divided by deaths plus the number of patients who progressed in the Flatiron dataset, assumed to be the same in both arms.

- The most common 2L treatments in Flatiron were DPd (15.6%), daratumumab, bortezomib, and dexamethasone (DVd) (11.0%), and other MM combinations (15.1%)

### Modeling

- A Markov model including 2L, 3L+, and death was used (**Figure 3**)
  - A lognormal distribution was chosen as the most appropriate distribution for statistical and visual fitting of the data and was used as the base case distribution, with an attrition rate of 15.8%

**Figure 3: Markov model**




a, % patients who stay on 2L treatment, derived from 2L TTNT; b, % patients who are newly progressed, derived from 2L TTNT and attrition rate; c, % death during 2L treatment, derived from 2L TTNT and attrition rate; d, % patients who stay on 3L+ treatment, derived from 2L TTNT and 3L OS; e, % death during 3L+ treatment, derived from 2L TTNT and 3L OS.

- Based on the simulation model, treatment with cilta-cel in 2L resulted in longer OS compared with using cilta-cel in 3L+ after SOC (median OS: 12.8 vs 9.3 years, respectively; **Table 2**)
  - When using cilta-cel in 2L, the estimated OS rate was 75.5% at 5 years and 57.2% at 10 years, compared with 61.6% and 48.6%, respectively, when using cilta-cel in 3L+
  - The OS rate difference (2L vs 3L+) was 14.0% at 5 years and 8.6% at 10 years

**Table 2: OS of IA2 by base case**

| | 2L cilta-cel to 3L+ SOC | 2L SOC to 3L+ cilta-cel | Δ |
|---|---|---|---|
| Median OS, years | 12.8 | 9.3 | 3.5 |
| 5 years | 75.5% | 61.6% | 14.0% |
| 10 years | 57.2% | 48.6% | 8.6% |

- Alternative attrition and distribution (exponential) assumptions consistently demonstrated the survival benefit of using cilta-cel in 2L compared with 3L+ (**Table 3**)
  - Different attrition assumptions using the lognormal distribution (base case) showed consistent improvements in OS benefit, with a difference in OS at 5 years between 13.4% and 27.4%
  - With the base case attrition assumption, the difference in OS at 5 years was 16.1% (exponential) vs 14.0% (lognormal)
  - The alternative survival assumption (exponential) also showed consistent benefits with cilta-cel in 2L with each alternative attrition rate

**Table 3: Incremental OS of using cilta-cel in 2L vs 3L+ with alternative attrition and distribution models**

| Distribution[a] | Attrition assumption | Attrition rate, % | Δ Median OS | Δ OS 5Y |
|---|---|---|---|---|
| Lognormal | **Base case:** Flatiron TTNT death only | 15.8 | 3.5 | 14.0% |
| | Flatiron TTNT death + censored[b] | 53.4 | 6.8 | 27.4% |
| | Trial death only[c] | Treatment specific | 3.3 | 13.4% |
| | Trial death + lost to follow-up[d] | Treatment specific | 5.8 | 23.8% |
| Exponential | Flatiron TTNT death only | 15.8 | 2.7 | 16.1% |
| | Flatiron TTNT death + censored | 53.4 | 4.2 | 27.1% |
| | Trial death only | Treatment specific | 2.5 | 15.4% |
| | Trial death + lost to follow-up | Treatment specific | 3.4 | 22.7% |

[a]Incremental OS was based on TTNT data for 2L and OS data for 3L+ for both base case and alternative distributions. [b]Flatiron TTNT death + censored is defined as number of deaths plus censored patients divided by deaths plus the number of patients who progressed in the Flatiron dataset. [c]Death only (treatment specific) is defined as number of treatment-related deaths divided by number of patients who initiated treatment at the start of the respective study periods. [d]Death + lost to follow-up (treatment specific) is defined as number of treatment-related deaths plus patients lost to follow-up divided by number of patients who initiated treatment at the start of the respective study periods.

### Limitations

- Attrition rates in patients receiving chimeric antigen receptor T-cell therapy in earlier lines in the real-world setting are unknown; therefore, the Markov model assumed the same attrition rates between the cilta-cel and SOC cohorts
- The model assumes that time spent in 2L does not impact survival outcomes in 3L+
- The model focuses on survival outcomes and does not measure other potential benefits of cilta-cel, such as health-related quality of life and economic benefits of patients remaining treatment free until relapse between cilta-cel and other MM treatments
- As randomized clinical trials comparing the use of cilta-cel in 2L vs 3L+ are not clinically or ethically feasible, the current modeling approach leverages data from different sources, where populations were matched and adjusted to minimize biases in cross-trial differences in patient characteristics

**References**

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Multiple Myeloma

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