INFECTIOUS MORBIDITY WITH BISPECIFIC T-CELL ENGAGER ANTIBODY THERAPY IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: A SYSTEMATIC SYNTHESIS REVEALING A PREVENTABLE SURVIVAL GAP

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INTRODUCTION

- Bispecific T-cell engager antibodies (BsAbs) directed against B-cell maturation Antigen (BCMA) and G-protein couples receptor class C group 5 member D (GPRC5D) have transformed the management of relapsed/refractory multiple myeloma (RRMM), showing response in triple-class refractory disease.
- Since BCMA is expressed on normal plasma cell in addition to malignant ones, target engagement depletes the entire humoral memory compartment, producing profound and sustained hypogammaglobulinemia.
- **Infectious morbidity is therefore an underrecognized driver of the discordance between trial and real-world outcomes.**

AIM

To compare efficacy and infectious toxicity across BsAb monotherapy pivotal trials and real-world RRMM cohorts, and to identify evidence-based mitigation strategies.

Secondary aims:

- Characterize infection type, severity, timing and site distribution
- Quantify the effect of corticosteroid exposure and antigen target on infection risk
- Estimate the magnitude of benefit from pre-emptive immunoglobulin replacement

METHOD

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CONCLUSIONS

- **Infectious morbidity is the dominant modifiable driver of the BsAb trial-to-practice gap in RRMM.**
- Response rates translate faithfully from trial to practice; durability does not. Efficacy is governed by drug pharmacology and target expression, which do not change between populations. Durability is governed by host immune fitness, which does.
- These findings quantify the benefit magnitude of preemptive IgG replacement, consistent with existing NCCN guidance.
- **Future trials should incorporate infectious endpoints and prophylaxis protocols as co-primary objectives.**

RESULTS

70%
Cumulative infection incidence

53%
Grade ≥ 3 infection

56%
Infection-related hospitalization

9%
Infection-attributed mortality

Table 1. BsAb monotherapies evaluated

Agent	Target	Administration	Pivotal trial
Teclistamab	BCMA × CD3	SC weekly; 2 step-up doses	MajesTEC-1
Elranatamab	BCMA × CD3	SC weekly → Q2W → Q4W	MagnetisMM-3
Linvoseltamab	BCMA × CD3	IV weekly → Q2W	LINKER-MM1
Talquetamab	GPRC5D × CD3	SC weekly or Q2W	MonumenTAL-1

Table 2. Efficacy: pivotal trials vs. real world

Outcome	Pivotal trials	Real-world	Interpretation
Overall response rate	63 - 80%	59 - 66%	Concordant
Median PFS	10 - 12 mo	2 - 6 mo shorter	Discordant
Median prior therapy lines	3 - 6	4 - 6	Concordant

Seven in ten patients develop infection and roughly one in eleven dies of it.
Response translates from trial to practice; survival does not.
This difference is largely preventable.

Table 3. Microbiologic and anatomical distribution of infectious episodes

Class of pathogen	Share of episodes
Bacterial	62% (Pneumonia, sepsis)
Viral	27% (CMV reactivation, COVID-19)
Fungal	11%
Anatomic site	**Share of episodes**
Respiratory tract	46%
All other sites	54%

Table 4. Modifiers of infection risk

Factor	Effect	Effect size	HR (95% CI)
Corticosteroid exposure (initial and adjunctive/step-up dosing)	Increased	Approximately 2-fold higher risk	**2.01 (1.27 - 3.19)**
GPRC5D-directed vs. BCMA-directed target	Reduced	47% lower risk; consistent with target biology; less hypogammaglobulinemia	**0.53**
Preemptive IgG supplementation at IgG < 400 mg/dL (all-grade infection)	Reduced	66% reduction in all-grade infection	**0.34 (0.19 - 0.60)**
Preemptive IgG supplementation at IgG < 400 mg/dL (severe infection)	Reduced	76% reduction in severe infection	**0.24 (0.08 - 0.69)**

CLINICAL IMPLICATIONS

- Monitor polyclonal IgG at baseline and monthly; replace to maintain IgG ≥ 400 mg/dL
- Minimize corticosteroid exposure beyond mandated step-up premedication
- De-escalate to biweekly or monthly dosing once response is established
- Front-load surveillance: risk is highest in the first two months of therapy
- Consider GPRC5D-directed monotherapy in patients with recurrent infection or profound hypogammaglobulinemia

CONTACT INFORMATION

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