CO108

Evaluating the impact of censoring on progression-free survival comparisons of BCMA-targeting bispecific antibodies in relapsed/refractory multiple myeloma

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Key Takeaway

Recently published indirect treatment comparisons between elranatamab (MagnetisMM-3) and teclistamab (MajesTEC-1) may have been biased by informative censoring resulting in an overestimation of elranatamab's PFS. After adjusting for informative censoring, PFS was found to be similar between both treatments.

Discussion & conclusions

There was more early censoring in the PFS data for elranatamab than for teclistamab, likely due to treatment discontinuations because of adverse events.

As older and frailer patients are more prone to discontinue treatment due to adverse events, these censorings are likely informative.

Informative censoring exploration (ICE) analyses indicate that MagnetisMM-3 median PFS may have been overestimated by up to 7.5 months (77%), while the potential overestimation of MajesTEC-1 PFS is less (up to 1.3 months; 11%).

Indirect comparisons indicate that observed differences in PFS between teclistamab and elranatamab may be explained by higher informative censoring of the elranatamab PFS curve, likely due to adverse event-driven discontinuation.

Therefore, cross-trial comparisons of PFS between MagnetisMM-3 and MajesTEC-1 not addressing early censoring, should be approached with caution due to potential bias.

Abbreviations

BCMA: B-cell maturation antigen; BsAbs: bispecific antibodies; CCO: clinical cut-off; HR: hazard ratio; ICE: informative censoring exploration; IPD: individual patient data; ITC: indirect treatment comparison; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival; RRMM: relapsed/refractory multiple myeloma; TEAE: treatment-emergent adverse events

Disclosures

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Introduction

- The relapsed/refractory multiple myeloma (RRMM) treatment landscape is evolving, with teclistamab and elranatamab offering promising therapeutic options for triple-class exposed patients.
- Efficacy and safety of first- and second-in-class BCMA-targeting bispecific antibodies (BsAbs) teclistamab and elranatamab were evaluated in the open-label, single arm clinical studies MajesTEC-1[1] and MagnetisMM-3[2], respectively.
- Several indirect treatment comparisons (ITCs) between these studies have been published, informing health economic evaluations and clinical decision-making. However, these ITCs may be biased by differences in trial design and factors such as treatment discontinuation.
- Here, we critically assess comparability of reported progression-free survival (PFS) outcomes between MajesTEC-1 and MagnetisMM-3, focusing on informative censoring. This is a known potential source of bias that can distort treatment effect estimates, e.g., if censoring is more frequent for one treatment due to increased toxicity, thereby removing the frailest individuals and introducing a bias favoring this treatment[3].

Methods

- Using individual patient data (IPD) from MajesTEC-1 and published data from MagnetisMM-3, we investigated censoring rules, early censoring rates, and underlying reasons for censoring.
- We focused on censoring in the first 24 months, as the time between last patient's initial dose and clinical cut-off (CCO) is ≥24 months in both studies, i.e., any censoring in this period is not due to study duration.
- For MajesTEC-1, we used PFS IPD from the August 2023 CCO[1] (median follow-up: 30.4 months); for MagnetisMM-3, we digitized the PFS Kaplan-Meier (KM) curve from the March 2024 CCO[2] (median follow-up: 28.4 months), to simulate IPD, using the Guyot method[4].
- We estimated the maximum potential impact of informative censoring on reported PFS in both studies, using the methodology behind the BREAKING-ICE app[3]. This tool reconstructs IPD from digitized KM curves, estimates censoring rates, and simulates how informative censoring could affect the curves. It assumes that toxicity-driven censored observations could actually be unobserved PFS events, thereby allowing users to explore how such informative censoring can distort treatment effect estimates in clinical trials.
- After adjusting for informative censoring, a matching-adjusted indirect comparison (MAIC) adjusting for 7 variables (*refractoriness, cytogenetics, R-ISS stage, extramedullary disease, prior lines of therapy, age, ECOG performance status*) was performed to compare teclistamab and elranatamab PFS.

Results

Censoring rules

- Both studies censored patients when they started a subsequent therapy before disease progression or death (Fig. 1).
- In MagnetisMM-3, patients were additionally censored if a PFS event occurred after a gap of 2 or more missing disease evaluations (Fig 1). This censoring rule may introduce informative censoring, as patients who miss scheduled visits could differ systematically from those with complete follow-up. Excluding these patients from the event count may bias PFS estimates by removing potentially higher-risk individuals from the analysis[7].

Early censoring percentage & reasons

- In MajesTEC-1, 12 patients (7.3%) were censored for PFS in the first 24 months (Table 1).
  - Reasons were withdrawal of consent (n=4) and receiving subsequent therapy before a disease progression event (n=8)
- Digitized MagnetisMM-3 KM data indicate that 27 patients (22.0%) were censored for PFS in the first 24 months (Table 1).
  - While specific reasons were not published, the large majority may have resulted from starting subsequent therapy before disease progression, as 24 (19.5%) MagnetisMM-3 patients permanently discontinued elranatamab due to treatment-emergent adverse events (TEAE)[8].
  - Patients who discontinued elranatamab treatment were older and frailer than those who did not[9]. As older and frailer patients are typically at a higher risk for progression, their censoring may have been informative, leading to an overestimation of elranatamab PFS.

Impact of informative censoring on PFS

- PFS curves were adjusted for early (24-month) censoring using the methodology behind the BREAKING-ICE app[3]. To estimate the maximum potential impact of informative censoring, we assumed all censored patients experienced an immediate event. Under this assumption, median PFS estimates decreased from 11.4 to 10.1 months for teclistamab and from 17.2 to 9.7 months for elranatamab (Fig. 2). This indicates that the originally reported median PFS for teclistamab may have been overestimated by 11%, while elranatamab PFS was potentially overestimated by up to 77%.

PFS comparisons before and after adjustment

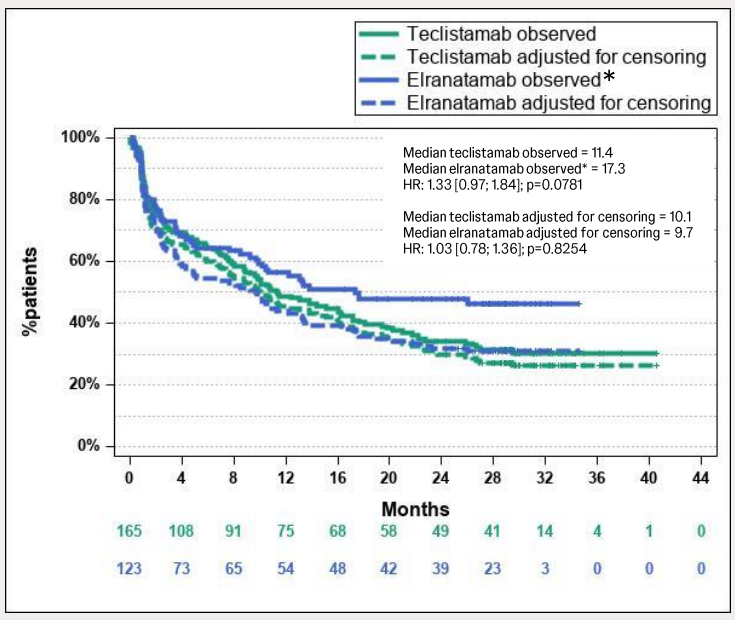
- A naive comparison of the reported PFS curves indicates a trend favouring elranatamab (HR: 1.33, p=0.08) (Fig. 2).
- A naive comparison after adjusting for early censoring indicates PFS similarity between both treatments (HR: 1.03; p=0.83) (Fig. 3).
- After additionally adjusting for baseline characteristics using MAIC, the HR remained similar (HR: 1.04; p=0.83) (Fig. 3), implying that differences in patient characteristics do not have a substantial additional impact on the relative efficacy estimation for PFS.

MajesTEC-1[5] (teclistamab)	MagnetisMM-3[6] (elranatamab)
PFS will be censored:	
• At the latest disease evaluation **before the start of any subsequent anti-myeloma therapy** for subjects who have not progressed and are alive	• On the date of the last adequate disease assessment **before the new anticancer therapy** for participants who start a new anticancer therapy prior to an event • On the date of the last adequate disease assessment before the gap, for participants with an **event after a gap of 2 or more missing disease evaluations**

Figure 1. Progression-free survival censoring rules

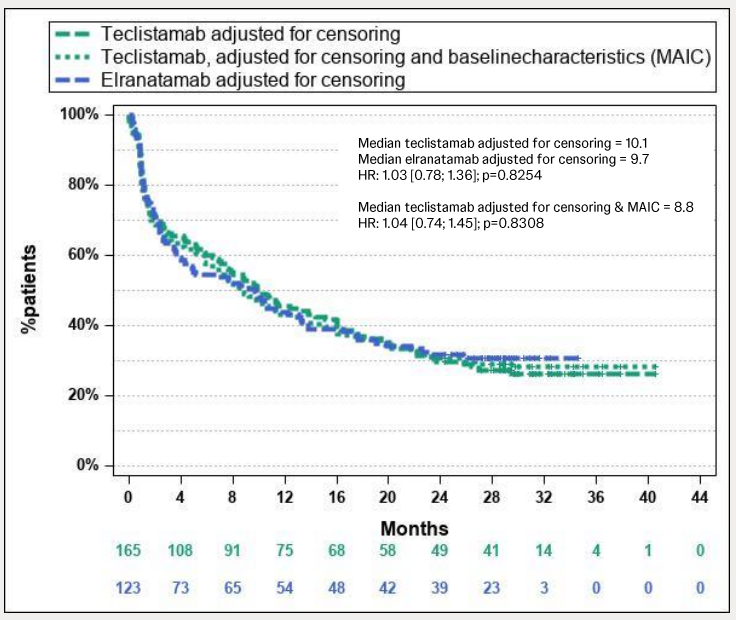
	Teclistamab MajesTEC-1 N=165	Elranatamab MagnetisMM-3 N=123
Median follow-up, months	30.4	28.4
Patients censored in first 24 months, n(%)	12 (7.3%)	27 (22.0%)
Discontinuations due to adverse events, n(%)	8 (4.8%)	24 (19.5%)

Table 1. MajesTEC-1 and MagnetisMM-3 censoring and discontinuation due to adverse events



*MagnetisMM-3 Kaplan-Meier data were digitized, and IPD were simulated using the Guyot approach

Figure 2. MajesTEC-1 and MagnetisMM-3 PFS curves, observed and adjusted for censoring.



MAIC: matching-adjusted indirect comparison

Figure 3. MajesTEC-1 and MagnetisMM-3 PFS curves, adjusted for censoring and baseline characteristics (matching-adjusted indirect comparison).

References

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Multiple Myeloma

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