Indirect Treatment Comparisons in Relapsed or Refractory Multiple Myeloma: Insights from Recent NICE Submissions

Shujun Li[1], Juan Idarraga[2], Denise Zou[1]

[1]Thermo Fisher Scientific, Waltham, MA, USA; [2]Thermo Fisher Scientific, Cali, Colombia

HTA111

Background

- The treatment landscape for relapsed or refractory multiple myeloma (RRMM) is crowded and rapidly evolving.
- Novel agents, such as anti-CD38 monoclonal antibodies, cereblon E3 ligase modulators, chimeric antigen receptor T-cells, and bispecific antibodies, have been introduced and are being adopted in different lines of therapy, with emerging data showing improvement in progression-free survival, response rates,[1-4] and the potential to overcome refractoriness to conventional therapies.
- As a result, the number of possible treatment comparisons has expanded substantially; therefore, it is infeasible for head-to-head trials to include all relevant comparators.
- Indirect treatment comparisons (ITCs) are frequently used to generate external comparative efficacy and support decision-making.
- Recent ITCs face increasing challenges due to differences in trial patient populations, driven by resistance to immunomodulatory agents and the expanding use of anti-CD38 monoclonal antibodies in earlier lines.

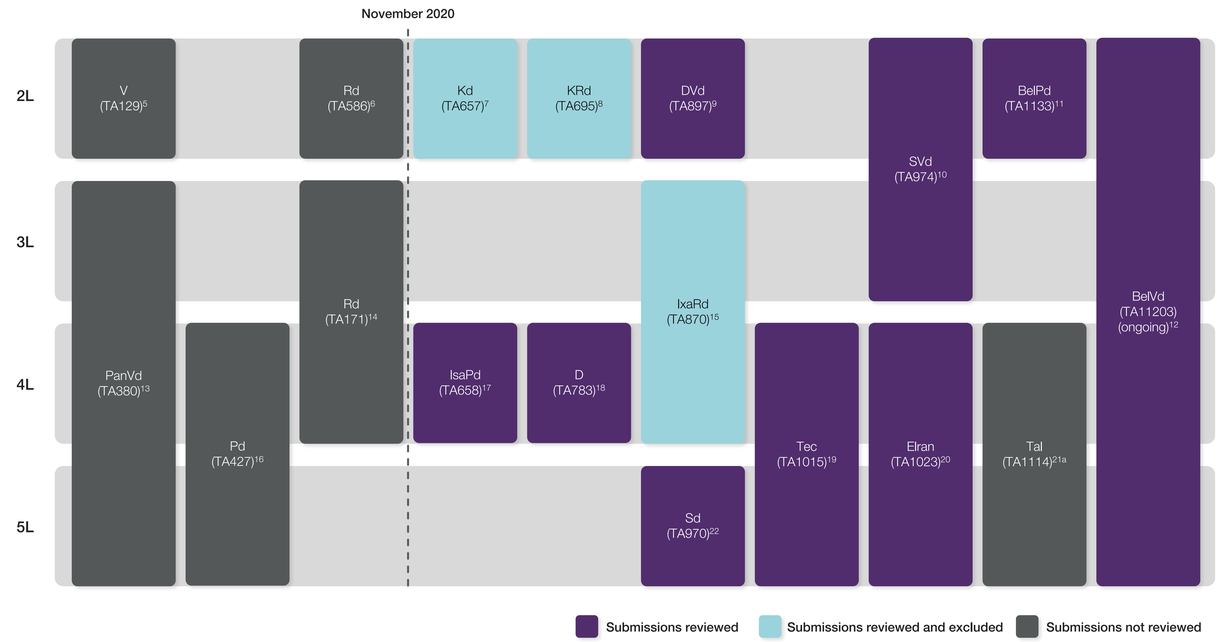
Objectives

- To identify key challenges in ITCs conducted for RRMM and highlight key areas of consideration for future studies, based on a review of recent National Institute for Health and Care Excellence (NICE) submissions.

Methods

- We reviewed 12 NICE submissions in RRMM identified from the NICE website, published between November 2020 and November 2025.
- Of the 12 submissions reviewed, three were excluded because only within-trial comparisons were considered (**Figure 1**).
- Full-text screening of committee papers and guidance was conducted to identify the ITC approaches applied and key critiques related to deriving out-of-trial comparative efficacy.

Figure 1. Current RRMM Treatments Recommended by NICE



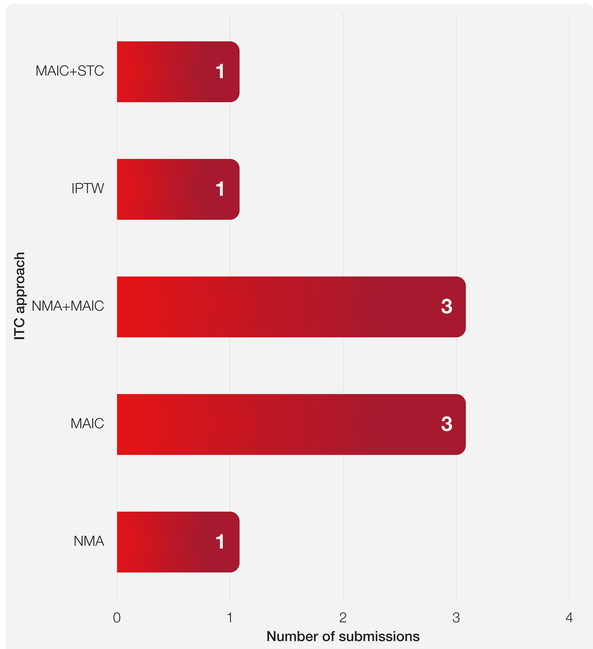
Abbreviations: BelPd = belantamab mafodotin + pomalidomide + dexamethasone; BelVd = belantamab mafodotin + bortezomib + dexamethasone; D = daratumumab monotherapy; DVd = daratumumab + bortezomib + dexamethasone; Elran = elranatamab; IsaPd = isatuximab + pomalidomide + dexamethasone; IxaRd = ixazomib + lenalidomide + dexamethasone; Kd = carfilzomib + dexamethasone; KRd = carfilzomib + lenalidomide + dexamethasone; PanVd = panobinostat + bortezomib + dexamethasone; Pd = pomalidomide + dexamethasone; Rd = lenalidomide + dexamethasone; Sd = selinexor + dexamethasone; SVd = selinexor + bortezomib + dexamethasone; TA = technology appraisal; Tal = talquetamab; Tec = teclistamab; V = bortezomib

[a] TA1114 was published on 03 December 2025; it was not reviewed due to its scope and findings overlapping with TA1015 and TA1023.

Results

- Among the nine included submissions, four were based on single-trial arms in the fourth-line or later setting, and the remainder were based on two-arm randomized controlled trials.
- One submission conducted a network meta-analysis; three employed unanchored matching-adjusted indirect comparisons (MAICs); three used both approaches; one applied inverse probability of treatment weighting; and one conducted an unanchored MAIC and a simulated treatment comparison (STC) (**Figure 2**).

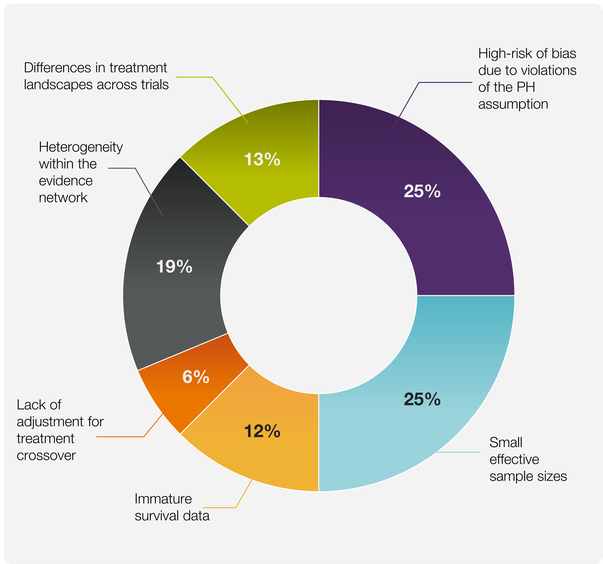
Figure 2. Approaches Used for ITC in the NICE Submissions



Abbreviations: IPTW = inverse probability of treatment weighting; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; STC = simulated treatment comparison

- Key critiques included high-risk bias due to violations of the proportional hazards assumption (25%) and small effective sample sizes (25%), particularly in unanchored MAICs. Additional concerns included immature survival data (12%), lack of adjustment for treatment crossover (6%), heterogeneity within the evidence network (19%), and differences in treatment landscapes across trials (13%) (**Figure 3**).

Figure 3. Summary of Key Critiques



Abbreviation: PH = proportional hazards

- In response to the critiques, solutions included conducting sensitivity and scenario analyses testing alternative assumptions; refining the study population to improve comparability; applying advanced adjustment techniques such as MAIC or STC to reduce bias; aligning comparators with current clinical practice; incorporating additional evidence, including longer follow-up, external datasets, or real-world data; and considering managed access approaches, such as Cancer Drugs Fund arrangements.
- Overall , the bias and high uncertainty in the ITC results tended to lead NICE to narrow the recommended population (restricting to subgroups where cost-effectiveness is more certain), or to limit access through managed access arrangements until further evidence is available.

Conclusions

- For ITCs in RRMM, improved handling of non-proportional hazards, thorough assessment of heterogeneity/inconsistency across trial populations, and robust identification and adjustment of effect modifiers are crucial to support decision-making.
- As more novel treatments continue to reshape the treatment landscape in RRMM, the comparative efficacy is going to increasingly rely on ITC. Future submissions should proactively align with NICE on comparators and subgroups, apply vigorous and transparent ITC methodologies, and supplement trial evidence with external data such as real-world data to strengthen the credibility of comparative estimates.

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Disclosures

Funding provided by Thermo Fisher Scientific. All authors are employees of PPD™ Evidera™ Health Economics & Market Access, Thermo Fisher Scientific.

Acknowledgments

The authors would like to acknowledge Shani Berger, Kawthar Nakayima, and Michael Grossi of Thermo Fisher Scientific for graphic design and editorial staff for figure generation and editorial services.

Presented at ISPOR—The Professional Society for Health Economics and Outcomes Research | 17–20 May 2026 | Philadelphia, PA, USA