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Systematic Review

Role of Durvalumab (Anti-PD-L1) in the Management of Mesothelioma: A Systematic Review of the Current Literature

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Abstract

Introduction

Mesothelioma is a rare and rapidly advancing tumor that usually emerges on the mesothelial surfaces of the pleura or peritoneum. Despite being a well-recognized rare disease for decades, the only approved primary treatment protocol has been platinum-based treatments plus pemetrexed, whether or not bevacizumab is administered. Immunotherapy-based immune checkpoint inhibitors demonstrated a promising antitumor efficacy in a variety of cancer types. This is a systematic review of the current role of durvalumab in the management of this condition.

Methods

A systematic search was carried out through the databases and search engines. Regardless of study design, line of therapy, mode of therapy, or Eastern Cooperative Oncology Group (ECOG) performance status, studies that primarily focused on the outcomes of treating this disease with durvalumab were eligible for inclusion. After the initial and full-text screenings, five studies were reviewed.

Results

The median age of the total 235 patients was 66.9 years. Males comprised 174 (74.04%) of the cases, with 61 (25.95%) cases being female. The Epithelioid mesothelioma

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subtype accounted for 194 (82.55%) of the patients. Durvalumab, in combination with pemetrexed cisplatin/carboplatin as therapy, was used in 109 (48.38%) cases. Durvalumab and tremelimumab were used in the treatment of 40 (17.02%) cases, of which 17 (7.23%) had retreatment with both immunotherapies. Among the patients who underwent durvalumab treatment, 69 (29.36%) of the individuals previously received carboplatin/pemetrexed and cisplatin/pemetrexed.

Conclusion

Durvalumab can be utilized as an effective alternative for malignant pleural mesothelioma treatment, providing positive results and acceptable safety profiles.

1. Introduction

Malignant mesothelioma is a deadly and rapidly advancing tumor most frequently linked to exposure to asbestos. Due to the ineffectiveness of available treatment options, the prognosis for mesothelioma patients remains bleak [1]. It exhibits a low cancer-specific survival rate characterized by a median overall survival duration spanning from half a year to two years and a 5-year survival rate falling between 4.7% to 6.1%.[2]. This devastating disease affects over 30,000 people worldwide annually [3]. In the past two decades, there has been no significant change in the primary systemic therapy for patients with unresectable mesothelioma [1].

Most patients are diagnosed with incurable diseases, and from 2004 to October 2020, the only approved primary treatment protocol has been platinum-based treatments plus pemetrexed, whether or not bevacizumab is administered [4]. However, there is limited clinical benefit and support for the implementation of alternative chemotherapy lines. In spite of a statistically notable enhancement in median overall survival, the incorporation of bevacizumab to chemotherapy doublets, as reported in the MAPS study, has had no impact on clinical practice [5,6].

Despite these challenges, there is a pressing need for the development of an effective systemic therapy for mesothelioma [7]. Immune checkpoint inhibitors (ICIs) represent a recently developed treatment for mesothelioma. The use of ICIs has shown promising results, particularly when used in combination regimens [1]. Durvalumab, an immunotherapeutic agent, blocks the interplay between the programmed cell death-1 (PD-1) receptor, which is expressed on T-cells, and the programmed cell death ligand-1 (PD-L1) on cancer cells [8].

The objective of this study is to assess the present role of durvalumab in the treatment of patients with malignant pleural mesothelioma (MPM).

2. Methods

2.1. Study design

This study was conducted by comprehensively reviewing the studies focusing on the treatment with anti-PD-L1 antibody durvalumab for MPM.

2.2. Data sources and search strategy

A systematic search was done in eligible databases and search engines such as PubMed/MEDLINE, EMBASE and Google Scholar. The keywords in the study were (durvalumab, Imfinzi, anti-PD-L1, anti-PD-L1 antibody, PD-L1 inhibitor, MEDI4136) 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 treatment of MPM with anti-PD-L1 durvalumab, not taking into account the study design, line of therapy or mode of therapy (either monotherapy or combination), and Eastern Cooperative Oncology Group (ECOG) performance status. For that, studies that had only abstracts available, pre prints, non-article and non-pleural mesothelioma were not included (except for a study that was conducted on treating 40 patients with only 2 cases of peritoneal mesothelioma were mentioned, and another one which was a follow-up of the previous study with only 1 case of peritoneal mesothelioma. Otherwise, both had all eligible criteria, hence they were included). All studies' publishers were assessed for reliability (fully peer-reviewed) using Kscien's List [9]. A total of 766 studies were found in the search process, of which 62 were excluded prior to the initial screening (duplicate = 7, non-english = 6, only abstract = 30, and non-article = 19). After the initial and full-text screenings, 7 studies were found to be eligible, of which 2 records were excluded owing to data insufficiency (one currently running trial/ongoing study, and the other one was window-opportunity) (Figure 1)[9].

2.4. Study selection and data items

The titles and abstracts of the identified studies were initially screened by several authors. Subsequently, they conducted a full-text screening to evaluate whether the studies met the inclusion criteria. Two independent authors evaluated the study's quality. 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 event and the gradings, treatment interruption due to adverse events, death due to adverse events, objective response rate (ORR), 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 includes five publications with study designs, consists of a multicentre, single-arm, open-label, phase II trial, a single-arm multicenter, phase II cohort study, phase II open-label, non-randomized study, and a follow-up of the open label, non-randomised, phase II NIBIT-MESO-1 study (Table1).). The main characteristics of the tumor, the basic demographics, and previous treatments are sumurized in table 1 and 2. There were 235 patients with a median age of 66.9 years. Sixty one (25.95%) cases were female, with a male predominance of 174 (74.04%). The most common type of mesothelioma in these patients was epithelioid 194 (82.55%), followed by biphasic mesothelioma 24 (10.21%) , 13 (5.53%) were sarcomatoid, 3 (1.27%) were desmoplastic and 1 (0.42%) was undefiend or missing. The frequent mode of therapy was durvalumab in combination with pemetrexed-cisplatin/carboplatin in 109 (48.38%) cases, forty cases (17.02%) underwent combination thrapy of durvalumab and tremelimumab; 17 (7.23%) of these patients were retreatment with durvalumab and tremelimumab in the follow-up trial. Sixty nine (29.36%) patients who had previously been treated with carboplatin-pemetrexed and cisplatin-pemetrexed before received durvalumab (Table 2). A total of 84 different adverse events (AEs) were recorded. The most frequently associated AEs were nausea (24.68%) fatigue (19.14%), maculopapular rash (18.29%), and pruritis (16.17%) (Table 3). AEs caused temporary and permanent treatment discontinuations equally (5.53%). All 17 retreatment patients had permanent or temporary discontinuation due to the progression of the disease, 13 of which received subsequent chemotherapy or immunotherapy. Only one case (0.42%) died due to the AEs by sudden death. Regarding the ORR of the patients (partial = 76 (32.34%), and SD was noticed in = 64 (27.23%) of cases (Table 4).

Table 1. The general characteristics of the studies on the use of durvalumab for the treatment of MPM.

Author/year	Study design	N. cases	Gender		Median Age	Histological subtype					Therapy Mode
			M	F		Biphasic	Epithelioid	Sarcomatoid	Desmoplastic	Undefined or missed	
Calabro 2021[1]	Follow-RCT	17	11	6	65	3	14	0	0	0	Combination
Forde 2021[2]	Cohort	55	45	10	68	6	41	7	1	0	Combination
Canova 2022[5]	RCT	69	44	25	69.9	4	62	3	0	0	Monotherapy
Anna 2020[6]	RCT	54	45	9	68	6	45	1	2	N/A	Combination
Calabro 2018[12]	RCT	40	29	11	64	5	32	2	0	1	Combination

* *RCT, Randomized controlled trial; N/A, Not applicable*

4. Discussion

The MPM is a type of cancer that develops in the pleural serous membrane lining due to prolonged exposure to silicate materials in the environment, such as asbestos. Extended contact with asbestos microparticles leads to an inflammatory response, infiltration of inflammatory macrophages, the emergence of an immunosuppressive protumoral microenvironment, and pathological neoangiogenesis with hypoxia. Ultimately, this confers aggressive characteristics to serous cells and results in the development of metastatic disease. The disease can be classified into three subgroups histologically: epithelioid, sarcomatoid, and mixed (biphasic). A favorable prognosis and better response to treatment are associated with the epithelioid subtype, affecting 50–60% of patients. Conversely, the sarcomatoid subtype, impacting 20% of patients, has a lower likelihood of responding to therapy [10]. Histology, tumor grade and stage, age, and sex have all been shown to independently predict prognosis in cancer. Notably, non-epithelioid histology is linked to a worse prognosis than the epithelioid subtype [11].

The studies included in this systematic review revealed that the average age of patients was 66.9 years, with a three-quarters preference for males. The majority of histologic subtypes (82.5%) were epithelioid, while biphasic subtypes accounted for 10.2%, and the sarcomatoid subtype around 5.5%. Similar to a prior study, which estimated that the percentage of epithelioid subtypes was approximately 76.7% and sarcomatoid subtypes were 7.9%, these results demonstrated a higher percentage of epithelioid subtypes and a lower percentage of sarcomatoid subtypes [10].

Advanced MPM is best managed using a dual theraputic regimen of cisplatin and pemetrexed. While, for advanced peritoneal disease, there are no approved first-line treatments, but cisplatin and pemetrexed are frequently employed among this particular group. According to the results of the randomized MAPS study in pleural mesothelioma patients reported in 2016, The inclusion of bevacizumab in the conventional cisplatin and pemetrexed regimen resulted in an extended overall survival by

2.7 months realtive to the standard cisplatin and pemetrexed alone. Nonetheless, this treatment protocol has not been acknowledged as the established standard of care at present for pleural mesothelioma patients in most countries [6,12,13].

Table 2. Baseline characteristics of patient who received Durvalumab treatment.

Characteristics	N. patients (%)
Age (mean of means) (years)	66.9
Sex	
Male	174 (74.05%)
Female	61 (25.95%)
Histological subtypes of mesothelioma	
Epithelioid	194 (82.05%)
Biphasic	24 (10.21%)
Sarcomatoid	13 (5.53%)
Desmoplastic	3 (1.27%)
Undefined or missed	1 (0.42%)
Previous treatment	
Carboplatin/prmetrexed/cisplatin pemetrexd	69 (29.36%)
Therapy line of durvalumab	
First-line chemotherapy	121 (51.48%)
Second-line chemotherapy	97 (41.27%)
Retreatment after first-line tremelimumb+durvalumab	4 (1.70%)
Retreatment after second-line tremelimumb+durvalumab	13 (5.53%)
Dose and mode of administration	
1500 mg, Q4W	69 (29.36%)
1.125mg then 1500 mg, Q3W then Q4W	54 (22.97%)
20mg/kg, Q4W	40 (17.02%)
1.120 mg, Q3W	55 (23.40%)
20mg/kg, Q4W	17 (7.23%)
Therapy mode	
Combination with pemetrexed/cisplatin and pemetrexed/carboplatin	109 (46.38%)
Combination with tremelimumab	57 (24.25%)
Monotherapy (pretreated with carboplatin/pemetrexed—cisplatin/pemetrexed monotherapy)	69 (29.36%)

There are no authorized secondary theraputic options for mesothelioma, and patients with suitable ECOG performance status scores and blood parameters for additional rounds of chemotherapy are best served by enrolling in a clinical trial. As a result, innovative treatment strategies are needed, and there is promise in exploring immunotherapy for mesothelioma [13]. Cancer immunotherapy stands out as one of the foremost breakthroughs in medical science. The contemproary era of immunotherapy gained significant momentum in the last two decades with the identification of antibodies that block cytotoxic T lymphocyte-associated protein 4 (CTLA-4), enhancing anti-tumor immunity. Despite the concept of neoplastic immunosurveillance and immunity against cancer extending back to the latter part of the twentieth century [4]. The US Food and Drug Administration (FDA) approved ipilimumab in 2011 for treating individuals with metastatic melanoma. Tremelimumab and ipilimumab were the first human anti-CTLA-4 antibodies to undergo clinical trials in patients with advanced cancer diseases [14]. Following the indentification of yet another crucial immune checkpoint, the protein known as (PD-1), which negatively regulates antitumor T cell function when bound to PDL-1, Pembrolizumab and nivolumab, the first PD-1-blocking antibodies, gained FDA approval in 2014 and 2015, respectively, for treating advanced non-small cell lung cancer (NSCLC). Since then, a range of other medications has been developed for use in clinical settings and are currently empolyed either in isolation or in conjunction with other theraoutic modalities (such as conventional chemotherapy, radiotherapy, surgery etc.) in initial or follow-up regimens for managing various solid tumors [4,15].

Durvalumab is a monoclonal human IgG antibody targeting the PDL-1 molecule. This molecule is expressed on the cell membranes of T cells, cancer cells, dendritic cells, and macrophages. The interaction of PDL-1 with PD-1 inhibits T cell activation and reduces the immune response directed at cancer cells. Granted FDA approval in 2017 for the initial treatment of stage 3 unoperable NSCLC and metastatic or locally advanced urothelial cancer, durvalumab is currently the subject of ongoing investigation in clinical research for treating numerous other solid tumors either independently or in conjunction with other therapeutic modalities [4]. The role of ICIs in mesothelioma is still not fully comprehended. Patients undergoing treatment after one or more rounds of chemotherapy have mainly been included in clinical trials and real-world data [7]. Considering the varied nature of clinical trials with respect to their inclusion criteria, research design, and the size of the patient population, the effectiveness of ICIs in a mesothelioma population has yielded mixed results and varying efficacy. The DIADEM study, the first phase II trial evaluating the safety and efficacy of durvalumab as a monotherapy in previously treated mesothelioma, reported median PFS and median OS of 1.9 and 7.3 months, respectively. Unfortunately, it did not meet its principal outcome measure of the proportion of patients alive and without progression at the 16 week markrs, demonstrating that durvalumab monotherapy did not show promising efficacy in mesothelioma patients who had previously received platinum/derivatives-pemetrexed treatment.

The regimen did not reveal any new safety concerns; AEs associated with treatment and their connection to the immune system were effectively controllable, with only a few cases necessitating permanent treatment discontinuation. Nonetheless, durvalumab provided a clinical benefit comparable to other ICIs in a similar context, even though The investigation did not reach its predefined primary endpoint [13]. Four ICIs were assessed as monotherapies for relapsed mesothelioma, and nivolumab was approved as the standard treatment after a phase III trial demonstrated its efficacy. However, other ICIs did not yield promising outcomes in terms of OS and PFS [5,12,16,17]. Untreated individuals appear to exhibit a greater efficacy in response to immune checkpoint inhibitors, as the overall response rate and disease control rate are higher in untreated patients than in those who have received previous treatments.

Table 3. The adverse events of the treatment with durvalumab.

Adverse events	N. patients (%)
Nausea	58 (24.68%)
Fatigue	46 (19.14%)
Maculopapular rash	43 (18.29%)
Pruritis	38 (16.17)
Skin disorders	37 (15.74%)
Constipation	30 (12.76%)
Diarrhea	28 (11.91%)
Vomiting	28 (11.91%)
Pustular rash	27 (11.48%)
GI disorders	26 (11.06%)
Peripheral sensory neuropathy	22 (9.36%)
Neutropenia	19 (8.08%)
Dyspnea	19 (8.08%)
Tinnitus	19 (8.08%)
Limb oedema	16 (6.80%)
Pain	16 (6.80%)
Decreased appetite	15 (6.38%)
MSK & connective tissue disorder	15 (6.38%)
GERD	15 (6.38%)
Cough	13 (5.53%)
Dysgeusia	13 (5.53%)
Watery eyes	12 (5.10%)
Hearing impaired	11 (4.68%)
Chest wall pain	11 (4.68%)
Dizziness	10 (4.25%)
Headache	10 (4.25%)
Fever	9 (3.82%)
Lethargy	9 (3.82%)
Dry mouth	8 (3.40%)
Anemia	8 (3.40%)
Back pain	7 (2.97%)
Atrial fibrillation	7 (2.97%)
Flu-like symptoms	7 (2.97%)
Blurred vision	7 (2.97%)
Creatinine Increased	7 (2.97%)
Lipase increased	7 (2.97%)
Upper respiratory infection	7 (2.97%)
Infections and infestations	6 (2.55%)
Dry eye	6 (2.55%)
Pleuritic pain	6 (2.55%)
Hypothyroidism	5 (2.12%)
Hyperthyroidism	5 (2.12%)
Oral mucositis	5 (2.12%)
Amylase increased	5 (2.12%)
Hypertension	4 (1.70%)
Pneumonitis	3 (1.27%)
Abdominal pain	3 (1.27%)
Infusion-related reactions	3 (1.27%)
ALT increased	3 (1.27%)
Muscular weakness	3 (1.27%)
Vascular disorders	3 (1.27%)
Weight loss	3 (1.27%)
Dry skin	2 (0.85%)
Hyponatremia	2 (0.85%)
Fall	2 (0.85%)
AST increased	2 (0.85%)
Ascites	2 (0.85%)
Cardiac disorders	2 (0.85%)
Neoplasms (benign & malignant)	2 (0.85%)
Pericarditis	2 (0.85%)
Sudden death	1 (0.42%)
Ischemic colitis	1 (0.42%)
Diabetes	1 (0.42%)
Flatulence	1 (0.42%)
Administration side conditions	1 (0.42%)
Mucosa infection	1 (0.42%)
Dermatitis acneiform	1 (0.42%)
Leucopenia	1 (0.42%)
Thrombocytopenia	1 (0.42%)
Anal pain	1 (0.42%)
Adrenal insufficiency	1 (0.42%)
Anorectal infection	1 (0.42%)
Anxiety	1 (0.42%)
Cholecystitis	1 (0.42%)
Constrictive pericarditis	1 (0.42%)
Articular mascle	1 (0.42%)
GGT increased	1 (0.42%)
Pancreatitis	1 (0.42%)
SVC syndrome	1 (0.42%)
SVT	1 (0.42%)
Surgical & medical procedures	1 (0.42%)
Limbic encephalitis	1 (0.42%)
AKI	1 (0.42%)

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

Nevertheless, PFS and OS rates did not significantly differ whether ICIs were administered as the first or subsequent lines of treatment. This is intriguing given the grim prognosis of pleural mesothelioma and the absence of effective second-line therapies, prompting speculation about potential sequential approaches [18].

Durvalumab has also been explored in combination with other agents. A common approach for advanced disease, following the NSCLC paradigm, involves combining first-line chemotherapy with PD-1 pathway blockade [7]. The efficacy of durvalumab, as demonstrated in patients with untreated MPM in the phase II, single-arm PrE0505 trial, was further validated when combined with chemotherapy doublet. In this scenario, the median OS for the combination was 20.4 months in a treatment-naive population, indicating potential additional synergy compared to chemotherapy alone, as evidenced in historical controls. Notably, patients with epithelioid MPM in the PrE0505 trial achieved a remarkable survival rate that exceeded two years. Following the publication of the PrE0505 trial results, several of these patients remained free of tumor progression. Treatment-related AEs in the PrE0505 trial aligned with established side effects of chemotherapy, and every immunotherapy-related AEs were grade 2 or lower [3]. The phase II DREAM study, which combined durvalumab with chemotherapy, demonstrated the regimen's tolerability and efficacy in the first-line setting by meeting its primary endpoint of PFS at 6 months. Thirty-one (57%) of the 54 patients were still alive and free of progression at 6 months, fulfilling the study's activity criteria and supporting the hypothesis that chemotherapy alone may not be the sole effective treatment. Partial responses were observed, with 21 (39%) patients experiencing more than a 50% reduction in tumor size from baseline [6]. After completing one year of treatment in both the DREAM and PrE0505 studies, Certain individuals may derive benefits from continued maintenance therapy until disease progression occurs. However, this issue varies among different tumor types. The ongoing phase III PrE0506/DREAM3R trial's investigative arm addresses this concern by including maintenance durvalumab therapy until confirmed disease progression [3,6], which led to approval by the US FDA for this indication [19].

Different pairings of monoclonal antibodies targeting CTLA-4 and PD-1 or PD-L1 have been explored in different tumor types, including malignant mesothelioma (NCT02899299), NSCLC (NCT02477826, NCT02938793), kidney cancer (NCT02231749), and head and neck cancer (NCT02551159). These findings prompted Calabrò, Morra et al. to investigate the effectiveness of combining tremelimumab with durvalumab as a first- or second-line treatment for mesothelioma patients. Moreover, it has been demonstrated that first-line combination therapy using anti-PD-1 and anti-CTLA-4 monoclonal antibodies significantly improves OS in patients with pleural mesothelioma compared to platinum-based therapy. It is foreseen that this treatment will be acknowledged as the emerging universal standard of care for these patients. [1,11,19]. In a phase 1b trial involving patients with NSCLC, the pharmacokinetic analyses of these combinations were previously reported, indicating their acceptability [19]. In the study by Calabrò, Morra et al., patients with malignant mesothelioma showed a favorable safety and tolerability profile with the combination therapy of tremelimumab and durvalumab. The primary endpoint of the study was met, with 11 (28%) of the 40 patients showing an immune-related partial response, which was confirmed in 10 (25%) patients. The duration of immune-related partial responses (observed in 65% of patients) and immune-related disease control (with a median duration of 10.6 months) suggest a sustained clinical benefit with this

Table 4. Outcomes of Durvalumab treatment for MM patients

Characteristics	N. patients (%)
Treatment interruption due to adverse events	
Combinant drug dose reduction owing to toxicity	5 (2.12%)
Treatment related toxicity	5 (2.12%)
Permanent interruption (grade 3-4 toxicity)	3 (1.27%)
Death due to adverse events	
Sudin death	1 (0.42%)
Objective response	
Stable disease	64 (27.23%)
Progressive disease	25 (10.63)
Partial response	76 (32.34)
Median duration of progression-free survival	4.94 months
Median overall survival	15.84 months

combination regimen. These findings suggest that the tremelimumab plus durvalumab regimen employed in this investigation can be further investigated without posing safety concerns. Notably, one patient developed diabetes insipidus, which is very rarely reported with ICIs, underscoring the potential for treatment-related toxicity affecting various organ systems [20]. In patients with metastatic melanoma, the combination of nivolumab, an anti-PD-1 monoclonal antibody, with ipilimumab, an anti-CTLA-4 monoclonal antibody, consistently improved OS compared to either drug used alone [21]. However, a study by Baas et al. found that the combination of nivolumab with ipilimumab was associated with a higher frequency of grade 3 or 4 serious treatment-related AEs and treatment discontinuations compared to chemotherapy. Nevertheless, most of these events were manageable and resolved with supportive treatment or steroids. Moreover, the overall incidence rate of treatment-related AEs was lower with nivolumab + ipilimumab when considering exposure to such events [11]. Based on previous data and the meta-analysis by Gemelli et al., and considering the lack of effective therapy in pre-treated pleural mesothelioma patients, Individuals who are not suitable candidates for combination treatments may still consider single-agent immune checkpoint inhibitors (ICIs) as a viable options such as the geriratric and frail demogaphic. There is a pressing necessity for predictive factors to identify patients who would benefit from this approach. As suggested by the Checkmate 743 trial, a sequential strategy involving platinum-pemetrexed chemotherapy followed by single-agent anti-PD-1/PD-L1 therapy upon disease progression may still be considered, particularly in epithelioid pleural mesothelioma patients who do not significantly benefit from ICI combinations [11,18].

There is limited available data on the therapeutic effectiveness of (ICIs) retreatment in cancer patients. who experience disease progression after initially benefiting from these agents, such as achieving a partial response or SD. The NIBIT-MESO-1 study, with a median follow-up duration of 52 months for mesothelioma patients receiving combination treatment with CTLA-4 and PD-L1, showed that despite not meeting the

primary objective of an OR, retreatment with ICIs led to disease stabilization in 41% of patients, primarily in those who had achieved an OR during their initial course of treatment in the NIBIT-MESO-1 study. Furthermore, the median PFS of patients who underwent retreatment (11.3 months) was better than the median PFS (8.0 months) monitored for each patient throughout their initial treatment regimen. In a post hoc analysis, OS exhibited a substantial improvement in patients who underwent retreatment with tremelimumab and durvalumab compared to those who were not retreated and received additional chemotherapy (25.6 months vs. 11.0 months). Additionally, in the NIBIT-MESO-1 study, no grade 3–4 immune-related AEs occurred in retreated patients. These results, although from a non-randomized study with a small cohort of retreatment patients, suggest that in 24% of mesothelioma patients who are ICI-refractory, retreatment with ICI may contribute to long-lasting tumor control. This strategy may be particularly relevant for previously-treated mesothelioma patients who currently lack effective treatment options. It should be noted that eligibility for retreatment in this follow-up study was limited to those who did not exhibit primary resistance to ICIs and had benefited from the initial ICI therapy (e.g., partial response or SD) [1].

Identifying biomarkers that can help in the selection of mesothelioma patients who are likely to benefit the most from both ICI retreatment and ICI therapy remains a significant challenge. The role of PD-L1 expression by neoplastic cells in this context is still a subject of debate [1]. The DIADEM study aimed to investigate the potential role of PD-L1 expression and found no evidence that durvalumab's performance differed based on positive or negative PD-L1 expression. This observation aligns with evidence from other trials evaluating the efficacy of durvalumab in MPM. In the NIBIT-MESO-1 study, no correlation was found between baseline PD-L1 expression, assessed as a continuous variable, and the endpoints of immune-related objective response, immune-related disease control, immune-related PFS, and 1-year OS [5]. Furthermore, there are currently no reliable biomarkers to predict the success of MPM treatment with dual-agent immunotherapy. In contrast, PD-L1 expression is an established biomarker for NSCLC immunotherapy with a single agent [11]. Similarly, patients with PD-L1-positive MPM showed considerable clinical efficacy with pembrolizumab, as reported by Alley et al. The absence of treatment-related mortality and the lack of treatment discontinuations due to AEs suggest that the study treatment has manageable toxicity and a favorable safety profile[10,16].

Regarding ICI retreatment, Calabrò et al. did not find any association between PD-L1 expression and clinical outcomes in patients who underwent ICI retreatment or those initially enrolled in the NIBIT-MESO-1 study. Similarly, no correlation was found between PD-L1 expression and the outcomes of salvage chemotherapy [1]. Consequently, in the DIADEM study, Canova et al. attempted to identify patient subgroups that would derive the most clinical benefit from durvalumab in a multivariate analysis. Since, histology is a recognized prognostic marker, the cohort was initially divided into epithelioid and non-epithelioid subtypes. In comparison to the non-epithelioid subtype, the epithelioid subtype had a more significant impact on PFS and overall OS. However, as seen in other clinical trials, sarcomatoid/biphasic MPMs were underrepresented [5]. According to the previous CheckMate 743 trial, which revealed a remarkable survival advantage favoring ipilimumab-nivolumab over chemotherapy for patients with non-epithelioid histology, this potential benefit from chemo-immunotherapy may apply particularly to patients with epithelioid MPM. Patients with epithelioid MPM did not show a significant difference in survival between the two treatment arms. Given the known chemosensitivity of epithelioid MPM and the greater chemo-resistance of non-epithelioid MPM, chemo-immunotherapy likely provides a synergistic advantage [11]. Additionally, several clinical trials have examined the potential relationship between tumor mutation burden with various cutoff values and the effectiveness of ICI therapy [1,22]. However, to date, no study has validated predetermined tumor mutation burden cutoffs to identify patients who will benefit most from ICI therapy. Calabrò et al. demonstrated an association between improved survival for all patients in the group and baseline tumor mutation burden values higher than the median population value, although their results did not reach statistical significance. A high mutation load at baseline appears to identify mesothelioma patients who are most likely to benefit from combined ICI therapy and retreatment with these agents. However, these findings should be interpreted cautiously as they are preliminary and derived from a post-hoc analysis of a small number of patients. Moreover, this approach may be limited by the highly invasive procedures required to obtain tumor biopsies at the onset of the disease [1].

At the first radiological evaluation, over half of the MPM patients receiving ICIs exhibited a pattern of disease progression. In the study by Canova et al., they observed a rate of disease progression of 42%, with a higher likelihood of this occurring in the first 2 months of treatment. Although it is not yet clear whether this phenomenon in MPM represents true hyperprogression, caution is warranted in selecting candidates for immunotherapy [5]. The most commonly reported ADEs included nausea, pruritus, maculopapular rash, fatigue, and gastrointestinal problems, which are comparable to the main ADEs in this review [12]. AEs in the DREAM trial were consistent with expectations when cisplatin-pemetrexed and durvalumab were used in combination. These drugs have non-overlapping toxicities that allow chemotherapy to be administered at the standard dose intensity. None of the five deaths that occurred during the DREAM trial could be directly attributed to durvalumab; they all resulted from mesothelioma or other factors, including chemotherapy. In the DETERMINE trial, 6% of patients in the placebo group died during the study treatment due to causes that also occurred in their trial (myocardial infarction, respiratory failure, and lung infection). The rate of deaths in the DREAM investigation reported a higher outcome than initially anticipated but consistent with the disease stage, age, and related comorbidities of their study population [7,12].

5. Conclusion

Durvalumab demonstrated no encouraging activity in patients with MPM when administered as a monotherapy after pretreated with platinum agents and pemetrexed. The treatment

was validated as being safe. Durvalumab can be used to treat pleural mesothelioma and has a useful safety and tolerability profile when used in combination with chemotherapy or combinations with other monoclonal antibodies targeting CTLA-4 and PD-1 or PD-L1. Combining tremelimumab and durvalumab also showed promising results. Retreatment was safe and led to clinically significant outcomes, implying its potential utilization in the clinical care of mesothelioma patients.

Declarations

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

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

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