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Generalizability Gaps in BCMA- and GPRC5D-Directed Immunotherapy Trials for Relapsed/Refractory Multiple Myeloma: A Trial-Level Eligibility Analysis

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BACKGROUND & METHODS

Background

BCMA- and GPRC5D-directed immunotherapies have transformed RRMM treatment, but pivotal trial populations may not reflect medically complex patients in routine practice.

Aim

Evaluate whether eligibility criteria in key RRMM immunotherapy trials limit enrollment of clinically vulnerable populations.

Evidence sources

ClinicalTrials.gov, PubMed/MEDLINE, FDA labels, primary publications, protocols, and sponsor protocol summaries were reviewed.

Scoring approach

Each trial received a vulnerability-restriction score from 0 to 6 across prespecified domains.

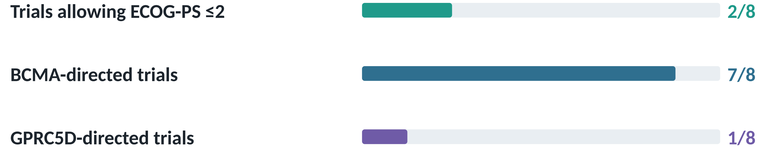
OVERALL GENERALIZABILITY GAP

8	5.5/6	6/8
Core trials analyzed pivotal/registrational	**Median restriction score** multidomain selection	**ECOG-PS 0-1 only** 2 allowed ECOG-PS ≤2

All trials restricted or did not clearly represent multiple vulnerability domains.

Eligibility criteria selected for clinically fit trial populations across performance status, organ function, hematologic, infection-related, disease-specific, and prior-therapy domains.

Quantifiable eligibility patterns



The median vulnerability-restriction score of 5.5/6 indicates broad multidomain selection for fit patients.

KEY ELIGIBILITY FINDINGS

Renal representation

Most trials specified renal function thresholds, commonly requiring CrCl or eGFR 30-45 mL/min; dialysis eligibility was generally absent or unclear.

Disease biology

Aggressive or atypical disease features were often restricted, including CNS/meningeal myeloma, plasma cell leukemia, amyloidosis, or POEMS syndrome.

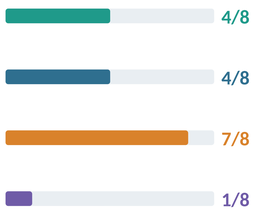
Prior therapy exposure

Prior BCMA exposure and prior T-cell-redirecting therapy were variably allowed, with many pivotal cohorts excluding or limiting these populations.

The combined pattern highlights limited external validity for medically complex RRMM populations.

TRIAL SET

Eight core pivotal or registrational trials were analyzed.



VULNERABILITY DOMAINS

ECOG performance status

Most trials limited enrollment to ECOG-PS 0-1.

Renal dysfunction/dialysis

Renal thresholds were common; dialysis eligibility was absent or unclear.

Cytopenias

Hematologic thresholds frequently limited patients with significant cytopenias.

Infection/immunosuppression

Active serious infection or significant immunosuppression was commonly excluded.

Aggressive biology

CNS/meningeal myeloma, plasma cell leukemia, amyloidosis, or POEMS were often restricted.

Prior immune redirection

Prior BCMA exposure and prior T-cell redirection were variably allowed or limited.

CONCLUSIONS

Pivotal BCMA- and GPRC5D-directed immunotherapy trials in RRMM largely enrolled clinically fit patients.

Patients with poor performance status, renal dysfunction, cytopenias, infection vulnerability, aggressive disease features, or prior immune-redirection exposure may be underrepresented.

These findings highlight gaps in trial representativeness and external validity.

Prospective and real-world studies are needed to define feasibility, toxicity, treatment persistence, and outcomes in clinically vulnerable RRMM populations.

Abbreviations: BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell; CNS, central nervous system; CrCl, creatinine clearance; ECOG-PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; GPRC5D, G protein-coupled receptor class C group 5 member D; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; RRMM, relapsed/refractory multiple myeloma.