Immune-Checkpoint Inhibitors in Malignant Pleural Mesothelioma: a meta-analysis

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Research Article

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Abstract

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive disease with poor prognosis. Many trials investigated the role of Immune Checkpoint Inhibitors (ICIs) in MPM, with contrasting results.

Methods

We performed a meta-analysis of clinical trials testing single-agent anti PD-1/PD-L1, anti-CTLA-4 or their combination in MPM patients. Objective response rate (ORR), disease control rate (DCR), 6 months progression-free survival (PFS) and 12 months overall survival (OS) rate were extracted, as well as safety data. The predictive role of PD-L1 was assessed, too.

Results

We selected 17 studies including 2328 patients. 12 months OS was 53% (95% CI 44–61%), 6 months PFS was 19% (95% CI 13–25%). Both OS and PFS were significantly higher with combined ICIs treatment than single agent anti PD-1/PD-L1 (respectively p < 0.001 and p = 0.006) or anti CTLA-4 (p < 0.001). ORR and DCR were 20% (95% CI 13–27%) and 56% (95% CI 45–67%) and did not significantly differ between combined and single agent ICIs (p = 0.088 and p = 0.058). 12 months OS and 6 months PFS rate did not differ significantly (p = 0.0545 and p = 0.1464) among pre-treated or untreated patients. Combined ICIs treatments have significantly higher rate of Adverse Events (AEs) (p = 0.01). PD-L1 positive patients have higher ORR, DCR and OS than PD-L1 negative patients.

Conclusion

ICIs are an efficient treatment option for MPM. Efficacy was independent from treatment line, so customized sequential strategy should still be speculated. PD-L1 expression could influence response to ICIs, however reliable biomarkers are warranted.

1. Introduction

Malignant pleural mesothelioma (MPM) is a highly aggressive disease associated with asbestos exposure [1–4]. The prognosis is poor and most of the patients have an inoperable disease at diagnosis. [3, 4] In this setting platinum-pemetrexed, with or without bevacizumab, has been the only approved first-line treatment regimen until October 2020 [2, 5, 6]. Gemcitabine and vinorelbine are widely used in pre-treated patients with only modest activity, while data on the use of PD-1 blocking in this setting are still contrasting. [7–12] More recently, the nivolumab and ipilimumab combination improved survival compared to platinum-pemetrexed chemotherapy in untreated patients in the Checkmate 743 trial, establishing a new standard for the first line treatment [13]. However, the small benefit in non-epithelioid histology and the higher rate of serious AEs, make it not suitable for frail and elderly patients. [13]

At present, the real clinical impact of immunotherapy in the management of MPM is difficult to ascertain due to several factors including the low number of patients included in early clinical trials, the different lines of treatment in which the ICIs are employed, and the different combinations of therapeutics used. For these reasons we decided to perform a meta-analysis of published data to assess the overall impact of ICIs in patients with MPM.

2. Methods

2. Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [14]. A protocol was created and registered on The International Prospective Register of Systematic Reviews (PROSPERO) website (Registration No.: CRD42021229532). Institutional review board permission was not necessary, as no individual patient-data was used for the meta-analysis.

2.1 Searching strategies and data sources
Studies published in English were searched among two database: MEDLINE® through Pubmed®, from 2005 to 05 December 2020, and EMBASE, from 2005 to 06 May 2021.

The following MeSH terms were applied: “Mesothelioma”, “Pleural Neoplasms”, “Immune Checkpoint Inhibitors”, “Immunotherapy”. Complete literature research string is reported on Suppl. Material.

2.2 Study selection and eligibility criteria

Randomized controlled trials (RCTS), phase I- II or III, assessing the efficacy of ICI (anti PD-1/PD-L1) monotherapy or in combination with chemotherapy or immunotherapy in patients affected from mesothelioma were included, as well as abstract from international congresses (ASCO- ESMO- WLCC) on immunotherapy and chemotherapy.

2.3 Objectives of the study

The main objective of this meta-analysis is to assess the efficacy of ICIs in MPM, comparing the effect of anti-CTLA-4 and PD-1/PD-L1 agents and between single or combination agents in first or second lines of therapy in terms of Overall Survival (OS) at 12 months, PFS at 6 months, Objective Response Rate (ORR), Disease Control Rate (DCR), Safety.

2.4 Data extraction

Two independent investigators (A.B and P.dM) extracted all data of the eligible studies. A third investigator checked the data (M.R.). Any inconsistency was discussed in the group. Data collected from the eligible studies were study name, year of publication, treatment regimen and line, information on PD-1, histologic subtypes, patients characteristics (median age, sex, ECOG PS), sample size, outcomes (OS, PFS, ORR, DOR), adverse events, and measures of effect (HR, OR, 95%CI, p-value) when available. If the HR and its 95% CI for OS or PFS were not reported, we calculated them according to published data. OS and PFS survival curves were digitized through a semi-automatic freely available tool, WebPlotDigitizer, that allows to extract OS and PFS estimates for each follow-up time-point. [15]

2.5 Statistical analysis

As the majority of the included studies were single-arm, OS and PFS could not be summarized in terms of hazard ratio (HR). Therefore, OS and PFS were synthetized across studies as proportions of patients surviving at 6- and 12-months. For the same reason, ORR, DCR and adverse events (AEs) were evaluated as proportions, too. For the stratified analyses according to PD-L1 expression, OS and PFS were synthetized in terms of HR. If eligible studies did not report HR estimates, we computed them from Kaplan-Meier curves using the methods described in Tierney et al [16]. ORR and DCR according to PD-L1 expression were summarized as odds ratio (OR). As we anticipate heterogeneity among RCTs, study-specific estimates were summarized across studies by means of a random-effects model. Moreover, each study-specific estimate was weighted by the inverse of its variance plus an estimate of the between-study variance component $\tau^2$ estimated through the DerSimonian and Laird moment estimator [17]. Results were displayed in forest plots. Between-studies heterogeneity was assessed through the Q test based on the $\chi^2$ statistics while the $I^2$ statistic was used to quantify the proportion of the total observed variability attributed to study heterogeneity. A leave-one-out sensitivity analysis was performed by iteratively removing 1 study at a time to assess whether the pooled estimate was influenced by any of the eligible studies. Publication biases were assessed by visual inspection of funnel plots for asymmetry, and by means of the Egger's test if the number of eligible studies was greater than 10.

2.6 RISK OF BIAS (quality) assessment

The Cochrane risk of bias tool (RoB) was used to assess risk of bias of eligible RCTs. Two independent investigators assessed the quality of the studies, and any divergences between them were resolved by discussion. Figure 1 suppl reports the risk of bias assessment.

3. Results

3.1 Literature research

We identified 46 studies from databases and registers. After electronic searching screening, title/abstract screening, and full-text review, 14 published studies and 3 studies from global conferences met our eligibility criteria. So, 17 trials were retained for analysis. The PRISMA 2020 flow diagram and reasons for study exclusion are presented in Fig. 1

The 17 trials included 2328 patients. [18–33] Characteristics of included trials and outcomes of interest are reported in Tables 1 and 2.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Blinding</th>
<th>Treatment</th>
<th>Dose</th>
<th>Control arm</th>
<th>Primary EPs</th>
<th>Stratification factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabrò et al. 2018, NIBIT-MESO-1&lt;sup&gt;18,19&lt;/sup&gt;</td>
<td>II</td>
<td>open label, single arm</td>
<td>durvalumab + tremelimumab</td>
<td>durva: 20 mg/kg 1q28 ipi: 1 mg/kg 1q28</td>
<td>/</td>
<td>ORR</td>
<td>/</td>
</tr>
<tr>
<td>Calabrò et al. 2013&lt;sup&gt;21&lt;/sup&gt;</td>
<td>II</td>
<td>open label, single arm</td>
<td>tremelimumab</td>
<td>15 mg/kg ev 1q90</td>
<td>/</td>
<td>ORR</td>
<td>EORTC prognostic score</td>
</tr>
<tr>
<td>Calabrò et al. 2015&lt;sup&gt;22&lt;/sup&gt;</td>
<td>II</td>
<td>open label, single arm</td>
<td>tremelimumab</td>
<td>10 mg/kg 1q28 for 4 cycles, then every 12 weeks</td>
<td>/</td>
<td>ORR</td>
<td>EORTC prognostic score</td>
</tr>
<tr>
<td>Nowak A.K et al. 2020, DREAM&lt;sup&gt;23&lt;/sup&gt;</td>
<td>II</td>
<td>open label, single arm</td>
<td>durvalumab + chemotherapy</td>
<td>durvalumab 1125 mg 1q21 cisplatin 75 mg/m2 or carboplatin AUC5 + pemetrexed 500 mg/m2</td>
<td>/</td>
<td>PFS</td>
<td>/</td>
</tr>
<tr>
<td>Baas P. et al. 2021, CheckMate 743&lt;sup&gt;16&lt;/sup&gt;</td>
<td>III</td>
<td>open label, randomized</td>
<td>nivolumab + ipilimumab</td>
<td>nivolumab 3 mg/kg 1q14 ipilimumab 1mg/kg 1q42</td>
<td>/</td>
<td>OS</td>
<td>Sex, Histology</td>
</tr>
<tr>
<td>Quispel-Janssen J. et al. 2018, NivoMes&lt;sup&gt;33&lt;/sup&gt;</td>
<td>II</td>
<td>open label, single arm</td>
<td>Nivolumab</td>
<td>3 mg/kg 1q14</td>
<td>/</td>
<td>DCR at 12 weeks</td>
<td>/</td>
</tr>
<tr>
<td>Popat A. et al. 2020, PROMISE-meso&lt;sup&gt;13&lt;/sup&gt;</td>
<td>III</td>
<td>open label, randomised</td>
<td>Pembrolizumab</td>
<td>200 mg 1q21 gemicitabine/vinorelbine</td>
<td>PFS</td>
<td>Histology</td>
<td>/</td>
</tr>
<tr>
<td>Fennel DA et al. 2021, CONFIRM&lt;sup&gt;14&lt;/sup&gt;</td>
<td>III</td>
<td>Double blind, randomized</td>
<td>Nivolumab</td>
<td>3 mg/kg 1q14 placebo</td>
<td>OS e PFS (IA, investigator assessed)</td>
<td>Histology</td>
<td>/</td>
</tr>
<tr>
<td>Okada M. et al. 2019, MERIT&lt;sup&gt;32&lt;/sup&gt;</td>
<td>II</td>
<td>open label, single arm</td>
<td>Nivolumab</td>
<td>240 mg 1q14</td>
<td>/</td>
<td>ORR (CA, centrally assessed)</td>
<td>/</td>
</tr>
<tr>
<td>Maio M. et al. 2017, DETERMINE&lt;sup&gt;26&lt;/sup&gt;</td>
<td>IIb</td>
<td>Double blind</td>
<td>Tremelimumab</td>
<td>10 mg/kg 1q28 for 7 doses, then every 12 weeks placebo</td>
<td>OS</td>
<td>EORTC status, line of therapy, anatomic site</td>
<td>/</td>
</tr>
<tr>
<td>Alley W et al. 2017, KEYNOTE-028&lt;sup&gt;29&lt;/sup&gt;</td>
<td>IIb</td>
<td>open label, single arm</td>
<td>Pembrolizumab</td>
<td>10 mg/kg 1q14 o 1q21 or 2 mg/kg 1q21</td>
<td>/</td>
<td>ORR</td>
<td>/</td>
</tr>
<tr>
<td>Trial</td>
<td>Phase</td>
<td>Blinding</td>
<td>Treatment</td>
<td>Dose</td>
<td>Control arm</td>
<td>Primary EPs</td>
<td>Stratification factors</td>
</tr>
<tr>
<td>--------------------------------------------</td>
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<tr>
<td>Yap T. et al. 2021, KEYNOTE-158</td>
<td>II</td>
<td>open label, single arm</td>
<td>Pembrolizumab</td>
<td>200 mg 1 q21</td>
<td>/</td>
<td>ORR (CA)</td>
<td>/</td>
</tr>
<tr>
<td>Hassan R. et al 2019, JAVELIN</td>
<td>Ib</td>
<td>open label, single arm</td>
<td>Avelumab</td>
<td>10 mg/kg 1q14</td>
<td>/</td>
<td>ORR (IA)</td>
<td>/</td>
</tr>
<tr>
<td>Desai et al. 2018</td>
<td>II</td>
<td>open label, single arm</td>
<td>Pembrolizumab</td>
<td>200 mg 1q21</td>
<td>/</td>
<td>ORR</td>
<td>/</td>
</tr>
<tr>
<td>Sherpereel A et al. 2019, MAPS-2</td>
<td>II</td>
<td>open label, randomized</td>
<td>Nivolumab or Nivolumab + Ipilimumab</td>
<td>Nivolumab 3 mg/kg</td>
<td>/</td>
<td>DCR</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ipilimumab 1 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venkatraman D et al. 2019</td>
<td>II</td>
<td>open label, single arm</td>
<td>Durvalumab + Tremelimumab</td>
<td>Durval: 1500 mg 1q28</td>
<td>/</td>
<td>ORR</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tremel: 75 mg 1q28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D Disselhorst MJ et al. 2019 INITIATE</td>
<td>II</td>
<td>open label, single arm</td>
<td>Nivolumab + Ipilimumab</td>
<td>nivo: 240 mg 1q14</td>
<td>/</td>
<td>DCR IA 12 W</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ipi: 1 mg/kg 1q42</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2

**Selected trials outcome by main endpoints.** ORR: Overall Response Rate, PFS: Progression Free Survival, OS: Overall Survival, DCR: Disease Control Rate, CA: Centrally Assessed, IA: Investigator Assessed; NE: Not evaluated; NR: Not Reached; CI: confidence interval; IQR: Inter Quantile Range

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pts n</th>
<th>mFUP (months; IQR)</th>
<th>mPFS (months; 95%CI)</th>
<th>mOS (months; 95%CI)</th>
<th>ORR (%)</th>
<th>mDOR (months; 95%CI)</th>
<th>DCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabrò et al. 2018, NiBIT-MESO-1&lt;sup&gt;21,22&lt;/sup&gt;</td>
<td>40</td>
<td>19.2 (13.8–20.5)</td>
<td>8.0 (6.7–9.3)</td>
<td>16.6 (13.1–20.1)</td>
<td>28 (15–44)</td>
<td>16.1 (IQR 11.5–20.5)</td>
<td>65 (48–79)</td>
</tr>
<tr>
<td>Calabrò et al. 2013&lt;sup&gt;21&lt;/sup&gt;</td>
<td>29</td>
<td>27 (23–35)</td>
<td>6.2 (1.3–11.1)</td>
<td>10.7 (0–21.9)</td>
<td>6.9% (0–0.16.1)</td>
<td>12.4 (6–30)</td>
<td>31.0 (14.0–47.9)</td>
</tr>
<tr>
<td>Calabrò et al. 2015&lt;sup&gt;22&lt;/sup&gt;</td>
<td>29</td>
<td>21.3 (18.7–25.9)</td>
<td>6.2 (5.7–6.7)</td>
<td>11.3 (3.4–19.2)</td>
<td>3.4%; 0–10.0</td>
<td>NE</td>
<td>37.9 (20.2–55.6)</td>
</tr>
<tr>
<td>Nowak A.K et al. 2020, DREAM&lt;sup&gt;23&lt;/sup&gt;</td>
<td>54</td>
<td>28.2 (26.5–30.2)</td>
<td>6.9 (5.5–9.0)</td>
<td>18.4 (13.1–24.8)</td>
<td>48 (35–61)</td>
<td>5.6 (4.9–12.3)</td>
<td>87 (80–91)</td>
</tr>
<tr>
<td>Baas P. et al. 2021, CheckMate 743&lt;sup&gt;16&lt;/sup&gt;</td>
<td>605 (303)</td>
<td>29.7 (26.7–32.9)</td>
<td>6.8 (5.6–7.4)</td>
<td>18.1 (16.9–22.0)</td>
<td>40 (34.1–45.4)</td>
<td>11 (1.45–3.27)</td>
<td>77 (71.4–81.2)</td>
</tr>
<tr>
<td>Quispel-Janssen J. et al. 2018, NivoMes&lt;sup&gt;33&lt;/sup&gt;</td>
<td>34</td>
<td>27.5 (19.3–NR)</td>
<td>2.6 (2.23–5.49)</td>
<td>11.8 (9.7–15.7)</td>
<td>24 (NR)</td>
<td>7.0 (&gt;3)</td>
<td>47 (NR)</td>
</tr>
<tr>
<td>Popat A. et al. 2020, PROMISE-meso&lt;sup&gt;13&lt;/sup&gt;</td>
<td>144 (73)</td>
<td>17.5 (9.9–14.5)</td>
<td>2.5 (2.1–4.2)</td>
<td>10.7 (7.6–15.0)</td>
<td>22 (13–33)</td>
<td>4.6 (2.1–NR)</td>
<td>45 (39–55)</td>
</tr>
<tr>
<td>Fennel DA et al. 2021, CONFIRM&lt;sup&gt;14&lt;/sup&gt;</td>
<td>332 (221)</td>
<td>11.6 (7.2–16.8)</td>
<td>3.0 (2.8–4.1)</td>
<td>10.2 (8.5–12.1)</td>
<td>11 (NR)</td>
<td>4.6 (3.0–6.9)</td>
<td>12 (NR)</td>
</tr>
<tr>
<td>Okada M. et al. 2019, MERIT&lt;sup&gt;32&lt;/sup&gt;</td>
<td>34</td>
<td>16.8 (1.8–20.2)</td>
<td>6.1 (2.9–9.9)</td>
<td>17.3 (11.5–NR)</td>
<td>29 (16.8–46.2)</td>
<td>11.1 (3.5–16.2)</td>
<td>68 (50.8–80.9)</td>
</tr>
<tr>
<td>Maio M. et al 2017, DETERMINE&lt;sup&gt;26&lt;/sup&gt;</td>
<td>571 (382)</td>
<td>NE</td>
<td>NE</td>
<td>7.7 (6.8–8.9)</td>
<td>4.5 (2–6–7.0)</td>
<td>4.8 (2.6–8.3)</td>
<td>27.7 (16.0–28.3)</td>
</tr>
<tr>
<td>Alley W et al 2017, KEYNOTE-028&lt;sup&gt;29&lt;/sup&gt;</td>
<td>25</td>
<td>18.7 (10.4–24.0)</td>
<td>5.4 (3.4–7.5)</td>
<td>18 (9.4–NR)</td>
<td>20 (6.8–40.7)</td>
<td>12.0 (3.7–NR)</td>
<td>72 (NE)</td>
</tr>
<tr>
<td>Yap T. et al. 2021, KEYNOTE-158&lt;sup&gt;30&lt;/sup&gt;</td>
<td>118</td>
<td>38.5 (37.5–39.2)</td>
<td>2.1 (2.1–3.9)</td>
<td>10.0 (7.6–13.4)</td>
<td>8 (4–15)</td>
<td>14.3 (4–33.9)</td>
<td>46 (NE)</td>
</tr>
<tr>
<td>Hassan R. et al 2019, JAVELIN&lt;sup&gt;28&lt;/sup&gt;</td>
<td>53</td>
<td>24.8 (16.8–27.8)</td>
<td>4.1 (1.4–6.2)</td>
<td>10.7 (6.4–20.2)</td>
<td>19 (3.1–20.7)</td>
<td>15.2 (11.1–NR)</td>
<td>58</td>
</tr>
<tr>
<td>Desai et al. 2018&lt;sup&gt;37&lt;/sup&gt;</td>
<td>65</td>
<td>NR</td>
<td>4.5 (2.3–6.2)</td>
<td>11.5 (7.6–14)</td>
<td>19</td>
<td>NE</td>
<td>66</td>
</tr>
<tr>
<td>Sherpereel A et al. 2019, MAPS-2&lt;sup&gt;31&lt;/sup&gt; (nivo cohort)</td>
<td>125 (63)</td>
<td>20.1 (19.6–20.3)</td>
<td>4.1 (2.8–5.7)</td>
<td>11.9 (6.7–17.7)</td>
<td>19 (8–29)</td>
<td>7.4 (4.1–11.9)</td>
<td>40 (28–52)</td>
</tr>
<tr>
<td>Sherpereel A et al. 2019, MAPS-231 (nivo-ipi cohort)</td>
<td>125 (62)</td>
<td>20.1 (19.6–20.3)</td>
<td>5.6 (3.1–8.9)</td>
<td>15.9 (10.7–NR)</td>
<td>28 (16–40)</td>
<td>8.3 (3.0–14.0)</td>
<td>52 (39–64)</td>
</tr>
<tr>
<td>Venkatraman D et al. 2019&lt;sup&gt;38&lt;/sup&gt;</td>
<td>19</td>
<td>7.1 (NE)</td>
<td>2.8 (2.0–5.7)</td>
<td>7.8 (6.2–NR)</td>
<td>5 (NE)</td>
<td>NE</td>
<td>52.6 (NE)</td>
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<tr>
<td>Trial</td>
<td>Pts n (experimental arm)</td>
<td>mFUP (months; IQR)</td>
<td>mPFS (months (95%CI))</td>
<td>mOS (months (95%CI))</td>
<td>ORR (%) (IQR)</td>
<td>mDOR (months (95%CI))</td>
<td>DCR (%) (IQR)</td>
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<tr>
<td>D Disselhorst MJ et al 2019 INITIATE 27</td>
<td>35</td>
<td>14.3 (12.7–15.7)</td>
<td>6.2 (4.1–NR)</td>
<td>NR (12.7–NR)</td>
<td>29 (NE)</td>
<td>14.3 (6.4–NR)</td>
<td>68 (NE)</td>
</tr>
</tbody>
</table>

3.2 Meta-analysis: overall outcomes

Overall, 12 months OS rate with ICIs treatment is 53% (95% CI 44–61%). The pooled estimate 12 months OS rate is significantly higher with combination treatment (66%; 95% CI 61–70%) than single agent anti PD-1/PD-L1 (51%, 95% CI 45–57%; p < 0.0001) or anti CTLA-4 (40%, 95% CI 27–54%; p < 0.0001) (Fig. 2A) The 6 months PFS rate with ICIs is 19% (95% CI 13–25%). 6 months PFS rate is significantly higher with combination treatment (29%; 95% CI 24–33%) compared to single agent anti PD-1/PD-L1 (16%, 95% CI 12–20%; p = 0.006) or anti-CTLA4 (5%, 95% CI 1–12%; p < 0.0001). (Fig. 2B)

No studies have a significant influential effect. However, when considering studies grouped by agent, the DREAM trial [20] has an influential effect on 12months OS, as well as the DETERMINE [23] and CHECKMATE 743 trials [13]. The NIBIT-MESO-1 [18] and MAPS2 [28] trials exhibited an influential effect on 6 months PFS. Supplementary Fig. 2 reports funnel plots for 12months OS (Panel A), 6 months PFS (Panel B), ORR (Panel C) and DCR (Panel D). Evidence of asymmetry emerged for 6 months PFS (p = 0.001).

Taken together, ICIs show 20% ORR (95% CI 13–27%): 21% for anti PD-1/PD-L1 (CI 95% 13–28%), 5% for anti CTLA-4 (CI 95%, 2–9%), 26% for the combination of anti CTLA-4 and anti PD-1/PD-L1 (CI 95% 12–39%). (Fig. 2C). The pooled estimate DCR was 56% (CI 95% 45–67%). Combination treatments have the highest DCR (64%, 95% CI 52–76%), followed by single-agent PD-1/PD-L1 (59%, 95% CI 47–71%) and single agent anti CTLA-4 (35%, 95% CI 21–48%). (Fig. 2D

Overall, no studies have a significant influential effect on ORR and DCR pooled estimates. ORR and DCR were not statistically significant different between combined treatment or single agent anti PD-1/PD-L1 (respectively, p = 0.088 and p = 0.058), while they were significantly higher when compared to anti CTLA-4 (p < 0.0001). When considering studies grouped by agent, the DREAM trial [20] has an influential effect, as well as the DETERMINE trial [23], the MESOTREM – 2008 [21] for ORR only and the MESOTTREM-2012 [22] for DCR only. For the combination of anti CTLA-4 and anti PD-1/PD-L1, the NCT03075527 [32] and the MAPS2 trials [28] exhibited an influential effect on ORR and DCR, respectively.

PD-L1 positive patients have 2.24 (95% CI, 1.27, 4.12) higher chance of response with respect to PD-L1 negative with anti PD-1/PD-L1 or combination treatment. The OR was higher with single agent anti PD-1/PD-L1 (OR 2.49, 95% CI 1.06–5.84) than with combined anti PD-1 and CTLA-4 (OR 2.04, 95% CI, 0.92–4.54). (Fig. 3A Suppl.)

Furthermore, PD-L1 positive patients have 1.59 higher chance of achieving disease control than PD-L1 negative (OR 1.59, 95% CI 1.06–2.41). The OR was similar considering single agent (OR 1.50, 95% CI 0.74–3.03) or combination treatment (OR 1.66, 95% CI 0.26–10.68). (Fig. 3B Suppl.) Finally, PD-L1 positive patients have 29% (HR 0.71, 95% CI 0.52–0.96) lower risk of death and 28% (HR 0.72, 95% CI 0.55–0.95) lower risk of disease progression than PD-L1 negative. (Fig. 3C and 3D Suppl.)

Overall, ADRs of any grade were reported in 84% (95% CI 78–89%). ADRs of any grade were slightly higher with combined treatment (87%, 95% CI 77–97%) than single agent therapy (82%, 95% CI 74–90%), p = 0.01. G3-G4 ADRs occurred in 24% (95% CI 13–34%). Higher rate of G3-G4 ADRs were observed in combination treatment (28%, 95% CI 21–35%) than mono therapy (22%, 95% CI 8–36%). (Fig. 3)

3.3 Meta-analysis: first line outcomes

Patients treated in first line have a 68% (95% CI 63–72%) probability of survival at 12 months with combined treatment. The 6 months PFS rate was 28% (95% CI, 21–35%), while ORR and DCR were respectively 41% (95% CI, 36–46%) and 79% (95% CI, 68–89%).

ORR and DCR were statistically significant higher in first line rather than in pretreated patients with the combination treatment (respectively p < 0.0001 and p = 0.0112). However, 12 months OS and 6 months PFS rate did not differ significantly (p = 0.0545 and p = 0.1464) Fig. 4 Suppl.

3.4 Meta-analysis: second line treatment
The 12 months OS rate for second and third line of treatment was 52% (95% CI 44–61%) for patients treated with either anti PD-1/PD-L1, anti CTLA-4 or the combination of both. Respectively, the probability of survival at 12 months was higher with ICIs combination (60%, 95% CI 50–70%), followed by single agent anti PD-1/PD-L1 (48%, 95% CI 43–53%) and CTLA-4 (40%, 95% CI 27–54%). The difference was statistically significant (p < 0.01).

The pooled 6 months PFS estimate was 16% (95% CI 11–21%). This was higher for combination treatment 25% (95% CI 17–34%), followed by single agent anti PD-1/PD-L1 (15%, 95% CI 11–19%) and anti CTLA-4 (5%, 95% CI 0–10%). This difference was statistically significant (p < 0.01).

Taken together, ICIs treatment registered a 16% ORR (95% CI, 11–21%) and 52% DCR (95% CI, 44–61%). ORR was higher with combination (21%, 95% CI 8–33%), than single agent anti PD-1/PD-L1 (17%, 95% CI 12–22%) and anti CTLA-4 (5%, 95% CI 2–9%).

The overall DCR was 52% (95% CI, 44–61%). It was higher with combination treatment 60% (95% CI 50–69%), followed by anti PD-1/PD-L1 (55%, 95% CI 46–63%) and single agent anti-CTLA 4 (35%, 95% CI 21–48%).

**Figure 4 Suppl.**

**4. Discussion**

We performed a systematic review and meta-analysis to assess the impact of immunotherapy, anti-PD-1/PD-L1 and anti- CTLA-4, in MPM patients in terms of PFS, OS, ORR, DCR and safety. MPM is an aggressive disease somehow refractory to traditional cytotoxic chemotherapy.

MPM is considered a highly inflammatory TME, as the consequence of an inflammatory response to asbestos exposure. [34–37] However, a deeper characterization of its tumor microenvironment revealed the prevalence of chemokines and suppressive immune cells, M2-like macrophages and regulatory T cells, low tumor mutational burden and paucity of activated T cells, which make MPM less sensitive to immunotherapy. [38, 39]

Data on the use of ICIs are contrasting and it might be difficult to drive conclusion on their real clinical impact in MPM. Recently, the combination of nivolumab and ipilimumab significantly increased OS as compared to platinum plus pemetrexed chemotherapy, becoming a new gold standard of treatment in the first-line setting. [13, 40] However, while the magnitude of benefit was clearly superior for ICIs combination in non-epithelioid tumors, it was less evident in patients with epithelioid MPM. [13] Thus, whether ICIs combination should be the preferred choice in these patients in the first line setting is still a matter of debate. In the meantime results of the phase III randomized clinical trial with chemo-immunotherapy combination are awaiting. [41, 42]

Vinorelbine or gemcitabine have only modest efficacy as second-line treatment, with ORR of 8.63%, a DCR of 54.8%, and a median PFS and OS of 3.4 and 7.86 months, respectively. [43]

More recently in the phase II randomized VIM trial vinorelbine demonstrated an impact on mPFS compared to active supportive care (4.2 vs 2.8 months); the primary end point was met even if the use of chemotherapy didn't seem to impact on secondary outcome measure mOS. [8] On the contrary, a randomized phase II trial showed that the addition of ramucirumab, an anti-vascular endothelial growth factor receptor 2 (VEGFR-2) monoclonal antibody, improved OS compared to gemcitabine and placebo, without, however, any improvement in PFS or ORR. [44]

Data on the use of ICIs in pre-treated patients are contrasting and suggest only mild efficacy. [45]

Our meta-analysis confirmed the activity of ICIs in MPM patients in terms of OS, PFS and response rate in any line of treatment. As expected, combination of anti-CTLA-4 and anti-PD-1 showed the higher OS, PFS, ORR and DCR both in first and second line setting, buried however by higher rate of AEs, particularly G3-G4. Interestingly, in the second line setting single agent anti PD-1/PD-L1 reported a 17% ORR and 55% DCR, which are slightly higher compared to historical data of standard second line gemcitabine or vinorelbine chemotherapy and do not significantly differ from the combination treatment (respectively 21% ORR and 60% DCR). Therefore, single agent ICI could represent an option for those patients who cannot be candidates for combined ICIs treatment, as elderly and frail patients. Furthermore, data coming from the Checkmate 743 trial, suggest that in patients with epithelioid MPM, who did not derive meaningful benefit from combined ICIs treatment, a sequential strategy of platinum-pemetrexed chemotherapy and single agent anti PD-1/PD-L1 at disease progression should still be taken into account. Single agent anti CTLA-4 also confirmed lack of activity also in our meta-analysis.
There are two meta-analysis already published that underpinned our results focusing on ICIs efficacy in pretreated setting.\textsuperscript{46, 47} However, one meta-analysis didn't analyze the role of ICIs combination in first line setting \textsuperscript{46} and the second one has investigated not only the role of immunotherapy but also further experimental agents including antiangiogenics in a population of pretreated patients \textsuperscript{47}.

Since most of the studies included in our meta-analysis lack a comparison arm, we were not able to compare ICIs with single-agent chemotherapy nor to carry out a network meta-analysis. In addition, we should acknowledge that the DOR outcome could not be synthetized in a meta-analysis of published data since its confidence interval is asymmetric and could not be considered normally distributed. The selected trials have used different criteria for response evaluation such as mRECIST and iRECIST, and some of the considered cases did not have independent assessment. Furthermore, we could not evaluate the activity of ICIs in pre-treated patients according to histology since a few studies reported specific data.

The results of our meta-analysis suggest a role of ICI combinations in first line setting showing a more robust activity and efficacy than in pretreated populations in which the use of immunotherapy could be reserved to a frail MPM subpopulation.

Although the early use of ICIs in the first line has proved beneficial in other cancers, it is not possible to conclude that this will be the case in all patients with pleural mesothelioma.

The lack of predictors of response and the confounding effects between predictive and prognostic factors make the issue of immunotherapy efficacy still confusing.

Our data showed that PD-L1 positive patients have higher probability of response or achieving disease control with ICIs treatment than PD-L1 negative, considering 1\% of expression as cut-off for positivity. This is in line to what reported Tagliamento et al. \textsuperscript{46}. However, the role of PD-L1 is still debating. A recent meta-analysis on this topic performed on 29 trials concluded that PDL1 status was not an established prognostic nor predictive biomarker. \textsuperscript{48} In many trials employing chemotherapy agents PD-L1 > 1\% patients had a higher risk of death compared to PDL1 negative counterparts with a proportional association of the degree of expression. \textsuperscript{49} With the introduction of ICIs, some clinical trials demonstrated a trend of favorable effect leading to a longer survival rate in patients with PD-L1–positive tumors than patients with PD-L1–negative tumors. \textsuperscript{49} The small size of studies analyzed, the heterogeneity of other clinical variables (like histology, PS, line of treatment), different PD-L1 essay and clones, and cut-off points are all factors that negatively influence a definitive conclusion about the role of this biomarker. Curiously, in our metanalysis the OR was higher for single agent than for combined ICIs. These data may suggest that combining anti PD-1/PD-L1 with anti-CTLA- 4 should increase the chance of response in PD-L1 negative patients.

Many other confounding effects can determine the uncertainty of the use of ICIs in an unselected population, as the BAP1 loss of expression, which emerges as a predictor of response to chemotherapy, or chromosomal rearrangements (chromoplexy and chromothripsis).\textsuperscript{50–53} All these other predictors of response may affect the final efficacy results of immunotherapy. Such interesting data deserve more studies in the context of ICIs therapy to identify better predictors of response.

Finally, new therapeutic approaches are under investigation, as adoptive immunotherapy as well as vaccines, alone or in combination with ICIs.\textsuperscript{54} Results from ongoing phase III trial of chemo-immunotherapy combination in the first line setting, along with the results of the Checkmate 743, are expected to change the treatment landscape in the next features.

5. Conclusions

In conclusion, our meta-analysis confirmed the activity of combined ICIs treatment and suggests that anti-PD-(L)1 single agents might be useful in some chemotherapy pre-treated patients. Reliable predictive biomarkers are needed to personalize and customize treatment.

Declarations

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

**Figure 1**

**PRISMA Flowchart of selected trials.** †The studies by Hayashi et al., 2020 and Calabrò et al., 2021 are updates of the MERIT (Okada et al., 2019) and NIBIT-MESO1 (Calabrò et al., 2018) RCTs.
Figure 2

Efficacy end-point by agent. A) OS probability at 12 months B) PFS probability at 6 months C) ORR D) DCR

Figure 3

Efficacy end-point by agent. A) G3/G4 AEs posted estimate (p<0.01) B) G3/G4 AEs posted estimate (p<0.01)
**Adverse Events.** A) Any grade B) G3-G4

**Supplementary Files**

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