World Journal of Clinical Oncology

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World J Clin Oncol 2022 April 24; 13(4): 267-275

DOI: 10.5306/wjco.v13.i4.267

ISSN 2218-4333 (online)

MINIREVIEWS

Tsunami of immunotherapy reaches mesothelioma

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Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ying S, China

Received: April 3, 2021
Peer-review started: April 3, 2021
First decision: July 6, 2021
Revised: September 4, 2021
Accepted: April 3, 2022
Article in press: April 3, 2022
Published online: April 24, 2022

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Abstract

Malignant pleural mesothelioma (MPM) is the most common type of malignant mesothelioma. It is a rare tumor linked to asbestos exposure and is associated with a poor prognosis. Until very recently, patients with advanced or unresectable disease had limited treatment options, primarily based on doublet chemotherapy with cisplatin and pemetrexed. In 2020 and 2021, after more than a decade with no major advances or new drugs, two phase III clinical trials published results positioning immunotherapy as a promising option for the first- and second-line treatment of MPM. Immunotherapy has revolutionized the treatment of many cancers and is also showing encouraging results in malignant mesothelioma. Both immune checkpoint inhibition and dual cytotoxic T-lymphocyte–associated antigen 4 and programmed death-ligand 1 pathway blockade resulted in

significantly improved overall survival in randomized phase III trials. In the CheckMate 743 trial, first-line therapy with nivolumab plus ipilimumab outperformed standard chemotherapy, while in the CONFIRM trial, nivolumab outperformed placebo in patients previously treated with chemotherapy. These two trials represent a major milestone in the treatment of MPM and are set to position immunotherapy as a viable alternative for treatment-naïve patients and patients with progressive disease after chemotherapy.

Key Words: Mesothelioma; Malignant pleural mesothelioma; Immunotherapy; Immune checkpoint inhibitors; Cytotoxic T-lymphocyte–associated antigen 4; Programmed cell death protein 1; Nivolumab; Ipilimumab; Immunotherapy combo; CheckMate 743; CONFIRM

Core Tip: Malignant pleural mesothelioma (MPM) is the most common type of malignant mesothelioma and is associated with a poor prognosis. The treatment options for advanced MPM were limited until very recently, when the results from two phase III trials showed improved survival in patients treated with immunotherapy. In the first trial, CheckMate 743, nivolumab plus ipilimumab as first-line therapy achieved better overall survival than standard chemotherapy, while in the second trial, CONFIRM, nivolumab *vs* placebo significantly improved overall survival in patients previously treated with chemotherapy. In this article, we discuss recent advances and highlights in the treatment of MPM.

Citation: Mielgo-Rubio X, Cardeña Gutiérrez A, Sotelo Peña V, Sánchez Becerra MV, González López AM, Rosero A, Trujillo-Reyes JC, Couñago F. Tsunami of immunotherapy reaches mesothelioma. *World J Clin Oncol* 2022; 13(4): 267-275
URL: https://www.wjgnet.com/2218-4333/full/v13/i4/267.htm
DOI: https://dx.doi.org/10.5306/wjco.v13.i4.267

INTRODUCTION

Malignant mesothelioma (MM) is a rare tumor, with just 30870 cases diagnosed in 2020. The annual incidence is 0.3 cases per 100000 inhabitants worldwide, but rates vary depending on the region. In more developed areas, such as Europe, the annual incidence of MM is > 1 case per 100000 population [1]. MM arises from the mesothelial cells of serous membranes such as the pleura, peritoneum, pericardium, and tunica vaginalis of the testes. Malignant pleural mesothelioma (MPM) accounts for approximately 80% of all cases and carries a poor prognosis, with an overall 5-year survival rate of just 10%. There is a clear causal link between MM and a history of asbestos exposure, although the latency period between exposure and tumor development is between 20 years and 50 years. MPM mainly affects men (male to female ratio, 3:1) and is considered an occupational disease. The mean age at presentation is 74 years[2]. MPM has three subtypes with distinct histologic, biologic, and prognostic features: The epithelioid subtype, which accounts for 50%-70% of cases; the sarcomatoid subtype, which accounts for 7%-20% of cases and carries the worst prognosis; and the biphasic subtype, which carries a moderate prognosis[3].

The standard treatment for MM up to 2020 was doublet chemotherapy with cisplatin and pemetrexed, and no relevant advances had been made in this area for over a decade. As has occurred in many cancers, the advent of immunotherapy is changing the landscape of MM treatment and has already shown promising results[4].

In this article, we review the history of treatment options for MPM, including attempts to add immunotherapy-based strategies to the existing armamentarium. We then analyze the recent results from two phase III clinical trials set to position immune checkpoint inhibitors as effective first- and second-line treatments for MPM.

HISTORICAL HIGHLIGHTS IN THE TREATMENT OF MESOTHELIOMA IN THE PRE-IMMUNOTHERAPY ERA

Polychemotherapy, with or without antiangiogenic therapy, was the only option for treating MPM until the recent approval of nivolumab plus ipilimumab. The standard first-line treatment, based on the results of a phase III trial of 456 patients published in 2003, is pemetrexed 500 mg/m^2 plus cisplatin 75

mg/m^2 every 21 d. In the trial, this combination significantly outperformed cisplatin alone in terms of overall survival (OS) [12.1 mo *vs* 9.3 mo; hazard ratio (HR) = 0.77; P = 0.02], progression-free survival (PFS) (5.7 mo *vs* 3.9 mo; HR = 0.68; P = 0.001), and response rates (41.3% *vs* 16.7%; P < 0.001). The most common adverse effect was hematologic toxicity (grade 3/4 neutropenia, 27.9%; grade 3/4 leukopenia, 17.7%)[5].

Contrasting with the situation for non-small cell lung cancer, it has not been confirmed that maintenance treatment with antifolates improves survival in patients with MM after four to six cycles of chemotherapy with cisplatin plus pemetrexed[6]. In 2019, the results of a phase II trial of patients who had achieved at least stable disease with cisplatin plus pemetrexed showed no significant differences for PFS [3.4 mo *vs* 3.0 mo; HR = 0.99; 95% confidence interval (CI): 0.51-1.9; P = 0.9733] or OS (11.8 mo *vs* 16.3 mo; HR = 0.86; 95%CI: 0.44-1.71; P = 0.6737) between patients randomized to maintenance treatment with pemetrexed and those randomized to placebo[7]. In the same year, however, another phase II trial showed a survival benefit for maintenance gemcitabine *vs* palliative treatment only (median DFS, 6.2 mo *vs* 3.2 mo; HR = 0.42; 95%CI: 0.28-0.63)[8], but the improvement was not considered important enough for this option to be included in clinical guidelines.

Carboplatin plus pemetrexed can be used in patients unfit for cisplatin, as several phase II trials have shown that it has comparable efficacy to the cisplatin-pemetrexed doublet[9-11].

Attempts to improve survival outcomes in patients treated with standard chemotherapy include the addition of antiangiogenic therapy (bevacizumab or nintedanib). The rationale is that vascular endothelial growth factor (VEGF) is a key mitogen for MM cells[8]. The open-label phase III MAPS trial showed that adding bevacizumab 15 mg/kg to first-line cisplatin plus pemetrexed chemotherapy improved median OS (18.8 mo *vs* 16.1 mo; HR = 0.77; 95%CI: 0.62-0.95; P = 0.0167). It also allowed the use of bevacizumab as maintenance therapy. Patients treated with bevacizumab plus chemotherapy, however, showed higher rates of hypertension (26% *vs* 0%, grade 3/4) and thrombotic events (6% *vs* 1%, grade 3/4)[12]. The addition of bevacizumab to cisplatin and pemetrexed chemotherapy is recommended in clinical guidelines but has not yet received regulatory approval. The phase III LUME-Meso trial found no significant improvements in PFS following the addition of nintedanib, a tyrosine kinase inhibitor, to the combination of cisplatin and pemetrexed. Other studies of second-line vascular endothelial growth factor receptor tyrosine kinase inhibitors used as second-line treatments have also reported no significant benefits, but their findings may have been influenced by the profile of patients studied[13].

Chemotherapy combining cisplatin and gemcitabine showed promising activity against MM in two phase II multicenter trials conducted before the approval of pemetrexed in this setting[14,15]. This combination thus would be the treatment of choice for previously treated patients, unless, of course, they had not received first-line treatment with pemetrexed[16]. Poor results have been reported for other second- and third-line treatments investigated. The only drugs that have shown a slight survival benefit to date are weekly vinorelbine (median PFS, 2.3 mo and median OS, 6.2 mo)[17] and weekly gemcitabine[18]. The use of these drugs is supported by data from small phase II trials, subgroup analyses from first-line studies, and retrospective analyses. Nonetheless, the phase II trial, RAMES, whose results were published in 2020, showed a significant OS benefit for gemcitabine plus ramucirumab *vs* gemcitabine only in previously treated patients (13.8 mo *vs* 7.5 mo; HR = 0.71; 95%CI: 0.59-0.85; P = 0.057), positioning this combination as a promising second-line option[19].

IMMUNOTHERAPY-BASED TREATMENT STRATEGIES FOR MESOTHELIOMA

MM is considered to be an inflamed tumor. High programmed death-ligand 1 (PD-L1) expression is associated with a worse prognosis and increased immune infiltration[20,21]. Immunotherapy is thus an attractive option for this tumor and has attracted increasing attention from researchers in recent years. Numerous types of immunomodulatory treatments have been investigated, including interferon, interleukin 2, tumor necrosis factor-α, granulocyte/macrophage colony-stimulating factor, oncolytic viruses, dendritic cell immunotherapy, and, currently at the forefront of efforts, immune checkpoint inhibitors[4,22]. Currently, most developed ICIs in the treatment of solid tumors are anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1)/PD-L1 monoclonal antibodies (mabs), each of which acts at a different level of activation of immune response. Anti-CTLA-4 mabs promote T cell proliferation and trigger antitumor response acting in the priming of immune response in peripheral lymphoid organs. On the other hand, anti-PD-1/PD-L1 mabs make their action in the tumor restoring the antitumor function of T cells, avoiding to become exhausted T lymphocytes. Attempts to find an effective immunotherapy-based treatment, however, were largely unsuccessful, until the phase III CheckMate 743 and CONFIRM trials, whose results were released in 2020 and 2021.

Tremelimumab, a CTLA-4 inhibitor, was investigated as an option for progressive disease after chemotherapy in two open-label single-arm trials - MESOT-TREM-2008[23] and MESOT-TREM-2012[24] - and a randomized, placebo-controlled, phase IIb trial - DETERMINE[25]. The two single-arm trials evaluated different dosages of tremelimumab, but only MESOT-TREM-2012 met the primary endpoint,

with an objective response rate (ORR) of 52%. The results for the secondary endpoints, OS and PFS, were promising and the drug also showed a favorable safety profile. The larger DETERMINE trial, which compared tremelimumab and placebo in patients who progressed after chemotherapy, did not demonstrate any significant differences in OS, PFS, or ORR.

Anti-PD-1/PD-L1 monotherapy as both a first- and second-line option has also been studied but mostly in phase Ib and II trials. The multicenter phase II DREAM trial evaluated the combination of durvalumab and standard first-line chemotherapy[26]. Its results were encouraging, with a median OS of 6.9 mo, a median PFS of 18.4 mo, an ORR of 48%, and an acceptable safety profile. They have not, however, been validated in comparative study or phase III trial. In a phase Ib trial, avelumab, an anti-PD-L1 drug, showed a good ORR in previously treated patients, with a complete response rate of 2% and a partial response rate of 8%[27]. Nonetheless, although the adverse events reported were to be expected, 8% of patients had an event that resulted in death[27].

The ETOP-PROMISE-Meso-Trial is the only phase III trial conducted in the setting of previously treated MM. It compared pembrolizumab and chemotherapy (gemcitabine or vinorelbine) in patients with MM that had progressed after at least one treatment but found no significant differences for PFS (primary endpoint) or OS[28]. While ORR was significantly higher in the pembrolizumab group (22% *vs* 6%; $P = 0.004$), responses were mostly short lived. Nivolumab, another anti-PD-1 drug, was studied in patients with pretreated MM in two single-arm phase II trials. The results for ORR, disease control rate, and OS were promising and were further investigated in the phase III placebo-controlled CONFIRM trial, whose results were recently published. The results for the two primary endpoints - OS and PFS - were positive, with an OS of 9.2 mo (*vs* 6.6 mo in the placebo group) (HR = 0.72; 95%CI: 0.55-0.94; $P = 0.02$) and a PFS of 3 mo (*vs* 1.8 mo) (HR = 0.6; 95%CI, 0.48-0.77; $P < 0.001$). These results undoubtedly represent a milestone in the management of previously treated mesothelioma, but as the comparator was placebo, it remains unclear whether nivolumab is truly a better option than chemotherapy or gemcitabine plus ramucirumab in this setting[29-31].

Combination immunotherapy with the immune checkpoint inhibitors CTLA-4 (ipilimumab) and PD-1 (nivolumab) showed promising results in two phase II trials - MAPS2[32] and INITIATE[33], leading to further investigation in the phase III CheckMate 743 trial. Combined tremelimumab and durvalumab therapy also showed activity against mesothelioma and an acceptable safety profile in the phase II NIBIT-MESO-1 trial[34] (Table 1).

NIVOLUMAB AS NEW SALVAGE THERAPY OPTION

Stand-Up-To-Cancer Cancer Research United Kingdom CONFIRM trial is a double blind phase 3 randomized study evaluating nivolumab (3 mg/kg/q2w) *vs* placebo with 2:1 ratio in patients with previously treated unresectable MM (pleural or peritoneal) until disease progression or a maximum of 12 mo. Co-primary objectives were investigator-assessed PFS and OS. 221 patients were randomized to nivolumab and 111 to placebo. Preliminary data were presented in World Conference of Lung Cancer 2020, and although OS was not mature, longer survival was achieved with nivolumab (9.2 mo *vs* 6.6 mo; HR = 0.72; 95%CI: 0.55-0.94; $P = 0002$), and PFS was also better for nivolumab arm (3.0 mo *vs* 1.8 mo; HR = 0.62; 95%CI: 0.49-0.78; $P < 0.001$). In the subgroup analysis of OS by histologic subtype, significant benefit was found in the epithelioid subtype but not significant benefit in non-epithelioid one. Grade 3-4 treatment-related adverse effects were reported in 19% on nivolumab *vs* 6.3% on placebo arm[29] (Table 2).

NIVOLUMAB AND IPILIMUMAB AS NEW FRONTLINE OPTION

The pivotal open-label, multicenter CheckMate 743 trial represented a major step forward in the treatment of mesothelioma, as it was the first phase III trial to publish results on the use of immunotherapy as first-line therapy. It compared nivolumab plus ipilimumab against standard chemotherapy in previously untreated patients with unresectable MPM[35]. In total, 605 patients were randomly assigned (1:1) to receive nivolumab 3 mg/kg every 2 wk plus ipilimumab 1 mg/kg every 6 wk for 2 years or standard chemotherapy with six cycles of cisplatin 75 mg/m^2 or carboplatin with an area under the curve value of 5 plus pemetrexed 500 mg/m^2. Patients in both arms continued to receive treatment until disease progression or unacceptable toxicity; the maximum time established for the experimental arm was 24 mo. The characteristics of the two groups were comparable; 77% of the participants were men and 75% had an epithelioid subtype. The results of the first prespecified interim analysis, at 29.7 mo, showed higher median OS (the primary endpoint) in the immunotherapy group (18.1 mo *vs* 14.1 mo; HR: 0.74; $P = 0.002$). OS in the immunotherapy *vs* chemotherapy group was 68% *vs* 58% at 1 year and 41% *vs* 27% at 2 years. Median duration of response was 11.0 *vs* 6.7 mo. All the subgroup analyses showed trends that favored nivolumab plus ipilimumab over chemotherapy. On stratifying the results by MPM subtype and PD-L1 expression, the survival benefit was higher for patients in the immunotherapy group, with a median OS of 18.1 mo *vs* 8.8 mo for patients with non-epithelioid MPM and 18

Table 1 Main pre-phase III clinical trials of immunotherapy-based strategies for the treatment of mesothelioma

Clinical trial (Phase): Drug analyzed	Setting	Primary endpoint
MESOT-TREM 2008 (Phase II): Tremelimumab 15 mg/kg every 90 d[23]	Salvage setting	ORR: 6.9%
MESOT-TREM 2012 (Phase II): Tremelimumab 10 mg/kg every 4 wk[24]	Salvage setting	ORR: 13.7%
DETERMINE (Phase IIb): Tremelimumab 10 mg/kg every 4 wk *vs* Placebo[25]	Salvage setting	OS: 7.7 mo *vs* 7.3 mo (HR = 0.92; P = 0.41)
DREAM (Phase II): Durvalumab 1125 mg + Cisplatin 75 mg/m^2 or Carboplatin AUC 5 + Pemexetrad 500 mg/m^2 every 3 wk[26]	Front-line setting	6-mo PFS: 57%
JAVELIN Solid (Phase Ib): Avelumab 10 mg/kg every 2 wk[27]	Salvage setting	ORR: 9%

AEs: Adverse events; AUC 5: Area under the curve value of 5; HR: Hazard ratio; ORR: Overall response rate; OS: Overall survival; PFS: Progression free survival.

Table 2 Recently published practice changing phase 3 studies in Malignant Pleural Mesothelioma

Clinical trial (Phase)	Population	Treatment arms	mOS		mPFS		AEs G3
CheckMate 743 (Phase III)[35]	Untreated MPM	Nivolumab 3 mg/kg every 2 wk + ipilimumab 1 mg/kg every 6 wk	18.1 mo	HR: 0.74, P = 0.002	6.8 mo	HR: 1.00	30%
		Cisplatin + pemetrexed	14.1 mo		7.6 mo		32%
CONFIRM (Phase III)[29]	Relapsed MPM	Nivolumab 3 mg/kg every 2 wk	9.2 mo	HR: 0.72, P = 0.002	3 mo	HR: 0.61; P < 0.001	19%
		Placebo	6.6 mo		1.8 mo		6.3%

MPM: Malignant pleural mesothelioma; MM: Malignant mesothelioma (pleural or peritoneal); AEs: Adverse events; mOS: Median overall survival; mPFS: Median progression free survival; G: Grade; HR: Hazard ratio.

mo *vs* 13.3 mo for those with PD-L1 expression > 1%. In the nivolumab plus ipilimumab group, the survival outcomes were similar across the different subtypes and were independent of PD-L1 expression. The incidence of grade 3-4 adverse events was similar in both groups: 30.3% in the immunotherapy group and 32% in the chemotherapy group. Adverse events led to treatment discontinuation in 15% of the patients treated with immunotherapy and 7.4% of those treated with chemotherapy. The most common adverse effect of any grade in immunotherapy arm was diarrhea (21%), and nausea in the chemotherapy group (37%). Most commonly reported any-grade immunotherapy-related adverse effects were skin (36%), gastrointestinal (22%), endocrine (17.3%), hepatic (12%), hypersensitivity/infusion reaction (12%), pulmonary (6.7%), and renal (5%).

The safety profile observed for the combined use of nivolumab and ipilimumab was comparable to that reported elsewhere[36]. Based on these results, the United States Food and Drug Administration approved nivolumab plus ipilimumab as a first-line treatment for MPM in October 2020 (Table 3).

IMMUNOTHERAPY BIOMARKERS IN MESOTHELIOMA

Numerous biomarkers of response to immunotherapy have been investigated in recent years, but the results have varied widely, precluding any definitive conclusions. In this section, we review the most promising results reported to date.

Approximately 38%-75% of MMs express PD-1/PD-L1, and this variability is partly due to the immune microenvironment that characterizes this tumor. PD-1/PD-L1 expression has been linked to significantly worse OS, suggesting that it might be a marker of poor prognosis, especially at values > 30%[22,37]. PD-1/PD-L1 Levels are higher in sarcomatoid tumors, which have a worse prognosis than epithelioid subtypes. Nonetheless, contradictory findings have been reported for the relationship between PD-1/PD-L1 expression and response to different forms of immunotherapy. The CONFIRM trial performed subgroup analyses according to PD-L1 expression but found no significant differences supporting the predictive value of this marker. In the PD-L1 ≥ 1% subgroup, patients treated with nivolumab had a median OS of 8 mo *vs* 8.7 mo for those treated with placebo (HR = 0.95; 95%CI: 0.51-1.76; P = 0.864), while in the < 1% PD-LI group, they had a median OS of 9 mo *vs* 6.4 mo for those in the placebo group (HR = 0.74; 95%CI: 0.51-1.08; P = 0.115)[29]. The predictive value of PD-L1 expression was a secondary endpoint in the CheckMate 743 trial, and the data showed a significant OS benefit for immunotherapy *vs* chemotherapy in patients with PD-L1 ≥ 1% (HR = 0.69; 95% CI 0.55-0.87). By

Table 3 Comparison of safety and efficacy of frontline Nivolumab + Ipilimumab *vs* chemotherapy in malignant pleural mesothelioma

Clinical trial	Phase	Treatment arm	mOS		mPFS		ORR	AEs G3
CheckMate-743 [35]	III (open-label)	Nivolumab 3 mg/kg every 2 wk + Ipilimumab 1 mg/kg every 6 wk	18.1 mo	HR: 0.74, P = 0.002	6.8 mo	HR: 1.00	32%	30%
		Cisplatin + Pemetrexed	14.1 mo		7.6 mo		8%	32%
EMPHACIS[5]	III (single blind)	Pemetrexed 500 mg/m^2 and Cisplatin 75 mg/m^2	12.1 mo	HR: 0.77, P = 0.002	5.7 mo	HR: 0.68, P = 0.001	41.3% *vs* 16.7% (P < 0.001)	
		Cisplatin 75 mg/m^2	9.3 mo		3.9 mo		16.7%	
MAPS[12]	III (open-label)	Pemetrexed 500 mg/m^2 and Cisplatin 75 mg/m^2 with 15 mg/kg Bevacizumab in	18.8 mo	HR: 0.77, P = 0.0167	9.2 mo	HR: 0.61, P < 0.0001	NR	71%
		Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2	16.1 mo		7.3 mo			62%

AEs: Adverse events; mOS: Median overall survival; mPFS: Median progression free survival; ORR: Overall response rate; G: Grade; HR: Hazard ratio.

contrast, OS rates were similar in the two groups with < 1% PD-L1 expression (HR = 0.94; 95%CI: 0.62-1.40)[35].

The V-domain Ig-containing suppressor of T-cell activation (*VISTA*) gene has also shown promise as an immunotherapy biomarker in MM. It has been detected in > 85% of patients with MPM, and in two-thirds of cases, it was present in > 50% of cells. Unlike PD-1/PD-L1, it was primarily detected in epithelioid tumors and was associated with significantly improved OS, especially at an expression level > 40%[38]. The *VISTA* gene is thus a promising immunotherapy target and is currently being analyzed in prospective studies.

Tumor mutational burden (TMB) is another potential target, but expression levels vary considerably according to tumor type and are low in mesothelioma. Nonetheless, a recent study of pembrolizumab in the treatment of advanced solid tumors, including MM, showed that high tumor mutational burden expression (> 10 mutations) could identify patients with a better response to pembrolizumab monotherapy[39].

FUTURE PERSPECTIVES IN MESOTHELIOMA

Further advances in immunotherapy for MM in the near future will probably involve combinations of strategies with proven efficacy drugs and continued investigation of new targets and approaches, such as immune checkpoint inhibition combined with chemotherapy and/or antiangiogenic drugs (BEAT-Meso, PrE0506/DREAM3R, PEMBIB)[40]; targeted therapy with AXL inhibitors[41]; other checkpoint inhibitors such as VISTA (NCT02812875), BH73, lymphocyte activation gene-3 (LAG-3), and T cell immunoglobulin and mucin-domain containing-3 (TIM-3); radiotherapy; vaccine-based strategies (MESOVAX); and mesothelin-targeted and metabolism-based therapies.

Other immunomodulatory strategies under investigation are vaccination, T-cell transduction pathway therapies, dendritic cell immunotherapy, adoptive cell therapy (chimeric antigen receptor T-cell) (MesoCancerVa, DENIM)[42], and oncolytic viruses.

Vaccination with Wilms Tumor antigen (WT1) combined with chemotherapy (MESODEC, NCT02649829) and autologous tumor-infiltrating lymphocytes plus interleukin-2 is also being investigated.

Apart from exploring different treatment combinations in advanced MM, researchers should also analyze the benefits of immunotherapy in earlier-stage disease and its perioperative use with multimodal treatment approaches.

CONCLUSION

The treatment options for patients with MPM were very limited until recently and had remained largely unchanged for more than a decade. Recent years, however, have witnessed dramatic improvements in our understanding of this disease and a surge in new research and treatments. From a practical perspective, the main breakthrough has been made in the field of immunotherapy, with two phase III trials set to mark a paradigm shift positioning immune checkpoint inhibitors as first- and second-line

treatment options for MPM. CheckMate 743 is the first phase III trial in over a decade to show a survival benefit for a new treatment—combined CTLA-4 and PD-L1 inhibition–over standard chemotherapy in MPM. The data showed that nivolumab plus ipilimumab significantly improved OS and, as was to be expected based on data from other settings, had an acceptable safety profile. This new strategy is set to become a priority alternative for the frontline treatment of unresectable MPM. The results of the CONFIRM trial signaled another major milestone. In this double-blind randomized phase III trial, intravenous nivolumab 240 mg every 2 wk achieved a significant improvement in OS compared with placebo in patients with previously treated MPM, positioning it as a very likely alternative for the second-line treatment of patients with progressive disease after chemotherapy. Efforts to identify reliable biomarkers to help select the best candidates for immunotherapy must be intensified in the coming years. The evolving landscape will also drive further research into treatment combinations that will hopefully continue to improve OS in this population.

FOOTNOTES

Author contributions: All authors contributed equally to the elaboration of the manuscript.

Conflict-of-interest statement: Xabier Mielgo-Rubio declares the following conflicts of interest: Advisory role; Boehringer-Ingelheim, Astra Zeneca, Brystol Myers Squibb. Speakers' bureau; Roche, Astra Zeneca, Brystol Myers Squibb, MSD, Abbott. Research funding; Brystol Myers Squibb. Rest of authors declare declare any conflicts of interest.

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S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Gong ZM

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