


SYSTEMATIC REVIEW

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Safety and efficacy of PD-1/PD-L1 immune checkpoint inhibitors in patients with pre-treated advanced stage malignant mesothelioma: a systematic review and meta-analysis

Amjad Zafar¹, Asma Abdul Rashid², Abdul Moeed², Muhammad Junaid Tahir³, Ahmad Jamal Khan⁴, Oadi N. Shrateh^{5*}  and Ali Ahmed⁶

Abstract

Background Malignant mesothelioma is an aggressive cancer with poor prognosis. Programmed cell death protein-1 (PD-1) and its ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) have recently presented as a viable option in some first line but primarily as a second-line treatment of advanced-stage malignant mesothelioma (asMM). Therefore, this systematic review and meta-analysis aims to assess the safety and efficacy of PD-1/L-1 ICIs in advanced-stage malignant mesothelioma.

Methods PubMed, Scopus, and Cochrane databases were searched for all studies assessing the safety and efficacy of anti PD-1/PD-L1 agents. Primary outcomes were objective response rate (ORR) and disease control rate (DCR). Secondary outcomes were median progression free (mPFS) and overall survival (mOS). Safety outcomes were treatment- (TRAEs) and immune-related adverse events (IRAEs). A random-effects meta-analysis was performed to pool medians and to derive event rates.

Results A total of 15 studies were included with total of 1064 asMM patients. ORR and DCR were 16% and 57%, respectively. A pooled mPFS was 4.53 (CI: 3.40–5.65) and mOS was 10.51 (CI: 9.03–12.00). Overall TRAEs had an event rate of 0.69 (0.50–0.83) whereas IRAEs had an event rate of 0.28 (0.15–0.46). There were no significant differences between pembrolizumab, nivolumab primarily, and avelumab subgroups for all the outcomes. Additionally, meta-regression found no covariate to be a significant factor in ORR and DCR.

PROSPERO registration This systematic review has been registered with PROSPERO under the registration number (CRD42023442350).

*Correspondence:

Oadi N. Shrateh
oadi.shrateh@students.alquds.edu

Full list of author information is available at the end of the article



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Conclusion In this meta-analysis we found that anti-PD1/PD-L1 treatment could be useful in pretreated asMM as they had at least comparable or greater mPFS, mOS, ORR, and DCR than other second-line agents currently being used.

Registration number This systematic review was registered at PROSPERO prior to the literature search, **CRD42023442350**.

Keywords PD-1, PD-L1, Immune checkpoint inhibitors, Malignant mesothelioma

Background

Malignant mesothelioma (MM) is an aggressive cancer with a poor prognosis that typically results from being exposed to asbestos fibres [1]. It commonly develops in the outer lining of the chest cavity or, less often, in the lining of the abdominal cavity, the sac around the heart, or the testes. There are three main histological subtypes of mesothelioma, each with decreasing levels of survival rates: epithelioid, biphasic, and sarcomatoid [2, 3]. Palliative chemotherapy is often recommended for many individuals diagnosed with MM who are not eligible for surgery due to factors such as advanced stage, advanced age, underlying health conditions, or limited physical well-being. The combination of cisplatin and pemetrexed is a standard first-line treatment for unresectable malignant pleural mesothelioma which was approved in 2004 [4]. From 1990 to 2017, global mesothelioma deaths varied between 18,200 and 32,400 [5]. However, one study by Driscoll et al. [6] showed an estimate of 43,000 deaths. Currently, the burden of global mesothelioma deaths is shouldered by high-income countries [7]. However, a group of studies led by Takahashi found that a rise in global mesothelioma deaths is inevitable, especially in the developing countries [8–10]. To date, there have been no randomized phase 3 clinical trials that have demonstrated any improvement in the overall survival of patients with malignant mesothelioma after the progression of the disease, regardless of the use of new drugs or drug combinations [11, 12].

Recently, modest improvements in progression-free and overall survival were observed with bevacizumab as compared to chemotherapy alone [13]. Over the past few years, the treatment landscape of numerous solid tumors has been significantly transformed by the introduction of immune checkpoint inhibitors (ICIs). Although cytotoxic T lymphocyte antigen-4 (CTLA-4) directed agents did not show any benefit in advanced-stage malignant mesothelioma (asMM) [12], programmed cell death protein-1 (PD-1) and programmed death ligand 1 (PD-L1) antagonists have shown benefit in increasing survival [14]. Studies such as those by Sahin et al. [15] and Guven et al. [16] demonstrate that novel combinatorial strategies have led to incremental improvements in patient survival in other solid tumors, and these findings are shaping the framework for treatment in malignant mesothelioma. Studies

have emphasized the role of molecular biomarkers in guiding immune-oncology (IO) therapy for advanced cancers, including MM [17]. However, the heterogeneity and low mutation burden in MM present challenges in pinpointing reliable predictors of response. Additionally, Rizzo et al. [18] identified potential markers beyond PD-L1 that may influence the efficacy of IO therapies, suggesting an expanding research focus for this cancer.

The findings from various clinical phase I or III trials have shown varying effectiveness of different second line and onward ICI monotherapies in treating MM. Nivolumab demonstrated median progression-free survival (mPFS) and median overall survival (mOS) durations ranging from 2.6 to 5.9 months and 9.2 to 17.3 months, respectively [19–22]. Similarly, Pembrolizumab achieved comparable outcomes with mPFS and mOS durations of 2.1 to 5.4 months and 10 to 11.5 months, respectively [23–25]. Avelumab, on the other hand, resulted in mPFS and mOS durations of 4.1 and 10.7 months, respectively [26]. However, it is essential to note that these outcomes were observed in carefully selected patients, and their reproducibility in a broader population of non-selected patients in routine therapeutic settings remains uncertain.

Due to the inconsistent efficacy outcomes of PD-1/PD-L1 ICIs across various trials, this systematic review and meta-analysis aims to synthesize existing evidence on the safety and efficacy of second-line PD-1 and PD-L1 ICI monotherapies in patients with advanced-stage malignant mesothelioma (asMM) who have already undergone treatment. By compiling data from multiple studies, we aim to provide a more comprehensive understanding of these therapies' potential benefits and risks, ultimately offering valuable insights to guide clinical decisions and support the development of more effective treatment strategies for asMM.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systemic Review and Meta-analysis (PRISMA) [27] and Cochrane Collaboration guidelines [28]. A protocol was registered at PROSPERO prior to the literature search, **CRD42023442350**.

Data sources and search strategy

Two independent (AZ and AM) investigators conducted a systematic literature search using electronic databases, including PubMed, Scopus, and Cochrane Central, from inception to July 2023. Online databases such as www.clinicaltrials.gov, medRxiv.org, and conference proceedings and presentations were also searched to identify grey literature. The following keywords were used: pleural neoplasms, mesothelioma, avelumab, nivolumab, durvalumab, and pembrolizumab. A detailed search strategy used for each database is shown in the supplementary material (Table S1).

Screening of studies

All articles initially retrieved from the systematic search of the electronic databases were transferred to Endnote Reference Library (Version X7.5; Clarivate Analytics, Philadelphia, Pennsylvania) software, where duplicates were identified and removed. Two researchers (AM and AAR) independently shortlisted the remaining articles based on the titles and abstracts and subsequently screened the full texts of the articles to assess relevance. Any discrepancy was settled by consulting a third reviewer (AZ) until a consensus was reached. The reference list of included articles was also sifted manually to identify relevant articles. All discrepancies between the reviewers were resolved by discussion.

Inclusion and exclusion criteria

Articles were shortlisted based on the following eligibility criteria (a) PD-1 or PD-L1 immune checkpoint inhibitors (ICIs) monotherapy in patients with advanced-stage malignant mesothelioma (asMM), (b) studies with at least one outcome of interest, (c) retrospective and prospective cohorts, and randomized controlled trials (RCTs). The primary outcomes included efficacy outcomes which were objective response rate (ORR), disease control rate (DCR), median progression free survival (mPFS), PFS at 6- and 12-month interval, median overall survival (mOS), and OS at 6- and 12-month interval. The safety outcomes secondary outcomes which were treatment- and immune-related adverse events divided in two cohorts: (a) adverse event grade 1–5 and (b) adverse event grade 3–5. Articles in languages other than English were excluded. Review articles, editorials, and commentaries were also excluded.

Data extraction and quality assessment

Two independent reviewers (AZ and AM) conducted data extraction of the relevant articles shortlisted. In each study following data was extracted: (a) study name and year, (b) study design, (c) the number of patients in each group, (d) general patient characteristics (age and gender), (e) tumor histology, (f) all the outcomes of interest.

Two independent reviewers performed a quality assessment to gauge the validity and reliability of the included studies. The risk of bias in the included non-randomized studies was evaluated independently by two investigators (AA and AB) using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool [29]. Further, the score assigned to each study was categorized into ratings. The risk of bias-2 tool (RoB-2) of the Cochrane collaboration [30] was used to evaluate quality of the included randomized controlled trials. Any disagreement was resolved by consensus.

Statistical analysis

This meta-analysis was conducted using Review Manager (RevMan) [Computer program] Version 5.4 Cochrane Collaboration, Comprehensive Meta Analysis Version 3.3.070, and OpenMetaAnalyst. A random-effects model was used to calculate event rates for dichotomous variables, whereas the Mantel-Haenszel (MH) method was used to pool medians and 95% CI for median PFS and median OS. A p-value less than 0.05 was considered significant in all cases. The Higgins I^2 index was utilized to examine heterogeneity among the included studies. The I^2 values of 0–25% were labeled as low, 25–50% as mild, 50–75% as moderate, and 75% above as critical. For each clinical outcome, forest plots were generated to show the relative effect sizes of the comparison groups. Publication bias assessment was carried out by performing Egger's regression test. A subgroup analysis was performed for all outcomes based on the type of immune checkpoint inhibitor to evaluate their individual impact on the overall effect size. Additionally, meta-regression was performed for primary outcomes and various covariates.

Results

A total of 1170 potentially relevant citations were identified and screened from the initial search. After the removal of duplicated studies, we retrieved 195 full-text articles for evaluation of which 15 studies fulfilled the set selection criteria. The PRISMA flow chart of the study selection is shown in Fig. 1. From the 15 studies, two were RCTs [20, 23], four were phase 2 trials [21, 24, 31, 32], two were phase 1b trials [26, 33], and seven were retrospective cohorts [34–40]. Of the 14, six assessed efficacies of pembrolizumab, seven evaluated nivolumab, and one tested avelumab. A total of 1133 patients with advanced-stage malignant mesothelioma were identified. The mean age of the patients was 66.8 (10.2) years and 74.5% were males. Study characteristics are shown in Table 1 and detailed patient characteristics are shown in Table 2. All the included studies had a low risk of bias. Detailed quality assessment is shown in Figures S1 and S2.

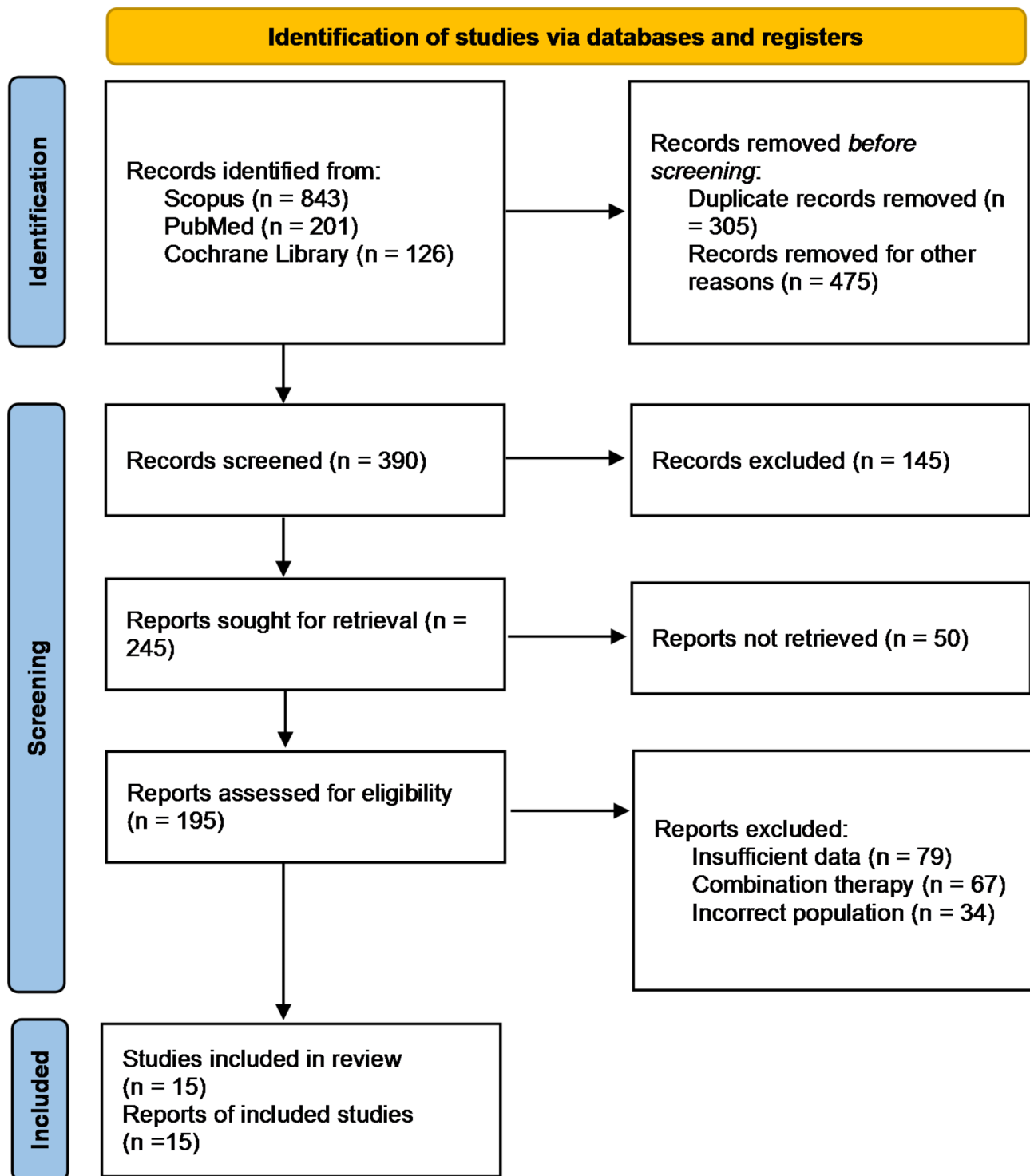


Fig. 1 PRISMA flowchart

Primary outcomes

A total of 13 studies were included in the outcome objective response rate (ORR). A pooled overall event rate of 0.16 ([0.13–0.20]; $p < 0.05$, $I^2 = 48\%$) (Fig. 2). For nivolumab, the ORR was 0.15 [0.11–0.20] and 0.17

[0.13–0.23] for pembrolizumab. Thirteen studies evaluating disease control rate (DCR) found an overall event rate of 0.57 ([0.49–0.65]; $p = 0.07$, $I^2 = 46\%$) (Fig. 3). No difference was seen in DCRs of nivolumab (0.57 [0.46–0.68]),

Table 1 General characteristics of the included studies

Study Name	Type	Sample size	Patient Population	Mean Age	Male %
Pembrolizumab					
Alley 2017 (34)	Phase 1b trial	25	PD-L1 ^b positive MPM	65 (12.6)	68
Metaxas 2018 (37)	Retrospective	93	MPM	63.8 (14)	91
Ahmadzada 2020 (35)	Retrospective	98	MPM	-	92
Popat 2020 (23)	RCT ^c	73	MPM	68.3 (6.5)	79.4
Yap 2021 (24)	Phase 2 trial	118	MPM ^a	64.3 (2.3)	72
Marmarelis 2023 (36)	Retrospective	24	Diffuse MPM	61.7 (14.4)	41.7
Nivolumab					
Okada 2019 (31)	Phase 2 trial	34	MPM	64.3 (8.4)	85
Scherpereel 2019 (21)	Phase 2 trial	63	MPM	71.2 (9.5)	75
Cantini 2020 (39)	Retrospective	107	Pretreated MPM	64 (9.9)	87
Nakamura 2020 (40)	Retrospective	35	Postoperative recurrence MPM	68 (5.2)	88.6
Fennell 2021 (20)	RCT	221	Mesothelioma	69.7 (6.7)	76
Yoneda 2021 (41)	Retrospective	11	MPM	71 (8.8)	72.7
Assie 2022 (38)	Retrospective	109	MPM	69 (7.5)	67.9
Avelumab					
Hassan 2019 (26)	Phase 1b trial	53	Mesothelioma	62.5 (11.3)	60
Durvalumab					
Canvo 2022	Phase 2 trial	69	Mesothelioma	69.9 (8.9)	63.8

pembrolizumab (0.57 [0.44–0.69]), and avelumab (0.58 [0.32–0.81]).

Secondary outcomes

Median progression free survival (mPFS) was assessed in 13 studies. An aggregate mPFS was found to be 4.53 ([3.40–5.65]; $p < 0.00001$, $I^2 = 88\%$) (Fig. 4). No difference was found between the pembrolizumab (5.32 [2.92–7.71]), nivolumab (3.46 [2.51–4.42]), and avelumab (4.10 [1.40–6.80]) subgroups. 6- and 12-month progression free survival was found to be (event rate 0.41 95% CI [0.25–0.59]) (Figure S3) and (event rate 0.18 95% CI [0.11–0.28]) (Figure S4). Similarly, median overall survival (mOS) was found in 14 studies. Pooled mOS was 10.51 ([9.03–12.00]; $p < 0.00001$, $I^2 = 58\%$) across the studies (Fig. 5). No significant difference was observed between pembrolizumab (10.25 [7.94–12.56]), nivolumab

(11.62 [8.97–14.27]), avelumab (10.70 [6.40–15.00]), and durvalumab (7.3 [4.00–10.60]) subgroups. 6- and 12-month overall survival was found to be (event rate 0.70 95% CI [0.60–0.79]) (Figure S5) and (event rate 0.44 95% CI [0.37–0.51]) (Figure S6).

Safety outcomes

Treatment-related adverse events grade 1–5 were found to be nine studies (Table 3). An overall event rate of 0.69 (0.50–0.83) was found (Figure S7). In grades 3–5, the event rate was 0.15 (0.10–0.23) (Figure S8). An overall event rate of immune-related adverse events grade 1–5 was found to be 0.28 (0.15–0.46) (Figure S9) and 0.05 (0.03–0.11) in grades 3–5 (Figure S10).

Meta-regression and publication bias

Meta-regression was performed for the primary outcomes against the following covariates: mean age, mean male sex percentage, percentage of PD-1 positive patients, and percentage of ECOG status 0 patients. For ORR and DCR, none of the covariates were found to be a significant predictor. Bubble plots are added to the supplementary material Figures S11–12. There was no significant publication bias detected in all the outcomes. Results of Egger's regression test is shown in supplementary Table S2.

Discussion

This meta-analysis was performed by pooling all the data of relevant studies to date evaluating safety and efficacy of anti PD-1/PD-L1 immune checkpoint inhibitors as a monotherapy in patients with pre-treated advanced-stage malignant mesothelioma (asMM). In this meta-analysis, we found an objective response rate of 0.16 (0.13–0.20) and a disease control rate of 0.57 (0.49–0.65). Additionally, we observed a median progression free survival of 4.53 (3.40–5.65) and a median overall survival of 10.80 (9.26–12.35). For the safety outcomes, treatment- and immune-related adverse events grade 1–5 had an event rate of 0.69 (0.50–0.83) and 0.28 (0.15–0.46), respectively.

In this meta-analysis, the majority of studies lacked in reporting asbestos exposure in patients with asMM as greater efficacy of anti PD-1/PD-L1 is noted in tumors with an etiology related to carcinogens exposure [41, 42]. Additionally, MM is inherently resistant to cytotoxic chemotherapy [43] and second line treatments have not exclusively shown an increase in overall or progression free survival. The choice of second line agents is based on various factors: choice of patient, response with first-line therapy, and performance status.

The Third Italian Consensus Conference on MM highlighted the need for new treatment options in the second-line setting, as there is currently a lack of approved agents. This situation presents an excellent opportunity

Table 2 Baseline patient and tumor characteristics

Study Name	ECOG ^a			PD-L1 ^b expression		Histology			
	0	1	≥ 2	Pos	Neg	Epithelioid	Biphasic	Sarcomatoid	Not specified
Pembrolizumab									
Alley 2017 (34)	9	16		25	0	18	2	2	3
Metaxas 2018 (37)	11	55	27			67	10	15	1
Ahmadzada 2020 (35)	21	55	18	31	45	74	8	8	8
Popat 2020 (23)	21	51	1	33	36	66			7
Yap 2021 (24)	44	74		77	31	82	9	10	17
Marmarelis 2023 (36)	5	15	1	6	11	18	4	1	1
Nivolumab									
Okada 2019 (31)	13	21		20	12	27	4	3	
Scherpereel 2019 (21)	19	42	0	21	31	52	11		
Cantini 2020 (39)	20	68	6	11	22	78		22	7
Nakamura 2020 (40)	11	21	3			32	2	1	
Fennell 2021 (20)	44	177		60	101	195			
Yoneda 2021 (41)	4	6	1			11			
Assie 2022 (38)	91		14			90	11	8	
Avelumab									
Hassan 2019 (26)	14	39		22	21	43		2	2
Durvalumab									
Canvo 2022 (33)	43	26		22	21	62	4	3	

^aEastern Cooperative Oncology Group

^bProgrammed death-ligand 1

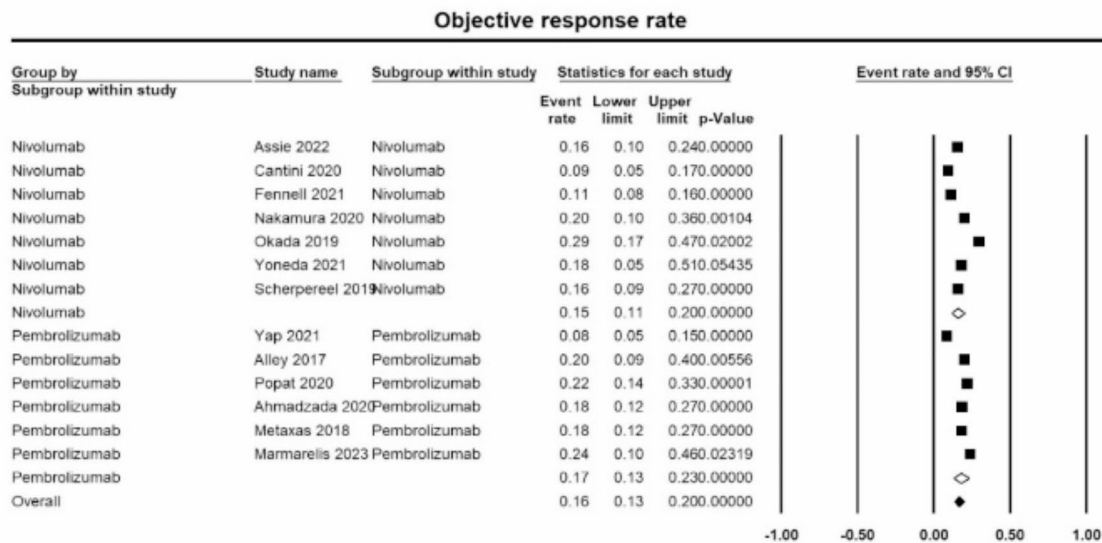


Fig. 2 Forest plot of objective response rate

to evaluate and test novel drugs. In cases where patients are unable to participate in a clinical trial, single-agent chemotherapy can be considered as a treatment option for those who are medically suitable, although best supportive care remains a valid choice [44]. Vinorelbine and gemcitabine monotherapy are most commonly used in practice for second-line treatment of MM as stated by

international guidelines reporting an ORR of 7–16% [45–47]. Moreover, the ESMO clinical practice guidelines suggested the role of platinum-premetrexed or premetrexed alone as a second-line agent as a meta-analysis reported a median overall survival of 7.93 and 7.78 months, respectively [48, 49].

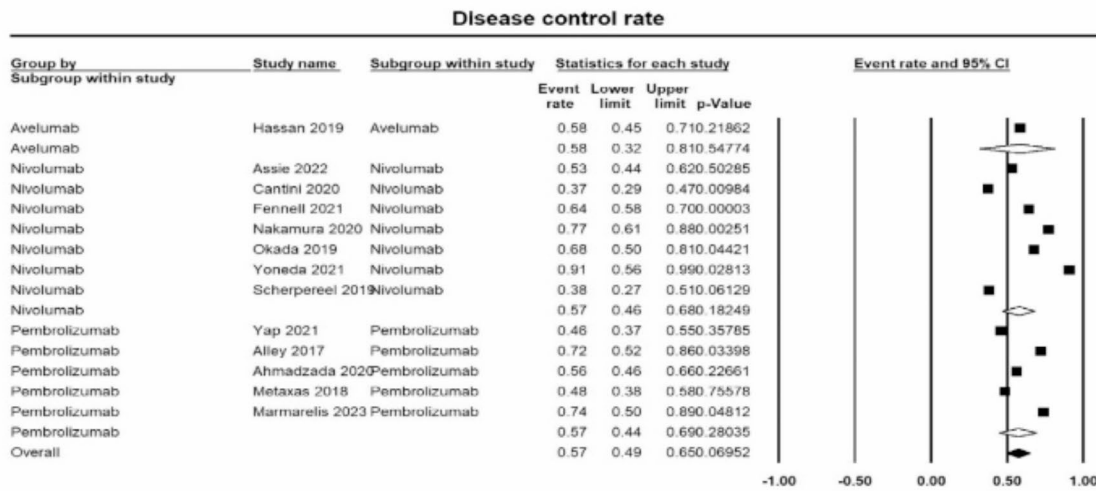


Fig. 3 Forest plot of disease control rate

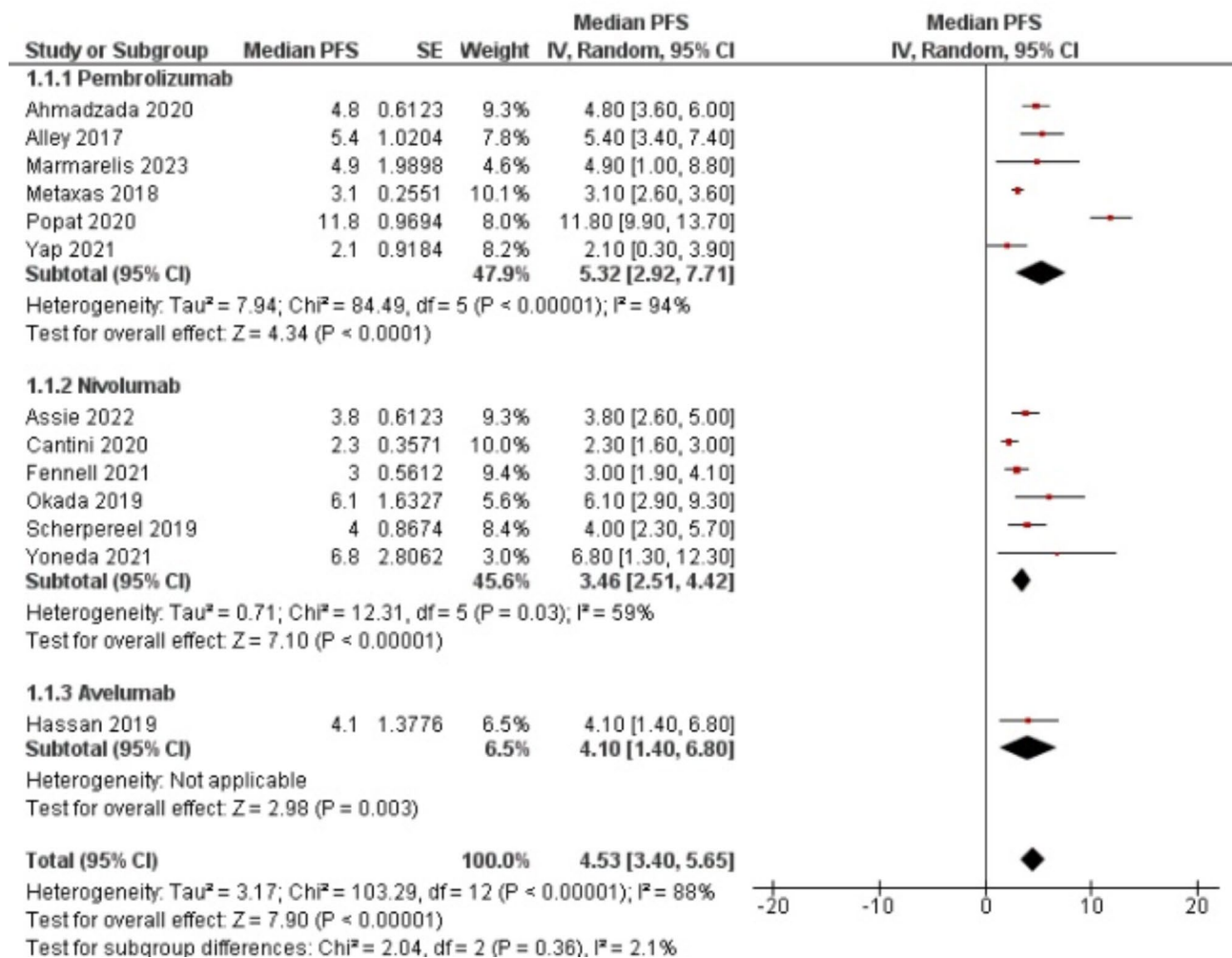


Fig. 4 Forest plot of median progression free survival

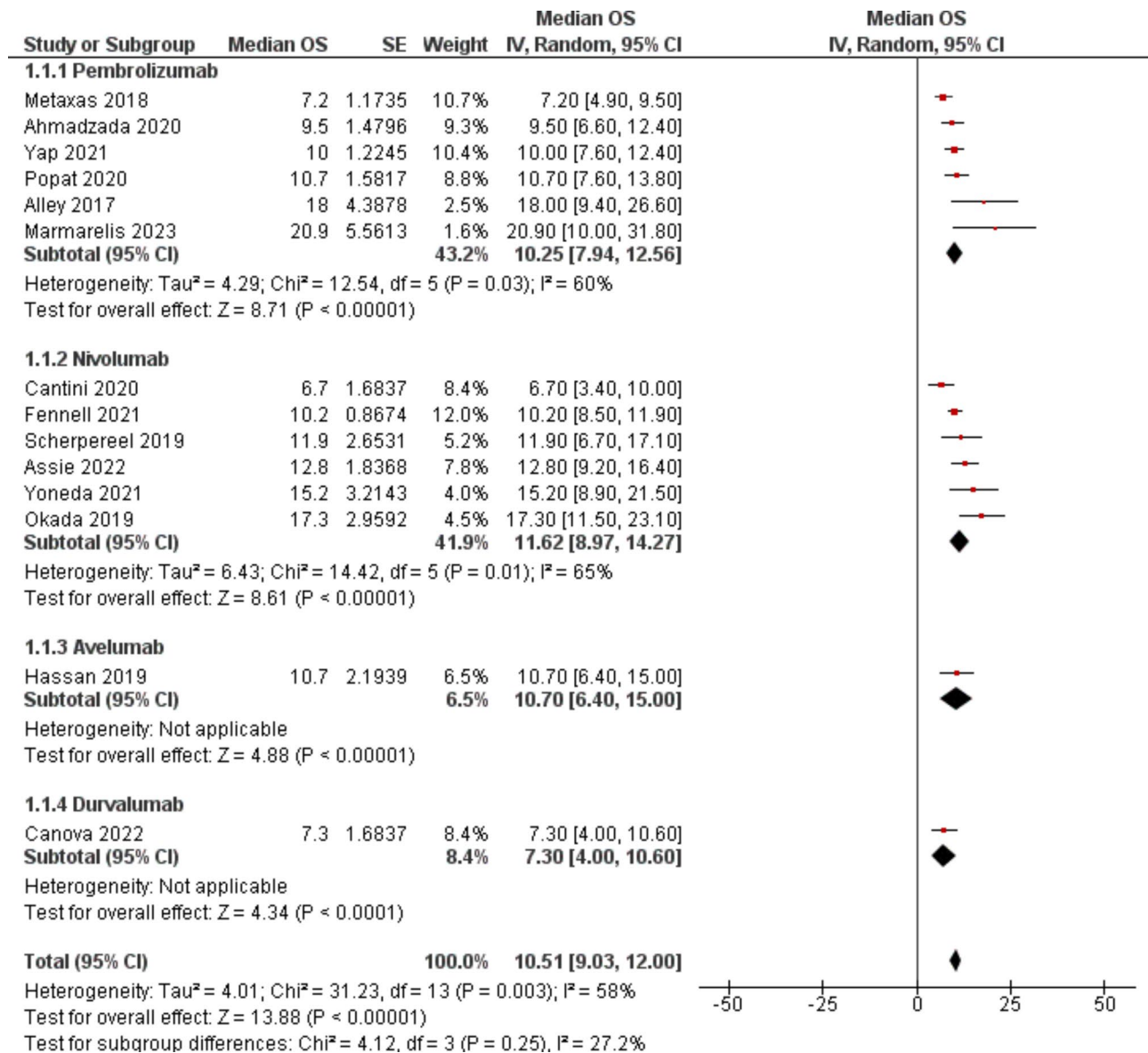


Fig. 5 Forest plot of median overall survival

As a second-line agent, our study found anti-PD1/PD-L1 agents to have an ORR of 16% and a DCR of 57% which is consistent with previous meta-analysis [50]. These findings are also found in the PROMISE-meso phase III trial which found pembrolizumab to have a greater ORR than chemotherapy (22% vs. 6%). Our findings were found to be superior to that of gemcitabine and vinorelbine monotherapy in MM patients [46, 47].

Additionally, we found a median PFS of 4.53 months and a median OS of 10.80 months with no significant difference between pembrolizumab, nivolumab, and avelumab. Previous meta-analysis did not pool these parameters however, they found a similar range of mPFS (2.1 to 5.9 months) and mOS (6.7 to 20.9 months) [50]. These findings are consistent with a recent study by

Marmarelis et al. reporting an mPFS and mOS of 4.9 and 20.9 months, respectively. Median PFS was comparable to studies evaluating vinorelbine monotherapy for MM (4.2 months) [47] however, mOS was significantly better in our study as compared to gemcitabine (13.8 months) and vinorelbine monotherapy (9.3 months) [47, 51].

We also measured progression free and overall survival at 6- and 12-month intervals. The PFS decreased from an event rate of 0.41 to 0.18 and OS decreased from 0.70 to 0.44. This decline in survival rate could be attributed to various factors. With increasing age, there is decreasing patient survival rate with approximately 6% survival in patients between ages 65 to 74 years. Since pleural mesothelioma is more difficult to remove during surgery as they attack chest linings, they have shorter survival rates

Table 3 Treatment- and immune-related adverse events

Subgroup	Treatment-related adverse events grade 1–5 (event rate and 95% confidence interval)	Treatment-related adverse events grade 3–5 (event rate and 95% confidence interval)
Avelumab (26)	0.75 (0.39–0.94)	0.09 (0.02–0.32)
Nivolumab (20,31,32,38)	0.77 (0.60–0.88)	0.17 (0.09–0.30)
Pembro-lizumab (23,24,34,37)	0.56 (0.37–0.74)	0.15 (0.10–0.23)
	Immune-related adverse events grade 1–5 (event rate and 95% confidence interval)	Immune-related adverse events grade 3–5 (event rate and 95% confidence interval)
Avelumab (26)	0.21 (0.04–0.65)	0.05 (0.02–0.15)
Nivolumab (20,32,41)	0.39 (0.16–0.67)	0.02 (0.00–0.1)
Pembrolizumab (24,34,35)	0.22 (0.08–0.46)	0.07 (0.04–0.11)

as compared to peritoneal mesothelioma. This could explain the decrease in survival rates since the majority of our studies had patients with pleural mesothelioma [52, 53].

In our study, we found a 69% occurrence of grade 1–5 treatment-related adverse events grade, however, only 15% were of a grade 3 or above. Similarly, serious immune-related adverse events were found in only 5% of the patients with asMM. These findings are consistent with RCTs with pembrolizumab and nivolumab monotherapies as interventions [20, 23]. Previous meta-analysis on anti PD-1/PD-L1 agents did not take adverse effects of the drugs into account [50]. Through meta-regression, our study did not find PD-L1 expression to be a significant predictor of increased ORR or DCR. These findings differ from those found by Cantini et al., as they demonstrated PD-L1 positive tumors to be linked with higher ORR however, no difference in PFS or OS was seen [38]. These results are also different from those of the meta-analysis conducted by Tagliamento et al. They found PD-L1 positive tumors to be more responsive to single-agent immunotherapy [50]. The reason for this difference could be as we conducted meta-regression to derive a linear relationship, while they performed subgroup analysis. Regardless, trials are highly heterogeneous when accounting for PD-L1 assessment as inconsistent immunohistochemical clones and cut-offs were applied. Moreover, a recent study found that the neoantigenic potential of MM could be attributed to structural chromosomal rearrangements [54]. Due to lack of specific data, meta-regression could not be performed based on the histology of the tumor.

This study highlights PD-1/PD-L1 inhibitors as promising second-line treatments for advanced-stage malignant mesothelioma (MM), demonstrating efficacy and

safety profiles that may improve patient outcomes. For clinicians, these results offer evidence-based support for integrating ICIs into treatment strategies for patients with prior therapies. Significant gaps remain, particularly around biomarkers like PD-L1 expression as predictors of response. Inconsistent study designs and PD-L1 assessment methods underscore the need for standardized biomarker evaluation. Future multi-institutional studies should address these gaps, focusing on MM's diverse subtypes and molecular characteristics. Over the next five years, we anticipate advances in combination IO therapies and personalization based on molecular profiling. These developments could transform the treatment landscape of MM, offering new, more effective options and a better quality of life for patients.

Our meta-analysis has some limitations. Firstly, we were restricted to a single-arm meta-analysis without any comparator as phase III trials are underway and results are yet to be posted. However, this study provides landmark results for pretreated asMM patients, which can provide a basis for future clinical trials. Secondly, there was moderate heterogeneity in several outcomes which was due to the retrospective nature of the studies. In this review, we could only search three major electronic databases/ EMBASE and PsycINFO could not be searched due to lack of access. Moreover, most of the studies were retrospective cohort studies which could potentially add biases to our results.

Conclusion

In this meta-analysis we found that anti-PD1/PD-L1 agents could be useful in pretreated asMM patients regardless of the current known predictive factors of treatment. Our study found relatively lower incidence of severe adverse events, greater ORR and DCR as compared to other second-line agents for MM and at least comparable, if not better, mOS and MPFS.

Abbreviations

MM	Malignant mesothelioma
ICIs	Immune checkpoint inhibitors
CTLA-4	cytotoxic T lymphocyte antigen-4
PD-1	programmed cell death protein-1
asMM	advanced-stage malignant mesothelioma
PD-L1	programmed death ligand 1
mPFS	median progression-free survival
mOS	median overall survival
RCTs	randomized controlled trials
ORR	objective response rate
DCR	disease control rate
mPFS	median progression free survival

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12885-024-13127-3>.

Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions

AZ, AAR, and AM conceived the idea; A.M, AZ, AAR, AA, and AJK did write up of the manuscript; and finally, A.A, M.J.T, O.N.S, and AZ reviewed and revised the manuscript for intellectual content critically. All authors approved the final version of the manuscript.

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Data availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Declarations**Ethics approval and consent to participate**

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Hameed Latif Hospital, Lahore, Pakistan

²Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan

³Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan

⁴Lahore General Hospital, Lahore, Pakistan

⁵Faculty of Medicine, Al-Quds University, Jerusalem, Palestine

⁶Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California, San Diego, CA, USA

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