GPRC5D-TARGETED THERAPIES IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: A SYSTEMATIC REVIEW AND SINGLE-ARM META-ANALYSIS

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INTRODUCTION

GPRC5D has emerged as a clinically actionable target in relapsed/refractory multiple myeloma (RRMM). Talquetamab, a GPRC5D×CD3 bispecific antibody, received FDA approval in 2023, and multiple GPRC5D-directed CAR-T therapies are in active development. Despite growing evidence, no meta-analysis had consolidated efficacy and class-specific toxicity data across the full landscape of GPRC5D-targeted agents. We aimed to pool overall response rate (ORR), depth of response, and on-target adverse events across all available clinical trials.

AIM

To pool overall response rate (ORR), depth of response, and on-target adverse events across all available clinical trials of GPRC5D-targeted monotherapy in relapsed/refractory multiple myeloma.

METHODS

A systematic search of PubMed, EMBASE, ClinicalTrials.gov, and major conference proceedings identified single-arm phase 1–2 clinical trials of GPRC5D-targeted monotherapy in RRMM.

A single-arm meta-analysis using the DerSimonian-Laird random-effects model was performed on logit-transformed proportions.

The primary outcome was ORR; secondary outcomes included ≥VGPR, ≥CR, and pooled rates of GPRC5D-class toxicities (skin, nail, dysgeusia, and grade ≥3 infections).

CONCLUSIONS

GPRC5D-targeted therapies achieve high and deep responses in heavily pretreated RRMM, with a pooled ORR exceeding 80%.

CAR-T approaches appear to deliver higher response rates and deeper remissions than BsAb therapy, although cross-modal comparisons are limited by small CAR-T sample sizes and trial heterogeneity.

The class-defining on-target toxicity profile—skin, nail, and taste toxicities—is frequent but manageable.

RESULTS

Study Population

8 cohorts comprising 549 efficacy-evaluable patients: 4 bispecific antibody (BsAb) cohorts from MonumenTAL-1 (talquetamab; N=405) and 4 CAR-T cohorts (arlo-cel, MCARH109, OriCAR-017, RD118; N=124).

Response Rates

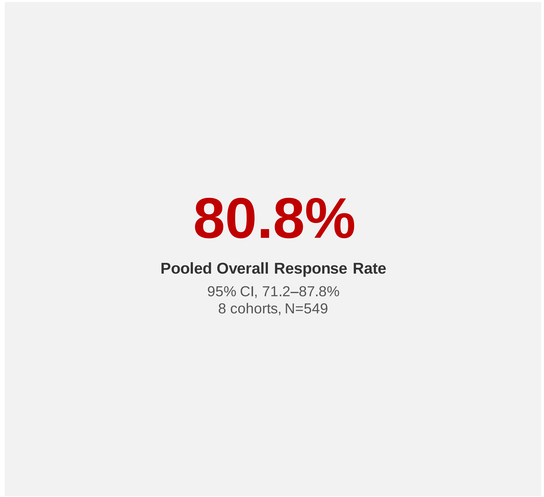
Pooled ORR 80.8% (95% CI 71.2–87.8%; I²=84.0%). By modality: BsAb 72.5% (95% CI 67.9–76.7%; I²=0.0%) vs CAR-T 89.1% (95% CI 76.2–95.5%; I²=76.4%). Pooled ≥VGPR 62.2% (95% CI 54.0–69.7%); pooled ≥CR 42.5% (95% CI 34.6–50.8%).

On-Target Toxicity (BsAb cohorts)

Any-grade skin, nail, and dysgeusia toxicities occurred in 68.2%, 52.8%, and 66.1% of patients, respectively. Grade ≥3 infections occurred in 21.0% (95% CI 15.5–27.8%)—substantially lower than published rates for BCMA-directed BsAbs.

CAR-T Safety

Cytokine release syndrome was near-universal with CAR-T therapy (82–100%) but predominantly grade 1–2.



BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T-cell therapy; ORR, overall response rate; I², heterogeneity index.

ACKNOWLEDGEMENTS

The authors declare no conflicts of interest and report no external funding for this study.

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