

Cytokine Release Syndrome and Immune Effector Cell–Associated Neurotoxicity Syndrome With Bispecific Antibodies in Relapsed/Refractory Multiple Myeloma

A Three-Target Systematic Review With Trial-versus-Real-World Stratification

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Background

Bispecific antibodies (BsAbs) targeting BCMA, GPRC5D, or FcRH5 have transformed relapsed/refractory multiple myeloma (RRMM). Cytokine release syndrome (CRS) and ICANS remain key safety concerns, and their incidence varies by target and by setting.

Aim

To provide a comprehensive cross-target comparison of CRS and ICANS with BsAb therapy in RRMM across BCMA, GPRC5D, and FcRH5, contrasting clinical-trial versus real-world incidence to inform target-specific risk stratification.

Methods

Systematic search of PubMed, EMBASE, ClinicalTrials.gov, and Cochrane for RCTs and observational studies reporting CRS and/or ICANS with BsAbs in adults with RRMM. Median incidence and IQR were calculated descriptively, stratified by tumour target and study design. A descriptive synthesis was performed.

Studies included

31

cohorts

2,999

patients

By target

BCMA

20

GPRC5D

7

FcRH5

3

By setting

Clinical trials

23

Real-world

8

0 10 20 31

Number of cohorts (31 total)

23 clinical-trial and 8 real-world cohorts; includes 1 dual-target cohort (n=90).

Median CRS & ICANS by target

Target	Cohorts (pts)	CRS %	ICANS %
BCMA	20 (2,159)	56.1	7.7
GPRC5D	7 (536)	75.0	3.3
FcRH5	3 (214)	78.6	13.1
Overall	31 (2,999)	57.1	8.8

Cytokine release syndrome

57.1%

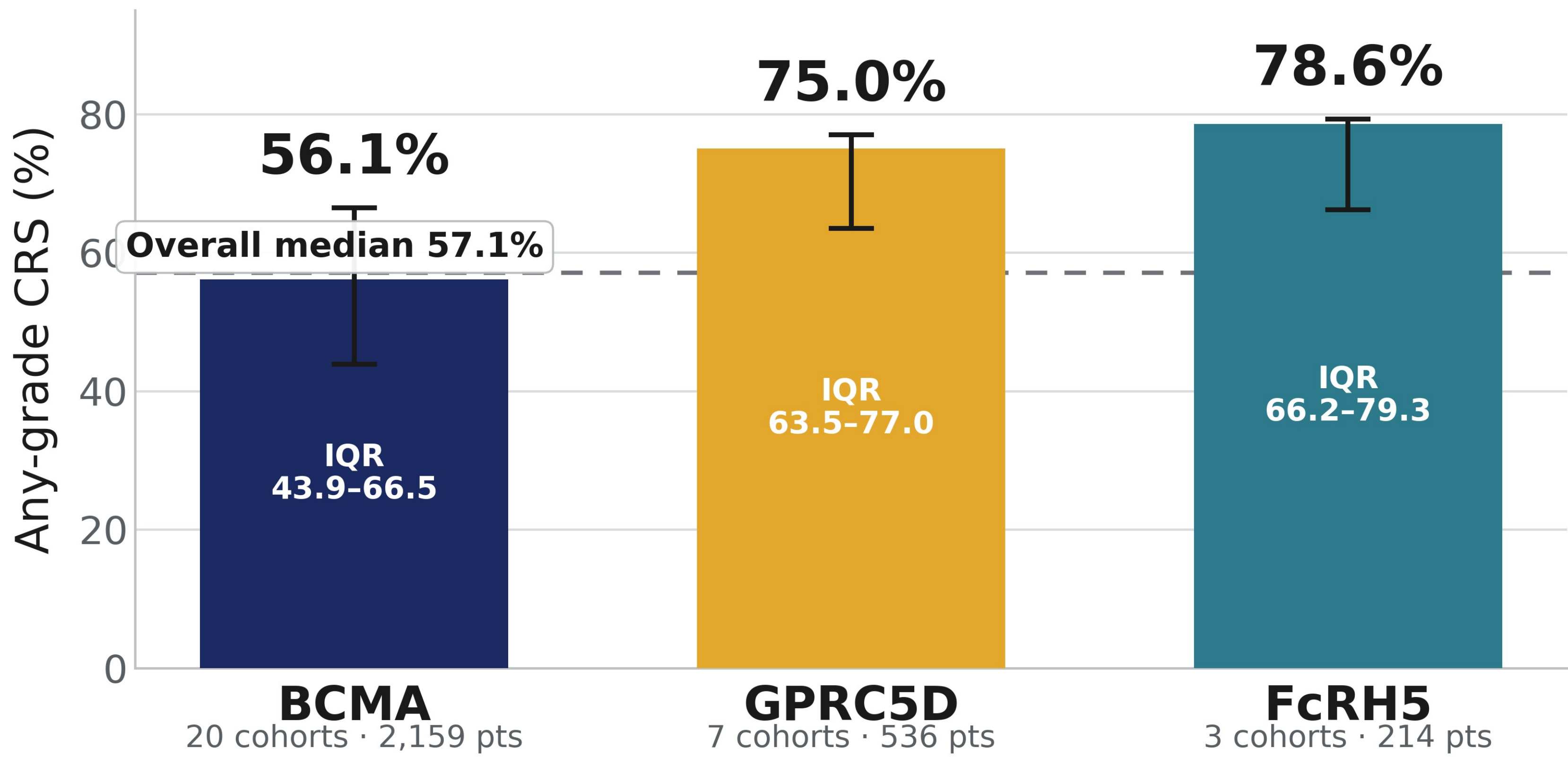
any-grade CRS

0.3%

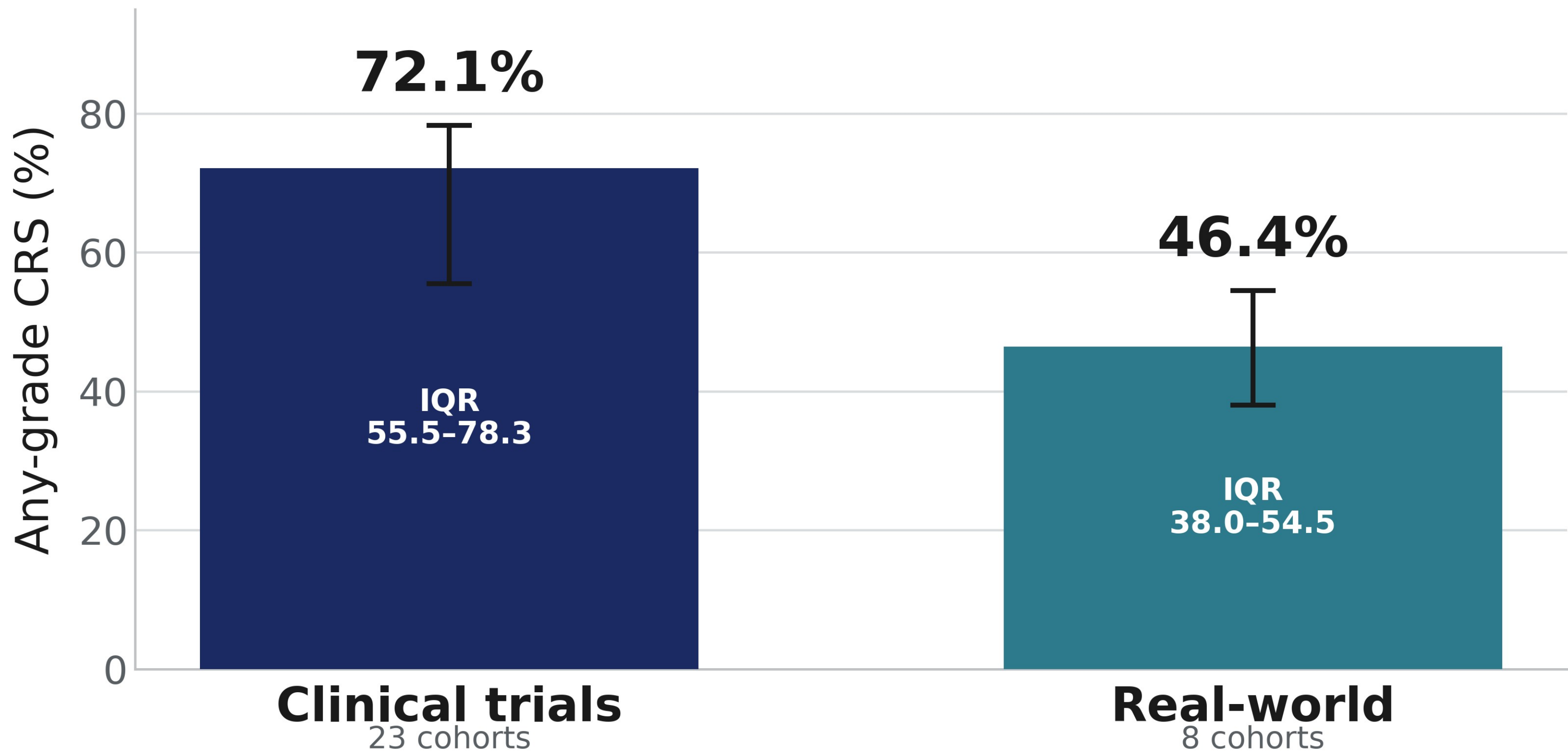
grade ≥3

0

fatal CRS



Any-grade CRS was highest for FcRH5 and GPRC5D and lowest for BCMA.



Trial cohorts reported markedly higher CRS than real-world cohorts.

New-onset CRS is common but overwhelmingly low-grade — no fatal CRS event was reported across any of the 31 cohorts.

Neurotoxicity (ICANS)

Immune effector cell–associated neurotoxicity syndrome

8.8%

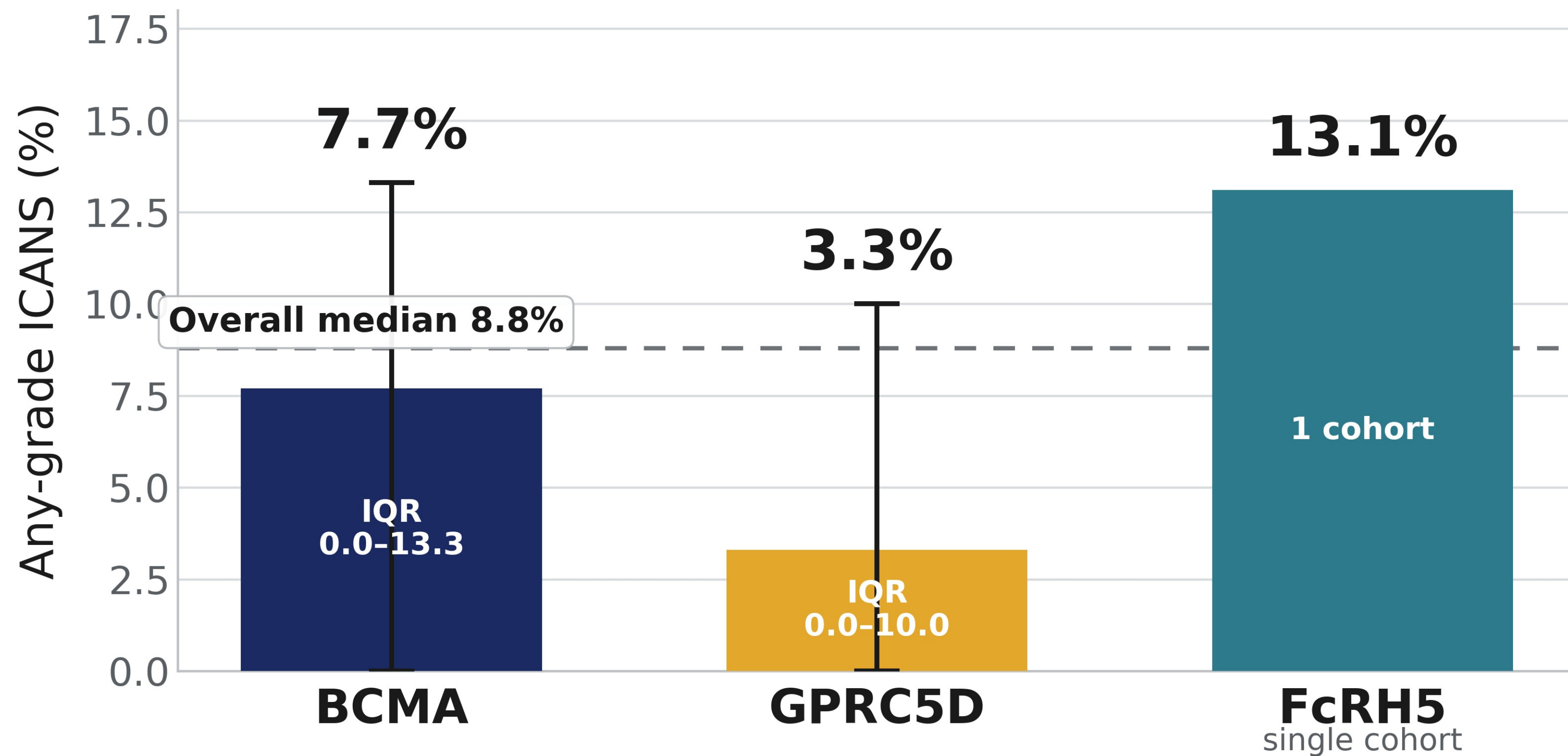
any-grade ICANS

Rare

grade ≥3

1

fatal event



ICANS was infrequent overall and lowest for GPRC5D despite its high CRS burden.

36.0%

received tocilizumab

Overall median across cohorts (IQR 28.9–45.4%)

Interpretation

- CRS is common but overwhelmingly low-grade, with no fatal CRS events.
- Neurotoxicity is uncommon and rarely severe.
- Toxicity is target-dependent: GPRC5D and FcRH5 carry more CRS, yet GPRC5D shows the least ICANS.
- CRS ran lower in real-world practice than in clinical trials.

Conclusions

- Low-grade CRS is common with BsAbs in RRMM; severe CRS is rare and non-fatal.
- GPRC5D- and FcRH5-targeting agents show higher CRS and tocilizumab use than BCMA.
- ICANS is infrequent overall; GPRC5D shows the lowest ICANS despite the highest CRS.
- Real-world CRS runs lower than trial rates (grading & observation-window differences).

These findings support target-specific CRS / ICANS risk stratification in clinical practice.