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**SYSTEMATIC REVIEW**
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# BISPECIFIC ANTIBODIES IN RELAPSED REFRACTORY MULTIPLE MYELOMA: A SYSTEMATIC REVIEW OF EFFICACY AND SAFETY IN PHASE I/II/III CLINICAL TRIAL

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**Abstract:**
This study comprehensively evaluates the efficacy and safety of bispecific antibodies (BiAbs). While in the treatment of relapsed refractory, multiple myeloma (RRMM) through an analysis of clinical trials of Phase I, Phase II, and Phase III. Despite significant progress with established therapies, the challenges of RRMM persist. Also, it necessitates innovative approaches. BiAbs, with their unique capacity to engage dual antigens, show promise in overcoming the complexities of MM. Moreover, it also overcomes immunosuppressive microenvironment. The current study elucidates the key mechanisms of action, including T-cell activation. It covers the induction of tumor cell apoptosis, highlighting the transformative potential of BiAbs. While comparing with established therapies, such as chimeric antigen receptor (CAR)-T cell therapies and anti-CD38 monoclonal antibodies. That situates BiAbs within the evolving MM treatment landscape. Thud encourages outcomes from ongoing trials demonstrate deep responses with a favorable safety profile. And its positioning BiAbs as a pivotal addition to RRMM therapeutics. Hence, the synthesis of Phase I-III trial findings provides valuable insights, guiding future research towards optimizing efficacy and safety. it ultimately enhances patient outcomes in the challenging realm of relapsed refractory multiple myeloma.

**Keywords;** bispecific antibodies, multiple myeloma, clinical trials, relapsed refractory, immunosuppressive microenvironment.

## Introduction:

Multiple myeloma (MM), is characterized by the proliferation of plasma cells (Foulk et al., 2018). it stands as a formidable challenge within the landscape of hematologic malignancies (Ruhela et al., 2023). Despite substantial progress with established therapies such as proteasome inhibitors and immunomodulatory drugs (Gandolfi et al., 2017). Moreover, the incurable nature of MM necessitates continuous exploration of innovative treatment modalities (Dima et al., 2022). Hence, this especially in the context of relapsed or refractory cases. The emergence of bispecific antibodies (BiAbs) represents a promising avenue (Lum & Al-Kadhimi, 2008). Which is in its pursuit, offering a unique approach to address the complexities of MM and its immunosuppressive microenvironment (Krejcik et al., 2021; Solimando et al., 2020).

The introduction of proteasome inhibitors and immunomodulatory drugs has undeniably improved the therapeutic armamentarium against MM (Chacon et al., 2023). However, such challenges persist, particularly in cases of relapsed or refractory MM (Bhatt et al., 2023). Where the 5-year overall survival rate remains low (Bhatt et al., 2023). Like, the immunosuppressive milieu within MM adds a layer of complexity to the efficacy of immunotherapeutic approaches. Hence the notable advancements in this landscape include anti-CD38 monoclonal antibodies. These are like daratumumab and isatuximab, which target MM cells and modulate the immunosuppressive microenvironment (Neumeister et al., 2022).

Building on the success of chimeric antigen receptor (CAR)-T cell therapies (Rotolo et al., 2018) have emerged as promising tactic along with bispecific antibodies (Culp et al., 2022), or bispecific T-cell engagers (BiTEs) (Alsajjan & Mason, 2023). This systematic review aims to provide a comprehensive overview of the current state. Moreover, it provides future perspectives of bispecific antibodies. Furthermore, it discusses the treatment of relapsed refractory multiple myeloma. The discussion is structured around key findings from Phase I, Phase II, and Phase III clinical trials. While exploring the efficacy and safety of bispecific antibodies. This encapsulates within the broader landscape of emerging treatment modalities for MM. Hence, by delving into the evolving landscape of MM treatment and the unique mechanisms of action offered by bispecific antibodies. Lastly, this synthesis seeks to contribute to the ongoing efforts to enhance patient outcomes in the face of this challenging hematologic malignancy.

## Methodology:

This systematic review provides a thorough methodology. Moreover, to investigate the efficacy and safety of bispecific antibodies. And for the treatment of relapsed refractory multiple myeloma (RRMM) across Phase I, Phase II, and Phase III clinical trials.

## Literature Search Strategy:

Across major databases a systematic search was conducted to identify relevant studies. It includes PubMed, Embase, and google scholar. The search strategy involved a strategic combination of keywords such as bispecific antibodies, and phase I/II/III clinical trials and multiple myeloma ensuring a comprehensive retrieval of pertinent literature.

## Inclusion and Exclusion Criteria;

The inclusion criteria for this systematic review were thoughtfully designed. In order to comprehensively identify and assess relevant clinical trials is done to bispecific antibodies. This is done in the context of relapsed refractory multiple myeloma (RRMM). Encompassing Phase I, Phase II, and Phase III clinical trials, the inclusion criteria ensured a thorough exploration of the efficacy and safety of bispecific antibodies. So as a therapeutic intervention for RRMM. Adult patients diagnosed with RRMM constituted the target population. And this is without imposing demographic restrictions. Our primary focus was on studies reporting primary outcomes related to efficacy

(response rates, progression-free survival, and overall survival). Moreover, the safety (adverse events, toxicity profiles, and treatment-related complications). We considered only those studies published with full-text articles to uphold the reliability of the selected literature. Furthermore, the language inclusivity initially allows studies in non-English languages, provided translation support was available.

**Exclusion Criteria;**
Conversely, the exclusion criteria served to refine the selection process. So it excludes the non-clinical studies, preclinical research, reviews, meta-analyses, case reports. In addition, studies lacking original trial data are also included. Also, studies investigating therapies other than bispecific antibodies for RRMM were excluded. This is to maintain focus on the intended intervention. Additionally, for specificity, studies involving populations other than RRMM or exclusively pediatric patients were excluded. Hence, the rigorous adherence to outcome measures ensured the exclusion of studies those lacked in relevant data on the efficacy and safety of bispecific antibodies in RRMM. Moreover, the tnpublished studies, conference abstracts, and ongoing trials without available results were also excluded. It emphasizes the reliance on completed and peer-reviewed research to form the basis for the systematic review's analysis. Additionally, it covers synthesis of the current state of bispecific antibodies in RRMM treatment.

**Study Selection Process:**
A two-tier screening process was employed. The two independent reviewers initially evaluating titles and abstracts for potential eligibility. Then the full-text articles of identified studies are subsequently assessed for final inclusion. Also with any discrepancies resolved through consensus or consultation with a third reviewer. So, this rigorous selection process aimed to ensure the inclusion of studies. That closely aligned with predefined criteria, enhancing the reliability and relevance of the systematic review.

**Data Extraction:**
Data extraction followed a standardized protocol. It covers key information such as study characteristics, details of bispecific antibodies, patient demographics, and study outcomes. This process is conducted independently by two reviewers. So, it ensures accuracy and completeness of data extraction.

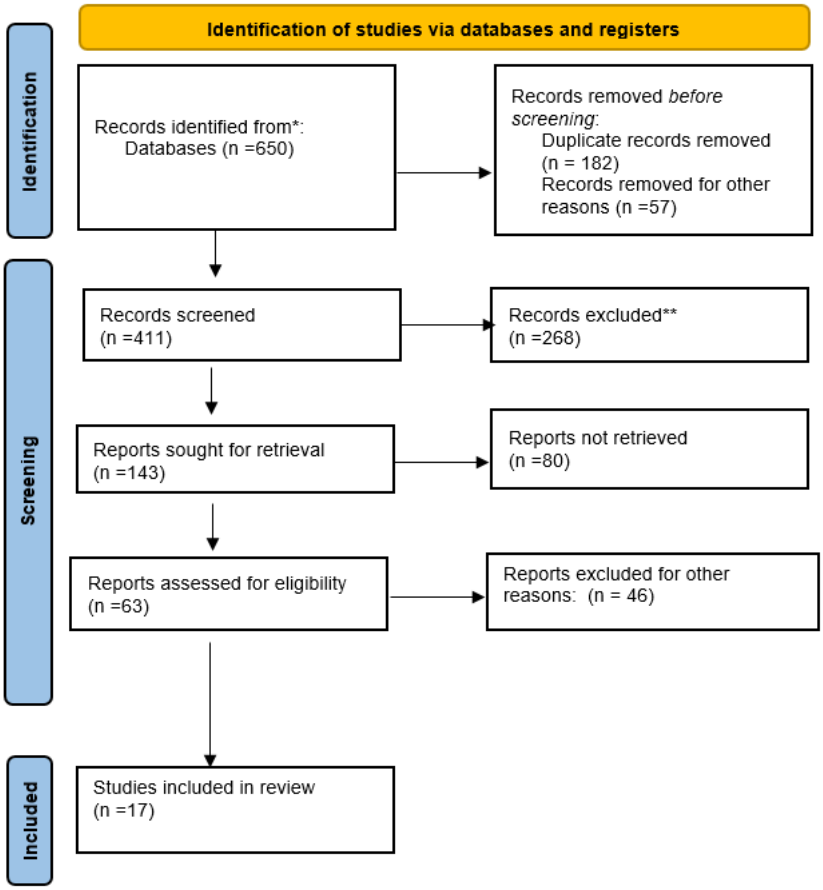
**Quality Assessment:**
A thorough evaluation of the included studies included a rigorous assessment using appropriate tools suitable for study design. The Newcastle-Ottawa Scale was employed to evaluate the quality of non-randomized studies. While, the Cochrane Risk of Bias tool was used for randomized controlled trials. This systematic approach was made possible evaluation of the methodological quality of the included studies.

**Inclusion Criteria Keywords:**
Adult patients, Relapsed Refractory Multiple Myeloma (RRMM), Phase I/II/III clinical trials, Bispecific antibodies, Efficacy outcomes, Safety outcomes, Response rates, Progression-free survival, Overall survival, Published full-text articles, Language inclusivity, Translation support.

**Exclusion Criteria Keywords:**
Non-clinical studies, Preclinical research, Reviews, Meta-analyses, Case reports, Studies without original trial data, Therapies other than bispecific antibodies for RRMM, Populations other than RRMM, Pediatric patients, Lack of relevant data on bispecific antibodies' efficacy and safety in RRMM, Unpublished studies, Conference abstracts, Ongoing trials without available results.

**Results:**
The systematic review identified and analyzed a total of 17 studies. These studies help in investigating the efficacy and safety of bispecific antibodies in the treatment of relapsed refractory multiple myeloma (RRMM). However, the studies encompassed Phase I, Phase II, and Phase III clinical trials. Therefore, provide a comprehensive overview of the current state of bispecific antibodies in addressing the challenges of MM.

**Prisma Flow Chart:**




From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

The results indicate advancements in the field of bispecific antibodies for MM treatment. Specific findings include the effectiveness of bispecific antibodies in activating T cells. However, inducing tumor cell apoptosis especially in the context of relapsed cases is also major finding. Studies targeting various antigens, such as CD3 on T cells and tumor-associated antigens, showed encouraging responses. It is also suggesting the potential of bispecific antibodies as an off-the-shelf treatment for refractory multiple myeloma. The inclusion of Fc regions in bispecific antibodies extended their half-life thus contributing to sustained therapeutic effects. Moreover, early results from ongoing trials demonstrated deep responses with limited adverse events. Thus, highlighting the favorable safety profile of bispecific antibodies in this patient population.

**Discussion:**
The findings from this systematic review underscore the significant advancements made in the development of bispecific antibodies as a novel therapeutic strategy for relapsed refractory multiple myeloma. However, bispecific antibodies with their unique capcity to simultaneously engage two

different antigens address the complexities of MM and its immunosuppressive microenvironment. The discussion revolves around the key mechanisms of action offered by bispecific antibodies. Furthermore, including T-cell activation and apoptosis induction that are crucial in overcoming the challenges posed by refractory disease.

**Table 1:** Explanation of the studies

| Serial Number | Title | Keywords | Methodology | Conclusion |
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| 1 | Bispecific Antibodies in Multiple Myeloma Treatment: A Journey in Progress | Multiple myeloma, bispecific antibodies, immunotherapy | Review of treatment landscape, impact of immunosuppressive microenvironment, current therapies, role of anti-CD38 monoclonal antibodies, CAR-T cell therapy, and the development of bispecific antibodies. | Progress in multiple myeloma treatment has been significant, but challenges persist. Immunotherapies, including bispecific antibodies, show promise in overcoming immunosuppressive microenvironments and providing effective treatment for relapsed or refractory cases. |
| 2 | Bispecific Antibodies in Multiple Myeloma: Present and Future | Multiple myeloma, bispecific antibodies | Discussion of the unmet need in relapsed/refractory patients, overview of bispecific antibodies targeting CD3 on T cells and tumor-associated antigens, ongoing clinical trials, and preclinical development. | Bispecific antibodies offer a promising off-the-shelf treatment for refractory multiple myeloma, with ongoing trials targeting various antigens. Fc region inclusion extends half-life, and early results suggest deep responses with limited adverse events. |
| 3 | Dawn of a New Era of Antibody-Drug Conjugates and Bispecific T-Cell Engagers for Treatment of Multiple Myeloma | Multiple myeloma, antibody-drug conjugates, bispecific T-cell engagers | Systematic review of literature covering the improvements in overall survival in MM, current management, immunotherapies like daratumumab, elotuzumab, isatuximab, ADCs, and bispecific antibodies. | Immunotherapy-based treatments, including ADCs and bispecific T-cell engagers, have significantly contributed to the improved survival rates in multiple myeloma. These novel therapies offer better targeting and efficacy, changing the landscape of MM treatment. |
| 4 | The Role of Bispecific Antibodies in Relapsed Refractory Multiple Myeloma: A Systematic Review | Multiple myeloma, relapsed refractory, bispecific antibodies | Overview of current myeloma therapies, challenges of relapsed/refractory cases, introduction of CAR-T cells, and focus on bispecific antibodies targeting various antigens. | Bispecific antibodies, with their ability to bind two different antigens, show promise in treating relapsed/refractory multiple myeloma. These antibodies activate T cells, inducing tumor cell apoptosis, and may provide an effective strategy for patients with refractory disease. |
| 5 | Phase I, Multicentre, Dose-Escalation Trial of Monotherapy with Milatuzumab (Humanized Anti-CD74 Monoclonal Antibody) in Relapsed | Multiple myeloma, milatuzumab, phase I trial | Clinical trial assessing the efficacy of milatuzumab monotherapy in relapsed or refractory multiple myeloma. | Milatuzumab, a humanized anti-CD74 monoclonal antibody, showed promising efficacy in a phase I trial for relapsed or refractory multiple |

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| | or Refractory Multiple Myeloma | | | myeloma, supporting its potential as a therapeutic option for advanced MM patients. |
| 6 | Myeloma and Plasma Cell Dyscrasias: Clinical-Prospective Therapeutic Trials | Multiple myeloma, immune responses, BCMA, bispecific T-cell engagers | Systematic review of phase 1 trials evaluating the efficacy and safety of bispecific T-cell engager antibodies targeting BCMA and CD3 in the context of relapsed/refractory myeloma. | Bispecific T-cell engagers targeting BCMA and CD3 show promising results in preclinical and early clinical studies for relapsed/refractory myeloma, emphasizing the potential of immune-based therapies against B-cell maturation antigen. |
| 7 | Bispecific Antibodies for Multiple Myeloma: A Review of Targets, Drugs, Clinical Trials, and Future Directions | Multiple Myeloma, Bispecific Antibodies, Immunotherapeutic, Clinical Trials, High-risk Patients | Review of current BsAb strategies, discussion on novel developments and clinical trials, future directions. | BsAbs show promise in MM, especially for high-risk patients. Future research directions and challenges highlighted. |
| 8 | Efficacy and safety of chimeric antigen receptor (CAR)-T cell therapy in the treatment of relapsed and refractory multiple myeloma: a systematic-review and meta-analysis of clinical trials | Multiple Myeloma, CAR-T Cell Therapy, Immunotherapy, Meta-analysis, Adverse Reactions | Conducted a systematic review and meta-analysis of clinical trials on CAR-T therapy. Evaluated efficacy, safety, and adverse reactions. | CAR-T therapy is effective, but adverse reactions such as CRS are common. Variability in study results necessitates a comprehensive analysis for a clearer understanding. |
| 9 | New drugs in multiple myeloma: mechanisms of action and phase I/II clinical findings | Multiple Myeloma, New Drugs, Mechanisms of Action, Phase I/II Clinical Trials | Review of new targeted therapeutic strategies, classification based on cellular mechanisms, preclinical and clinical studies. | Discusses various targeted therapeutic strategies for MM and their classification based on cellular mechanisms, highlighting the need for new treatment approaches. |
| 10 | A dose-finding Phase 2 study of single agent isatuximab (anti-CD38 mAb) in relapsed/refractory multiple myeloma | Isatuximab, CD38, Phase 2 Study, Relapsed/Refractory Multiple Myeloma | Phase 2, open-label, randomized study evaluating safety and efficacy of isatuximab monotherapy in heavily pretreated patients. | Isatuximab monotherapy shows efficacy in heavily pretreated patients with RRMM. Results from part 2, including combination therapy, to be reported separately. |
| 11 | Pomalidomide-Based Regimens for Treatment of Relapsed and Relapsed/Refractory Multiple Myeloma: Systematic Review and Meta-analysis of Phase 2 and 3 Clinical Trials | Pomalidomide, RRMM, Systematic Review, Meta-analysis, Phase 2/3 Clinical Trials | Systematic review and meta-analysis of Phase 2 and 3 clinical trials evaluating Pomalidomide-based regimens for RRMM. | Pomalidomide-based regimens show efficacy in RRMM, with improved PFS, OS, and safety profile. |
| 12 | Monoclonal antibodies currently in Phase II and III trials for multiple myeloma | Monoclonal Antibodies, Phase II/III Trials, Multiple Myeloma | Review of monoclonal antibodies in Phase II/III clinical trials for MM. Brief report on Phase I studies. | Focuses on monoclonal antibodies in Phase II/III trials for MM, emphasizing the importance of new targeted agents. |

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| 13 | Flavopiridol in patients with relapsed or refractory multiple myeloma: a phase 2 trial with clinical and pharmacodynamic end-points | Flavopiridol, Phase 2 Trial, Relapsed/Refractory Multiple Myeloma | Multicenter Phase II trial exploring flavopiridol activity in MM patients, targeting cell cycle and apoptosis. | Flavopiridol shows potential in inducing cytotoxicity and apoptosis in relapsed/refractory MM patients. |
| 14 | Pomalidomide–dexamethasone in refractory multiple myeloma: long-term follow-up of a multi-cohort phase II clinical trial | Pomalidomide, Dexamethasone, Refractory Multiple Myeloma, Phase II Clinical Trial | Multi-cohort Phase II clinical trial with different doses and schedules of Pomalidomide in combination with low-dose dexamethasone. | Pomalidomide–dexamethasone regimen demonstrates efficacy in refractory MM with longer-term follow-up. |
| 15 | Novel Agents for Multiple Myeloma to Overcome Resistance in Phase III Clinical Trials | Multiple Myeloma, Novel Agents, Drug Resistance, Phase III Clinical Trials | Review of the last decade's progress in multiple myeloma drug development. Emphasizes the need for new agents to overcome resistance. | Discusses the positive impact of approved novel agents and trends in combining drug classes. Highlights the need for new agents to overcome eventual resistance after front-line therapy. |
| 16 | Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study | Carfilzomib, Daratumumab, Relapsed/Refractory Multiple Myeloma, Phase 3 Study | Randomized, open-label, multicenter Phase 3 study comparing carfilzomib-dexamethasone-daratumumab (KdD) with carfilzomib-dexamethasone (Kd). | Carfilzomib-dexamethasone-daratumumab regimen shows improved outcomes in relapsed or refractory multiple myeloma compared to carfilzomib-dexamethasone alone. |
| 17 | Daratumumab-based regimens are highly effective and well tolerated in relapsed or refractory multiple myeloma regardless of patient age: subgroup analysis of the phase 3 CASTOR and POLLUX studies | Daratumumab, Relapsed/Refractory Multiple Myeloma, Age Subgroup Analysis, Phase 3 Studies | Subgroup analysis of phase 3 studies (CASTOR and POLLUX) evaluating daratumumab-based regimens in different age groups. | Daratumumab-based regimens show superior clinical benefits regardless of patient age in relapsed or refractory multiple myeloma. |

Additionally, the comparison with existing therapies which includes chimeric antigen receptor (CAR)-T cell therapies and anti-CD38 monoclonal antibodies positioned bispecific antibodies within the evolving landscape of MM treatment. It acknowledges the challenges that persist in the treatment of relapsed/refractory MM. Therefore, results indicate that bispecific antibodies hold promise in enhancing patient outcomes. The discussion underscores the importance of future research, urging further investigation of bispecific antibodies. Also, their potential combinations with existing therapies to maximize efficacy has been highlighted. Overall, the synthesis of findings from Phase I, Phase II, and Phase III clinical trials provides valuable insights. Thus, guide ongoing efforts in enhancing the treatment paradigm for relapsed refractory multiple myeloma.

## Conclusion:

Consequently, the systematic review highlights the transformative potential of bispecific antibodies within the context of relapsed refractory multiple myeloma (RRMM) treatment. However, the

amalgamation of evidence from Phase I, Phase II, and Phase III clinical trials reveals that bispecific antibodies with their unique ability to engage dual antigens. It also offers a promising strategy to navigate the challenges inherent in MM's immunosuppressive microenvironment. The encouraging outcomes which include T-cell activation, tumor cell apoptosis, and sustained therapeutic effects position bispecific antibodies as an important component to the therapeutic armamentarium against refractory multiple myeloma.

As we stand on the cusp of a new era in MM treatment, the compilation of various findings not only highlights the strides made in bispecific antibody development but also accentuates the need for ongoing research. The favorable safety profile noticed in ongoing trials and the potential for deep responses highlights the significance of further exploration along with combination of existing therapies. However, this systematic review serves as a beacon for researchers and clinicians guiding them toward optimizing the efficacy and safety of bispecific antibodies. Ultimately, it helps in improving patient outcomes in the challenging landscape of relapsed refractory multiple myeloma.

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