FROM BCMA TO GPRC5D: SEQUENCING T-CELL-REDIRECTING THERAPIES IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

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INTRODUCTION

- BCMA-directed CAR-T cells and bispecific antibodies have transformed the treatment of RRMM.
- Most patients eventually relapse after BCMA-targeted therapy.
- GPRC5D has emerged as an alternative target with limited antigen overlap.
- The optimal sequencing of BCMA- and GPRC5D-directed therapies remains unknown.

AIM

To evaluate the efficacy and safety of sequential BCMA- and GPRC5D-directed therapies in relapsed/refractory multiple myeloma using a systematic review and pooled proportional meta-analysis.

METHOD

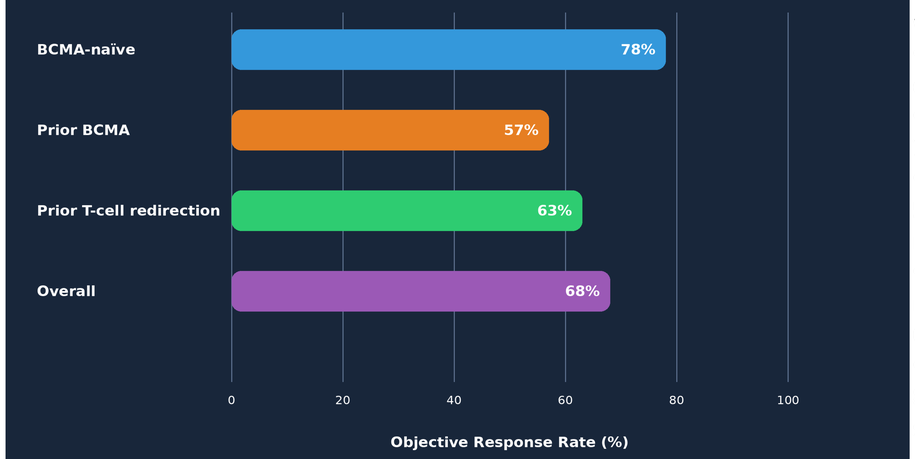
- **Study Design:** Systematic review and proportional meta-analysis
- **Data Sources:** Prospective clinical trials and real-world cohorts evaluating BCMA- and GPRC5D-directed therapies in RRMM
- **Population:** Patients receiving sequential T-cell–redirecting therapies
- **Cohorts:** 8 sequencing-relevant cohorts (n = 708)
- **Subgroups:**
- BCMA-naïve
- Prior BCMA exposure
- Prior T-cell redirection
- **Primary Outcome:** Objective response rate (ORR)
- **Secondary Outcome:** Cytokine release syndrome (CRS)
- **Statistical Analysis:**
- Random-effects proportional meta-analysis
- Logit-transformed pooled proportions
- Results reported with 95% confidence intervals
- Heterogeneity assessed using I^2 statistics

CONCLUSIONS

- Sequential T-cell–redirecting therapies remain effective despite prior BCMA exposure.
- Repeat BCMA targeting demonstrates lower response rates.
- GPRC5D-directed therapies retain meaningful activity following prior T-cell redirection.
- Prospective sequencing studies are warranted.

RESULTS

Figure 1. Objective Response Rate by Sequencing Strategy



- Eight sequencing-relevant cohorts comprising **708 patients** with RRMM were included.
- The **overall pooled objective response rate (ORR)** across all cohorts was **68%** (95% CI, 54–79; I^2 = 78.7%).
- **BCMA-naïve** patients demonstrated the highest pooled ORR of **78%** (95% CI, 50–93).
- Patients with **prior BCMA exposure** achieved a pooled ORR of **57%** (95% CI, 49–65), indicating reduced but clinically meaningful efficacy.
- **GPRC5D-directed therapy** following prior T-cell redirection maintained substantial activity, with a pooled ORR of **63%** (95% CI, 48–76).
- The **pooled incidence of CRS** was **77%** (95% CI, 62–87; I^2 = 87.6%), with no significant differences observed across sequencing subgroups.

Figure 2. Key Results

Study Population
- 8 sequencing-relevant cohorts
- 708 patients with relapsed/refractory multiple myeloma

Efficacy
- Overall pooled ORR: 68% (95% CI, 54–79)
- BCMA-naïve: 78% (95% CI, 50–93)
- Prior BCMA exposure: 57% (95% CI, 49–65)
- Prior T-cell redirection: 63% (95% CI, 48–76)

Safety
- Overall CRS incidence: 77% (95% CI, 62–87)
- No significant differences across sequencing subgroups

Target switching to GPRC5D preserves clinically meaningful activity after prior BCMA-directed therapy.