Real-world comparison of progression-free and overall survival between idecabtagene vicleucel and teclistamab in triple-class exposed relapsed/refractory multiple myeloma

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Objective

- To perform an indirect treatment comparison of the effectiveness of ide-cel and teclistamab for the treatment of patients with TCEx RRMM in terms of PFS and OS using individual-level patient data from the Flatiron Health RW dataset

Conclusions

- In this RW analysis, ide-cel was associated with superior PFS and OS compared with teclistamab in patients with TCEx RRMM
- These findings support emerging RW evidence favoring BCMA-directed CAR T cell therapies over bispecific antibodies and may inform treatment sequencing decisions in this difficult-to-treat population

Introduction

- Patients with triple-class exposed (TCEx) relapsed/refractory multiple myeloma (RRMM) have historically experienced poor clinical outcomes, prompting the development of novel therapeutic options[1]
- Idecabtagene vicleucel (ide-cel) was the first chimeric antigen receptor (CAR) T cell therapy approved for this population,[2] while teclistamab became the first approved bispecific antibody[3]
- Ide-cel and teclistamab both target B-cell maturation antigen (BCMA) and are used increasingly in real-world (RW) settings
- Most comparative evidence to date is derived from single-arm clinical trials with cross-trial adjustments; RW studies offer an opportunity to compare these therapies and assess their relative effectiveness in routine clinical practice

Methods

Data source

- Individual-level patient data from the Flatiron Health United States electronic health record-derived, deidentified database (data cut: January 2011 to April 2025)

Definitions

- The index treatment of interest was defined as the first qualifying index therapy (either ide-cel or teclistamab) at any subsequent line after becoming TCEx (ie, exposed to an immunomodulatory drug [IMiD®] agent, a proteasome inhibitor [PI], and an anti-CD38 monoclonal antibody [mAb])
- The index date was defined as the date that patients received the first qualifying index therapy

Patient eligibility

- Included: adult patients who received an index therapy of ide-cel or teclistamab at any line after becoming TCEx
- Excluded: patients without an index therapy; patients with prior exposure to CAR T cell therapy, bispecific antibodies, or belantamab mafodotin prior to the index therapy; or patients without post-index follow-up data

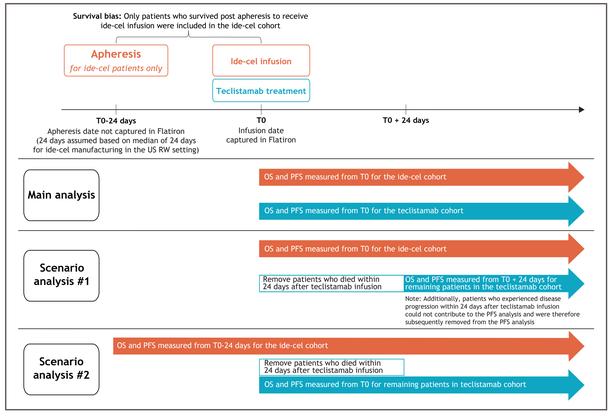
Patient weighting

- Average treatment effect in the exposed weights was estimated to balance patient characteristics of interest between the ide-cel and teclistamab cohorts
- Model covariates (N = 17) were selected a priori based on published rank orderings of prognostic relevance in TCEx RRMM[4,5] that were available in the Flatiron Health database
- Multiple imputation was performed for covariates with ≤ 30% missing data, which created 30 imputed datasets for the analysis
- Weights were trimmed at the 99th percentile (one-sided) in each imputed dataset to reduce the impact of extreme weights
- Balance in patient characteristics before and after weighting/trimming was assessed using absolute standardized differences (ASD) with values ≤ 20% indicating a balance

Summary of relative treatment effects (ide-cel vs teclistamab)

- Cox proportional hazards models were used to estimate unadjusted and inverse probability of treatment weighting (IPTW)-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for progression-free survival (PFS) and overall survival (OS)
  - Comparisons were performed for each of the 30 imputed datasets, which were combined using Rubin's rules to obtain pooled adjusted HRs for each outcome[6,7]
- **Sensitivity analyses**
  - The proportional hazards assumption was assessed by the Grambsch-Therneau test with visual inspection of the log-cumulative hazard plot and the Schoenfeld residuals plot
  - Due to potential violations in the proportional hazards assumption, sensitivity analyses were performed to estimate unadjusted and adjusted differences in restricted mean survival time (dRMST) up to 12 months and 25.9 months (maximum available follow-up for each outcome in the teclistamab cohort)
- **Scenario analyses to explore potential survivor bias**
  - The ide-cel cohort included infused patients only, who by the nature of the analysis had to survive between apheresis and infusion, potentially inducing immortal time bias
  - To emulate a RW intention-to-treat population and address the immortal time bias, alternative scenarios were explored using an alternative index date (T0) for either the ide-cel or teclistamab group (**Figure 1**) based on a median ide-cel manufacturing turnaround time of 24 days per 2024 RW data in the United States[8]

Figure 1. Alternative definitions of index date (T0) in main and scenario analyses

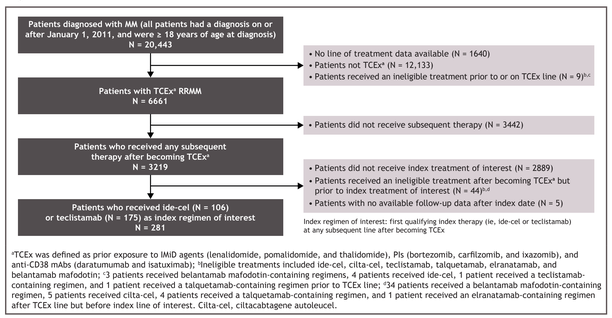


Results

Patient eligibility criteria/weighting

- A total of 281 patients met the inclusion criteria, including 106 patients treated with ide-cel (median follow-up: 22.4 months) and 175 patients treated with teclistamab (median follow-up: 13.7 months; median duration of treatment: 5.2 months) (**Figure 2**)
- Patient characteristics before and after weighting are summarized in **Table 1**
  - Before weighting, imbalances were observed in the following key characteristics: ISS stage, number of prior LOTs, age, Hb levels, LDH levels, prior SCT, Ig isotype, and platelet count
  - Following IPTW adjustment, patient characteristics were balanced between the treatment cohorts, with balance achieved in every imputed dataset for each model covariate
  - Mean ASD ranged from 1.2 (sex) to 77.8 (prior SCT) before weighting and ranged from 1.8 (platelet count) to 15.2 (ISS stage I at diagnosis) after weighting

Figure 2. Selection of cohort of interest



[a]TCEx was defined as prior exposure to IMiD agents (lenalidomide, pomalidomide, and thalidomide), PIs (bortezomib, carfilzomib, and ixazomib), and anti-CD38 mAbs (daratumumab and isatuximab); [b]Ineligible treatments included ide-cel, cilta-cel, teclistamab, talquetamab, elranatamab, and belantamab mafodotin; [c]3 patients received belantamab mafodotin-containing regimens, 4 patients received ide-cel, 1 patient received a teclistamab-containing regimen, and 1 patient received a talquetamab-containing regimen prior to TCEx line; [d]34 patients received a belantamab mafodotin-containing regimen, 5 patients received cilta-cel, 4 patients received a talquetamab-containing regimen, and 1 patient received an elranatamab-containing regimen after TCEx line but before index line of interest. Cilta-cel, ciltacabtagene autoleucel.

Table 1. Patient characteristics of ide-cel and teclistamab cohorts before and after weighting/trimming

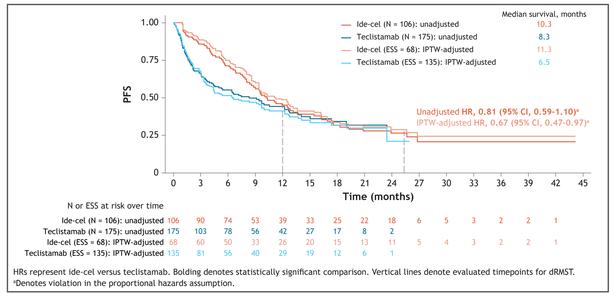
			Before IPTW				After IPTW			
Category	Rank[a]	Detail	Ide-cel (N = 106)	Teclistamab (N = 175)	ASD, mean (SD)	Number of balance reached[b]	Weighted ide-cel (ESS = 67.9)	Weighted teclistamab (ESS = 134.7)	ASD, mean (SD)	Number of balance reached[b]
Refractory status[c], %	1	Triple-class refractory	87.7	90.9	10.11 (0)	30/30	89.5	90.0	2.53 (2.12)	30/30
Cytogenetic risk profile[d], %	2	High risk: t(4;14), t(14;16), or del(17p)	30.3	39.1	18.89 (7.14)	17/30	35.4	36.1	2.92 (2.37)	30/30
ISS stage[e], %	3	I	42.5	29.1	28.22 (6.37)	3/30	40.3	33.0	15.19 (3.99)	27/30
		II	26.9	34.5	16.71 (8.09)	20/30	28.6	31.7	6.96 (4.11)	30/30
		III	30.7	36.4	12.23 (6.05)	28/30	31.0	35.3	9.17 (4.67)	30/30
TTP on last regimen, %	5	≤ 4 months	43.4	45.7	4.67 (0)	30/30	40.9	43.6	5.52 (2.65)	30/30
Exposure status, mean (SD)	6	Number of prior LOTs	5.34 (2.17)	4.56 (1.88)	38.44 (0)	0/30	4.91 (2.02)	4.89 (2.11)	3.12 (2.14)	30/30
Time since diagnosis, %	7	≥ 5 years	58.5	48.6	19.99 (0)	30/30	55.7	52.5	6.32 (2.47)	30/30
Age, mean (SD)	8	Years	65.42 (10.36)	70.19 (9.53)	47.87 (0)	0/30	68.26 (9.89)	68.59 (9.73)	3.58 (2.84)	30/30
Hb level, %	9	< 10 g/dL	63.7	47.8	32.38 (3.26)	0/30	51.8	53.4	3.64 (2.67)	30/30
LDH, %	10	≥ 300 U/L	12.1	23.8	30.95 (5.75)	1/30	15.9	19.4	9.33 (3.15)	30/30
Prior SCT, %	11	Yes	81.1	46.3	77.75 (0)	0/30	62.6	59.2	7.02 (3.42)	30/30
ECOG PS, %	12	0	24.2	21.4	6.77 (5.40)	30/30	24.1	23.3	3.35 (2.74)	30/30
		1	49.8	45.9	8.18 (5.12)	29/30	46.3	46.5	3.53 (2.28)	30/30
		≥ 2	26.0	32.6	14.67 (6.10)	24/30	29.6	30.2	2.98 (2.62)	30/30
Race, %	13	White	64.2	68.0	8.02 (1.85)	30/30	70.6	67.8	6.06 (2.35)	30/30
Sex, %	14	Male	56.6	56.0	1.22 (0)	30/30	60.8	58.6	4.61 (2.16)	30/30
Ig isotype, %	15	IgG	74.5	84.0	23.52 (0)	0/30	79.9	80.9	3.13 (2.19)	30/30
Albumin, %	-	< 3.5 g/dL	36.3	33.4	6.19 (2.70)	30/30	38.3	35.6	5.99 (2.58)	30/30
Platelet count, %	-	< 150 × 10^9/L	66.2	49.8	33.77 (5.32)	0/30	56.3	56.5	1.83 (1.58)	30/30
Calcium, %	-	≥ 12 mg/dL	2.4	3.6	9.23 (6.27)	29/30	2.5	3.0	5.54 (4.64)	29/30

Purple boxes represent key characteristics that showed imbalances before weighting. [a]Rank 4 (extramedullary disease) was not included due to lack of data availability; [b]Balance represents number of balanced datasets across the 30 imputed datasets; [c]Refractory status was defined as patients who progressed on current treatment or progressed within 60 days after current treatment end or before subsequent line start date, whichever came first; [d]High-risk defined as ≥ 1 yes/positive for any of the following markers: t(4;14), t(14;16), or del(17p), not high-risk defined as no/negative for ≥ 1 marker and the absence of a yes/positive for any marker, missing defined as no information available (or inconclusive) for all markers; [e]At diagnosis. ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; Hb, hemoglobin; Ig, immunoglobulin; ISS, International Staging System; LDH, lactate dehydrogenase; LOT, line of treatment; SD, standard deviation; SCT, stem cell transplantation; TTP, time to progression.

Relative treatment effects

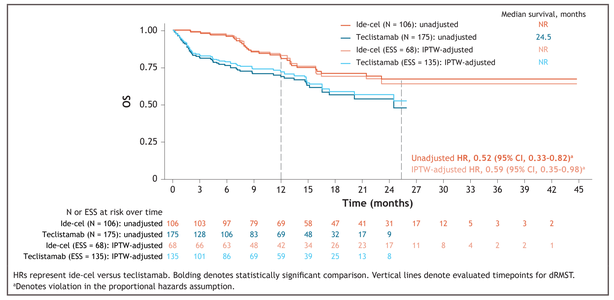
- Following IPTW adjustment, ESSs were 68 for ide-cel and 135 for teclistamab
- Adjusted analyses showed statistically significant improvement in PFS with ide-cel versus teclistamab (HR, 0.67; 95% CI, 0.47-0.97), with a median PFS of 11.3 (ide-cel) and 6.5 (teclistamab) months (**Figure 3**)
- OS also showed a significant improvement with ide-cel compared with teclistamab (HR, 0.59; 95% CI, 0.35-0.98); median OS was not reached (NR) in either group due to insufficient follow-up (**Figure 4**)

Figure 3. PFS among patients treated with ide-cel and teclistamab (unadjusted and IPTW-adjusted)



HRs represent ide-cel versus teclistamab. Bolding denotes statistically significant comparison. Vertical lines denote evaluated timepoints for dRMST.
[a]Denotes violation in the proportional hazards assumption.

Figure 4. OS among patients treated with ide-cel and teclistamab (unadjusted and IPTW-adjusted)



HRs represent ide-cel versus teclistamab. Bolding denotes statistically significant comparison. Vertical lines denote evaluated timepoints for dRMST.
[a]Denotes violation in the proportional hazards assumption.

- The proportional hazards assumption was violated in PFS and OS analyses (ie, the difference in risk between groups changed over time); therefore, sensitivity analyses were performed using dRMST (dRMST is the difference in expected survival between treatments, up to a prespecified timepoint and does not rely on the proportional hazards assumption), which confirmed statistically significant improvements for ide-cel versus teclistamab in both PFS and OS
  - Adjusted dRMST (95% CI) at 12 months: +2.11 months (0.87-3.35) for PFS and +1.56 months (0.50-2.61) for OS
  - Adjusted dRMST (95% CI) at 25.9 months: +2.71 months (0.72-4.69) for PFS and +2.90 months (1.02-4.78) for OS
- Results from the scenario analyses examining the potential immortal time bias also showed a consistent trend favoring ide-cel versus teclistamab for both PFS and OS in terms of HRs and dRMST

Limitations

- This analysis is limited by the small sample size and short follow-up available in Flatiron (ie, median follow-up of 13.7 months for patients treated with teclistamab)
- There is the potential for residual bias due to missing data (ie, analysis did not adjust for extramedullary disease [ranked #4 prognostic factor], given the lack of data availability in Flatiron); similarly, β2-microglobulin and best responses to last prior treatment (a priori identified potential prognostic factors) were not adjusted for, given the > 30% missing rate
- The proportional hazards assumption was violated for PFS and OS; additional analyses were performed comparing treatment effects based on dRMST to supplement the HRs
- There are potential differences in treatment eligibility, despite adjusting for group differences
  - For example, certain patients treated with teclistamab may have been ineligible for CAR T cell therapy due to older age, poor PS, and/or comorbidities; this potential bias was challenging to explore given that eligibility is driven by multiple characteristics

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