INFECTIOUS COMPLICATIONS IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS TREATED WITH BISPECIFIC ANTIBODIES: META-ANALYSIS

PRANATI SHAH, DO1, EMILY FOURT, DO2, SOFIA YEREMIAN, BS3, DANIEL PARK, DO4, JERRY QI. MD1, ANGEL NGUYEN, PHARMD 5, MOJTABA AKHTARI, MD6

1. LOMA LINDA UNIVERSITY MEDICAL CENTER, DEPARTMENT OF MEDICINE, LOMA LINDA, CA.
2. UNIVERSITY OF CALIFORNIA SAN FRANCISCO, FRESNO CAMPUS, DEPARTMENT OF MEDICINE, FRESNO, CA.
3. KIRK KERKORIAN SCHOOL OF MEDICINE AT UNLV, LAS VEGAS, NV.
4. UNIVERSITY OF CALIFORNIA SAN FRANCISCO, FRESNO CAMPUS, DEPARTMENT OF MEDICINE, FRESNO, CA.
5. UNIVERSITY OF CALIFORNIA SAN DIEGO, SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCE, LA JOLLA, CA.
6. LOMA LINDA UNIVERSITY HEALTH, DIVISION OF TRANSPLANT, CELLULAR THERAPY, AND HEMATOLOGICAL MALIGNANCIES, LOMA LINDA,

BACKGROUND

- Multiple myeloma (MM) is a plasma cell malignancy diagnosed by >10% clonal plasma cells and CRAB criteria (hypercalcemia, renal failure, anemia, bone lesions).
- R-ISS staging uses β2-microglobulin, albumin, LDH, and cytogenetics to assess prognosis.
- Initial treatment includes PIs, IMiDs, steroids, and monoclonal antibodies, with autologous stem cell transplant (ASCT) as destination therapy.
- In relapsed/refractory MM (RRMM), disease becomes resistant to standard therapies, prompting the use of novel agents like bispecific antibodies (BsABs).
- Teclistamab and elranatamab target BCMA/CD3, while talquetamab targets GPRC5D/CD3, activating T-cells to lyse myeloma cells.
- BsABs can cause cytokine release, cytopenias, and hypogammaglobulinemia, increasing the risk for bacterial, viral, fungal, and opportunistic infections.
- This meta-analysis evaluates the infectious complication profiles of teclistamab, talquetamab, and elranatamab in RRMM.

METHODS

- Systematic literature review conducted using MEDLINE, Embase, and Cochrane databases
- Included trials evaluating infectious adverse events of bispecific antibodies (BsABs) in relapsed/refractory multiple myeloma (RRMM)
- Extracted data:
  - Total number of patients
  - Number of grade ≥ 3 infectious adverse events
  - Number of non–grade ≥ 3 infectious adverse events
- Statistical analysis performed using R software with the meta package
- Random-effects model used to account for heterogeneity

RESULTS AND FIGURES

- Eight studies included (6 RCTs, 2 retrospective), totaling 946 patients:
  - Teclistamab: 394 patients
  - Talquetamab: 374 patients
  - Elranatamab: 178 patients
- Teclistamab group:
  - Pooled proportion (PP) of infections: 0.517 (95% CI: 0.183–0.837)
  - Grade ≥ 3 infections: 0.233 (95% CI: 0.058–0.598)
- Talquetamab group:
  - PP of infections: 0.636 (95% CI: 0.305–0.874)
  - Grade ≥ 3 infections: 0.201 (95% CI: 0.110–0.339)
  - Most reported infections: COVID-19 and pneumonia
- Elranatamab group:
  - PP of infections: 0.714 (95% CI: 0.397–0.904)
  - Grade ≥ 3 infections: 0.344 (95% CI: 0.015–0.948)
- Common infections across BsABs:
  - Adenovirus, CMV, COVID-19, Pneumocystis jirovecii

Medication	Author/Year	Trial	# of Patients	Mean/Median Age	Number of Prior Treatments	All-grade Infection	Grade≥3 Infection	Median Follow-Up (months)
Teclistamab	Saad Z et. al. 2021	-	157	63 (57-69)	6 (4-7)	94/157	9/40	6.1 months
Teclistamab	P. Moreau, et. al. 2022.	MajesTEC-1	165	64 (33-84)	5 (2-14)	129/165	-	14.1 months
Teclistamab	Adam Stepanovic et. al. 2023	-	33	75 (39-85)	5 (2-21)	11/33	3/33	17.6 weeks
Teclistamab	Danai Dima et. al. 2024	-	39	66.5 (35-87)	6 (4-17)	33/106	18/106	3.8 months
Talquetamab	Jeffrey Matous et. al. 2023	MonumenTAL-2	35	QW: 69.5 (49-78) QW: 63 (43-78)	3	25/35	8/35	11.4 months
Talquetamab	Paula Rodriguez-Otero et. al. 2023	MonumenTAL-1	339	N/A	N/A	213/339	15.9, 10.1, 13.1 months over 3 groups	15.9, 10.1, 13.1 months over 3 groups
Elranatamab	Nizar J. Bahlis et. al. 2023	MagnetisMM-1	55	64 (42-80)	5 (2-14)	41/55	15/55	12 months

Table 1: Table 2: Characteristics of included studies using Bispecific Antibodies in RRMM.
RRMM: relapsed/refractory multiple myeloma; - : Not available.

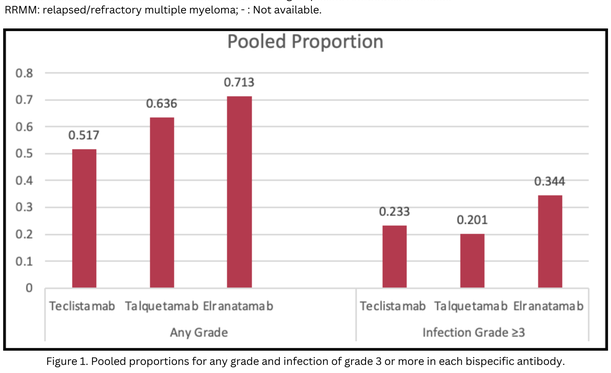


Figure 1. Pooled proportions for any grade and infection of grade 3 or more in each bispecific antibody.

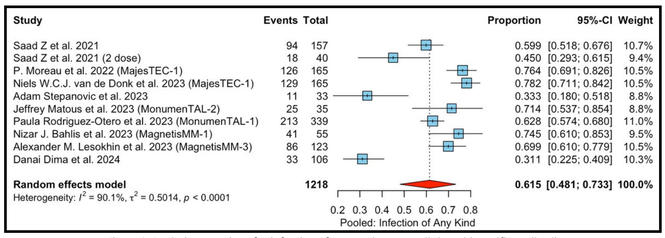


Figure 2. Pooled proportions for infection of any grade across all three bispecific antibodies.

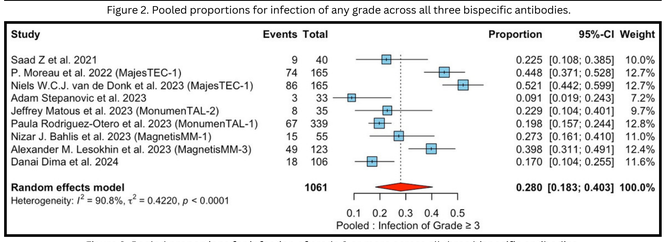


Figure 3. Pooled proportions for infection of grade 3 or more across all three bispecific antibodies.

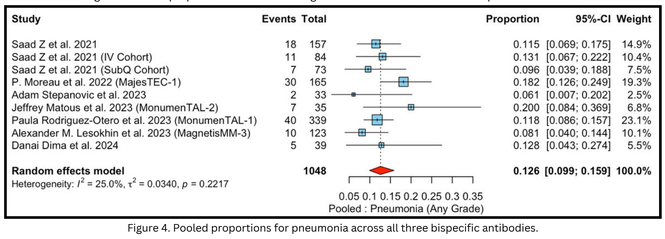


Figure 4. Pooled proportions for pneumonia across all three bispecific antibodies.

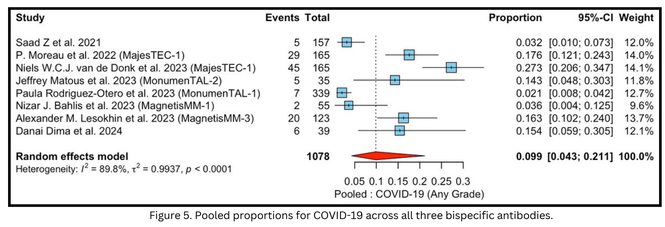


Figure 5. Pooled proportions for COVID-19 across all three bispecific antibodies.

DISCUSSION

- High Infection Risk in RRMM Patients: All included patients had relapsed/refractory multiple myeloma (RRMM) with ≥3 prior immune-compromising therapies, placing them at elevated baseline risk for infections when treated with bispecific antibodies (BsAbs).
- Promising Efficacy of BsAbs: Despite the risk, BsAbs demonstrate strong response rates in RRMM, underscoring the importance of balancing efficacy with infection risk.
- Mechanism-Driven Immunosuppression: The mechanisms of BsAbs—T-cell engagement and immune modulation—likely contribute to the increased incidence of infectious adverse events (AEs).
- Need for Proactive Infection Prevention:
  - Consider prophylactic antimicrobials, IVIG for hypogammaglobulinemia, and routine vaccinations (e.g., COVID-19, pneumococcus).
  - HSV and HBV infections were largely absent in trials, likely due to existing prophylactic strategies—serving as a model for preventing CMV and COVID-19 infections.
- Monitoring Recommendations:
  - Routine CBC with differential to detect cytopenias.
  - Monitor T-cell function and screen for viral reactivations (CMV, EBV).
  - Maintain a low threshold for broad-spectrum antibiotics, especially for febrile neutropenia.
- Supportive Measures:
  - Consider G-CSF in prolonged neutropenia or recurrent infections.
  - Optimize timing and sequencing of BsAb therapy, particularly in patients previously treated with BCMA-targeted therapies or with baseline immune compromise.
- Clinical Practice Implication: A multifaceted, preventive approach is essential to mitigate infectious complications while maintaining the therapeutic potential of BsAbs in RRMM.

CONCLUSION

- Bispecific antibodies (teclistamab, talquetamab, elranatamab) carry a significant risk of infectious complications in RRMM patients.
- Meta-analysis of eight clinical trials showed heterogeneity in infection rates due to differences in:
  - Patient populations
  - Dosing regimens
  - Infection prevention protocols
- Immunosuppressive effects—including T-cell exhaustion, hypogammaglobulinemia, neutropenia, and immune dysregulation—increase infection risk.
- Supportive care variability (e.g., vaccinations, prophylactic antibiotics, IVIG use) contributes to outcome differences across studies.
- Infection prevention strategies must be optimized when initiating BsABs:
  - Routine screening
  - Prophylactic antimicrobials
  - Timely vaccinations
  - IVIG support
- Proactive management can enhance safety and reduce infectious morbidity in RRMM patients treated with BsABs.

REFERENCES

1. Malard F, Neri P, Bahlis NJ, Terpos E, Moukalled N, Hungria VTM, et al. Multiple myeloma. Nat Rev Dis Primers [Internet]. 2024 Jun 27 [cited 2025 Feb 11];10(1):45. Available from: https://www.nature.com/articles/s41572-024-00529-7
2. Rajkumar SV. Multiple myeloma: 2024 update on diagnosis, risk-stratification, and management. American J Hematol [Internet]. 2024 Sep [cited 2025 Feb 11];99(9):1802–24. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ajh.27422
3. Ramasamy K, Gay F, Weisel K, Zweegman S, Mateos MV, Richardson P. Improving outcomes for patients with relapsed multiple myeloma: Challenges and considerations of current and emerging treatment options. Blood Reviews [Internet]. 2021 Sep [cited 2025 Feb 11];49:100808. Available from: https://linkinghub.elsevier.com/retrieve/pii/S026896042100014X
4. Chim CS, Kumar SK, Orłowski RZ, Cook G, Richardson PG, Gertz MA, et al. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. Leukemia [Internet]. 2018 Feb [cited 2025 Feb 11];32(2):252–62. Available from: https://www.nature.com/articles/leu2017329
5. Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ, Miles Prince H, Niesvizky R, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med [Internet]. 2023 Sep [cited 2025 Feb 11];29(9):2259–67. Available from: https://www.nature.com/articles/s41591-023-02528-9
6. Chari A, Minnema MC, Berdeja JG, Oriol A, Van De Donk NWCJ, Rodríguez-Otero P, et al. Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. N Engl J Med [Internet]. 2022 Dec 15 [cited 2025 Feb 11];387(24):2232–44. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2204591
7. Nooka AK, Rodriguez C, Mateos MV, Manier S, Chastain K, Banerjee A, et al. Incidence, timing, and management of infections in patients receiving teclistamab for the treatment of relapsed/refractory multiple myeloma in the MajesTEC-1 study. Cancer [Internet]. 2024 Mar 15 [cited 2025 Feb 11];130(6):888–900. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.35107
8. Ludwig H, Terpos E, Van De Donk N, Mateos MV, Moreau P, Dimopoulos MA, et al. Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network. The Lancet Oncology [Internet]. 2023 Jun [cited 2025 Feb 11];24(6):e255–69. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204523001596
9. Moreau P, Garfall AL, Van De Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med [Internet]. 2022 Aug 11 [cited 2025 Mar 5];387(6):495–505. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2203478
10. Usmani SZ, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, et al. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet. 2021 Aug 21;398(10301):665–74.
11. Dima D, Davis JA, Ahmed M, Jia X, Sannareddy A, Shaikh H, et al. Safety and Efficacy of Teclistamab in Patients with Relapsed/Refractory Multiple Myeloma: A Real-World Experience. Transplant Cell Ther. 2024 Mar;30(3):308.e1-308.e13.
12. Stepanovic A, Abonour R, Abu Zaid M, Farag S, Lee KP, Suvannasankha A. Teclistamab in Relapsed/Refractory Multiple Myeloma: Real-World Outcomes at a Single Academic Center in the Midwest. Blood [Internet]. 2023 Nov 2 [cited 2025 Mar 9];142(Supplement 1):7359–7359. Available from: https://ashpublications.org/blood/article/142/Supplement%201/7359/501270/Teclistamab-in-Relapsed-Refractory-Multiple
13. Matous J, Biran N, Perrot A, Berdeja JG, Dorritie K, Elsaen JV, et al. Talquetamab + Pomalidomide in Patients with Relapsed/Refractory Multiple Myeloma: Safety and Preliminary Efficacy Results from the Phase 1b MonumenTAL-2 Study. Blood [Internet]. 2023 Nov 2 [cited 2025 Mar 9];142(Supplement 1):1014–1014. Available from: https://ashpublications.org/blood/article/142/Supplement%201/1014/501614/Talquetamab-Pomalidomide-in-Patients-with-Relapsed
14. Bahlis NJ, Costello CL, Raje NS, Levy MY, Dholaria B, Solh M, et al. Elranatamab in relapsed or refractory multiple myeloma: the MagnetisMM-1 phase 1 trial. Nat Med. 2023 Oct;29(10):2570–6.
15. Carpenter RO, Evbuomwan MO, Pittaluga S, Rose JJ, Raffeld M, Yang S, et al. B-cell Maturation Antigen Is a Promising Target for Adoptive T-cell Therapy of Multiple Myeloma. Clinical Cancer Research [Internet]. 2013 Apr 15 [cited 2025 Mar 5];19(8):2048–60. Available from: https://aacrjournals.org/clincancerres/article/19/8/2048/208469/B-cell-Maturation-Antigen-Is-a-Promising-Target
16. Rodriguez-Otero P, Schinke CD, Chari A, Lipe B, Lavi N, Raschle L, et al. Analysis of infections and parameters of humoral immunity in patients (pts) with relapsed/refractory multiple myeloma (RRMM) treated with talquetamab (tal) monotherapy in MonumenTAL-1. JCO [Internet]. 2023 Jun 1 [cited 2025 Mar 12];41(16_suppl):8020–8020. Available from: https://ascopubs.org/doi/10.1200/JCO.2023.41.16_suppl.8020
17. Zahr A, Kotchi T, Gill L, Parfrey N. T cell exhaustion in multiple myeloma. Expert Rev Hematol. 2024 Jul;17(7):295–312.