Meta-Analysis on the Combination of Chemotherapy With Programmed Death-Ligand 1 and Programmed Cell Death Protein 1 Blockade as First-Line Treatment for Unresectable Pleural Mesothelioma.

Brief report: Meta-analysis on chemotherapy and PD-(L)1 blockade combination as first-line treatment for unresectable pleural mesothelioma

Marco Tagliamento[1,2], Massimo Di Maio[3,4], Jordi Remon[1], Paolo Bironzo[4,5], Carlo Genova[2,6], Francesco Facchinetti[7], Mihaela Aldea[1,8], Cecile Le Pechoux[9], Silvia Novello[4,5], Fabrice Barlesi[1,8], Benjamin Besse[1,8], David Planchard[1,8]

[1] Department of Cancer Medicine, Gustave Roussy, Villejuif (France)
[2] Department of Internal Medicine and Medical Specialties, University of Genova, Genova (Italy)
[3] Medical Oncology, Ordine Mauriziano Hospital, Turin (Italy)
[4] Department of Oncology, University of Turin, Turin (Italy)
[5] Thoracic Oncology, San Luigi Gonzaga Hospital, Orbassano (Italy)
[6] UO Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova (Italy)
[7] Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, (USA)
[8] Paris-Saclay University, Orsay, France
[9] Department of Radiation Oncology, Gustave Roussy, Villejuif (France)

Corresponding author:

Dr. David Planchard
Medical Oncology Department, Gustave Roussy
114 Rue Edouard Vaillant
94805 Villejuif (France)
David.PLANCHARD@gustaveroussy.fr

ABSTRACT

Background: Dual immune checkpoint blockers (ICBs) regimen represents a standard first-line therapy in unresectable pleural mesothelioma (PM). Novel combination strategies, including ICBs and antiangiogenic drugs, are currently under investigation in this setting. We aimed to assess the efficacy of chemo-immunotherapy combination by reference of literature evidence.

Methods: A systematic review and meta-analysis of trials with first-line platinum-based chemotherapy associated with anti-PD(L)1 agents in unresectable PM. We estimated weighted summary proportion of disease response, along with landmark probability of survival outcomes.

Results: 349 patients with unresectable PM from four trials (DREAM, PrE0505, JME-001, IND.227) were included, 79% (n=274) with epithelioid and 21% (n=75) with non-epithelioid histologic type. In aggregate, objective response rate (ORR) was 59.2% (95%CI: 50.3%-67.9%) and disease control rate (DCR) was 92.2% (95%CI: 89.2%-94.8%). Comparing epithelioid vs. non-epithelioid tumors, the ORR was 64.5% vs. 46.4%, ($p<0.001$) and the DCR was 92.3% vs. 80.0%, ($p=0.043$), with on odds ratio of 2.56 (95%CI: 1.51-4.32) for disease response and of 3.37 (95%CI: 0.99-11.47) for disease control. Aggregated estimated probability of progression-free survival was 63% (95%CI: 53%-71%) at 6 months and 25% (95%CI: 21%-31%) at 12 months, whereas 6-, 12- and 24-month overall survival rates were 88% (95%CI: 81%-93%), 71% (95%CI: 61%-79%) and 39% (95%CI: 34%-45%), respectively.

Conclusion: According to our analysis, first-line chemo-immunotherapy shows promise as a potential novel treatment approach for PM, exhibiting encouraging survival outcomes and an enhanced response rate, including for the epithelioid subtype. Ongoing studies are necessary to establish its precise placement within the treatment algorithm.

INTRODUCTION

The natural history of unresectable pleural mesothelioma (PM) is characterized by an unfavorable clinical scenario with dismal 1-year survival rates. Platinum and pemetrexed has long been the standard therapy in this setting.[1] Bevacizumab added to platinum-doublet increased the overall survival (OS) over the sole chemotherapy.[2] The advent of immune checkpoint blockers (ICBs) has marked a turnaround point in the approach to this tumor.[3,4] Based on OS improvement with nivolumab plus ipilimumab over standard chemotherapy, dual immunotherapy obtained approval from FDA and EMA as frontline treatment approach.[5] Nevertheless, the heterogeneity behind histologic subtypes and response to treatment leave rooms for exploring combination strategies aiming to improve the performance of ICBs and optimize the therapeutic sequence[6].

We have conducted a systematic review and meta-analysis of trials that assessed the combination of platinum-based chemotherapy and programmed cell death-(ligand)-1 [PD-(L)1] ICBs as first-line therapy in unresectable PM, to provide a synthesis of the measures of activity and of the time-to-event outcomes.

METHODS

Search Strategy and Selection Criteria

A systematic literature search of PubMed/Medline and Cochrane databases was performed on June 25, 2023. The searching strategy was: Mesothelioma AND (Nivolumab OR Pembrolizumab OR Atezolizumab OR Avelumab OR Durvalumab) AND (Chemotherapy OR Platinum). We also reviewed conference proceedings from European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), World Conference on Lung Cancer (WCLC) and European Lung Cancer Congress (ELCC) from 2016 onwards. All included articles were cross-referenced to identify pertinent records. We considered only the most updated data when multiple reports of the same study were available. The criteria for inclusion in the meta-analysis were: (1) studies enrolling adult patients with unresectable PM; (2) prospective trials testing first-line combination treatment between chemotherapy and anti-PD-(L)1; (3) availability or possibility to estimate objective response rate (ORR), disease control rate (DCR), rate of progression-free survival (PFS) and OS; (4) papers or abstracts in English.

Data Analysis

We extracted the following variables from each study: first author; year of publication; study design and methodology; number of patients included in each study/arm; patient's and disease's

characteristics; number of patients treated with chemo-immunotherapy combination; number of patients achieving a complete response (CR), partial response (PR) or stabilization of disease (SD) as best response per RECIST modified for mesothelioma; median PFS and OS; rate of PFS and OS and number of patients at risk at survival landmark times; response and survival data according to histologic subtype. Main objectives were: 1) To estimate weighted summary proportion of ORR and DCR with chemo-immunotherapy combination, 2) To estimate the probability of being progression free and/or alive at 6, 12 and 24 months with chemo-immunotherapy combination. Subgroup analyses by histologic type were also conducted. We calculated weighted summary proportion of ORR and DCR under the fixed and the random effect model with Freeman-Tukey transformation, with differences according to histology tested as odds ratio by Mantel-Haenszel test. The probability of being progression free and/or alive at 6, 12 and 24 months were estimated by Kaplan-Meier method, by pooling the number of patients at risk and censored at each defined landmark time. Heterogeneity was measured by Cochran's Q, while Inconsistency was computed by I^2 statistic. The likelihood of publication bias was assessed by both Egger's and Begg's tests and by visual inspection of funnel plots. Tests were two-sided, and a p-value <0.05 was considered statistically significant. Analyses were performed by M.D.M. with MedCalc Statistical Software version 20.015 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

RESULTS

Out of 257 identified records, four phase II or III trials were included in the meta-analysis (Figure 1)[7–10]: two testing durvalumab (the DREAM and PrE0505 trials),[7,8] one testing nivolumab (the JME-001 trial)[9] and one with pembrolizumab (IND.227, chemotherapy + immunotherapy arm)[10]. 349 patients with unresectable PM were eligible and evaluable. In all the trials, chemotherapy with platinum and pemetrexed was administered for up to 6 cycles. Nivolumab was continued until disease progression, durvalumab for maximum of 12 months while pembrolizumab up to two years. Table S1 summarizes patients' characteristics and results of the selected trials. 78% of the patients were male, 46% and 54% had an ECOG performance status 0 and 1, respectively. Overall, 274 patients (79%) had epithelioid PM, and 187 cases who had been analyzed for PD-L1 had a tumor-proportion score $\geq$1%. The median follow-up ranged between 15.2 and 28.2 months.

Disease response: ORR and DCR

Weighted summary proportion of ORR and DCR results are shown in Figure 2. ORR was 59.2% (95%CI: 50.3%-67.9%) among the overall population including epithelioid and non-epithelioid tumors. The Cochran's Q had a p level of 0.101, the I^2 test showed a moderate inconsistency (51.83%). The funnel plot for publication bias is given in Figure S1. In aggregate, DCR was 92.2% (95%CI: 89.2%-94.8%) when evaluating any histology. The Cochran's Q test for heterogeneity was not significant (p=0.465, I^2 not evaluable). Publication bias is given in Figure S2. Forest plots for ORR and DCR according to histologic type are shown in Figure S3 and S4.

ORR was significantly higher in patients with epithelioid PM than in those with non-epithelioid tumors: 64.5% (95%CI: 58.7%-70.0%; Cochran's Q p=0.396, I^2=not evaluable) vs. 46.4% (95%CI: 23.3%-70.5%, Cochran's Q p=0.015, I^2=71.55%), with an odds ratio (OR) for disease response of 2.56 (95%CI: 1.51-4.32, p<0.001). Publication bias is given in Figure S5. DCR was also improved in epithelioid tumors than non-epithelioid subtype: 92.3% (95%CI: 85.4%-97.1%, Cochran's Q p=0.287, I^2=19.89%) vs. 80.0% (95%CI: 64.0%-92.1%, Cochran's Q p=0.521, I^2 not evaluable). The OR for disease control was 3.37 (95%CI: 0.99-11.47, p=0.043). Publication bias is given in Figure S6.

Survival analysis: landmark probabilities of PFS and OS

Overall, median PFS in the four evaluated studies ranged from 6.7 to 8.0 months, and median OS from 17.3 to 20.8 months. Landmark survival estimates are reported in Table 1.

The estimated aggregated probability of being alive and progression-free at 6 and 12 months was 63% (95%CI: 53%-71%) and 25% (95%CI: 21%-31%), respectively. With regard to OS, 6-, 12- and 24-month rates were 88% (95%CI: 81%-93%), 71% (95%CI: 61%-79%) and 39% (95%CI: 34%-45%), respectively. Two trials reported survival outcomes by histology. In the PrE0505 trial, the results demonstrated significantly longer median OS for patients with epithelioid compared to non-epithelioid PM (24.3 months vs. 9.2 months, hazard ratio [HR] 0.27, 95%CI: 0.13–0.57, log-rank p<0.001). Similarly, patients with epithelioid PM exhibited prolonged median PFS (8.2 vs. 4.9 months, HR 0.30, 95%CI: 0.16–0.58, log-rank p<0.001).[8] In the IND.227 trial, median OS was also significantly longer in patients with epithelioid PM than non-epithelioid PM (19.8 vs. 12.3 months). Nevertheless, at an exploratory analysis, the magnitude of benefit with the addition of ICBs to chemotherapy was more pronounced in non-epithelioid tumors (HR 0.57), given the poorer performance of the control arm in this subtype of disease.[10]

DISCUSSION

Our metanalysis suggests that chemo-immunotherapy strategy as first-line setting in unresectable PM achieves a clinically meaningful ORR, with 39% of patients alive at 2 years. The CheckMate 743 trial defined a significant OS improvement with nivolumab plus ipilimumab as first-line treatment in unresectable PM as compared with standard chemotherapy, with 2-years OS rate of 41% vs. 27%, respectively.[5] Similarly, the addition of bevacizumab in selected patients with PM improved OS from 16.1 to 18.8 months in the randomized MAPS trial.[2] However, the OS curves in the CheckMate 743 trial cross approximately during the first four months after treatment initiation, with chemotherapy performing better during this time period.[11] It may be surmised that survival data from our meta-analysis mirror those from the CheckMate743 trial, but potentially combining ICBs to chemotherapy might avoid the risk of early progression observed with immunotherapy alone as reported in other malignancies such as non-small cell lung cancer[12] and in the IND.227 trial (4% of progressive disease as best response). Risk of early progression for PM was indeed higher with dual ICBs than with chemotherapy alone in the CheckMate 743 trial (18% vs. 5%).[5] Moreover, although the median OS with nivolumab plus ipilimumab was similar regardless of the histologic subtype, the magnitude of benefit was more pronounced in non-epithelioid than in epithelioid histology,[5] suggesting that other immune-strategies for epithelioid PM are awaited.[13] This point is of particular interest. Biological differences between histologic types manifest in high heterogeneity of treatments effect, with chemotherapy and immunotherapy performing similarly in epithelioid tumors, and ICBs rescuing the poor effectiveness of chemotherapy in non-epithelioid PM.[6]

We estimated that chemo-immunotherapy achieves 59% ORR and 92% DCR. By indirect speculative comparison, which anyway should be considered with caution, it can be observed that these rates are higher than what achieved with dual immunotherapy (ORR 40% and DCR 77%),[5] which could be clinically meaningful in a population that can present with symptomatic disease. In addition, we found significantly higher ORR and DCR in epithelioid as compared to non-epithelioid tumors. This combination may then represent an intriguing first-line approach in unresectable PM and is currently under investigation face-to-face vs. ipilimumab and nivolumab in the phase 3 DREAM3R trial (NCT04334759).

Our meta-analysis has some limitations. It is based on literature results including also phase 2 trials, hence on a selected population. Moreover, we did not provide aggregated outcomes data according to tumor PD-L1 expression level, particularly due to lack of these results in some of the included study, and the different PD-L1 testing methods used across the trials. Nevertheless, in the DREAM and IND.227 trials there was no correlation between survival outcomes and PD-L1 expression.

We were unable to provide a comprehensive estimation of survival outcomes based on histology due to a heterogeneity in reporting these data in the selected trials. However, it is worth noting that previous reports suggested that a reduction in tumor burden resulting from first-line therapy may serve as a surrogate for PFS and OS,[14,15] and survival results from the phase III study from the Canadian Cancer Trials Group seems to confirm the promising long-term efficacy of chemotherapy plus ICBs combination.[10]

To conclude, our meta-analysis is a proof of concept regarding the efficacy of this strategy that is being compared with nivolumab plus ipilimumab in a phase III clinical trial. Considering the potential additional effect of antiangiogenic and ICBs in this disease,[2,3] there may be also a place for a four-drugs regimen (BEAT-meso trial, NCT03762018), in patients fit for receiving it. Results of the ongoing randomized trials will better clarify which will be the best first-line strategy for unresectable PM in the ICBs era. In this panorama, ICBs confirm to be a significant milestone in the treatment of non-epithelioid PM, while chemotherapy combined with immunotherapy shows a highly promising response rate. Chemo-immunotherapy could become a potential therapeutic approach, alternative to first-line ipilimumab plus nivolumab or sequentially, expanding the therapeutic options for patients with PM.

DISCLOSURES

MT: Travel, accommodation, expenses: Roche, Bristol-Myers Squibb, AstraZeneca, Takeda, Eli Lilly. Honoraria as medical writer: Novartis, Amgen, MSD. None within this work.
MDM: Received Honoraria and had roles as consultant or advisor for AstraZeneca, Pfizer, Novartis, Roche, Takeda, Eisai, Merck Sharp & Dohme, Janssen, Astellas, Boehringer Ingelheim, Amgen, Merck, outside this work; received institutional research grant by Tesaro – GlaxoSmithKline, outside this work.
JRM: Advisory board: MSD, Boehringer Ingelheim, BMS, AstraZeneca, Roche, Bayer. Speaker bureau: Pfizer. Travel reimbursement: Ose Immunotherapeutics, BMS, AstraZeneca, Roche. None within this work.
PB: Sponsored Research at University of Torino: Pfizer, Roche. Advisor/speaker bureau: AstraZeneca, BeiGene, Roche, BMS, Takeda. Travel, Accommodations, Expenses: Amgen, Daiichi Sankyo. None within this work.
CG: Honoraria from Amgen, AstraZeneca, Bristol-Myers-Squibb, Merck-Sharp-Dohme, Roche, Sanofi, Takeda. Research funds from Bristol-Myers-Squibb and from the Italian Ministry of Health (5x1000 funds; CO-2016-02361470; Ricerca Corrente 2022-2024). None within this work.
FF: Advisory board for BeiGene, outside this work.
MA: Expenses: Sandoz; Advisory Board: Viatris; Research funding: Sandoz. None within this work.
CLP: Institutional honoraria for participation to boards (AstraZeneca, BMS, Roche, Varian). Travel: Janssen. None within this work.
SN: Advisor/speaker bureau: AstraZeneca, Boehringer Ingelheim, BeiGene, Amgen, Eli Lilly, Roche, MSD, Takeda, Pfizer, Sanofi, Novartis, Janssen. None within this work.
FB: Personal financial interests: AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, Mirati, MSD, Pierre Fabre, Pfizer, Seattle Genetics and Takeda. None within this work.
BB: Sponsored Research at Gustave Roussy Cancer Center: Abbvie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgene, Eli Lilly, GSK, Ignyta, IPSEN, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, Tiziana Pharma. Investigator or co-investigator of trials: Nerviano, GSK, Pfizer, Roche-Genentech, Lilly, OSE Pharma, MSD, Celgene, Stemcentrx, Ignyta, Abbvie, Loxo Oncology, AstraZeneca, Blueprint Medicines. None within this work.
DP: Consulting/advisory board: AstraZeneca, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche, Samsung, Sanofi, Janssen, Abbvie. Clinical trials research as principal or co-investigator (institutional financial interests): AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, MedImmune, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo, Janssen, Abbvie, Sanofi. None within this work.

ACKNOWLEDGMENTS
Marco Tagliamento is the recipient of the 2022 International Lung Cancer Foundation (ILCF) Heine A. Hansen Fellowship Grant.

FUNDING
This study did not receive funding.

FIGURE'S TITLE AND LEGEND

Figure 1
TITLE: The PRISMA flowchart summarizing the process for the identification of eligible studies

Figure 2
TITLE: Weighted summary proportion of ORR (A) and DCR (B) in the overall population

REFERENCES

1. Carbone M, Adusumilli PS, Alexander HR, et al. Mesothelioma: Scientific clues for prevention, diagnosis, and therapy. *CA Cancer J Clin*. 2019;69(5):402-429. doi:10.3322/caac.21572
2. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *The Lancet*. 2016;387(10026):1405-1414. doi:10.1016/S0140-6736(15)01238-6
3. Tagliamento M, Bironzo P, Curcio H, et al. A systematic review and meta-analysis of trials assessing PD-1/PD-L1 immune checkpoint inhibitors activity in pre-treated advanced stage malignant mesothelioma. *Crit Rev Oncol Hematol*. 2022;172:103639. doi:10.1016/j.critrevonc.2022.103639
4. Cantini L, Laniado I, Murthy V, Sterman D, Aerts JGJV. Immunotherapy for mesothelioma: Moving beyond single immune check point inhibition. *Lung Cancer*. 2022;165:91-101. doi:10.1016/j.lungcan.2022.01.016
5. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *The Lancet*. 2021;397(10272):375-386. doi:10.1016/S0140-6736(20)32714-8
6. Di Maio M, Tagliamento M. Heterogeneity of treatment effects in malignant pleural mesothelioma. *The Lancet*. 2021;398(10297):301-302. doi:10.1016/S0140-6736(21)00882-5
7. Nowak AK, Lesterhuis WJ, Kok PS, et al. Durvalumab with first-line chemotherapy in previously untreated malignant pleural mesothelioma (DREAM): a multicentre, single-arm, phase 2 trial with a safety run-in. *Lancet Oncol*. 2020;21(9):1213-1223. doi:10.1016/S1470-2045(20)30462-9
8. Forde PM, Anagnostou V, Sun Z, et al. Durvalumab with platinum-pemetrexed for unresectable pleural mesothelioma: survival, genomic and immunologic analyses from the phase 2 PrE0505 trial. *Nat Med*. 2021;27(11):1910-1920. doi:10.1038/s41591-021-01541-0
9. Miyamoto Y, Kozuki T, Aoe K, et al. JME-001 phase II trial of first-line combination chemotherapy with cisplatin, pemetrexed, and nivolumab for unresectable malignant pleural mesothelioma. *J Immunother Cancer*. 2021;9(10):e003288. doi:10.1136/jitc-2021-003288
10. Chu QS, Piccirillo MC, Greillier L, et al. IND227 phase III (P3) study of cisplatin/pemetrexed (CP) with or without pembrolizumab (pembro) in patients (pts) with malignant pleural mesothelioma (PM): A CCTG, NCIN, and IFCT trial. *J Clin Oncol*. 2023;41(17_suppl):LBA8505-LBA8505. doi:10.1200/JCO.2023.41.17_suppl.LBA8505
11. Peters S, Scherpereel A, Cornelissen R, et al. First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743. *Ann Oncol*. 2022;33(5):488-499. doi:10.1016/j.annonc.2022.01.074
12. Paz-Ares LG, Ciuleanu TE, Cobo M, et al. First-Line Nivolumab Plus Ipilimumab With Chemotherapy Versus Chemotherapy Alone for Metastatic NSCLC in CheckMate 9LA: 3-Year Clinical Update and Outcomes in Patients With Brain Metastases or Select Somatic Mutations. *J Thorac Oncol*. 2023;18(2):204-222. doi:10.1016/j.jtho.2022.10.014
13. Aldea M, Benitez JC, Chaput N, Besse B. New Immunotherapy Combinations Enter the Battlefield of Malignant Mesothelioma. *Cancer Discov*. 2021;11(11):2674-2676. doi:10.1158/2159-8290.CD-21-1046
14. Hasan B, Greillier L, Pallis A, et al. Progression free survival rate at 9 and 18weeks predict overall survival in patients with malignant pleural mesothelioma: An individual patient pooled analysis of 10 European Organisation for Research and Treatment of Cancer Lung Cancer Group studies and an independent study validation. *Eur J Cancer*. 2014;50(16):2771-2782.

doi:10.1016/j.ejca.2014.07.020
15. Mansfield AS, Peikert T, Vogelzang NJ, Symanowski JT. Effects of Reduction in Tumor Burden on Survival in Epithelioid Malignant Pleural Mesothelioma. *Mayo Clin Proc*. 2018;93(8):1026-1033. doi:10.1016/j.mayocp.2018.01.032