Barw Medical Journal | 2023;1(3):6-13
Journal home page: https://barw.krd/index.php/BMJ

Systematic Review

Pembrolizumab (Anti-PD-1) Immunotherapy in Malignant Pleural Mesothelioma: A Systematic Review of the Current Literature

Rebaz M. Ali[1], Fahmi H. Kakamad[2*], Hiwa O. Abdullah[3], Shalaw H. Abdulla[1], Shaho F. Ahmed[4], Bnar J. Hama Amin[5], Marwan N. Hassan[3], Sabah J. Hasan[4], Hussein M. Hamasalih[3], Berun A. Abdalla[3], Rawezh Q. Salih[4], Gasha S. Ahmed[6]

1. *Hiwa Cancer Hospital, Sulaimani Directorate of Health, Sulaimani, Kurdistan, Iraq.*
2. *College of Medicine, University of Sulaimani, Madam Mitterrand Street, Sulaimani, Kurdistan, Iraq*
3. *Smart Health Tower, Scientific Affairs Department, Madam Mitterrand Street, Sulaimani, Kurdistan, Iraq*
4. *Smart Health Tower, Madam Mitterrand Street, Sulaimani, Kurdistan, Iraq*
5. *Shar Hospital, Department of Medicine, Sulaimani, Kurdistan, Iraq*
6. *Faculty of Medicine, Tokat Gaziosmanpasa University, Tokat, Turkey*

[*] ***Corresponding author***: *fahmi.hussein@univsul.edu.iq (F.H. Kakamad). Doctor City, Building 11, Apartment 50, Zip code: 46001, Sulaimani, Iraq*

Keywords:
Pembrolizumab
Malignant mesothelioma
Pleural cancer
Immunotherapy
PD-1 inhibitor

Received: July 10, 2023
Revised: July 19, 2023
Accepted: July 23, 2023
First Published: July 27, 2023

Citation: Ali RM, Kakamad FH, Abdullah HO, Abdulla SH, Ahmed SF, Hama-Amin BJ. Pembrolizumab (Anti-PD-1) immunotherapy in malignant pleural mesothelioma: A systematic review of the current literature. Barw Medical Journal. 2023;1(3):6-13. https://doi.org/10.58742/bmj.v1i2.34

Abstract

Introduction

Malignant pleural mesothelioma is an infrequent and aggressive type of cancer that is difficult to treat, and standard therapies have shown limited effectiveness. There have been recent advances in the development of targeted therapies for malignant pleural mesothelioma, including immunotherapy with pembrolizumab.

Methods

This is a systematic review of the current role of pembrolizumab in the treatment of this disease. A systematic search was conducted through the databases and search engines. The eligible studies to be included were those that primarily focused on the outcomes of treating this disease with pembrolizumab, regardless of study design, line of therapy, mode of therapy, and ECOG performance status.

Results

After the initial and full-text screenings, 15 studies were reviewed. The number of cases was 454 with a mean age of 68.13 years, of which males (79.7%) were the predominant gender. Most of the cases were affected by epithelioid mesothelioma (76.7%). Pembrolizumab had been used as the first line of treatment in 62 (13.7%) cases. In 92.73% of cases, the therapy mode was pembrolizumab monotherapy. A total of 68 different adverse events were recorded. The most commonly associated adverse events were fatigue (14.8%), pruritis/rash (13.7%), and diarrhea (9.7%). Two patients died due to adverse events. The overall objective response was 17.8%, stable disease was 35.7%, progression-free survival was about 47.6% with a mean of 4.73 months, and 117 cases (25.8%) could reach treatment-related survival.

Conclusion

Pembrolizumab can serve as a viable alternative in the management of malignant pleural mesothelioma, offering satisfactory outcomes and acceptable safety profiles.

1. Introduction

Pembrolizumab is a monoclonal antibody that targets the programmed death-1 (PD-1) receptor on T cells and is used in the treatment of various types of cancer [1]. PD-1 is a key immune checkpoint that plays a critical role in regulating the immune response and preventing autoimmunity. However, cancer cells can hijack this pathway and use it to evade the immune system. Pembrolizumab blocks the PD-1 receptor, enabling T cells to recognize and attack cancer cells [1,2]. Pembrolizumab has been approved for use in several types of cancer, including melanoma, head, and neck squamous cell carcinoma, urothelial carcinoma, classical Hodgkin's lymphoma, non-small cell lung cancer, and gastric cancer. It has also shown promising results in clinical trials for the treatment of other cancer types, such as hepatocellular carcinoma and renal cell carcinoma [3-10]. Malignant pleural mesothelioma (MPM) is an infrequent and aggressive type of cancer that emerges in the lining of the lungs (pleura) and is primarily caused by exposure to asbestos [11]. Symptoms of MPM can include chest pain, shortness of breath, persistent coughing, and fatigue, but these can often be mistaken for other respiratory illnesses. The MPM is often not diagnosed until it has reached an advanced stage. Unfortunately, MPM is notoriously difficult to treat, and standard therapies such as surgery, radiation, and chemotherapy have shown limited effectiveness [1,12-14]. Despite these challenges, there have been recent advances in the development of targeted therapies for MPM, including immunotherapy with pembrolizumab [1,2].

The aim of this study is to review the current role of pembrolizumab in the treatment of MPM.

2. Methods

2.1. Study design

This study was a comprehensive systematic review of the studies focusing on the treatment of MPM with anti-PD-1 pembrolizumab. It was conducted in accordance with the PRISMA 2020 guidelines.

2.2. Data sources and search strategy

A systematic search was conducted in eligible databases and search engines like Web of Science, PubMed/MEDLINE, EMBASE, Science Direct, CINAHL, the Cochrane Library, and Google Scholar. The search keywords were (pembrolizumab OR Keytruda OR MK-3475 OR lambrolizumab OR anti-PD-1 OR PD-1 inhibitor) AND (pleura OR pleural OR pleurae) AND (mesothelioma OR asbestos cancer OR cancer OR carcinoma OR tumor OR tumors OR cancers OR malignancy OR malignancies OR neoplasm OR malignance OR cancerous OR mesothelium).

2.3. Eligibility criteria

The eligible studies to be included were those that primarily focused on the outcomes of treating MPM with pembrolizumab, regardless of study design, line of therapy, mode of therapy (either monotherapy or combination), and ECOG performance status. Studies that had only abstracts available, pre-prints and non-pleural mesothelioma were not included. All studies' publishers were assessed for reliability (fully peer-reviewed) using Kscien's List [15]. A total of 54 studies were found in the search, of which 28 were excluded prior to the initial screening (only abstract = 15, duplicate = 11, non-article = 2). After the initial and full-text screenings, 15 studies remained eligible (Figure 1) [1,14,16-28].

2.4. Study selection and data items

Several authors initially screened the titles and abstracts of the identified studies. Subsequently, they conducted a full-text screening to assess whether the studies met the inclusion criteria. In case of any discrepancies, a third author intervened to resolve them.

The variables extracted from the studies included the study design, number of cases, demographics, histological subtypes of mesothelioma, treatment lines, and modes, previous treatment, doses, and modes of administration, adverse events, treatment interruption due to adverse events, death due to adverse events, objective response (OR), progression-free survival (PFS), stable disease (SD), and overall survival (OS).

2.5. Data analysis and synthesis

The Statistical Package for the Social Sciences software (version 25) was utilized to analyze the data qualitatively (descriptive analysis). The data were represented as frequencies, mean, and percentages.

3. Results

The review included 15 publications: one randomized controlled trial, three non-randomized controlled trials, two cohort studies, two case series, and seven case reports. The total number of cases was 454 with a mean age of 68.13 years (calculated as the mean of means), of which males (79.7%) were the predominant gender (Tables 1 and 2). Most of the cases were affected by epithelioid mesothelioma (76.7%), followed by sarcomatoid mesothelioma (7.9%). Regarding the previous treatment prior to pembrolizumab, platinum pemetrexed was more commonly used (28.2%), followed by carboplatin/pemetrexed (25.3%), and cisplatin/pemetrexed (20.5%). Pembrolizumab was used as the first line of treatment in only 62 (13.7%) cases. In 92.73% of cases, the therapy mode was pembrolizumab monotherapy. The second frequent mode was a combination of pembrolizumab and nintedanib (Table 2). A total of 68 different adverse events were recorded. The most commonly associated adverse events were fatigue (14.8%), pruritis/rash (13.7%), and diarrhea (9.7%) (Table 3). Adverse events caused temporary and permanent treatment interruptions equally (4.6%). Only two cases (0.4%) died due to the adverse events; one due to dyspnea, lung infiltration, and worsening pleural effusion, and the other due to cardiopathy. An OR was achieved in 17.8% of the patients (partial = 16.7%, complete = 1.1%), and SD was noticed in 35.7% of cases. In addition, PFS was about 47.6% with a mean

of 4.73 months, and 117 cases (25.8%) could reach treatment-related survival (Table 4).

4. Discussion

The MPM is a cancer form that develops in the pleural serous membrane lining due to long-term exposure to environmental silicate minerals like asbestos. Persistent exposure to asbestos microparticles causes inflammation, inflammatory macrophage recruitment, formation of an immunosuppressive protumoral microenvironment, and pathological neoangiogenesis with hypoxia. It ultimately transforms serous cells into an aggressive phenotype, leading to the development of metastatic disease [17]. The disease can be categorized into three histological subtypes: epithelioid, sarcomatoid, and mixed (biphasic). The epithelioid subtype is associated with a better prognosis and a better response to treatment, affecting approximately 50–60% of patients. On the other hand, the sarcomatoid subtype has a lower probability of responding to therapy and occurs in about 20% of patients. Furthermore, several remarkable predictors are linked to improved survival in mesothelioma, including female gender, being under 45 years old, undergoing a combination of chemotherapy and radiation therapy in addition to surgery, and having no history of smoking [21].

The MPM is commonly diagnosed at an advanced stage, making it challenging to effectively treat. Common treatment approaches including surgery, radiation, and chemotherapy have demonstrated limited efficacy in managing the disease [1,12-14]. At present, the FDA has exclusively approved the cisplatin/pemetrexed combination regimen as the primary treatment option for MPM [21]. In a phase III trial comparing pemetrexed/cisplatin to cisplatin alone, the pemetrexed/cisplatin arm exhibited a superior median OS of 12.1 months, whereas the cisplatin arm demonstrated a median OS of 9.3 months [29].

In patients with MPM, angiogenesis inhibitors like bevacizumab have also indicated anti-tumor activity. In a phase III trial evaluating the use of bevacizumab for unresectable MPM, the cisplatin/pemetrexed/bevacizumab treatment group showed a median OS of 18.8 months in comparison to the cisplatin/pemetrexed group, which yielded a median OS of 16.1 months [30]. Even though the utilization of this treatment was

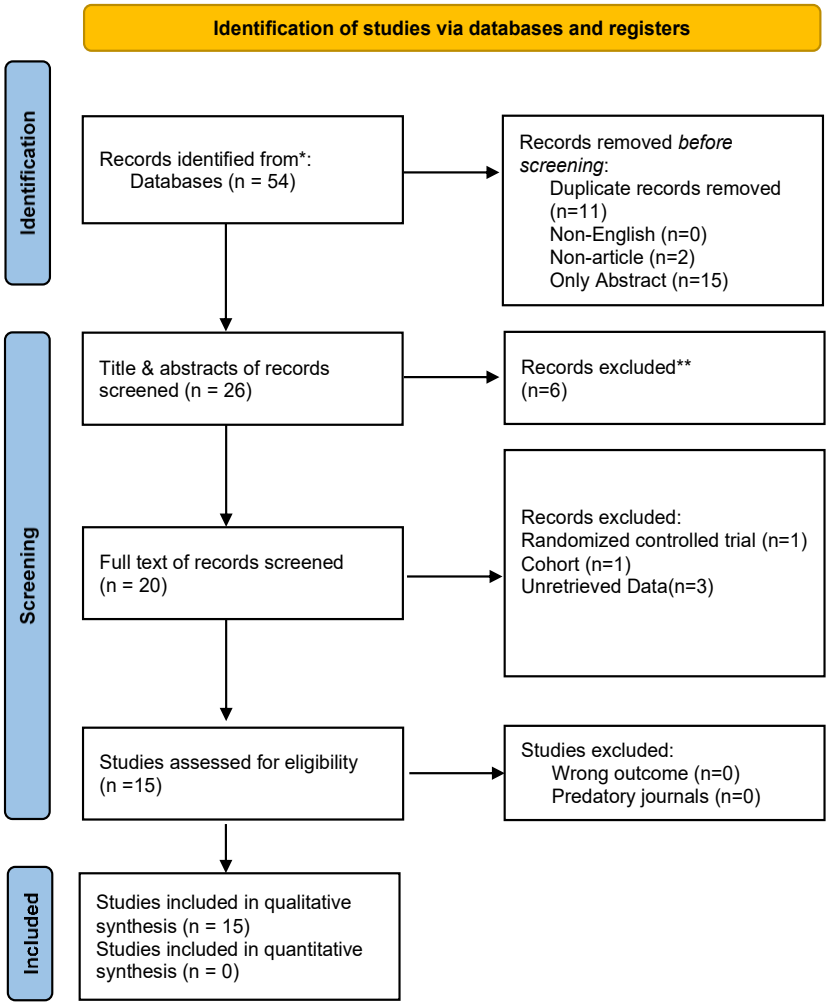

Figure 1. Study selection PRISMA flow chart.

Table 1. The general characteristics of the studies on the treatment of MPM with pembrolizumab.

Author	Study design	N. cases	Gender		Age	Histological subtype				Therapy Mode
			M	F		Biphasic	Epithelioid	Sarcomatoid	Mixed/ Unknown	
Alley et al. [1]	NRCT	25	17	8	65[a]	2	18	2	0/3	MT
Ahmadzada et al. [14]	Cohort	95	87	8	70[a]	8	74	8	0/5	MT
Popat et al. [16]	RCT	73	58	15	67.7[a]	0	66	0	0/7	MT
Danlos et al. [17]	NRCT	30	20	10	69[a]	4	25	1	0	C
Yap et al. [18]	NRCT	118	85	33	68[a]	9	82	10	0/17	MT
Metaxas et al. [19]	Cohort	93	85	8	68[a]	0	67	15	10/1	MT
Shalata et al. [20]	Case series	1	0	1	50	0	1	0	0	C
Zhou et al. [21]	Case series	12	5	7	71[b]	0	11	0	1/0	MT
Bickel et al. [22]	Case report	1	1	0	62	1	0	0	0	MT
Hearon et al. [23]	Case report	1	1	0	66	0	1	0	0	MT
Mampuya et al. [24]	Case report	1	1	0	72	0	0	0	0/1	C
Minchom et al. [25]	Case report	1	0	1	77	0	1	0	0	MT
Rittberg et al. [26]	Case report	1	1	0	68	0	1	0	0	C
Baldauf et al. [27]	Case report	1	0	1	61	0	0	0	0/1	MT
Schiopu et al. [28]	Case report	1	1	0	75	0	1	0	0	MT

** RCT, Randomized controlled trial; NRCT, Non-Randomized controlled trial; [a], Mean age; [b], Median age; MT, Monotherapy; C, Combination*

Table 2. The baseline characteristics of the cases treated with pembrolizumab.

Characteristics	N. patients (%)
Age (mean of means) (years)	68.13
Sex	
Male	362 (79.7%)
Female	92 (20.3%)
Histological subtypes of mesothelioma	
Epithelioid	348 (76.7%)
Sarcomatoid	36 (7.9%)
Biphasic (Mixed)	35 (7.7%)
Not-reported	35 (7.7%)
Previous treatment	
Platinum pemetrexed	128 (28.2%)
Carboplatin/pemetrexed	115 (25.3%)
Cisplatin/pemetrexed	93 (20.5%)
Radiotherapy	52 (11.5%)
Pemetrexed	42 (9.3%)
Carboplatin	23 (5%)
Cisplatin	23 (5%)
Gemcitabine	18 (4%)
Bevacizumab	16 (3.5%)
Vinorelbine	12 (3%)
Surgery	10 (2.2%)
Cisplatin/pemetrexed and carboplatin/pemetrexed	8 (2%)
Carboplatin/Gemcitabine	7 (1.5%)
Platinum gemcitabine	4 (0.9%)
Carboplatin/Pemetrexed + Bevacizumab	4 (0.9%)
Cisplatin/pemetrexed + durvalumab	1 (0.2%)
NGR-hTNF	1 (0.2%)
CB 839 glutaminase inhibitor	1 (0.2%)
Non-reported	118 (26%)
Therapy line of pembrolizumab	
1	62 (13.7%)
≥2	392 (86.3%)
Dose and mode of administration	
200 mg, Q3W	323 (71.14%)
10 mg, Q2W	26 (5.72%)
Varying dose, Q2W and Q3W	93 (20.5%)
Non-reported	12 (2.64%)
Therapy mode	
Monotherapy	421 (92.73%)
Combination with nintedanib	30 (6.61%)
Combination with radiotherapy	2 (0.44%)
Combination with lenvatinib + gemcitabine +Ipilimumab	1 (0.22%)

Table 3. The adverse events of the treatment with pembrolizumab

Adverse events	N. patients (%)
Fatigue	67 (14.8%)
Pruritis/ rash	62 (13.7%)
Diarrhea	44 (9.7%)
Arthralgia	29 (6.4%)
Nausea	27 (6%)
Loss of appetite	24 (5.3%)
Pneumonitis	24 (5.3%)
Dyspnea	18 (4%)
Hypothyroidism	17 (3.7%)
Vomiting	14 (3%)
Dry skin	12 (2.6%)
Colitis	12 (2.6%)
Rash maculopapular	11 (2.4%)
Fever	9 (2%)
Cough	8 (1.8%)
CNS+PNS* disorder	7 (1.5%)
Hyperthyroidism	6 (1.3%)
Nephrotic syndrome	6 (1.3%)
Constipation	5 (1.1%)
Hypomagnesemia	5 (1.1%)
Dry mouth	5 (1.1%)
Anemia	4 (0.9%)
Cardiac disorder	4 (0.9%)
Aspartate aminotransferase increased	4 (0.9%)
Alanine aminotransferase increased	4 (0.9%)
Lipase increased	4 (0.9%)
Mucositis	4 (0.9%)
Hepatitis	4 (0.9%)
Creatine Phosphokinase increased	3 (0.7%)
Dyspepsia	3 (0.7%)
Weight loss	3 (0.7%)
Musculoskeletal stiffness	3 (0.7%)
Gamma-glutamyl Transferase (GGT) increased	3 (0.7%)
Chest pain	2 (0.4%)
Mucosal inflammation	2 (0.4%)
Headache	2 (0.4%)
Paresthesia	2 (0.4%)
Polyarthralgia	2 (0.4%)
Scleroderma	2 (0.4%)
Thyroiditis	2 (0.4%)
Myasthenia Gravis	2 (0.4%)
Synovitis	2 (0.4%)
Abnormal thyroid function test	2 (0.4%)
Creatinine increased	1 (0.2%)
Rhabdomyolysis	1 (0.2%)
White blood cell count decreased	1 (0.2%)
Vitreous floaters	1 (0.2%)
Thrombosis	1 (0.2%)
Thrombocytopenia	1 (0.2%)
Pleuritic pain	1 (0.2%)
Platelet count decreased	1 (0.2%)
Neutrophil count decreased	1 (0.2%)
Myalgia	1 (0.2%)
Irritability	1 (0.2%)
Iridocyclitis	1 (0.2%)
Infusion-related reaction	1 (0.2%)
Hypocalcemia	1 (0.2%)
Haemoglobin decreased	1 (0.2%)
Dysgeusia	1 (0.2%)
Cancer pain	1 (0.2%)
Blood alkaline phosphatase increased	1 (0.2%)
Balance disorder	1 (0.2%)
Lung infiltration	1 (0.2%)
Worsening pleural effusion	1 (0.2%)
Diabetes mellitus	1 (0.2%)
Minimal change disease	1 (0.2%)
Nonsystemic vasculitic mononeuritis multiplex (NSVM)	1 (0.2%)
Myocarditis	1 (0.2%)

**CNS+PNS, central and peripheral nervous system.*

Table 4. The outcomes of treating cases of MPM with pembrolizumab

Characteristics	N. patients (%)
Treatment interruption due to adverse events	
None	305 (67.2%)
Temporary	21 (4.6%)
Permanent	21 (4.6%)
Death due to adverse events	
Dyspnea, lung infiltration and worsening pleural effusion	1 (0.2%)
Cardiopathy resulting in thrombosis and mesenteric ischemia	1 (0.2%)
Objective response	
Partial response	76 (16.7%)
Complete response	5 (1.1%)
Stable disease	162 (35.7%)
Progression-free survival	216 (47.6%)
Mean and median duration of progression-free survival (Min-Max), months	4.73 & 4.8 (2.1 – 9)
Overall survival (cases alive till the end of the study)	117 (25.8%)

linked to a substantial level of toxicity, among the individuals who received bevacizumab, 71% reported experiencing grade 3–4 adverse events, whereas the percentage was 62% for those who did not receive bevacizumab [30]. In a randomized phase II trial, nintedanib, an oral triple receptor tyrosine kinase inhibitor, showed notable efficacy when used in combination with chemotherapy for treating MPM [31]. However, this positive outcome could not be replicated in a later phase III trial [32]. By reviewing the included studies in this systematic review, it was found that the mean age of the patients was 68.13 years, with a predilection towards males. The epithelioid subtype accounted for the majority (76.7%) of histologic subtypes, while the sarcomatoid subtype constituted approximately 7.9%. These findings revealed a higher percentage of epithelioid and a lower percentage of sarcomatoid subtypes compared to a previous study that reported epithelioid to be around 50-60% and sarcomatoid to be approximately 20% [21]. Over 86% of the patients in this review had previously undergone various treatment regimens without achieving satisfactory outcomes. Among them, the most commonly administered regimen was platinum pemetrexed, which was received by 28.2% of the patients. This was followed by carboplatin/pemetrexed (25.3%) and cisplatin/pemetrexed (20.5%). Only 13.7% of the cases had been directly treated with pembrolizumab, highlighting the need for further studies to investigate the efficacy of this treatment as a first-line therapy for patients with MPM.

Despite all of that, there are currently no approved treatments available for patients with relapsed MPM after being treated with standard first-line therapy [18]. Gemcitabine and vinorelbine are often considered potential second-line treatment options. Recently, the use of immune checkpoint inhibitors (ICI) has gained interest as a promising approach for managing MPM [24]. The introduction of ICI has revolutionized the treatment approach for patients with metastatic cancer. However, it is important to acknowledge that only a minority of patients with different tumor types show a positive response to these therapies. Investigating PD-L1 inhibitors in MPM has shown overall response rates (ORR) ranging from 10% to 29%. Ongoing endeavors are focused on improving therapeutic outcomes by synergistically combining immunotherapy with classic oncological interventions such as chemotherapy, radiotherapy, and anti-angiogenic therapy [24].

PD-1 is a complex protein found on activated T lymphocytes that functions as an inhibitory receptor. When tumor cells express the corresponding ligands, known as PD-L1, and engage with these receptors, it causes the suppression of tumor-specific T effector cells, permitting the tumor to evade immune detection. By binding to PD-1, pembrolizumab, a humanized IgG4 antibody, disrupts the inhibitory interaction between T cells and the tumor microenvironment (TME) at this specific immune checkpoint. This blockade leads to an enhancement of the immune response against the tumor, facilitating a more potent antitumor reaction by T cells [22,23]. Compared to the standard burdensome nine-month trimodal regimen with its potential for severe complications, the use of this ICI as the primary treatment option appeared preferable to both the physician and the patient. Furthermore, the positive response of MPM to pembrolizumab persisted even after discontinuation of the drug, as previously observed in patients with melanoma [23].

Previous clinical studies have provided evidence supporting the effectiveness and safety of pembrolizumab in individuals with advanced MPM, particularly those who have undergone prior chemotherapy without experiencing improvement [1,18,19]. In the KEYNOTE-028 phase Ib trial conducted by Alley et al., it was observed that out of 25 patients with PD-L1-positive MPM who had previously not responded to standard therapy, five individuals achieved a partial metabolic response (PMR) when treated with pembrolizumab. Furthermore, 13 patients (52%) experienced stable disease and an overall disease control rate (DCR) of 72% with a median PFS of 5.4 months was achieved [1]. In a study conducted by Metaxas et al., a group of 93 patients with MPM who received palliative treatment with pembrolizumab as a first-line or second-line therapy was examined. Among the included cases, 16 individuals (17.2%) achieved a PMR, and one patient (1%) achieved a complete metabolic response, resulting in an ORR of 18% with a median PFS of 3.1 months [19]. Desai et al. conducted a phase II trial evaluating pembrolizumab in a population of 65 patients with malignant mesothelioma, including 56 individuals with pleural involvement, who had experienced disease progression after platinum/pemetrexed chemotherapy. The results showed that 19% of the cases achieved a PMR, and 47% had stable disease, with a DCR of 66% [33].

Another study showed that the combined administration of pembrolizumab and radiotherapy can result in a favorable response in cases of MPM [24]. In a case managed by Mampuya et al., following an initial partial response to pembrolizumab, the patient experienced disease progression in the right mediastinum and pleura after one year. While pembrolizumab treatment was ongoing, palliative radiotherapy was administered to the mediastinum. Remarkably, the patient exhibited a systemic abscopal response in the non-irradiated pleural areas. The authors considered the observed response to be an abscopal effect, as it occurred following disease progression despite 20 cycles of pembrolizumab. This suggested that radiotherapy triggered a systemic immune response. The upregulation of PD-L1 induced by radiation was mediated through the increased production of IFNc by T cells that infiltrated the TME after radiotherapy. Consequently, this caused the expression of PD-L1 on tumor cells. Thus, the concurrent application of radiotherapy and an anti-PD-L1 antibody might have circumvented tumor T-cell exhaustion, ultimately enhancing the potential for an effective immune response against the tumor [24]. The combination of pembrolizumab (200 mg every three weeks (Q3W)) and nintedanib (150 mg) has also shown remarkable antitumor activity and manageable toxicity in MPM cases who have not received prior immunotherapy and have been refractory to platinum-based chemotherapy as the first-line treatment [17].

Another study suggested that the administration of pembrolizumab as monotherapy in MPM patients was deemed safe. Nonetheless, the authors mentioned that not all patients could get benefit from this therapeutic approach [14]. This assumption aligns with the outcomes of phase III prospective randomized PROMISE-Meso trial [16]. The results of the trial demonstrated that there was no improvement in PFS when using pembrolizumab compared to chemotherapy in patients with MPM. In the trial, 144 patients with relapsed MPM were

randomly assigned in a 1:1 ratio. One group received a fixed dose of 200 mg pembrolizumab intravenously (Q3W) (n=73), while the other group received chemotherapy, which consisted of gemcitabine (1000 mg/m2 - Q3W), vinorelbine (30 mg/m2 - Q3W), or vinorelbine (60 or 80 mg/m2 - Q3W) (n=71). The PFS was 2.5 months for the pembrolizumab group, whereas it was 3.4 months for the chemotherapy group. In addition, the grade 3 treatment-related adverse events were similar for both groups [16].

Out of the studies reviewed in this review, pembrolizumab monotherapy was the predominant therapy mode. However, a combination of pembrolizumab and nintedanib was utilized in 30 cases, pembrolizumab with radiotherapy in 2 cases, and pembrolizumab in combination with lenvatinib, gemcitabine, and ipilimumab in one case, respectively. The effectiveness of these combination therapies in treating MPM seems to demand further investigation, particularly through trials with larger sample sizes. The most common associated adverse events were fatigue, pruritus/rash, and diarrhea. Unfortunately, we were unable to classify the adverse events precisely based on their grades, as the grades were not specified in all studies. Treatment interruptions due to adverse events in the management with pembrolizumab were found to occur in 9.2% of cases, with 4.6% of those interruptions being permanent due to the high grade of the adverse events. Among the adverse events, two cases resulted in fatalities. One case involved dyspnea, lung infiltration, and worsening pleural effusion, while the other involved cardiopathy leading to thrombosis and mesenteric ischemia. This systematic review showed that the overall OR of MPM to pembrolizumab was 17.8%, with 16.7% partial and 1.1% complete responses. Stable disease, PFS, and OS were achieved in 35.7%, 47.6%, and 25.8%, respectively. The median duration of PFS was 4.8 months.

Considering the relatively underwhelming results of the PROMISE-Meso trial [16], two general strategies have been proposed to enhance patient outcomes. The first approach entails combining PD-1 or PD-L1 inhibition with other treatment modalities with the aim of augmenting the efficacy of the overall therapeutic approach. Positive outcomes were observed in both mesothelioma and other tumor types when immunotherapy was combined with chemotherapy or when different ICIs were targeted in combination [34]. The second strategy involves identifying individuals who are more likely to benefit from immunotherapy as a standalone treatment. In MPM cases, the expression of PD-L1 has been proposed as an unfavorable prognostic biomarker, particularly in the nonepithelioid subtype [35]. In contrast, patients with strong PD-L1 expression (≥50%) have shown a noteworthy association with a higher ORR (44%) and an increased DCR (89%) [19]. Other scholars also confirmed that patients who had a PD-L1 tumor proportion score of ≥ 1% demonstrated a greater likelihood of responding positively to pembrolizumab treatment. Moreover, these individuals tended to experience prolonged PFS and OS when compared to those who did not show PD-L1 staining [14,36]. Alley et al. reported that pembrolizumab demonstrated notable clinical effectiveness in patients with PD-L1-positive MPM. Moreover, the treatment exhibited a manageable toxicity and safety profile, as evidenced by the absence of treatment-related mortality and no discontinuations caused by treatment-related adverse events [1]. However, it is worth noting that responses to pembrolizumab have also been observed in MPM patients, regardless of their PD-L1 status. The findings of the Yap et al. study have shown antitumor activity in both positive and negative PD-L1 MPM patients [18]. Currently, no definitive correlation has been established between PD-L1 expression and the response to immunotherapy involving PD-1 or PD-L1 checkpoint blockade in MPM [14]. A study discussed that the most favorable prognostic biomarker during and after treatment for MPM was a significant reduction in tumor FDG avidity on interim positron emission-computed tomography scans. This reduction has been demonstrated to correlate with improved PFS and OS in MPM patients who received non-surgical treatment [37]. Given the heterogeneity of the included studies, variations in study designs, and the use of different detection methods, it was not possible for us to draw any conclusions regarding the role of PD-L1 expression as a biomarker in determining the effectiveness of MPM.

5. Conclusion

Pembrolizumab can serve as a viable alternative in the treatment of MPM, offering satisfactory outcomes and acceptable safety profiles. However, there is a need for further research to identify biomarkers that can predict treatment efficacy in MPM, and investigations are necessary to explore the optimal utilization of pembrolizumab, whether as a monotherapy or in combination with other treatments, to enhance patient outcomes in MPM management.

Declarations

Conflicts of interest: The author(s) have no conflicts of interest to disclose.

Ethical approval: Not applicable, as systematic reviews do not require ethical approval.

Patient consent (participation and publication)**:** Not applicable.

Funding: The present study received no financial support.

Acknowledgements: None to be declared.

Authors' contributions: BAA, GSA and HMH participated in data collection; FHK designed the study; RQS performed the data analysis; MNS, HOA, and SJH participated in preparing the manuscript; BHA, GSA, SFA and RMA critically revised the manuscript; FHK, HOA confirmed the authenticity of the data; all authors approved the final version of the manuscript.

Data availability statement: Note applicable.

References

1. Alley EW, Lopez J, Santoro A, Morosky A, Saraf S, Piperdi B, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. The Lancet Oncology. 2017 ;18(5):623-30. doi:10.1016/S1470-2045(17)30169-9

2. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56-61. doi:10.1126/science.aaa8172
3. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non–small-cell lung cancer. New England Journal of Medicine. 2015;372(21):2018-28. doi:10.1056/NEJMoa1507643
4. Mehra R, Seiwert TY, Gupta S, Weiss J, Gluck I, Eder JP, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. British journal of cancer. 2018;119(2):153-9. doi:10.1038/s41416-018-0131-9
5. Maly J, Alinari L. Pembrolizumab in classical Hodgkin's lymphoma. European journal of haematology. 2016;97(3):219-27. doi:10.1111/ejh.12770
6. Bellmunt J, De Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. New England Journal of Medicine. 2017;376(11):1015-26. doi:10.1056/NEJMoa1613683
7. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. New England Journal of Medicine. 2015;372(26):2521-32. doi:10.1056/NEJMoa1503093
8. Shitara K, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandalà M, Ryu MH, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. The Lancet. 2018 ;392(10142):123-33. doi:10.1016/S0140-6736(18)31257-1
9. Finn RS, Ryoo BY, Merle P, Bouattour M, Lim HY, Breder V, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. 2019; 38(3): 193-202. doi:10.1200/JCO.19
10. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. New England Journal of Medicine. 2019 ;380(12):1116-27. doi:10.1056/NEJMoa1816714
11. Robinson BW, Lake RA. Advances in malignant mesothelioma. New England Journal of Medicine. 2005;353(15):1591-603. doi:10.1056/NEJMra050152
12. Ismail-Khan R, Robinson LA, Williams Jr CC, Garrett CR, Bepler G, Simon GR. Malignant pleural mesothelioma: a comprehensive review. Cancer control. 2006;13(4):255-63. doi:N/A
13. Gray SG. Emerging avenues in immunotherapy for the management of malignant pleural mesothelioma. BMC Pulmonary Medicine. 2021;21(1):1-24. doi:10.1186/s12890-021-01513-7
14. Ahmadzada T, Cooper WA, Holmes M, Mahar A, Westman H, Gill AJ, et al. Retrospective evaluation of the use of Pembrolizumab in malignant mesothelioma in a real-world Australian population. JTO Clinical and Research Reports. 2020;1(4):100075. doi:10.1016/j.jtocrr.2020.100075
15. Muhialdeen AS, Ahmed JO, Baba HO, Abdullah IY, Hassan HA, Najar KA, et al. Kscien's List; A New Strategy to Discourage Predatory Journals and Publishers (Second Version).Barw Medical Journal. 2023; 1(1);30-32. doi:N/A
16. Popat S, Curioni-Fontecedro A, Dafni U, Shah R, O'Brien M, Pope A, et al. A multicentre randomised phase III trial comparing pembrolizumab versus single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial. Annals of Oncology. 2020;31(12):1734-45. doi:10.1016/j.annonc.2020.09.009
17. Danlos FX, Texier M, Job B, Mouraud S, Cassard L, Baldini C, et al. Genomic Instability and Protumoral Inflammation Are Associated with Primary Resistance to Anti–PD-1+ Antiangiogenesis in Malignant Pleural Mesothelioma. Cancer Discovery. 2023;13(4):858-79. doi:10.1158/2159-8290.CD-22-0886
18. Yap TA, Nakagawa K, Fujimoto N, Kuribayashi K, Guren TK, Calabrò L, et al. Efficacy and safety of pembrolizumab in patients with advanced mesothelioma in the open-label, single-arm, phase 2 KEYNOTE-158 study. The Lancet Respiratory Medicine. 2021;9(6):613-21. doi:10.1016/S2213-2600(20)30515-4
19. Metaxas Y, Rivalland G, Mauti LA, Klingbiel D, Kao S, Schmid S, et al. Pembrolizumab as palliative immunotherapy in malignant pleural mesothelioma. Journal of Thoracic Oncology. 2018 ;13(11):1784-91. doi:10.1016/j.jtho.2018.08.007
20. Shalata W, Iraqi M, Bhattacharya B, Fuchs V, Roisman LC, Cohen AY, et al. Rapid Response to the Combination of Lenvatinib and Pembrolizumab in Patients With Advanced Carcinomas (Lung Adenocarcinoma and Malignant Pleural Mesothelioma). Cancers. 2021;13(14):3630. doi:10.3390/cancers13143630
21. Zhou M, Joshi N, Raj KP, Wakelee H, Neal JW. PD-1/PD-L1 Checkpoint Inhibitor Immunotherapy for Malignant Pleural Mesothelioma: Case Series and Literature Review. Clinical Lung Cancer. 2021;22(3):e329-35. doi:10.1016/j.cllc.2020.05.012
22. Bickel A, Koneth I, Enzler-Tschudy A, Neuweiler J, Flatz L, Früh M. Pembrolizumab-associated minimal change disease in a patient with malignant pleural mesothelioma. BMC cancer. 2016; 16:1-3. doi:10.1186/s12885-016-2718-y
23. Hearon BF, Redelman KN, Elhomsy GC, Moore Jr DF. Exceptional Regression of Malignant Pleural Mesothelioma with Pembrolizumab Monotherapy. Case Reports in Oncology. 2020;13(3):1483-9. doi:10.1159/000512013
24. Mampuya WA, Bouchaab H, Schaefer N, Kinj R, La Rosa S, Letovanec I, et al. Abscopal effect in a patient with malignant pleural mesothelioma treated with palliative radiotherapy and pembrolizumab. Clinical and Translational Radiation Oncology. 2021; 27:85-8. doi:10.1016/j.ctro.2020.12.006
25. Minchom A, Yuan W, Crespo M, Gurel B, Figueiredo I, Wotherspoon A, et al. Molecular and immunological features of a prolonged exceptional responder with malignant pleural mesothelioma treated initially and rechallenged with pembrolizumab. Journal for Immunotherapy of Cancer. 2020;8(1): e000713. doi:10.1136/jitc-2020-000713
26. Rittberg R, Chan E, Yip S, Alex D, Ho C, Chan EK. Radiation Induced Abscopal Effect in a Patient With Malignant Pleural Mesothelioma on Pembrolizumab. Cureus. 2022;14(2): e22159. doi:10.7759/cureus.22159
27. Baldauf MC, Kapauer M, Joerger M, Flatz L, Rodriguez R, Frank S, et al. Pembrolizumab-Associated CD8+ Vasculitic Mononeuritis Multiplex in a Patient with Mesothelioma. Neurology® Neuroimmunology & Neuroinflammation. 2021;8(4): e993. doi:10.1212/NXI.0000000000000993
28. Schiopu SR, Käsmann L, Schönermarck U, Fischereder M, Grabmaier U, Manapov F, et al. Pembrolizumab-induced myocarditis in a patient with malignant mesothelioma: plasma exchange as a successful emerging therapy—case report. Translational Lung Cancer Research. 2021;10(2):1039-1046. doi:10.21037/tlcr-20-1095
29. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. Journal of clinical oncology. 2003;21(14):2636-44. doi:10.1200/jco.2003.11.136
30. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. The Lancet. 2016 ;387(10026):1405-14. doi:10.1016/S0140-6736(15)01238-6
31. Grosso F, Steele N, Novello S, Nowak AK, Popat S, Greillier L, et al. Nintedanib plus pemetrexed/cisplatin in patients with malignant pleural mesothelioma: phase II results from the randomized, placebo-controlled LUME-Meso trial. Journal of Clinical Oncology. 2017;35(31):3591-600. doi:10.1200/JCO.2017.72.9012
32. Scagliotti GV, Gaafar R, Nowak AK, Nakano T, van Meerbeeck J, Popat S, et al. Nintedanib in combination with pemetrexed and cisplatin for chemotherapy-naive patients with advanced malignant pleural mesothelioma (LUME-Meso): a double-blind, randomised, placebo-controlled phase 3 trial. The Lancet Respiratory Medicine. 2019;7(7):569-80. doi:10.1016/S2213-2600(19)30139-0
33. Desai A, Karrison T, Rose B, Tan Y, Hill B, Pemberton E, et al. OA08. 03 phase II trial of pembrolizumab (NCT02399371) in previously-treated malignant mesothelioma (MM): final analysis. Journal of Thoracic Oncology. 2018;13(10):S339. doi:10.1016/j.jtho.2018.08.277
34. Forde PM, Sun Z, Anagnostou V, Kindler HL, Purcell WT, Goulart BH, et al. PrE0505: Phase II multicenter study of anti-PD-L1, durvalumab, in combination with cisplatin and pemetrexed for the first-line treatment of unresectable malignant pleural mesothelioma (MPM)—A PrECOG LLC study. Journal of Clinical Oncology. 2020;38(15):9003. doi:10.1200/JCO.2020.38.15_suppl.9003
35. Kao SC, Cheng YY, Williams M, Kirschner MB, Madore J, Lum T, et al. Tumor suppressor microRNAs contribute to the regulation of PD-L1 expression in malignant pleural mesothelioma. Journal of Thoracic Oncology. 2017;12(9):1421-33. doi:1016/j.jtho.2017.05.024
36. Okada M, Kijima T, Aoe K, Kato T, Fujimoto N, Nakagawa K, et al. Clinical Efficacy and Safety of Nivolumab: Results of a Multicenter, Open-label, Single-arm, Japanese Phase II study in Malignant Pleural Mesothelioma (MERIT) Nivolumab In Japanese Patients With Advanced/Metastatic MPM. Clinical Cancer Research. 2019;25(18):5485-92. doi:10.1158/1078-0432.CCR-19-0103
37. Lopci E, Zucali PA, Ceresoli GL, Perrino M, Giordano L, Gianoncelli L, et al. Quantitative analyses at baseline and interim PET evaluation for response assessment and outcome definition in patients with malignant pleural mesothelioma. European journal of nuclear medicine and molecular imaging. 2015; 42:667-75. doi:10.1007/s00259-014-2960-y