

DURABILITY OF RESPONSE, MECHANISMS OF RESISTANCE, AND RETREATMENT OUTCOMES FOLLOWING CAR T-CELL THERAPY IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: A SYSTEMATIC REVIEW

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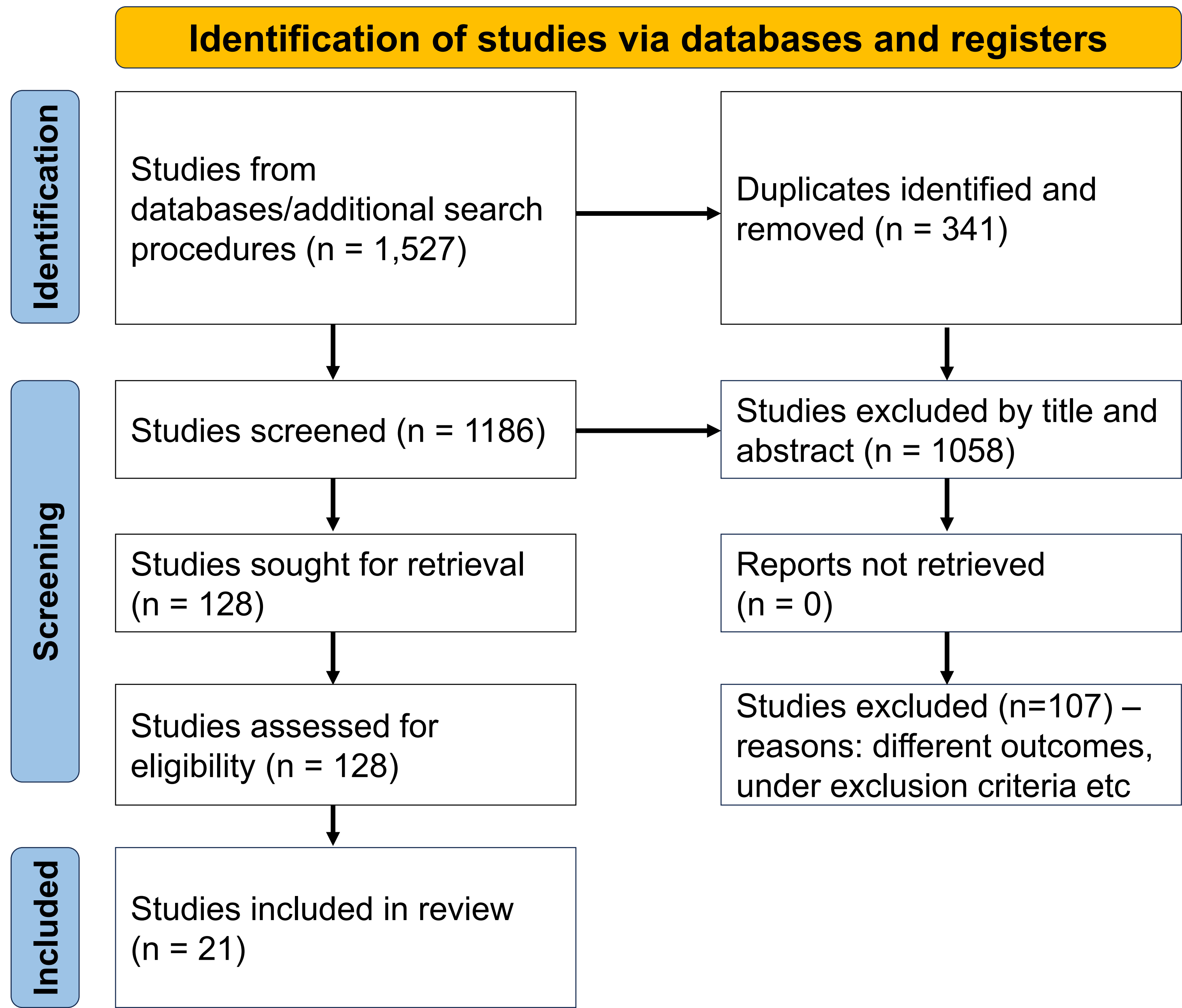
Background

- BCMA-directed CAR T-cell therapy has improved outcomes in relapsed/refractory multiple myeloma (RRMM) by producing high response rates and deep remissions.
- However, long-term disease control remains inconsistent, and relapse is common.
- Resistance appears to involve both antigen escape and T-cell dysfunction.

Methods

Systematic review conducted according to PRISMA 2020 guidelines.

- **Search period:** 2017 to May 2026
- Eligible studies reported response durability, PFS, relapse timing, resistance mechanisms, or salvage outcomes following CAR T-cell therapy in RRMM.
- **21 studies (>2,500 patients)** were included:
 - 4 randomized phase III trials
 - 10 single-arm trials
 - 7 observational cohorts
- Risk of bias was assessed using validated tools
- Findings were synthesized narratively due to study heterogeneity.



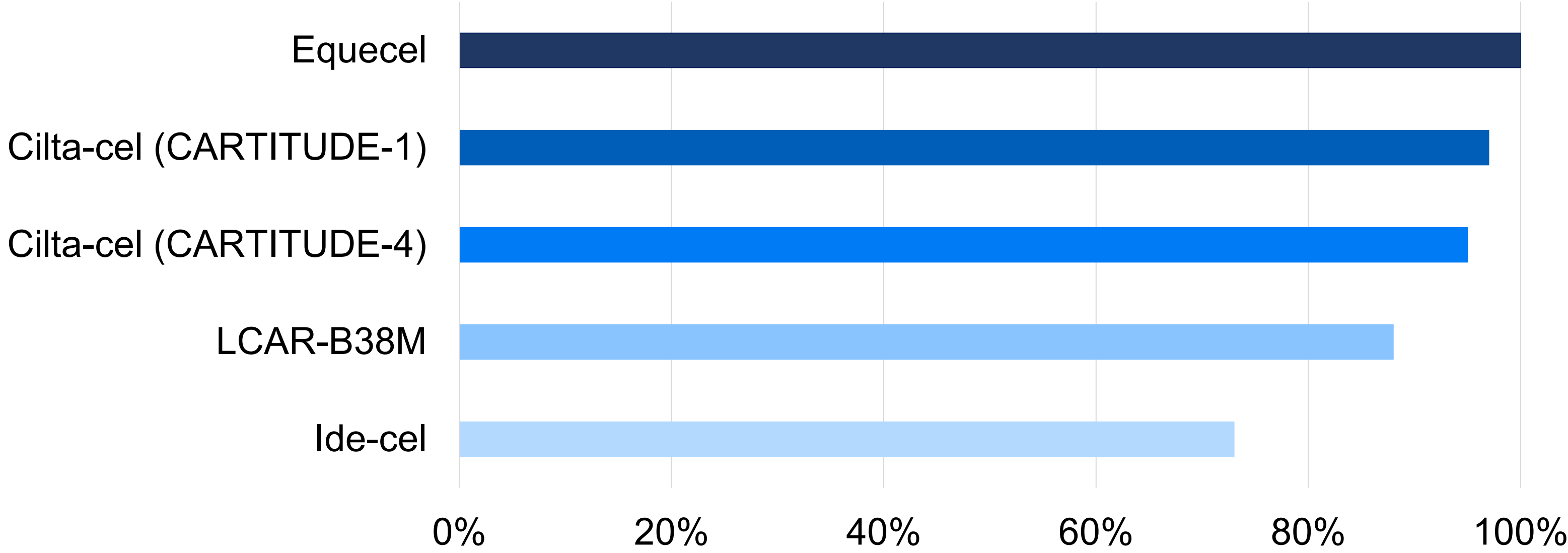
Objectives

- Evaluate response durability after BCMA-directed CAR T-cell therapy in RRMM.
- Characterize mechanisms of resistance and relapse and assess outcomes of post-CAR T retreatment strategies .

Results

- 21 studies (>2,500 patients): 4 randomized phase 3, 10 single-arm, and 7 observational cohorts.
- ORR: 73% with ide-cel; 100% with cilta-cel and equecel.
- Median PFS: 34.9 months with cilta-cel vs 8.8-13.8 months with ide-cel.
- MRD negativity was the strongest predictor of durable remission.
- Resistance was driven by BCMA loss, antigen shedding, and T-cell exhaustion.
- Sequential CAR-T: 100% ORR; 64.8% PFS at 6 months.
- Bispecific antibodies: 64-79% ORR; median PFS 4.4-5.1 months.

Overall Response Rates Across Major BCMA-Directed CAR T-Cell Therapies



Graph1: Graph 1: Overall response rates observed across major BCMA-directed CAR T-cell trials. Cilta-cel demonstrated the highest response rates.

Durability of Response Following BCMA-Directed CAR-T Therapy

CAR-T Therapy	Median PFS	5-Year PFS
Ide-cel	8.8–13.8 months	—
Cilta-cel	34.9 months	33%

Table 1. Durability of response following BCMA-directed CAR T-cell therapy. Cilta-cel demonstrated longer median PFS (34.9 months) compared with ide-cel (8.8–13.8 months), with a 5-year PFS of 33%.

Results

Clinical Outcomes of Salvage Therapies After CAR T-Cell Failure

Salvage Therapy	ORR (%)	PFS Outcome
Sequential CAR T	100%	64.8% PFS at 6 months
Talquetamab	79%	Median PFS: 5.1 months
Teclistamab	64%	Median PFS: 4.4 months

Table 2: Sequential CAR T-cell retreatment demonstrated the highest ORR (100%), with 64.8% PFS at 6 months.

Discussion

- BCMA-directed CAR T-cell therapy provides deep and durable responses, particularly with cilta-cel. Sustained **MRD negativity** was consistently associated with prolonged remission.
- Sequential CAR T-cell therapy and bispecific antibodies remain effective salvage strategies.

Clinical Implications

- Incorporate **MRD-guided monitoring** into post-CAR T surveillance. Consider **sequential CAR T-cell therapy** or **bispecific antibodies** after relapse.
- Early identification of resistance mechanisms may optimize treatment sequencing. Next-generation CAR T-cell constructs are needed to improve long-term durability.

Conclusion

- BCMA-directed CAR T-cell therapy achieves **high response rates and durable remissions** in RRMM.
- **MRD negativity** is a key predictor of sustained clinical benefit.
- Antigen escape and T-cell exhaustion remain the principal mechanisms of relapse.
- Improved CAR T-cell designs and optimized treatment sequencing are essential to enhance long-term outcomes.

References

1. Ludwig H, Novis Durie S, Meckl A, Hinke A, Durie B. Multiple Myeloma Incidence and Mortality Around the Globe; Interrelations Between Health Access and Quality, Economic Resources, and Patient Empowerment. *Oncologist*. 2020;25(9):e1406-e1413. doi:10.1634/theoncologist.2020-0141
2. Moreau P, Kumar SK, San Miguel J, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. *Lancet Oncol*. 2021;22(3):e105-e118. doi:10.1016/S1470-2045(20)30756-7
3. Danis R, et al. Outcomes of triple-class refractory multiple myeloma patients at a single clinic: a retrospective study. *Leuk Res*. 2023;151:107677.

