REVIEW

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Efficacy and Safety of Tebentafusp in Uveal Melanoma: A Systematic Review and Single-Arm Meta-Analysis

Majd M. AlBarakat[1], Ahmed Wadaa-Allah[2]*, Rana B. Altawalbeh[1], Khaled M. Hamam[3], Dana Y. Tarawneh[4], Abdullah Al Momani[1], Sakhr Alshwayyat[5,6,7], Arvind Kunadi[8,9]

Abstract

Background: Uveal melanoma, a rare and aggressive intraocular malignancy, poses significant challenges due to its high metastatic potential. Tebentafusp, an innovative immunotherapy targeting melanoma-associated antigens, has shown promise in early clinical trials for metastatic uveal melanoma. **Methods:** This systematic review adhered to PRISMA guidelines, analyzing four studies encompassing 475 patients until January 18, 2024. Meta-analysis techniques, utilizing RevMan software version 5.4, were employed to calculate hazard ratios (HR) or risk ratios (RR) with their respective 95% confidence intervals for each outcome. **Results:** The 1-year overall survival rate, pooled from the included studies, was 68% with moderate heterogeneity (I^2=56%, p=0.1). Cytokine release syndrome was observed in 83% of patients across three studies, with high heterogeneity (I^2=79%, p<0.01). **Conclusion:** Our findings underscore modest responses and manageable adverse effects such as cytokine release syndrome and fatigue, highlighting the necessity for careful monitoring and proactive management in the clinical application of Tebentafusp for metastatic uveal melanoma.

Keywords: Tebentafusp- Uveal melanoma- Systematic Review- Meta-analysis

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Introduction

Uveal melanoma is a rare and aggressive intraocular malignancy arising from melanocytes in the uveal tract. It accounts for approximately 3-5% of all melanomas and is characterized by a high metastatic potential, with liver metastasis identified as the predominant site of spread [1]. Blurred vision is the prevailing symptom observed in individuals with primary UM, although a significant number of patients remain asymptomatic during the initial diagnosis. Additional symptoms commonly experienced upon presentation encompass photopsia, floaters, visual field loss, visible tumor, pain, and metamorphopsia [2].

Uveal melanoma treatment aims to avoid the metastatic spread and to preserve the eye with useful vision [3]. Treatment modalities consist of observation, surgical enucleation or excision, and radiotherapy such as brachytherapy, proton beam radiotherapy and photon radiotherapy [4].

However, despite these interventions, the prognosis for patients with advanced disease is still unfavorable, as the long-term prognosis of UM is poor, and approximately half of the patients still suffer from metastases, irrespective of treatment for the primary tumor [5]. Metastatic uveal melanoma (UM) often proves fatal within a year of diagnosis, showing poor responsiveness to chemotherapy or targeted therapies [1]. Challenges persist as the efficacy of preventing metastasis and improving overall survival rates remains constrained [1, 6, 7].

These persistent challenges in effectively managing advanced uveal melanoma necessitate ongoing exploration of novel treatment modalities. One such emerging therapeutic agent is Tebentafusp, an innovative immunotherapy designed to target and activate T cells against melanoma-associated antigens [8]. This bispecific fusion protein, designed to target the melanocytic protein gp100 and the immune cell receptor CD3, has shown promising results in early clinical trials for metastatic uveal melanoma [8, 9]. By redirecting T cells to recognize and destroy melanoma cells, Tebentafusp stands for a novel approach in the evolving landscape of cancer immunotherapy [9].

*[1]Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan. [2]Biochemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt. [3]Research Scholar, Pharmaceutical Sciences Department, College of Health and Human Sciences, North Dakota State University, Fargo, North Dakota, USA. [4]School of Medicine, the University of Jordan, Amman, Jordan. [5]Research Associate, King Hussein Cancer Center, Amman, Jordan. [6]Research Fellow, Applied Science Research Center, Applied Science Private University, Amman, Jordan. [7]Internship, Princess Basma Teaching Hospital, Irbid, Jordan. [8]McLaren Health Care, Flint, USA. [9]Michigan State University, East Lansing, USA.*For Correspondence: a.m.wadaa-allah.p@sci.asu.edu.eg*

However, The current landscape highlights a knowledge gap in the optimal utilization of Tebentafusp for uveal melanoma, prompting the need for further exploration [10].

Our systematic review aims to address this critical gap in the literature by comprehensively analyzing existing evidence on the safety and efficacy of Tebentafusp compared to other modalities, including placebo, in patients with uveal melanoma. Through a rigorous examination of relevant studies, we seek to provide a comprehensive overview of the current landscape and identify areas where Tebentafusp may offer superior outcomes or present distinct safety profiles compared to existing interventions offering a comprehensive synthesis of evidence to guide clinicians in making informed decisions for the management of uveal melanoma.

Materials and Methods

Protocol Registration

This systematic review and meta-analysis adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11] and the Cochrane Handbook of Systematic Reviews and Meta-Analysis [12]. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number:CRD42024504367.

Data Sources & Search Strategy

Until January 18, 2024, a systematic search of five databases (PubMed, WOS, SCOPUS, EMBASE) was conducted by M.M.A and A.K. without any search limitations. The search strategy included the following terms: intraocular melanoma OR ocular melanoma OR uveal melanoma AND Tebentafusp OR kim tark. In addition, abstracts and unpublished studies were carefully reviewed, and authors of relevant studies were contacted for additional data where necessary. More details regarding the search strategy are shown in (Table S1).

Eligibility Criteria

The criteria for inclusion in this study were defined as follows: Population (P) encompassed patients diagnosed with metastatic melanoma; Intervention (I) consisted of Tebentafusp; Control (C) included any comparator, including placebo; and Outcome (O) focused on safety and efficacy data. Study design (S) Randomized controlled trials RCTs or observational comparative studies.

We excluded animal studies, reviews, pilot studies protocols, conference abstracts, editorial articles, papers published in languages other than english and book chapters.

Study Selection

Two reviewers (F.A. and A.A.) independently screened the gathered studies based on titles and abstracts using the online software Covidence, following the removal of duplicates. Subsequently, full-text screening was conducted by the same three reviewers, adhering to the previously outlined eligibility criteria. Any discrepancies were resolved through discussion.

Data extraction

Two reviewers (M.M.B. and A.K.) conducted a pilot test and created an extraction sheet to gather the following data: summary of Study Design, Country, Centers, Total Participants, Arms of Study, Primary Outcome; baseline information including Number of patients in each group, Mean Age (Years) with Standard Deviation, Gender Distribution (Male), ECOG performance status, Median time since primary diagnosis in years (with range), Median Number of prior anticancer therapy regimens in the metastatic setting (with range), and others; efficacy and safety outcomes data such as Overall Survival, 1-year Overall Survival, Confirmed Complete Response, Confirmed Partial Response, Stable Disease, Progressive Disease, Any Adverse Event, Cytokine Release Syndrome (CRS), Pyrexia, Nausea, Fatigue, and other side effects. Two reviewers (K.M. and A.W.) independently extracted the data, with any discrepancies resolved through discussion.

Quality Assessment

Two reviewers (F.A and A.A) assessed independently the quality of the included studies using the Modified Newcastle Ottawa Scale (NOS) that classifies studies as “low” (0-3), “moderate” (4-6), and “high” (7-9) quality, based on the calculated total score. NOS assessed three domains: selection, comparability, and outcome. Any conflicts between the reviewers were resolved by M.M.B In discussion.

Statistical analysis

A meta-analysis was conducted using RevMan software version 5.4. Hazard ratios (HR) or risk ratios (RR) with their respective 95% confidence intervals were employed for each outcome. We used the inverse variance method to estimate the overall effect size, REML for between-study variance (Tau^2), and the Q-Profile method for confidence intervals of Tau^2 and Tau. Untransformed proportions represented individual study effect sizes, and the Clopper-Pearson method calculated confidence intervals for them. These methods ensured rigorous analysis, providing reliable estimates of effect size while assessing heterogeneity and uncertainty.

Results

The search results

The initial search of literature produced a total of 1692 studies, all of which underwent screening based on their titles and abstracts. Following the application of pre-defined inclusion and exclusion criteria, 409 duplicate and 1192 irrelevant studies were excluded. This process resulted in 4 articles eligible for a thorough full-text review. Ultimately, 4 studies met the criteria for inclusion in the final analysis. The flow chart is shown in (Figure 1).

Summary of the included studies

We included four studies with a total of 475 patients. Two studies were multicentral open-labeled Phase 2

clinical trials [8, 13], one of them performed in United Kingdom [8] and the other was conducted in Canada, Germany, Spain, United Kingdom and United states of America [13]. The third study was phase 3 clinical trial, open-labeled, and multicentral performed in Australia, United states, Italy, Russia, Germany, Canada, France, Belgium, Ukraine, Poland, Spain, Netherlands, United Kingdom, and Switzerland [14], The fourth study was a multicentral retrospective study in Germany and Switzerland [15] (Table 1).

Two arms of doses were evaluated, Arm 1: Weekly dosing ranging from 5 to 900 ng/kg, with a later focus on a 600 ng/kg dose converted to 50 mcg, and Arm 2: Daily dosing for 4 consecutive days every 3 weeks, with doses ranging from 10 to 50 mcg [8].Tebentafusp applied initially at 20 µg on day 1, 30 µg on day 8, 68 µg on day 15 and then 68 µg then once weekly thereafter (total treatment in 28 days) [13]. Also, Tebentafusp 20 µg on day 1, 30 µg on day 8, and 68 µg weekly after that for three weeks [14] (Table 1).

Quality Assessment

As per the revised criteria outlined in the Newcastle Ottawa scale, it was found that all four studies demonstrated a high level of quality. Details of quality assessment regarding each domain of the criteria are shown in (Table 2).

Efficacy

The pooled estimate of the clinical trials' included studies using the random effect model of the 1-year overall survival was 68% with moderate heterogeneity (I^2=56%, p=0.1) [8, 13, 14] (Figure 2a), After applying sensitivity test, the heterogeneity became 0% after omitting Carvajal et al. [13] and Nathan et al. [14], but it became 77% after omitting Middleton et al. [8] (Figure 2b).

Regarding the pooled overall response rate of all the included studies (8,13–15), were 7% with no heterogeneity (I^2=5%, p=0.37) (Figure 3a). When subgroup performed, the pooled overall response rate of the clinical trials' included studies (8,13,14), using the random effect model was the same 7% but with higher heterogeneity but still low (I^2=31%, p=0.23) (Figure 3b).

Patients with initial assessment of progressive disease for all the included studies [8, 13–15], disclosed a pooled estimate of 52% with moderate heterogeneity (I^2=54%, p=0.09) (Figure 4a), The heterogeneity become 0% after performing sensitivity test and omitting Tomsitz et al. [15] (Figure 4b), and after conducting subgroup analysis for three included clinical trials [8, 13–15], the same results of heterogeneity obtained (I^2=0%, p=0.42) with pooled estimate of the progressive disease of 50% (Figure 4c).

The pooled estimate of the patients with stable disease for all the included studies [8, 13–15], were 37% with moderate heterogeneity (I^2=55%, p=0.08) (Figure 5a). After applying sensitivity test, the heterogeneity became 29% and 24% after omitting Carvajal et al. [13] and Tomsitz et al. [15] respectively (Figure 5b). Subgroup analysis for the clinical trials [8, 13, 14] showed a pooled estimate of 40% with no heterogeneity (I^2=24%, p=0.27) (Figure 5c).

The pooled estimate of the patients with partial response for all the included studies [8, 13–15], were 7% with no heterogeneity (I^2=22%, p=0.28) (Figure 5d). Subgroup analysis for the clinical trials [8, 13, 14], showed a pooled estimate of 7% with no heterogeneity (I^2=45%, p=0.16) (Figure 5e). Further, the results of the pooled estimate of the patients with complete response for all the included studies [8, 13–15], were 0% with no heterogeneity (I^2=0%, p=0.84) (Figure 5f).

Safety

The pooled estimate of the patients with Cytokine release syndrome those three included studies [13–15] were 83% with high heterogeneity (I^2=79%, p<0.01) (Figure 6a). Subgroup analysis for the two clinical

Table 1. Summary Included Studies

Study ID	Sample size	Study Design	Location	Doses	Follow up
Middleton et al. [8]	18	Multicenter, Open-label phase 2	UK	Arm 1: Weekly dosing ranging from 5 to 900 ng/kg, with a later focus on a 600 ng/kg dose converted to 50 mcg. Arm 2: Daily dosing for 4 consecutive days every 3 weeks, with doses ranging from 10 to 50 mcg	NA
Carvajal et al. [13]	127	Multicenter, open-label phase 2 study	Canada, Germany, Spain, UK and US	Tebentafusp, initially at 20 µg on day 1, 30 µg on day 8, 68 µg on day 15 and then 68 µg then once weekly thereafter (total treatment in 28 days).	19.5 months
Nathan et al. [14]	252	Multicenter, open labeled phase 3 trial	Australia, US, Italy, Russia, Germany, Canada, France, Belgium, Ukraine, Poland, Spain, Netherlands, UK, Switzerland,	Tebentafusp 20 µg on day 1, 30 µg on day 8, and 68 µg weekly thereafter for three weeks.	14.1 months
Tomsitz et al. [15]	78	Retrospective multicenter study	Germany & Switzerland	NA	15 months

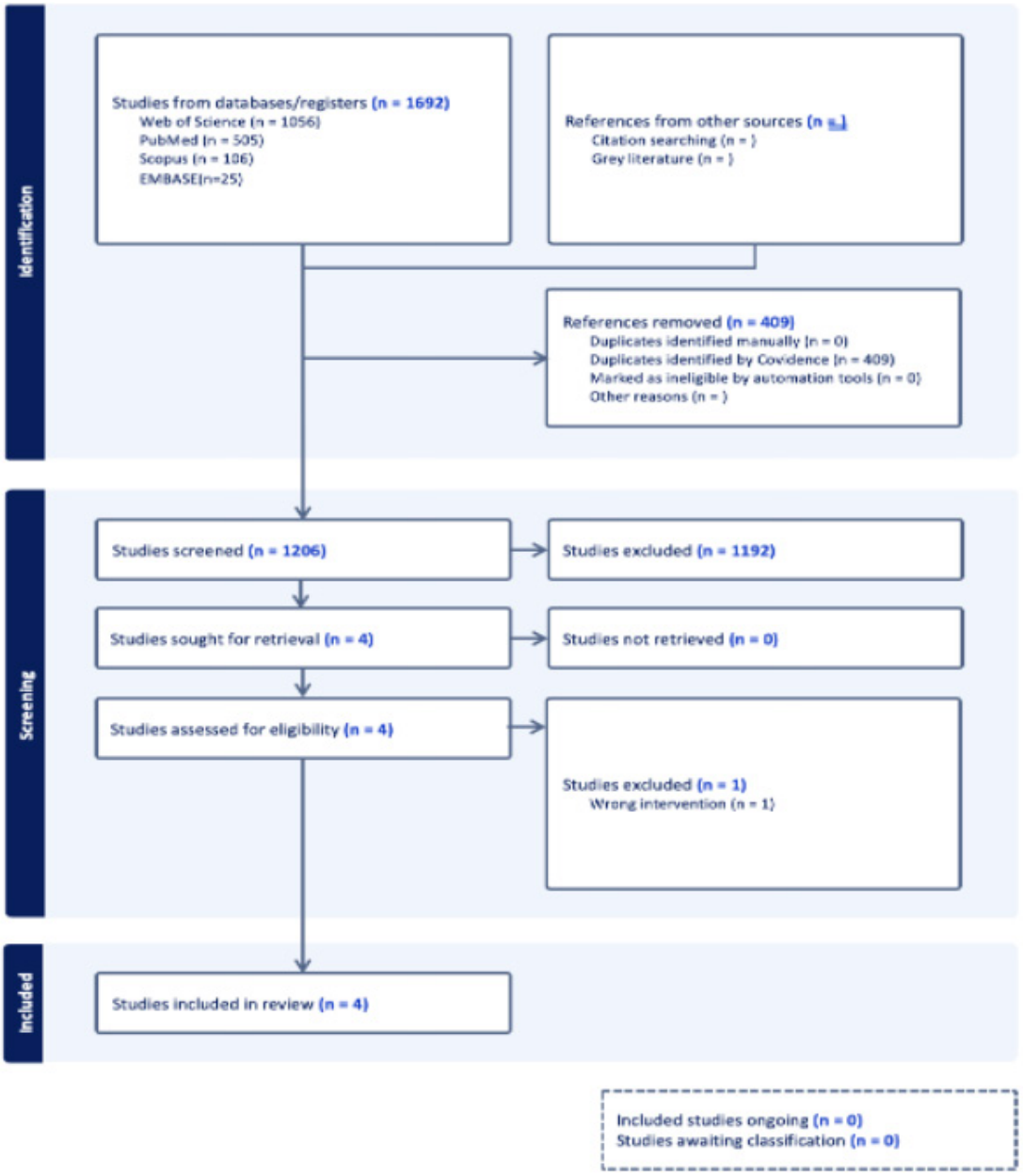

Figure 1. Flow Diagram of the Study Selection Process. A total of 1692 studies were identified, with 409 duplicates and 1192 irrelevant studies excluded, resulting in 4 studies eligible for inclusion.

trials [13, 14] showed a pooled estimate of 88% with no heterogeneity (I^2=0%, p=0.46) (Figure 6b).

The pooled estimate of the patients with fatigue for those three included studies [13–15] were 32% with very high heterogeneity (I2=99%, p<0.01) (Figure 6c). Subgroup analysis for the two clinical trials [13, 14] showed a pooled estimate of 46% with high heterogeneity (I^2=74%, p=0.05) (Figure 6d). The sensitivity test did not

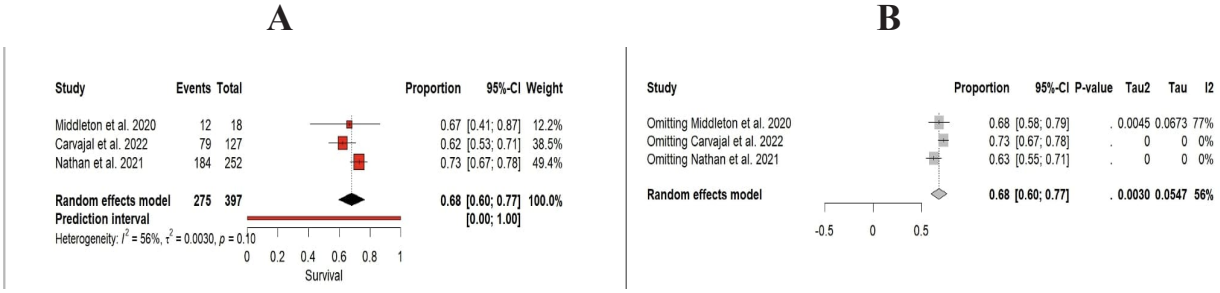

Figure 2. Pooled Estimate of 1-Year Overall Survival Across the Clinical Trials (Carvajal et al., 2022; Nathan et al., 2021; Middleton et al., 2020). (a) Pooled estimate with moderate heterogeneity (68%, I^2 = 56%, p = 0.1). (b) Sensitivity analysis showing heterogeneity reduction after omitting Carvajal et al., 2022 and Nathan et al., 2021, and increase after omitting Middleton et al., 2020.

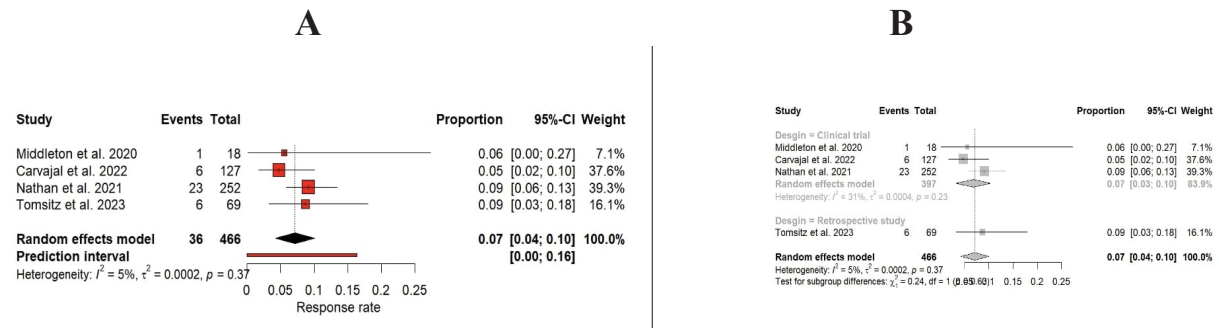

Figure 3. Pooled Overall Response Rate Across All Studies (Carvajal et al., 2022; Nathan et al., 2021; Middleton et al., 2020; Tomsitz et al., 2023), with subgroup analysis for clinical trials (Carvajal et al., 2022; Nathan et al., 2021; Middleton et al., 2020). Pooled estimate: 7%, with minimal heterogeneity (I^2 = 5%, p = 0.37).

decrease the heterogeneity (Figure 6e).

Same aspect with the pooled estimate of the patients with Nausea for those included studies [13–15] were 39% with very high heterogeneity (I^2=97%, p<0.01) (Figure 7a). Subgroup analysis for the two clinical trials [13, 14] showed a pooled estimate of 51% with high heterogeneity (I^2=89%, p<0.01) (Figure 7b). The sensitivity test did not decrease the heterogeneity (Figure 7c).

No major difference for the results of the pooled estimate of the patients underwent vomiting for those included studies [13-15] were 25% with very high heterogeneity (I^2=85%, p=0.0087) (Figure 7d). Subgroup analysis for the two clinical trials [13, 14] showed a pooled estimate of 30% with high heterogeneity (I^2=65%, p=0.09) (Figure 7e). The sensitivity test did not decrease the heterogeneity (Figure 7f).

The same results for any adverse events, the pooled estimate of the patients for those included studies [13–15] were 91% with very high heterogeneity (I^2=93%, p<0.01) (Figure 7g). On the other hand, subgroup analysis for the two clinical trials [8, 13–15] showed a pooled estimate of 100% with no heterogeneity (I^2=5%, p=0.31) (Figure 7h).

Discussion

This systematic review combines four studies with a total patient population of 475 to evaluate Tebentafusps' safety and efficacy in the treatment of uveal melanoma. The analysis included data from two phase 2 clinical trials, one phase 3 clinical trial, and a multi-center retrospective study, providing a comprehensive overview of the current research landscape.

The 1-year overall survival pooled estimate of the included studies was 68%, with moderate heterogeneity. Interestingly, the heterogeneity fluctuated with the exclusion of specific studies, suggesting their impact on the variability of outcomes.

As for the overall response rate, we found that the pooled estimate was 7%, indicating minimal heterogeneity. The subgroup analysis of included clinical trials yielded consistent results, although with slightly higher heterogeneity. These results are consistent with

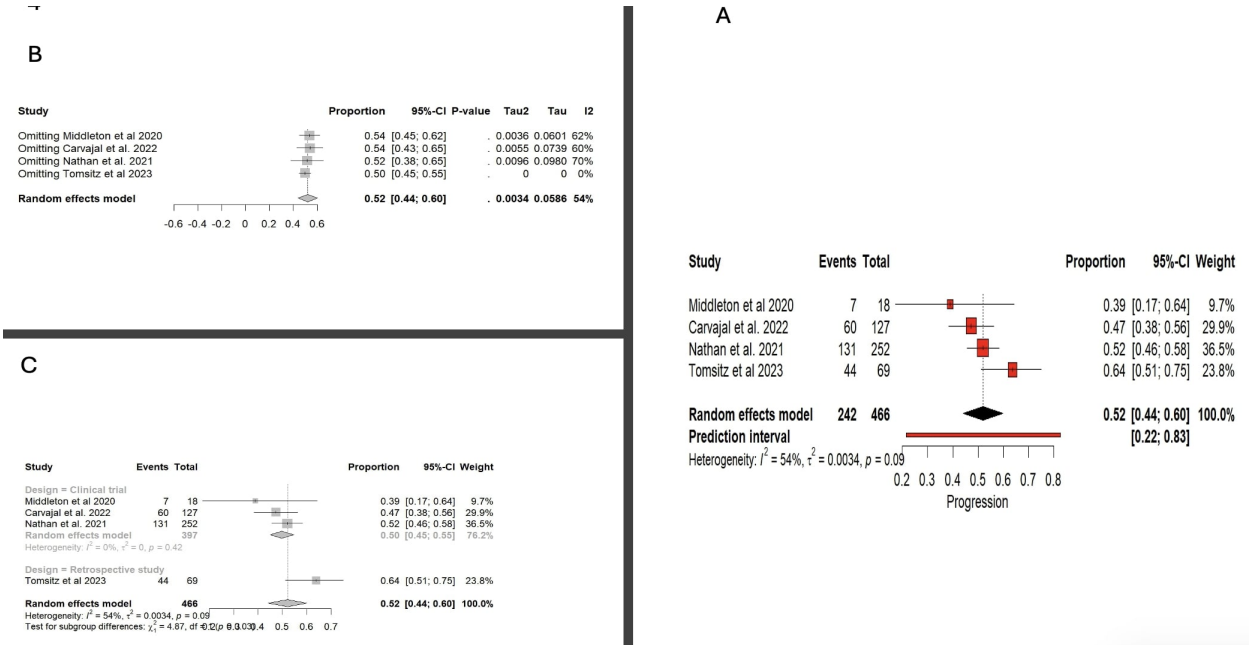

Figure 4. Pooled Estimate of Patients with Progressive Disease. (a) All studies: 52% with moderate heterogeneity (I^2 = 54%, p = 0.09). (b) Sensitivity analysis showing reduction to 0% heterogeneity after omitting Tomsitz et al., 2023. (c) Subgroup analysis for clinical trials: 50% with no heterogeneity (I^2 = 0%, p = 0.42).

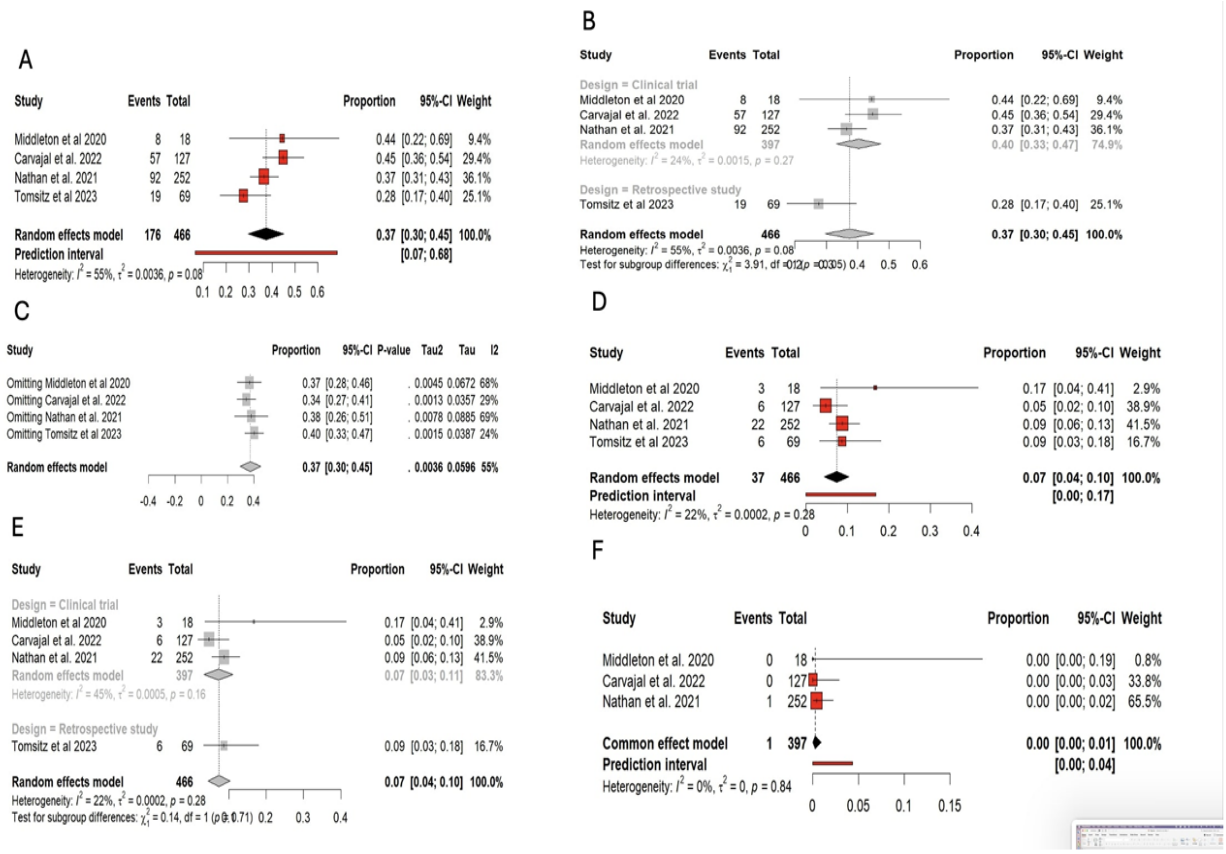

Figure 5. Pooled Estimates for Patients with Stable Disease, Partial Response, and Complete Response. (a) All studies: Stable disease: 37%, with moderate heterogeneity (I^2 = 55%, p = 0.08). (b) Sensitivity analysis showing reduced heterogeneity after omitting Carvajal et al., 2022 and Tomsitz et al., 2023. (c) Subgroup analysis for clinical trials: Stable disease: 40%, no heterogeneity (I^2 = 24%, p = 0.27). (d) Partial response: 7%, no heterogeneity (I^2 = 22%, p = 0.28). (e) Partial response for clinical trials: 7%, no heterogeneity (I^2 = 45%, p = 0.16). (f) Complete response: 0%, no heterogeneity (I^2 = 0%, p = 0.84).

the existing literature that shows modest responses to Tebentafusp therapy in patients with uveal melanoma [16].

The assessment of the progression of disease revealed a combined estimate of 52% for progressive disease and 37% for stable disease, with moderate heterogeneity observed. Sensitivity tests and subgroup analysis helped clarify the sources of heterogeneity and highlighted the robustness of certain findings, while also clarifying potential variability between studies.

As the mechanism of action of tebentafusp involves activating CD4+/CD8+ T cells to induce tumor cell death, which can cause several adverse effects [16,17]. Our study revealed that cytokine release syndrome (CRS), fatigue, nausea, and vomiting are significant side effects that should be considered for the safety and clinical use of tebentafusp in treating metastatic uveal melanoma.

Clinical trials have reported common treatment-related adverse events with tebentafusp, including cytokine-mediated events and skin-related events such as rash, pyrexia, and pruritus [15, 17]. Carvajal et al. reported a 71.2% incidence rate of CRS in patients treated with tebentafusp. However, they were manageable with

Table 2. Summary of the Quality Assessment, Using NOS

Studies	Selection				Comparability	Exposure			Totat
Author, yearStudy ID	Representatives of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcomes were not present at the start of study	Comparability of Cohorts on the basis of the design or analysis	Assessment of outcome	Adequate follow-up duration	Adequacy of follow-up of cohorts	Quality Score
Middleton et al. [8]	1	1	1	1	2	1	1	0	8
Carvajal et al. [13]	1	1	1	1	1	1	1	1	7
Nathan et al. [14]	1	1	1	1	1	1	0	1	7
Tomsitz et al. [15]	1	1	0	1	1	1	1	1	7

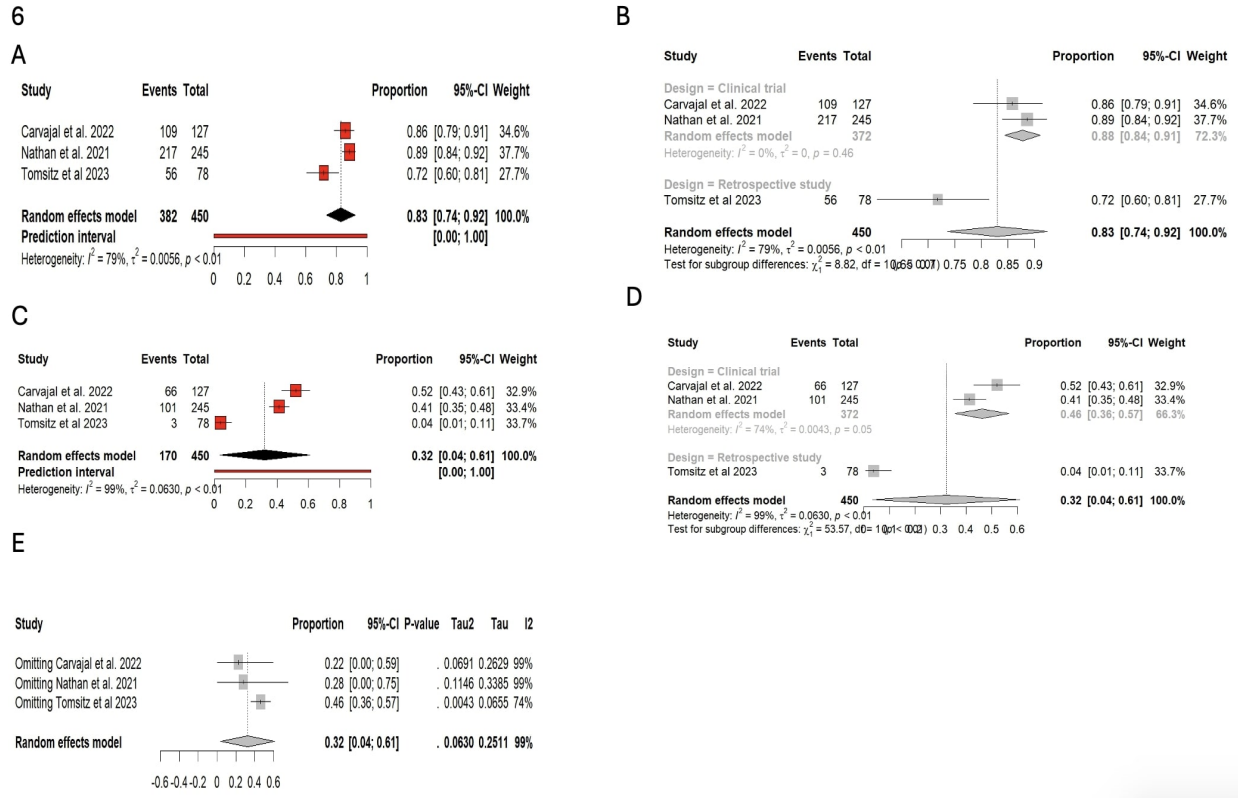

Figure 6. Pooled Estimates for Safety Events. (a) Cytokine Release Syndrome: 83% with high heterogeneity (I^2 = 79%, p < 0.01). (b) Subgroup analysis for two trials: 88%, no heterogeneity (I^2 = 0%, p = 0.46). (c) Fatigue: 32% with very high heterogeneity (I^2 = 99%, p < 0.01). (d) Subgroup analysis: 46%, high heterogeneity (I^2 = 74%, p = 0.05). (e) Sensitivity analysis for fatigue: heterogeneity remained unchanged.

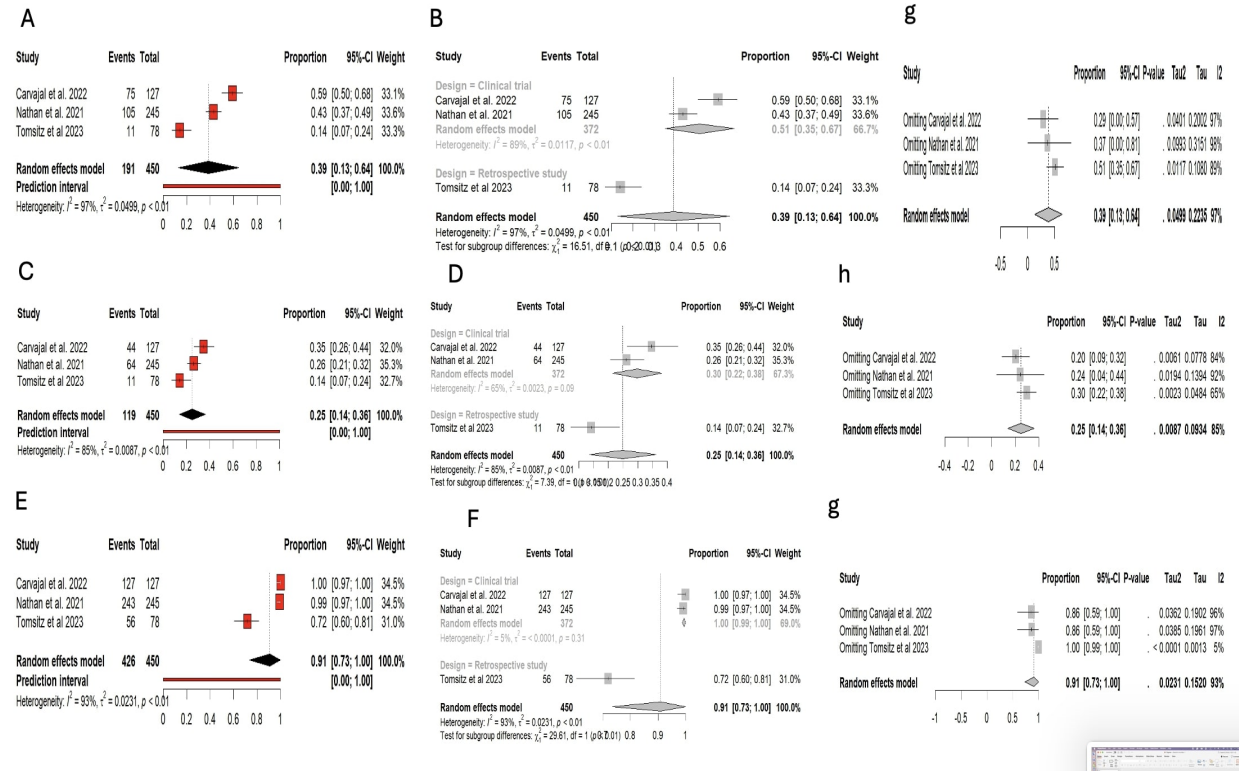

Figure 7. Pooled Estimates for Nausea, Vomiting, and any Adverse Events. (a) Nausea: 39%, very high heterogeneity (I^2 = 97%, p < 0.01). (b) Subgroup analysis: 51%, high heterogeneity (I^2 = 89%, p < 0.01). (c) Sensitivity analysis for nausea: heterogeneity remained unchanged. (d) Vomiting: 25%, very high heterogeneity (I^2 = 85%, p = 0.0087). (e) Subgroup analysis: 30%, high heterogeneity (I^2 = 65%, p = 0.09). (f) Sensitivity analysis for vomiting: heterogeneity remained unchanged. (g) Any adverse event: 91%, very high heterogeneity (I^2 = 93%, p < 0.01). (h) Subgroup analysis: 100%, no heterogeneity (I^2 = 5%, p = 0.31).

antipyretic drugs, intravenous fluids, and corticosteroids [13]. Additionally, nausea was identified as a side effect that was generally manageable and decreased in severity after the initial dose, and treatment discontinuation due to adverse events has been reported to be low [18,19].

Fatigue was identified as a common adverse event associated with tebentafusp treatment in a retrospective study that analyzed the outcomes of tebentafusp therapy in patients with metastatic uveal melanoma [20]. Additionally, in a Phase 3 study, tebentafusp-treated patients experienced fatigue, among other side effects [15]. This indicates that fatigue can be a potential adverse effect of the tebentafusp treatment. Although adverse events can occur with tebentafusp treatment, they are generally manageable and do not commonly lead to treatment discontinuation [16].

Limitations

This meta-analysis has several limitations. The small number of included studies limits the generalizability of the findings. Additionally, publication bias may have influenced the results, as studies with significant outcomes are more likely to be published. Heterogeneity across studies and variations in study quality also introduce uncertainty in the findings. Future updates with more studies will help address these limitations and provide stronger conclusions.

Author Contribution Statement

A.K. and M.M.A. conceived the idea. A.K. and M.M.A. designed the research workflow. M.A. and A.K. searched the databases. A.A. and R.B.A. screened the retrieved records, extracted relevant data, assessed the quality of evidence, and M.M.A. resolved the conflicts. K.M. and A.W. performed the analysis. M.M.A., D.T., S.A and R.B.A. wrote the final manuscript. A.K. supervised the project. All authors have read and agreed to the final version of the manuscript.

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None.

Conflicts of Interest

The authors declare no conflict of interest.

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