A systematic review and meta-analysis of trials assessing PD-1/PD-L1 immune checkpoint inhibitors activity in pre-treated advanced stage malignant mesothelioma

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Abstract:	Introduction Advanced stage malignant mesothelioma (asMM) patients have poor prognosis. Several trials investigated the role of programmed cell death protein-1 (PD-1) and its ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) in pre-treated asMM. Methods A systematic review of the literature of clinical trials testing single-agent anti PD-1/PD-L1 ICIs in pre-treated asMM was performed. Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) data were extracted. The predictive role of PD-L1 was assessed. Results We selected 13 studies including 888 patients. ORR and DCR were 18.1% (95%

	confidence interval [CI] 13.9-22.8%) and 55.4% (95% CI: 48.1-62.5%), respectively. Median PFS and OS ranged from 2.1 to 5.9 and from 6.7 to 20.9 months, respectively. ORR according to PD-L1 was 27.0% (95% CI: 18.7-36.2%). Conclusions Anti-PD-(L)1 ICIs might be considered a treatment option for chemotherapy-resistant asMM, even if reliable predictive factors are still lacking.

DIPARTIMENTO DI
ONCOLOGIA
UNIVERSITÀ DEGLI STUDI DI TORINO

Orbassano, January26th, 2022

Dear Sir,

We would like to submit a new version of our manuscript ”A systematic review and meta-analysis of trials assessing PD-1/PD-L1 immune checkpoint inhibitors activity in pre-treated advanced stage malignant mesothelioma” for publication on Critical Reviews in Oncology/Hematology. This systematic review and meta-analysis aims at elucidating the role of anti PD-1/PD-L1 monoclonal antibodies in pre-treated advanced malignant mesothelioma in terms of response rate (RR) and disease control rate (DCR). We found that these agents could led 18.1% RR and 55.4% DCR, with possibly higher activity in PD-L1 positive patients. Despite immune checkpoint inhibitors combinations in the first-line setting are changing treatment approach in non-epithelioid tumors, patients with epithelioid mesothelioma seem derive less benefit from this approach. Therefore, it is worth to investigate the activity of single agent anti PD1/PD-L1 agents chemotherapy pre-treated patients. Indeed, we think that our analysis could add more data in this evolving clinical scenario. According to reviewer’s comments we updated our original work submitted on December 2020, by including new published studies. We also modified the discussion section by highlighting novel evidences from recently published and presented trials. We hope that this works would we considered of interest for the readers of Critical Reviews in Oncology/Hematology.

This manuscript is not under consideration for publication to other journals.

Best regards

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Dear Sir,

according to reviewers' comments we revised our manuscript. Moreover, we updated our meta-analysis by including 3 more studies that have been published in the meantime. The attached manuscript has all changes tracked. The following reviewers'comments have been addressed:

- "Albeit out of the scope of this metanalysis ("Search was made on Pubmed/Medline and Cochrane library on September 13th, 2020"), the results of the recently published CONFIRM trial (Fennell et al. Lancet Oncol 2021) should be included, at least, in the Discussion. Similarly, the results of the recently published RAMES trial should be discussed (Pinto C, et al. Lancet Oncol 2021)". We thank reviewer for this valuable comment. We updated our meta-analysis by including CONFIRM trial along with other 2 novel studies. Moreover, we update previous selected series by retrieving data from more recent publications. CONFIRM results were also included in the introduction. We also discussed RAMES trial in the discussion section of the manuscript.

- "In the Discussion, the authors can more extensively explain the context of pretreated MPM, reporting in more details the outcomes obtainable with single agent chemotherapy (see for example Petrelli F, et al. Respir Med. 2018). This could be useful for readers less familiar with the topic". We thank the reviewer for his suggestion. We modified the discussion section by including the suggested reference as well as data form the VIM phase 2 trial presented at 2021 ASCO Annual Meeting.
- " Ref. 32 can be updated with the results of the full paper, recently published on Cancer Discovery (doi: 10.1158/2159-8290.CD-21-0407)". We thank the reviewer for this comment. We updated the reference accordingly.
- "KEYNOTE-158 data can be updated (Yap TA, et al. Lancet Respir Med. 2021)". We appreciated reviewer's comment. We update data from KEYNOTE-158 in our work.
- "Recent studies showed that PD-L1 expression has a prognostic role in MPM (Brcic L, et al. Transl Lung Cancer Res. 2021; Rrapaj E, et al. Pathology. 2021)". We really appreciated this comment. We updated our discussion by pointing out such data.
- "Quality of the images and graphical abstract is poor. Please reupload the relative files in a higher quality format". We thank reviewer for this comment. We uploaded images with higher quality.

A systematic review and meta-analysis of trials assessing PD-1/PD-L1 immune checkpoint inhibitors activity in pre-treated advanced stage malignant mesothelioma

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Paolo Bironzo
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Emmanuele De Luca is a Medical Oncologist at Humanitas Gradenigo, Turin, since February 2019. On 22/07/2013 he gradutated from the University of Catania with a thesis entitled "Role of the *ATP7A* gene in predicting the efficacy of therapy with platinum derivatives in patients with malignant pleural mesothelioma" On December 2019 he specialized in Medical Oncology at the University of Turin the thesis: "Systematic review and meta-analysis of the literature of the efficacy of immune checkpoint inhibitors in elderly patients with advanced solid cancer: the IMAGE (IMmunotherapy and AGE) study". His special interests are clinical and preclinical research in thoracic and genitourinary tumors as well as melanoma. He participated as a speaker at numerous conferences and have been involved in the writing of several thoracic oncology publications, collaborating in the drafting of guidelines for the Oncological Network of Piedmont and Valle D'Aosta.

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Her research experiences include: an internship at the Laboratory of Neurophysiology at the Department of Human Anatomy and Physiology of the University of Torino; post-graduate student at the Research Laboratory of Molecular and Cellular Biology, Department of Clinical Physiopathology, University of Torino; postdoctoral fellowship at the Monitoring & Cellular Products Laboratory, Department of Pathology, University of Pittsburgh Cancer Institute. USA.Her research interests include thoracic tumors and hereditary cancer syndromes.

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Clizia Zichi is a 34- years old Medical Oncologist, working in Turin, at Mauriziano Hospital. She graduated in October 2013 at the University of Turin and then completed the Oncology training speciality course in December 2019. Now she deals with gastrointestinal and neuroendocrine cancers, with a special interest in thyroid cancers.

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Lucio Buffoni

Lucio Buffoni has been an Oncologist since 2004. Since then, he always dealt with thoracic pathology including both lung cancer and tumors of the thymus and pleura. He always carried out his activity as an oncologist at reference hospitals for the diagnosis and treatment of cancer and, specifically, his main interest has always fallen on neoplasms of the thoracic district. The experience gained in these excellent structures allowed him to hold responsibility positions at the head of working groups dedicated to thoracic tumors. He was also responsible for the drafting and subsequent application of courses dedicated to the diagnosis and treatment of lung and pleural cancers. In these hospitals, he took part in research activities by participating in numerous national and international clinical trials. He also participated both as first author and as co-author in the publication of about 30 articles in international scientific peer-reviewed journals.

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Silvia Novello, MD, PhD is Full Professor of Medical Oncology in the Oncology Department at San Luigi Hospital in Orbassano, Italy, part of the University of Turin. She earned her medical degree and completed the postgraduate training in Respiratory Medicine and Medical Oncology at the University of Turin and partially at the Institut Gustave Roussy, in France. Currently, she is head of the Thoracic Oncology Unit at the San Luigi Hospital, Orbassano (Turin), where she also tutors medical students and Postgraduate students in Respiratory Medicine and Medical Oncology and Deputy Director of the Oncology Dept.

Prof. Novello's research interests include thoracic malignancies, primary prevention, gender differences in lung cancer, basic, translational and clinical applied research on lung cancer and mesothelioma, including pharmacogenomics. She is involved as PI in many International and national controlled clinical trials evaluating new approaches in diagnosis and lung cancer therapy. From July 2012 until 2016, Prof Novello has been a Member of the Board of Directors of the International Association for the Study of Lung Cancer and since October 2016 Member of the Board of Directors of the Italian Association of Medical Oncology, past Secretary and now part of the EORTC Lung Cancer Group and member of several scientific societies including the American Society of Clinical Oncology, American Thoracic Society and the European Society of Medical Oncology. Currently, she is the President of WALCE (Women Against Lung Cancer in Europe), a non profit European Association founded in 2006 in Turin, Italy, part of the scientific Committee of LuCe (Lung cancer Europe) and also member of the Scientific Committee of Bonnie J Addario Lung Cancer Foundation and Member of the Scientific Committee of ICAPEM (Investigación sobre Cáncer de Pulmón en Mujeres). She is the author or co-author of over 150 publications in peer-reviewed journals.

Giorgio V. Scagliotti

Prof. Scagliotti is Professor of Oncology at the University of Torino and former president of the International Association for the Study of Lung Cancer. He earned his medical degree and completed the postgraduate training in Respiratory Medicine, Internal Medicine, and Medical Oncology at the University of Torino. He is chief of the Medical Oncology Division at the S. Luigi Hospital, Orbassano (Torino).

Massimo Di Maio

Massimo Di Maio is associate professor of Medical Oncology at Department of Oncology, University of Turin, Italy, since 2014, and director of Medical Oncology at Mauriziano Hospital, Turin, since 2016. In 1999, he obtained degree *cum laude* in Medicine and Surgery at the University of Napoli "Federico II", Italy. Four years later, in 2003, he graduated from the Specialty School in Oncology at the same University. From 2000 to 2006 and from 2008 to 2014 he worked at the Clinical Trials Unit of the National Cancer Institute "G.Pascale" Foundation, in Naples, Italy, where he was involved in the planning, conducting and analysis of clinical trials. His main areas of interest are: methodology of clinical trials in oncology, conduction of meta-analyses based on individual patients' data, patient-reported outcomes in clinical research and in clinical practice. Prof Di Maio has been invited as speaker at many national and international meetings and has authored more than 340 publications in international peer-reviewed journals (H-Index November 2021: 45 according to Scopus, 45 according to Web of Science). Additionally, Prof. Di Maio is an active member of the Associazione Italiana di Oncologia Medica (Italian Society of Medical Oncology, AIOM) and the European Society of Medical Oncology (ESMO). Between 2009 and 2013, Prof. Di Maio acted as national coordinator of the AIOM Young Oncologists Working Group. Between 2013 and 2017, he was councillor (member of the National Board) of AIOM. Since October 2019, he is AIOM National Secretary.

A systematic review and meta-analysis of trials assessing PD-1/PD-L1 immune checkpoint inhibitors activity in pre-treated advanced stage malignant mesothelioma

Abstract

Introduction

Advanced stage malignant mesothelioma (asMM) patients have poor prognosis. Several trials investigated the role of programmed cell death protein-1 (PD-1) and its ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) in pre-treated asMM.

Methods

A systematic review of the literature of clinical trials testing single-agent anti PD-1/PD-L1 ICIs in pre-treated asMM was performed. Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) data were extracted. The predictive role of PD-L1 was assessed.

Results

We selected 10 studies including 497 patients. ORR and DCR were 20.1% (95% confidence interval [CI] 16.8-23.9) and 54.6% (95% CI: 50.2-59.0), respectively. Median PFS and OS ranged from 2.5 to 6.1 and from 6.36 to 20.9 months, respectively. ORR according to PD-L1 expression ranged from 19% to 55.5%.

Conclusions

Anti-PD-(L)1 ICIs might be considered a treatment option for chemotherapy-resistant asMM, even if reliable predictive factors are still lacking.

Keywords

Mesothelioma; immune checkpoint inhibitors; nivolumab; pembrolizumab; avelumab

Abbreviations

MM: malignant mesothelioma

OS: overall survival

PFS: progression-free survival

ICIs: immune checkpoint inhibitors

CTLA-4: cytotoxic T-lymphocyte antigen-4

PD-1: programmed cell death protein-1

PD-L1: programmed death-ligand 1

asMM: advanced stage malignant mesothelioma

mAbs: monoclonal antibodies

ASCO: American Society of Clinical Oncology

ESMO: European Society of Medical Oncology

IASLC: International Association for the Study of Lung Cancer

ELCC: European Lung Cancer Congress

HR: hazard ratio

CI: confidence interval

ORR: objective response rare

FDA: Food and Drug Administration

EMA: European Medicines Agency

q2w: every two weeks

q3w: every three weeks

ECOG: Eastern Cooperative Oncology Group

PS: performance status

IHC: immunohistochemistry

DoT: duration of treatment

RECIST: Response Evaluation Criteria in Solid Tumours

PD-L1+: PD-L1 positive

PD-L1-: PD-L1 negative

MPM: malignant pleural mesothelioma

mRECIST: modified RECIST

iRECIST: immune RECIST

DoR: duration of response

RR: response rate

PR: partial response

SD: stable disease

BAP1: BRCA1 associated protein 1

CAR-T: chimeric antigen receptor T-cell

1. Introduction

Malignant mesothelioma (MM) is a rare and aggressive tumour of mesothelial surfaces. Asbestos exposure is the main risk factor, even if this neoplasm can occur in non-exposed subjects and rarely can be due to germline mutations.[1] The combination of platinum and pemetrexed is the standard systemic first-line treatment, providing a small although significant survival benefit as compared to platinum alone, and better symptom control.[2] Recently, in one randomized study the addition of bevacizumab improved progression-free and overall survival (PFS and OS) as compared to chemotherapy alone.[3] Overall clinical results are still modest, claiming for novel approaches to significantly ameliorate the survival of MM patients. In the last few years, immune checkpoint inhibitors (ICIs) radically changed treatment paradigm of many solid tumours. While cytotoxic T-lymphocyte antigen-4 (CTLA-4) directed agents did not confer any benefit in advanced MM,[4] several trials and case-series suggest that programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) antagonists may increase survival in pre-treated advanced stage MM (asMM) patients.[5] However, such results are still debated because the only randomized trial did not show survival differences between pembrolizumab and single agent chemotherapy. To this end, we performed a systematic review and meta-analysis to define the activity and efficacy of PD-1/PD-L1 monoclonal antibodies (mAbs) in pre-treated asMM patients.

2. Material and Methods

2.1 Trial identification criteria

We identified all clinical trials testing ICIs in pre-treated asMM as single-agent in single-arm as well as multi-arm studies. The following Mesh terms were used: “mesothelioma”, “mesothelioma, malignant”, “atezolizumab”, “avelumab”, “durvalumab”, “nivolumab”, “pembrolizumab”. Search was made on Pubmed/Medline and Cochrane library on September 13th, 2020. Papers published in peer-reviewed journals and in English language were selected. We also searched proceedings of major International meetings such as American Society of Clinical Oncology- ASCO annual meetings, European Society of Medical Oncology- ESMO annual meetings, International Association for the Study of Lung Cancer- IASLC World Conferences on Lung Cancer, European Lung Cancer Congress-ELCC from 2014 onwards for relevant abstracts. When more than one report of the same study was available, the most recent data (with longer follow-up and/or higher number of patients) were considered (**Figure 1**).

2.2 Aims of the meta-analysis

- (i) To evaluate the activity of single-agent PD-1/PD-L1 directed ICIs in chemotherapy pre-treated asMM in terms of objective response rare (ORR) and disease control rate (DCR);
- (ii) To evaluate the efficacy of single-agent PD-1/PD-L1 directed ICIs in chemotherapy pre-treated asMM in terms of PFS and OS;
- (iii) To explore the potential role of PD-L1 expression as a predictive marker of activity. For this aim, the ORR and DCR analyses were repeated in the subgroup of patients included, within each trial, in the highest category of PD-L1 expression (even if with heterogeneous methods and cut-offs).

2.3 Data extraction for the meta-analysis

The following data were extracted from each study: (a) first author, phase of the study, and year of publication; (b) type of ICIs agent and number of patients assigned to the experimental treatment; (c) percentage of patients treated in second-line; (d) site of MM (pleural *vs* peritoneal *vs* others) and histology; (e) median follow-up and range; (f) ORR (number of patients obtaining objective response) in the whole study population and in the "PD-L1 high" subpopulation; in the randomized trial, ORR was collected for both treatment arms in order to calculate odds ratio; (g) DCR (number of patients obtaining objective response or disease stabilization) in the study population and in the "PD-L1 high" subpopulation; in the randomized trial, DCR was collected for both treatment arms in order to calculate odds ratio; (g) median PFS and median OS; in the randomized trial, hazard ratio (HR) and 95% confidence interval (CI) of experimental treatment compared to control arm, in the intention to treat population, were collected.

To obtain a quantitative measure of the degree of heterogeneity among studies included in the analysis, the Higgins I^2 index was computed. The likelihood of publication bias was assessed by both Egger's and Begg's tests. The MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used for statistical analyses.

3. Results

3.1 Systematic review of the literature

3.1.1 Atezolizumab

No results from clinical trials evaluating the anti PD-L1 mAb atezolizumab in pre-treated asMM were found. However, a single-arm phase trial with atezolizumab in this population is ongoing [NCT 03786419].

3.1.2 Avelumab

Avelumab, a humanized anti-PD-L1 IgG1 mAb, has been evaluated in MM within the phase Ib JAVELIN trial.[6] Fifty-three patients with unresectable pre-treated MM received avelumab 10 mg/Kg every two weeks (q2w). Median age was 67 years (range 32-84), and median number of previous lines was 2 (range 1-8). Thirty-two patients (60%) were male, and 39 (74%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1. Most patients had epithelioid histology (n:43, 81%). PD-L1 expression, evaluated with Dako PD-L1 immunohistochemistry (IHC) 73-10 pharmDx, was ≥1% in 21 patients (40%), negative in 22 patients (42%), not evaluable in 10 (19%). High PD-L1 expression(≥5% of positive tumour cells) was reported in 16 patients (30%), while 27 (51%) had a low/negative expression. The median duration of treatment (DoT) was 2.8 months (range 0.9-28.1), with a median of 6 delivered doses (range 2-59). At a median follow-up of 24.8 months (range 16.8-27.8), the ORR (by Response Evaluation Criteria in Solid Tumours- RECIST 1.1) was 9% (95% CI: 3.1-20.7) and the DCR was 58% (n:31). Median PFS and OS were 4.1 (95% CI: 1.4-6.2) and 10.7 (95% CI: 6.4-20.2) months, respectively. ORR was higher in PD-L1 high (19%, 3 out of 16 patients; 95% CI: 4.0-45.6) than in low/negative patients (7%, 2 out of 27 patients; 95% CI: 0.9-24.3) (p=0.34). Median PFS for PD-L1 high and PD-L1 low/negative patients was 5.3 (95% CI: 1.4-17.8) and 1.7 (95% CI: 1.4-8.3) months, respectively, while median OS was 20.2 (95% CI: 4.9-not estimable) and 10.2 (95% CI: 3.8-21.0) months, respectively. Using a 1% cut-off for PD-L1 positive (PD-L1+) and negative (PD-L1-) definition, ORR was 14% (3 patients; 95% CI: 2.9-34.9) and 10% (2 patients; 95% CI: 1.2-30.4), respectively (p= 1.00). In PD-L1+, the median PFS was 5.3 months (95% CI: 1.4-12.0) as compared to 1.6 months in PD-L1- patients (95% CI: 1.4-6.8). The median OS was 20.2 months (95% CI: 6.1- not estimable) and 7.5 months (95% CI: 3.8-21.0) in PD-L1+ and PD-L1-, respectively.

3.1.3 Durvalumab

No results from clinical trials evaluating the anti PD-L1 mAb durvalumab in pre-treated asMM were found. This agent has been studied in 2 single-arm phase 2 trials combined with

chemotherapy in treatment-naïve, unresectable malignant pleural mesothelioma (MPM) patients.[7,8] A phase 3 randomized trial comparing cisplatin plus pemetrexed plus durvalumab versus cisplatin plus pemetrexed is initiating enrolment [NCT 04334759].

3.1.4 Nivolumab

The fully human anti-PD-1 Ig G4 mAb nivolumab has been studied in MM alone or in combination with anti-CTLA-4 mAbs. Nivolumab was administered at 3 mg/kg q2w in a single-arm, single-centre, phase II trial in advanced stage MPM patients progressing to at least one prior chemotherapy, with ECOG-PS 0-1.[9] Tumour assessment was performed by RECIST modified for MM (mRECIST) and immune RECIST (iRECIST). The DCR at 12 weeks was the primary end-point. The study enrolled 38 patients, 34 received nivolumab. Median age was 67 years (range 50-81), 82% (n:28) were male, 47% (n:16) had ECOG-PS 1, 82% (n:28) had epithelioid histology, and most had stage I to III disease (n:24, 71%). All but one patient received second-line nivolumab. The median number of administered doses was 7, the median DoT was 2.8 months. The 12 weeks DCR was 47% (95% CI: 30-65), with 8 partial responses (PR) (24%; 95% CI: 11-42) and another patient PR after 18 weeks, leading to 26% ORR. Three pseudo-progressions were observed. At a median follow-up of 27.5 months (95% CI: 19.3-not reached), median duration of response (DoR) was 7.0 months, while median PFS and OS were 2.6 (95% CI: 2.23-5.49) and 11.8 (95% CI: 9.7-15.7) months, respectively. Nine cases (27%) were PD-L1+ (cut-off 1% by 28-8 antibody), mostly epithelioid. Among them, clinical benefit (PR or long-term stable disease- SD) was observed in 5 (55%), with 4 experiencing PR. Overall, 8 out of 23 (34.8%) evaluable PD-L1- patients had clinical benefit.

The single-arm phase 2 trial MERIT had a similar design differing for the nivolumab dose (240 mg q2w) and the number of previous chemotherapy lines (no more than 2, including platinum-pemetrexed combination).[10] The primary end-point ORR was centrally assessed by mRECIST. Thirty-four patients were enrolled, the median age was 68 years, 79% (n:27) had epithelioid histology. Median DoT was 6.8 months (median number of doses: 12.5). At a median follow-up of 12.8 months, ORR was 29% (95% CI: 16.8-46.2) and DCR was 68% (95% CI: 50.8-80.9). Median OS and PFS were 17.3 (95% CI: 11.5-not reached) and 6.1 (95% CI: 2.9-9.9) months, respectively. 59% of patients (n:20) was PD-L1+ (cut-off 1% by 28-8 antibody), 12% (n:4) PD-L1-, in 6% (n:2) not evaluable. ORR was higher in PD-L1+ patients as compared to PD-L1- (40% *vs* 8%, respectively), with similar trends using higher cut-offs (5% and 10%). At the same time, PD-L1+

patients had longer OS (HR 0.542; 95% CI: 0.208-1.415, p=0.2021) and PFS (HR 0.725; 95% CI: 0.316-1.668, p=0.4490) as compared to PD-L1-.

Single agent nivolumab was also investigated in a randomized phase II, non-comparative, multicentre trial (MAPS-2).[11] This study enrolled patients with MPM, already treated with one or two lines of chemotherapy. Patients were randomized 1:1 to nivolumab or nivolumab plus ipilimumab. Nivolumab was administered at 3 mg/Kg dose q2w. Disease assessment was performed every 12 weeks (mRECIST criteria), with central revision. PD-L1 expression was assessed using 28-8 pharmDx (n:99) and SP-263 clones (n:104), with high expression defined as ≥25% or ≥50% tumour cells expressing PD-L1. An exploratory cut-off threshold was defined on results from a post-hoc analysis. The primary end-point was DCR at 12 weeks, secondary objectives included OS and PFS. Among the 132 recruited patients, 68 were randomized to single agent nivolumab and 63 received the treatment. The median age was 72.3 years, most of the patients were male (75%), had stage III or IV disease (89%), while only 30% had ECOG-PS 0. Fifty-two patients (83%) had epithelioid histology, 44 (70%) had received one previous line. After a median follow-up of 20.1 months, the 12 weeks DCR was 44% (95% CI: 31-58), while the ORR was 19% (95% CI: 8-29). In the intention-to-treat population, the response rate (RR) was 17.5% (95% CI: 8-1-26.8), while the DCR at 12 weeks was 40% (95% CI: 28-52). The median DoR was 7.4 months (95% CI: 4.1-11.9), while median PFS and OS were 4.0 (95% CI: 2.8-5.7) and 11.9 (95% CI: 6.7-17.7) months, respectively. The subgroup analysis of ORR and DCR by PD-L1 expression were not reported separately by treatment. Overall, the ORR was significantly higher in PD-L1+ patients (using 1% cut-off with both clones) in both arms, while the 12 weeks DCR was not. Using a 25% cut-off for high expressors, both RR and DCR were significantly higher in patients with high PD-L1 expression as assessed by both clones.

Domoulin et al. reported real-world data about 59 patients affected by MPM treated with nivolumab 3 mg/Kg q2w.[12] All patients were pre-treated with at least one prior platinum-antifolate regimen (54 treated in second-line). Median age was 72 years (range 50-83), 90% of patients were male, 95% with ECOG-PS 0-1. Forty-one patients had epithelioid histology. Median PFS and OS were 2.64 and 6.36 months, respectively, and ORR was 12% by mRECIST.

Another series reported 27 patients with asMM treated with nivolumab 3mg/Kg q2w. The median age of 25 evaluable patients was 67 years (range 38-89), 72% were male, 56% had ECOG-PS $\geq$2, 76% had epithelioid histology.[13] Median PFS was 5 months, the ORR was 24% by RECIST

1.1 with a DCR of 60% in the whole group. Patients with PD-L1 ≥1% and <1% had a DCR of 63% and 55%, respectively.

Early results of a retrospective single-centre Japanese series including 79 patients (78.7% males, n:63) with MPM and treated with nivolumab as second- (63.2%), third- (19%) or ≥fourth-line (17.8%) were presented.[14] 21.5% (n=17) had an ECOG-PS ≥2, 81% (n=64) had epithelioid histology. Among 71 patients considered for efficacy, the ORR (by mRECIST) and DCR were 26.8% and 66.2%, respectively. ORR were 22.8%, 55.6%, and 20% for epithelioid, sarcomatoid, and biphasic MPM, respectively. At a median follow-up of 13.3 months (range 4.2-18.9), median PFS and OS were 4.1 and 14.3 months, respectively. At multivariate analysis, PS ≥2 was an independent negative factor for both PFS (HR 2.6; 95% CI: 1.46-4.62) and OS (HR 2.33; 95% CI: 1.30-4.15).

A randomized, double-blind, placebo-controlled clinical trial comparing nivolumab with placebo in previously treated MM is currently ongoing (CONFIRM Study, NCT 03063450).

3.1.5 Pembrolizumab

Pembrolizumab is a humanised Ig G4 mAb directed against PD-1. The phase IB KEYNOTE-028 study was a multicentre, non-randomised, open-label, multicohort trial of pembrolizumab in patients with advanced solid tumours with PD-L1 expression (≥1%, tested with 22C3 clone).[15] Among 38 MPM patients, 25 received pembrolizumab 10 mg/Kg q2w for a maximum of 24 months. The primary end-points were safety, tolerability and ORR (by RECIST based on investigator review); PFS, OS and DoR were secondary end-points. Eighteen (72%) patients had epithelioid MPM. At a median follow-up of 18.7 months, ORR was 20% (95% CI: 6.8-40.7) and the clinical benefit rate (defined as complete response plus PR plus SD for 6 months or more) was 40% (95% CI: 21.1-61.3). The DCR was 72%. Of note, two additional patients had a reduction in tumour size of more than 30% but were not included in the confirmed ORR as they did not have a subsequent confirmatory imaging. Median PFS and OS were 5.4 (95% CI: 3.4-7.5) and 18 (95% CI: 9.4-not reached) months, respectively.

A registry study enrolled 93 patients with unresectable MPM, both untreated and previously treated with chemotherapy.[16] Data collection was retrospective, with PD-L1 evaluation by SP263 clone or by E1L3N clone. Pembrolizumab was administered at different doses (200 mg q3w or q2w, 10 mg/Kg q2w, 2 mg/Kg q2w or q3w). Sixty-six patients (71%) had ECOG-PS 0-1, the median age was 68 years (range 25-94), most patients were male (91%, n:85), 67 (73%) had epithelioid

histology. Four patients received pembrolizumab as first-line, 48 as second-line (52%), and 41 (48%) as third-line or subsequent. At a median follow-up of 9 months, the ORR was 18% and the DCR was 48% in the whole cohort. Median PFS and OS were 3.1 (95% CI: 2.6-6.4) and 7.2 (95% CI: 4.9-10.0) months, respectively. PD-L1 expression was associated with ORR and DCR at the univariate analysis but not at the multivariate analysis.

Desai et al. conducted a two-part, phase II, single-centre, non-randomised trial enrolling patients with MM.[17] The part A enrolled 35 unselected patients to determine the ORR to pembrolizumab (200 mg q3w) and to find the optimal PD-L1 cut-off for positivity (22C3 clone). The part B was initiated when 7 responses were reported in part A, and intended to use a biomarker enrichment strategy for PD-L1. However, as no PD-L1 cut-off was established in part A, part B enrolled 30 patients irrespective of PD-L1 level. All enrolled patients previously received at least one previous line of therapy, including platinum and pemetrexed, but no more than 2 systemic regimens. eTh median age was 68 years (range 26-85), 77% were male, and 53% had ECOG-PS 0. 77% had epithelioid histology, 88% had pleural mesothelioma while 12% had peritoneal, and 61% had already received one previous systemic treatment. Disease assessment was performed by mRECIST. ORR was 22% and DCR was 63%. Median PFS and OS were 4.1 and 11.5 months, respectively. PD-L1 expression ≥50% was associated with higher RR and longer median PFS.

The cohort study by Cengel et al enrolled 82 patients and evaluated ORR (by mRECIST), PFS and OS.[18] Median age was 72 years, and 59 were male. Sixty-three patients had epithelioid histology, 42 treated in second-line. PD-L1 expression was not determined in 45 patients, <1% in 16, and ≥1% in 21. Median OS of the entire population was 8.5 months, median PFS 4.2 months, ORR 25%, and DCR 71%.

In 2019, the results of a phase III, open-label, randomized PROMISE-meso trial have been presented.[19] This trial randomized 1:1 MPM patients, who progressed to platinum-based chemotherapy, to receive either pembrolizumab 200 mg q3w or chemotherapy based on investigator choice (gemcitabine or vinorelbine). Histological subtype (epithelioid *vs* non-epithelioid) was the only stratification factor, while PD-L1 expression was exploratory. The primary end-point was PFS (assessed by blinded independent central review), and secondary end-points were ORR (by RECIST 1.1), time to treatment failure, OS, investigator-assessed PFS and adverse events. The study enrolled 144 patients (73 treated with pembrolizumab, 50.7%), 90% with epithelioid histology, 80% males. After a median follow-up of 11.8 months, pembrolizumab arm showed a median PFS of 2.5 months as compared to 3.4 months of the

control (HR 1.06, 95% CI: 0.73-1.53, p=0.76 stratified by histological subtype). Pembrolizumab led to a superior ORR (22% *vs* 6%, p=0.004), while the median DoR was higher with chemotherapy (11.2 months *vs* 4.6 months). Median OS was 10.7 and 11.7 months in the experimental and control arm, respectively (HR 1.04, 95% CI: 0.66-1.67, p=0.85), without differences even after adjusting for cross-over. The DCR in the pembrolizumab group was 45%, with 16 patients achieving PR and 17 SD. No differences were observed neither in median PFS nor in OS according to PD-L1 expression (TPS <1% *vs* ≥1%).

A retrospective single-centre cohort study of pembrolizumab in MPM included 13 non-papillary peritoneal tumours, all pre-treated with chemotherapy.[20] Median age of enrolled patients was 65.6 years, 62% had known asbestos exposure. Histology was epithelioid in 70% of cases. ORR was 18%, while DCR was 81%. Median PFS and OS were 5.7 and 20.9 months, respectively. No differences in PFS were observed comparing epithelioid histology *vs* others, or by PD-L1 status (positive *vs* negative, median PFS 5.1 *vs* 5.7 months respectively, p=0.73).

Another retrospective real-world study included 98 patients with MM (95 pleural, 3 peritoneal) treated with pembrolizumab.[21] Median age was 70 years (range 46-91), most patients were male (92%) and with ECOG-PS of 0-1 (78%), 76% had epithelioid histology. Four patients received pembrolizumab as first-line because unfit for chemotherapy, while the others were chemotherapy pre-treated (64% one previous line). Pembrolizumab was administered at 200 mg q3w (73%) or at 2 mg/Kg q3w (27%), the median number of cycles was 6 (range 1-35). PD-L1 was assessed with. Using a 1% cut-off, PD-L1 expression (E1L3N clone) resulted negative in 46%, positive in 32%, while for remaining data was missing. ORR was 18% (95% CI: 12-28%) as per investigator-assessed mRECIST, and DCR 56% (95% CI: 47-66). The median PFS and OS were 4.8 (95% CI: 3.6-6.2) and 9.5 (6.6-13.7) months, respectively. PD-L1 expression and BRCA1 associated protein 1 (BAP1) loss were not associated with objective response, although ORR was numerically higher in PD-L1+ patients (23% *vs* 11%) and those with BAP1 loss (20% *vs* 13%).

Finally, 4 patients affected by asMM were enrolled into the Keynote-158 trial, a phase 2 study assessing the efficacy of pembrolizumab in patients with non-colorectal high microsatellite instability/mismatch repair deficient tumours.[22] Among 233 enrolled patients, ORR was 34.3% (95% CI: 28.3-40.8) and the median PFS and OS were 4.1 (95% CI: 2.4-4.9) and 23.5 (95% CI: 13.5-not reached) months, respectively. However, data about patients with asMM are not available.

3.2 Meta-analysis

We selected 10 studies including 497 patients, most with pleural MM.[6,9–12,14,15,17,19,20] **Table 1** summarizes the main characteristics of the selected trials. Four studies were excluded due to the inclusion of treatment naïve patients,[13,16,18,21] while one study because no data on asMM patients were available.[22] The analysis of patients from the phase III PROMISE-meso trial was restricted to those assigned to pembrolizumab (n:73).[19] Data on responses were available for 487 patients, irrespective of PD-L1 levels. A total of 434 patients (89.1%) received anti-PD-1 inhibitors (nivolumab [N] or pembrolizumab [P]), while 53 (10.9%) were treated with avelumab (A) [**Table 1**]. In aggregate, ORR was 20.1% (95% CI: 16.8-23.9%) with no significant differences between drugs (N:21.5%, P:21.4%, A:9.4%; p=0.121. I^2=26.18%, p=0.2027) [**Figure 2**]. DCR was 54.6% (95% CI: 50.2-59.0%) without significant differences between agents (N:51.7%, P:57.8%, A:58.5%; p=0.385. I^2=68.14%, p=0.0009) [**Figure 2**]. In unselected patients, the median PFS ranged from 2.5 to 6.1 months, while the median OS from 6.36 to 20.9 months. Tumour response according to PD-L1 expression were reported in 6 out of 10 studies, with PD-L1 positivity defined using heterogeneous cut-offs depending of each different trial (ranging from 1% to 50%).[6,9–11,15,17] This subgroup included 125 and 131 patients, depending on the clone adopted in the study by Scherpereel et al. (n: 125 for 28-8, n: 131 for SP-263) [**Table 2**].[11] ORR was 34.4% (95% CI: 26.7-43.1%. I^2=28.52%, p=0.2210) and 32.1% (95% CI: 24.7-40.5%. I^2=22.23%, p=0.2667), respectively, although it ranged from 19% to 56% in different studies [**Figure 3**]. No publication biases were found at a significance level < 0.05 [**Figure 4**, **Figure 5**].

4. Discussion

The present study performed a systematic review and meta-analysis to evaluate the activity of anti-PD-1/PD-L1 in pre-treated asMM in terms of ORR and DCR. Notably, higher efficacy is observed in tumours whose aetiology is associated to carcinogens exposure.[23–25] Therefore, the assessment of the efficacy of ICIs in asMM finds a rationale as most of the cases are related to asbestos exposure. Unfortunately, most of the studies about ICIs in asMM do not report this information. At the same time, MM is partially resistant to cytotoxic chemotherapy and second-line treatments have never formally demonstrated to increase survival as compared to best supportive care. Indeed, international guidelines suggest the treatment with vinorelbine or gemcitabine in pre-treated patients, reporting ORR between 7% and 16%.[26–30] The present meta-analysis indicates that ICIs provide an ORR of 20.1% and a DCR of 54.6%, without significant differences between drugs. Overall, the heterogeneity between the studies was low

when evaluating the ORR, both in the entire population and in patients whose tumours expressed PD-L1, while the heterogeneity was significant for the evaluation of the DCR. We did not found significant evidence of publication bias.

However, the results of the phase 3 PROMISE-meso trial showed that, despite the higher ORR with pembrolizumab, no survival differences were observed as compared to single agent chemotherapy in pre-treated advanced stage MPM.[19] Notably, this trial was designed with PFS as primary end-point. OS events were 71 at the time of the analysis, leading to a 16% statistical power for a HR of 0.8, meaning that the study was not powered to allow meaningful conclusion about OS. Indeed, the interpretation of these results is challenging. Since most of the studies included in our meta-analysis lack of a comparison arm, we were not capable to compare ICIs with single-agent chemotherapy. However, to our knowledge, ORR has never been demonstrated to be a surrogate marker of survival in MM. Moreover, 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. For this latter reason, as most studies were single-arm trials, observer bias could not be ruled out.

The present meta-analysis suggests that PD-L1+ tumours might better respond to single-agent immunotherapy. However, trials are highly heterogeneous when accounting for PD-L1 evaluation because different IHC clones and cut-offs were used, so that these data should be taken with caution. Moreover, a recent publication reported that the antigenic potential of mesothelioma could be better predicted by other factors, including chromosomal rearrangements (chromoplexy and chromothripsis).[31] Such interesting data deserve more studies in the context of ICIs therapy for MM. Adoptive immunotherapy as well as vaccines, alone or in combination with ICIs, are another active field of investigation. Preliminary results of a phase I study of intrapleural injection of mesothelin-targeted chimeric antigen receptor T-cell (CAR-T) therapy, with or without anti PD-1 agents, showed 63% RR in 18 asMM patients, 37% of which already treated with 3 or more lines of therapy.[32] The treatment landscape of asMM is therefore expected to change, and immunotherapy may have a pivotal role both in treatment-naïve and pre-treated patients. The recent results of the Checkmate 743 trial, showing that nivolumab plus ipilimumab led to significantly longer OS as compared to platinum plus pemetrexed in untreated unresectable MPM, are starting this paradigm shift.[33] Non-epithelioid tumors seem to derive the most benefit. Unfortunately, due to the lack of specific data, we could not evaluate the activity of single-agent ICIs in different histologies. As results of other ongoing

studies are eagerly awaited, our meta-analysis suggests that anti-PD-(L)1 agents might be useful in some chemotherapy pre-treated patients, even if reliable predictive factors are still lacking.

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Figure legends

Figure 1. PRISMA flowchart of selected trials

Figure 2. Objective response rate of trials selected for the meta-analysis and aggregate data

Abbreviations. ORR: objective response rate.

Figure 3. Objective response rate of trials reporting activity according to PD-L1 expression and aggregate data

Abbreviations. ORR: objective response rate.

Figure 4. Funnel plot for objective response rate

Figure 5. Funnel plot for disease control rate

A systematic review and meta-analysis of trials assessing PD-1/PD-L1 immune checkpoint inhibitors activity in pre-treated advanced stage malignant mesothelioma

Abstract

Introduction

Advanced stage malignant mesothelioma (asMM) patients have poor prognosis. Several trials investigated the role of programmed cell death protein-1 (PD-1) and its ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) in pre-treated asMM.

Methods

A systematic review of the literature of clinical trials testing single-agent anti PD-1/PD-L1 ICIs in pre-treated asMM was performed. Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) data were extracted. The predictive role of PD-L1 was assessed.

Results

We selected 13 studies including 888 patients. ORR and DCR were 18.1% (95% confidence interval [CI] 13.9-22.8%) and 55.4% (95% CI: 48.1-62.5%), respectively. Median PFS and OS ranged from 2.1 to 5.9 and from 6.7 to 20.9 months, respectively. ORR according to PD-L1 was 27.0% (95% CI: 18.7-36.2%).

Conclusions

Anti-PD-(L)1 ICIs might be considered a treatment option for chemotherapy-resistant asMM, even if reliable predictive factors are still lacking.

Keywords

Mesothelioma; immune checkpoint inhibitors; nivolumab; pembrolizumab; avelumab

Abbreviations

MM: malignant mesothelioma

OS: overall survival

PFS: progression-free survival

ICIs: immune checkpoint inhibitors

CTLA-4: cytotoxic T-lymphocyte antigen-4

PD-1: programmed cell death protein-1

PD-L1: programmed death-ligand 1

asMM: advanced stage malignant mesothelioma

mAbs: monoclonal antibodies

ASCO: American Society of Clinical Oncology

ESMO: European Society of Medical Oncology

IASLC: International Association for the Study of Lung Cancer

ELCC: European Lung Cancer Congress

HR: hazard ratio

CI: confidence interval

ORR: objective response rare

FDA: Food and Drug Administration

EMA: European Medicines Agency

q2w: every two weeks

q3w: every three weeks

ECOG: Eastern Cooperative Oncology Group

PS: performance status

IHC: immunohistochemistry

DoT: duration of treatment

RECIST: Response Evaluation Criteria in Solid Tumours

PD-L1+: PD-L1 positive

PD-L1-: PD-L1 negative

MPM: malignant pleural mesothelioma

mRECIST: modified RECIST

iRECIST: immune RECIST

DoR: duration of response

RR: response rate

PR: partial response

SD: stable disease

BAP1: BRCA1 associated protein 1

CAR-T: chimeric antigen receptor T-cell

1. Introduction

Malignant mesothelioma (MM) is a rare and aggressive tumour of mesothelial surfaces. Asbestos exposure is the main risk factor, even if this neoplasm can occur in non-exposed subjects and rarely can be due to germline mutations.[1] The combination of platinum and pemetrexed has been for decades the standard systemic first-line treatment, providing a small although significant survival benefit as compared to platinum alone, and better symptom control.[2] One randomized study the addition of bevacizumab improved progression-free and overall survival (PFS and OS) as compared to chemotherapy alone.[3] Overall clinical results are still modest, claiming for novel approaches to significantly increase survival of MM patients. In the last few years, immune checkpoint inhibitors (ICIs) radically changed treatment paradigm of many solid tumours. While cytotoxic T-lymphocyte antigen-4 (CTLA-4) directed agents alone did not confer any benefit in advanced MM,[4] their combination with a programmed cell death protein-1 (PD-1) inhibitor recently demonstrated to be superior to platinum plus pemetrexed in a phase 3 randomized trial in treatment naïve advanced pleural MM patients.[5] However, the magnitude of benefit seems superior in non-epithelioid MM, while at best modest in epithelioid tumors.[6] Several trials and case-series suggest that PD-1) and programmed death-ligand 1 (PD-L1) antagonists may increase survival in chemotherapy pre-treated advanced stage MM (asMM) patients too.[7] However, such results are still debated because the only randomized trial with active control did not show survival differences between pembrolizumab and single agent chemotherapy, while another placebo-controlled study showed the superiority of nivolumab as compared to best supportive care.[8] To this end, we performed a systematic review and meta-analysis to define the activity and efficacy of PD-1/PD-L1 monoclonal antibodies (mAbs) in chemotherapy pre-treated asMM patients.

2. Material and Methods

2.1 Trial identification criteria

We identified all clinical trials testing ICIs in pre-treated asMM as single-agent in single-arm as well as multi-arm studies. The following Mesh terms were used: “mesothelioma”, “malignant mesothelioma”, “atezolizumab”, “avelumab”, “durvalumab”, “nivolumab”, “pembrolizumab”, “immunotherapy”, “PD-1”, “PD-L1”. Search was made on Pubmed/Medline and Cochrane library on January 20th, 2022. Papers published in peer-reviewed journals and in English language were selected. We also searched proceedings of major International meetings such as American Society of Clinical Oncology- ASCO annual meetings, European Society of Medical Oncology- ESMO annual

meetings, International Association for the Study of Lung Cancer- IASLC World Conferences on Lung Cancer, European Lung Cancer Congress- ELCC from 2014 onwards for relevant abstracts. When more than one report of the same study was available, the most recent data (with longer follow-up and/or higher number of patients) were considered (**Figure 1**).

2.2 Aims of the meta-analysis

- (i) To evaluate the activity of single-agent PD-1/PD-L1 directed ICIs in chemotherapy pre-treated asMM in terms of objective response rare (ORR) and disease control rate (DCR);
- (ii) To evaluate the efficacy of single-agent PD-1/PD-L1 directed ICIs in chemotherapy pre-treated asMM in terms of PFS and OS;
- (iii) To explore the potential role of PD-L1 expression as a predictive marker of activity. For this aim, the ORR and DCR analyses were repeated in the subgroup of patients included, within each trial, in the highest category of PD-L1 expression (even if with heterogeneous methods and cut-offs).

2.3 Data extraction for the meta-analysis

The following data were extracted from each study: (a) first author, phase of the study, and year of publication; (b) type of ICIs agent and number of patients assigned to the experimental treatment; (c) percentage of patients treated in second-line; (d) site of MM (pleural *vs* peritoneal *vs* others) and histology; (e) median follow-up and range; (f) ORR (number of patients obtaining objective response) in the whole study population and in the "PD-L1 high" subpopulation; in the randomized trial, ORR was collected for both treatment arms in order to calculate odds ratio; (g) DCR (number of patients obtaining objective response or disease stabilization) in the study population and in the "PD-L1 high" subpopulation; in the randomized trial, DCR was collected for both treatment arms in order to calculate odds ratio; (g) median PFS and median OS; in the randomized trial, hazard ratio (HR) and 95% confidence interval (CI) of experimental treatment compared to control arm, in the intention to treat population, were collected. Outcome results by histologic subtypes were also collected to provide a descriptive analysis.

2.4 Data analysis

Meta-analysis on response/disease control rates was performed with MedCalc Statistical Software version 20.015 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

Freeman-Tukey transformation (arcsine square root transformation) was used to calculate the weighted summary proportion under the fixed and random effects model.

Heterogeneity was measured by Cochran's Q, calculated as the weighted sum of squared differences between individual study proportion and the pooled proportion across studies. The I^2 statistic was used to describes the percentage of variation across studies that is due to heterogeneity The likelihood of publication bias was assessed by both Egger's and Begg's tests and by visual inspection of funnel plots.

3. Results

3.1 Systematic review of the literature

3.1.1 Atezolizumab

No results from clinical trials evaluating the anti PD-L1 mAb atezolizumab in pre-treated asMM were found. A randomized phase 3 trial comparing carboplatin plus pemetrexed plus bevacizumab with or without atezolizumab is ongoing in treatment-naive asMM [NCT03762018]

3.1.2 Avelumab

Avelumab has been evaluated in MM within the phase Ib JAVELIN trial.[9] Fifty-three patients with unresectable pre-treated MM received avelumab 10 mg/Kg every two weeks (q2w). Median age was 67 years (range 32-84), and median number of previous lines was 2 (range 1-8). Thirty-two patients (60%) were male, and 39 (74%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1. Most patients had epithelioid histology (n:43, 81%). PD-L1 expression, evaluated with Dako PD-L1 immunohistochemistry (IHC) 73-10 pharmDx, was ≥1% in 21 patients (40%), negative in 22 patients (42%), not evaluable in 10 (19%). High PD-L1 expression (≥5% of positive tumour cells) was reported in 16 patients (30%), while 27 (51%) had a low/negative expression. The median duration of treatment (DoT) was 2.8 months (range 0.9-28.1), with a median of 6 delivered doses (range 2-59). At a median follow-up of 24.8 months (range 16.8-27.8), the ORR (by Response Evaluation Criteria in Solid Tumours- RECIST 1.1) was 9% (95% CI: 3.1-20.7) and the DCR was 58% (n:31). Median PFS and OS were 4.1 (95% CI: 1.4-6.2) and 10.7 (95% CI: 6.4-20.2) months, respectively. ORR was higher in PD-L1 high (19%, 3 out of 16 patients; 95% CI: 4.0-45.6) than in low/negative patients (7%, 2 out of 27 patients; 95% CI: 0.9-24.3) (p=0.34). Median PFS for PD-L1 high and PD-L1 low/negative patients was 5.3 (95% CI:

1.4-17.8) and 1.7 (95% CI: 1.4-8.3) months, respectively, while median OS was 20.2 (95% CI: 4.9-not estimable) and 10.2 (95% CI: 3.8-21.0) months, respectively. Using a 1% cut-off for PD-L1 positive (PD-L1+) and negative (PD-L1-) definition, ORR was 14% (3 patients; 95% CI: 2.9-34.9) and 10% (2 patients; 95% CI: 1.2-30.4), respectively (p= 1.00). In PD-L1+, the median PFS was 5.3 months (95% CI: 1.4-12.0) as compared to 1.6 months in PD-L1- patients (95% CI: 1.4-6.8). The median OS was 20.2 months (95% CI: 6.1- not estimable) and 7.5 months (95% CI: 3.8-21.0) in PD-L1+ and PD-L1-, respectively.

3.1.3 Durvalumab

No results from clinical trials evaluating the anti PD-L1 mAb durvalumab in pre-treated asMM were found. This agent has been studied in 2 single-arm phase 2 trials combined with chemotherapy in treatment-naïve, unresectable malignant pleural mesothelioma (MPM) patients.[10,11] A phase 3 randomized trial comparing cisplatin plus pemetrexed plus durvalumab versus cisplatin plus pemetrexed is ongoing [NCT04334759].

3.1.4 Nivolumab

Nivolumab has been studied in MM alone or in combination with anti-CTLA-4 mAbs. Nivolumab was administered at 3 mg/kg q2w in a single-arm, single-centre, phase II trial in advanced stage MPM patients progressing to at least one prior chemotherapy, with ECOG-PS 0-1.[12] Tumour assessment was performed by RECIST modified for MM (mRECIST) and immune RECIST (iRECIST). The DCR at 12 weeks was the primary end-point. The study enrolled 38 patients, 34 received nivolumab. Median age was 67 years (range 50-81), 82% (n:28) were male, 47% (n:16) had ECOG-PS 1, 82% (n:28) had epithelioid histology, and most had stage I to III disease (n:24, 71%). All but one patient received second-line nivolumab. The median number of administered doses was 7, the median DoT was 2.8 months. The 12 weeks DCR was 47% (95% CI: 30-65), with 8 partial responses (PR) (24%; 95% CI: 11-42) and another patient PR after 18 weeks, leading to 26% ORR. Three pseudo-progressions were observed. At a median follow-up of 27.5 months (95% CI: 19.3-not reached), median duration of response (DoR) was 7.0 months, while median PFS and OS were 2.6 (95% CI: 2.23-5.49) and 11.8 (95% CI: 9.7-15.7) months, respectively. Nine cases (27%) were PD-L1+ (cut-off 1% by 28-8 antibody), mostly epithelioid. Among them, clinical benefit (PR or long-term stable disease- SD) was observed in 5 (55%), with 4 experiencing PR. Overall, 8 out of 23 (34.8%) evaluable PD-L1- patients had clinical benefit.

The single-arm phase 2 trial MERIT had a similar design differing for the nivolumab dose (240 mg q2w) and the number of previous chemotherapy lines (no more than 2, including platinum-pemetrexed combination).[13,14] The primary end-point ORR was centrally assessed by mRECIST. Thirty-four patients were enrolled, the median age was 68 years, 79% (n:27) had epithelioid histology. Median DoT was 6.8 months (median number of doses: 12.5). ORR was 29% (95% CI: 16.8-46.2) and DCR was 68% (95% CI: 50.8-80.9). At a median follow-up of 17.3 months, median OS and PFS were 17.3 (95% CI: 11.5-26.6) and 5.9 (95% CI: not reported) months, respectively. 59% of patients (n:20) was PD-L1+ (cut-off 1% by 28-8 antibody), 35% (n:12) PD-L1-, in 6% (n:2) not evaluable. ORR was higher in PD-L1+ patients as compared to PD-L1- (40% *vs* 8%, respectively). At the same time, PD-L1+ patients did not have longer OS (HR 0.98; 95% CI: 0.43-2.23, p=0.969) and PFS (HR 0.82; 95% CI: 0.37-1.82, p=0.629) as compared to PD-L1-.

Single agent nivolumab was also investigated in a randomized phase II, non-comparative, multicentre trial (MAPS-2).[15] This study enrolled patients with MPM, already treated with one or two lines of chemotherapy. Patients were randomized 1:1 to nivolumab or nivolumab plus ipilimumab. Nivolumab was administered at 3 mg/Kg dose q2w. PD-L1 expression was assessed using 28-8 pharmDx (n:99) and SP-263 clones (n:104), with high expression defined as ≥25% or ≥50% tumour cells expressing PD-L1. The primary end-point was DCR at 12 weeks, OS and PFS were secondary objectives Overall, 68 out of 132 patients were randomized to single agent nivolumab and 63 received the treatment. The median age was 72.3 years, most of the patients were male (75%), had stage III or IV disease (89%) and30% had ECOG-PS 0. Fifty-two patients (83%) had epithelioid histology, 44 (70%) had received one previous line. After a median follow-up of 20.1 months, the 12 weeks DCR was 44% (95% CI: 31-58), while the ORR was 19% (95% CI: 8-29). In the intention-to-treat population, the response rate (RR) was 17.5% (95% CI: 8-1-26.8), while the DCR at 12 weeks was 40% (95% CI: 28-52). The median DoR was 7.4 months (95% CI: 4.1-11.9), while median PFS and OS were 4.0 (95% CI: 2.8-5.7) and 11.9 (95% CI: 6.7-17.7) months, respectively. The subgroup analysis of ORR and DCR by PD-L1 expression were not reported separately by treatment. Overall, the ORR was significantly higher in PD-L1+ patients (using 1% cut-off with both clones) in both arms, while the 12 weeks DCR was not. Using a 25% cut-off for high expressors, both RR and DCR were significantly higher in patients with high PD-L1 expression as assessed by both clones.

Real-world data about 107 patients affected by MPM treated with nivolumab 3 mg/Kg q2w within the Dutch expanded access program were reported.[16,17] All patients were pre-treated

with at least one prior platinum-antifolate regimen (97 treated in second-line). Median age was 69 years (range 34-84), 87% of patients were male, 83% with ECOG-PS 0-1, 78 patients had epithelioid histology. Median PFS and OS were 2.3 (95% CI 1.6-2.9) and 6.7 (95% CI 6.2-10.0) months, respectively, and ORR and DCR by mRECIST were 10% and 37%, respectively.

Another series reported 27 patients with asMM treated with nivolumab 3mg/Kg q2w. The median age of 25 evaluable patients was 67 years (range 38-89), 72% were male, 56% had ECOG-PS $\geq$2, 76% had epithelioid histology.[18] Median PFS was 5 months, the ORR was 24% by RECIST 1.1 with a DCR of 60% in the whole group. Patients with PD-L1 ≥1% and <1% had a DCR of 63% and 55%, respectively.

Early results of a retrospective single-centre Japanese series including 79 patients (78.7% males, n:63) with MPM treated with nivolumab as second- (63.2%), third- (19%) or ≥fourth-line (17.8%) were presented.[19] 21.5% (n=17) had an ECOG-PS ≥2, 81% (n:64) had epithelioid histology. Among 71 patients considered for efficacy, the ORR and DCR by mRECIST were 26.8% and 66.2%, respectively. ORR were 22.8%, 55.6%, and 20% for epithelioid, sarcomatoid, and biphasic MPM, respectively. At a median follow-up of 13.3 months (range 4.2-18.9), median PFS and OS were 4.1 and 14.3 months, respectively. At multivariate analysis, PS $\geq$2 was an independent negative factor for both PFS (HR 2.6; 95% CI: 1.46-4.62) and OS (HR 2.33; 95% CI: 1.30-4.15).

The randomized, double-blind, placebo-controlled CONFIRM trial compared nivolumab with placebo in previously treated MM with a 2:1 allocation proportion.[8] Overall, 221 patients were assigned to the nivolumab arm. Their median age was 74 years (IQR 65-74), 76% (n:167) were male, 95% (n:211) had MPM, 88% (95%) had epithelioid histology. The ORR with nivolumab compared with placebo was significantly higher: 11% *vs* 1% (25 vs 1 partial responses, odds ratio 14.0, p=0.00086), while the DCR was 64% *vs* 55%. Tumors from 161 patients treated with immunotherapy were evaluable for PD-L1 expression and 60 resulted to be positive (defined as 1% threshold 1% with clone 22-C3 clone). Median OS was 10.2 months (95% CI 8.5-12.1) in the nivolumab group and 6.9 months (95% CI: 5.0-8.0;) in the placebo group (HR 0.69, 95% CI: 0.52-0.91, p=0·0090). Median PFS by investigators was 3.0 (95% CI: 2.8-4.1) and 1.8 months (1.4-2.6) months in the nivolumab and placebo group, respectively (HR 0.67, 95% CI: 0.53-0.85, p=0·0012). Seven out of 60 patients (12%) with PD-L1 positive MM achieved a partial response with nivolumab.

3.1.5 Pembrolizumab

The phase IB KEYNOTE-028 study was a multicentre, non-randomised, open-label, multicohort trial of pembrolizumab in patients with advanced solid tumours with PD-L1 expression (≥1%, tested with 22C3 clone).[20,21] Among 38 MPM patients, 25 received pembrolizumab 10 mg/Kg q2w for a maximum of 24 months. The primary end-points were safety, tolerability and ORR (by RECIST based on investigator review); PFS, OS and DoR were secondary end-points. Eighteen (72%) patients had epithelioid MPM. At a median follow-up of 18.7 months, ORR was 28% and the DCR (was 76%Median PFS and OS were 5.8 (95% CI: 3.4-8.2) and 18 (95% CI: 9.4-not reached) months, respectively.

A registry study enrolled 93 patients with unresectable MPM, both untreated and previously treated with chemotherapy.[22] Data collection was retrospective, with PD-L1 evaluation by SP263 clone or by E1L3N clone. Pembrolizumab was administered at different doses (200 mg q3w or q2w, 10 mg/Kg q2w, 2 mg/Kg q2w or q3w). Sixty-six patients (71%) had ECOG-PS 0-1, the median age was 68 years (range 25-94), most patients were male (91%, n:85), 67 (73%) had epithelioid histology. Four patients received pembrolizumab as first-line, 48 as second-line (52%), and 41 (48%) as third-line or subsequent. At a median follow-up of 9 months, the ORR was 18% and the DCR was 48% in the whole cohort. Median PFS and OS were 3.1 (95% CI: 2.6-6.4) and 7.2 (95% CI: 4.9-10.0) months, respectively. PD-L1 expression was associated with ORR and DCR at the univariate analysis but not at the multivariate analysis.

Desai et al. conducted a two-part, phase II, single-centre, non-randomised trial enrolling patients with MM.[23] The part A enrolled 35 unselected patients to determine the ORR to pembrolizumab (200 mg q3w) and to find the optimal PD-L1 cut-off for positivity (22C3 clone). The part B was initiated when 7 responses were reported in part A, and intended to use a biomarker enrichment strategy for PD-L1. However, as no PD-L1 cut-off was established in part A, part B enrolled 30 patients irrespective of PD-L1 level. All enrolled patients previously received at least one previous line of therapy, including platinum and pemetrexed, but no more than 2 systemic regimens. eTh median age was 68 years (range 26-85), 77% were male, and 53% had ECOG-PS 0. 77% had epithelioid histology, 88% had pleural mesothelioma while 12% had peritoneal, and 61% had already received one previous systemic treatment. Disease assessment was performed by mRECIST. ORR was 22% and DCR was 63%. Median PFS and OS were 4.1 and 11.5 months, respectively. PD-L1 expression ≥50% was associated with higher RR and longer median PFS.

The cohort study by Cengel et al enrolled 74 patients receiving pembrolizumab after disease progression to chemotherapy and evaluated ORR (by mRECIST), PFS and OS.[24] Median age was

73 years (range 52-92), and 55 (74%) were male. Three patients received immunotherapy as first-line. Fifty-eight (78%) patients had epithelioid histology. Median OS of the entire population was 7.9 months, median PFS 7.9 months, ORR 26%.

The PROMISE-meso was a phase III, open-label, trial that randomized 1:1 MPM patients, who progressed to platinum-based chemotherapy, to receive either pembrolizumab 200 mg q3w or chemotherapy based on investigator choice (gemcitabine or vinorelbine).[25] Histological subtype (epithelioid *vs* non-epithelioid) was the only stratification factor, while PD-L1 expression was exploratory. The primary end-point was PFS (assessed by blinded independent central review), and secondary end-points were ORR (by RECIST 1.1), time to treatment failure, OS, investigator-assessed PFS and adverse events. PD-L1 immunohistochemistry was assessed by using clone SP263. The study enrolled 144 patients (73 treated with pembrolizumab, 50.7%), 89% with epithelioid histology, 82% males. After a median follow-up of 11.8 months, pembrolizumab arm showed a median PFS of 2.5 months as compared to 3.4 months of the control (HR 1.06, 95% CI: 0.73-1.53, p=0.76 stratified by histological subtype). Pembrolizumab led to a superior ORR (22% *vs* 6%, p=0.004), while the median DoR was higher with chemotherapy (7.2 months *vs* 4.6 months). Median OS was not statistically different between study arms, being 10.7 and 12.4 months in the experimental and control arm, respectively (HR 1.12, 95% CI: 0.74-1.69, p=0.59), without differences even after adjusting for cross-over. The DCR in the pembrolizumab group was 45%, with 16 patients achieving PR and 17 SD. No differences were observed neither in median PFS nor in OS according to PD-L1 expression (TPS <1% *vs* ≥1%).

A retrospective single-centre cohort study of pembrolizumab in MPM included 13 non-papillary peritoneal tumours, all pre-treated with chemotherapy.[26] Median age of enrolled patients was 65.6 years, 62% had known asbestos exposure. Histology was epithelioid in 70% of cases. ORR was 18%, while DCR was 81%. Median PFS and OS were 5.7 and 20.9 months, respectively. No differences in PFS were observed comparing epithelioid histology *vs* others, or by PD-L1 status (positive *vs* negative, median PFS 5.1 *vs* 5.7 months respectively, p=0.73).

Another retrospective real-world study included 98 patients with MM (95 pleural, 3 peritoneal) treated with pembrolizumab.[27] Median age was 70 years (range 46-91), most patients were male (92%) and with ECOG-PS of 0-1 (78%), 76% had epithelioid histology. Four patients received pembrolizumab as first-line because unfit for chemotherapy, while the others were chemotherapy pre-treated (64% one previous line). Pembrolizumab was administered at 200 mg q3w (73%) or at 2 mg/Kg q3w (27%), the median number of cycles was 6 (range 1-35). PD-L1

was assessed with. Using a 1% cut-off, PD-L1 expression (E1L3N clone) resulted negative in 46%, positive in 32%, while for remaining data was missing. ORR was 18% (95% CI: 12-28%) as per investigator-assessed mRECIST, and DCR 56% (95% CI: 47-66). The median PFS and OS were 4.8 (95% CI: 3.6-6.2) and 9.5 (6.6-13.7) months, respectively. PD-L1 expression and BRCA1 associated protein 1 (BAP1) loss were not associated with objective response, although ORR was numerically higher in PD-L1+ patients (23% *vs* 11%) and those with BAP1 loss (20% *vs* 13%).

Kim et al evaluated 115 patients treated with pembrolizumab, nivolumab, or nivolumab in combination with ipilimumab after disease progression to first-line platinum-based chemotherapy.[28] The median age was 75 years (IQR 69-79.5), most were male (74%), and had epithelioid histology (67%). The median OS of the entire cohort was 8.7 months (95% CI: 7.7-10-9).

Finally, 118 patients with ECOG PS 0 to 1 who had disease progression on or intolerance to standard therapy were enrolled into the MPM cohort of Keynote-158 trial, a phase 2 single-arm study assessing the efficacy of pembrolizumab.[29] The median age was 68 years (IQR 61-64), 69% (n:82) had epithelioid histology, 48% (n:57) received immunotherapy as second-line; 77 out of 108 assessable tumours had positive PD-L1 expression ($\geq$ 1 by 22C3 clone). ORR was 8% (95% CI: 4-15), median DoR was 14.3 months, and the median PFS and OS were 2.1 (95% CI: 2.1-3.9) and 10 (95% CI: 7.6-13.4) months, respectively. ORR in PD-L1 positive patients was 12%.

3.2 Meta-analysis

We selected 13 studies including 888 patients, most with pleural MM.[8,9,12,14,15,17,19,20,23,25,26,29,30] **Table 1** summarizes the main characteristics of the selected trials. Four studies were excluded due to the inclusion of treatment naïve patients,[18,22,24,27] , and one due to the inclusion of patients treated with dual ICIs combination.[28] The analysis of patients from the phase III PROMISE-meso and CONFIRM trials was restricted to those assigned to immunotherapy.[8,25] Data on responses were available for 888 patients, irrespective of PD-L1 levels. A total of 835 patients (94%) received anti-PD-1 inhibitors (nivolumab or pembrolizumab []), while 53 (6%) were treated with avelumab [**Table 1**]. In aggregate, ORR was 18.1% (95% CI: 13.9-22.8%; Cochran's Q p=0.0011, I^2=63.35%) [**Figure 2**]. DCR was 55.4% (95% CI: 48.1-62.5%; Cochran's Q p<0.0001, I^2=76.57%) [**Figure 3**]. In unselected patients, the median PFS ranged from 2.1 to 5.8 months, while the median OS from 6.7 to 20.9 months. Tumour response according to PD-L1 expression were reported in 10 out of 13 studies, with PD-L1 positivity defined using

heterogeneous cut-offs depending of each different trial (ranging from 1% to 50%).[9,12,13,15,20,23] This subgroup included 304 and 310 patients, depending on the clone adopted in the study by Scherpereel et al. (the 28-8and SP-263, respectively) [**Table 2**].[15] ORR was 28.0% (95% CI: 19.0-38.0%; Cochran's Q p=0.0006, I^2=69.03%) and 27.0% (95% CI: 18.7-36.2%; Cochran's Q p=0.0021, I^2=65.22%), respectively, although it ranged from 12% to 56% in different studies [**Figure 4** forest plot of the analysis with the largest sample, accounting for the use of SP-263 clone in [15]; **sFigure 1** accounting for the use of 28-8 clone]. The funnel plots showed no evidence of publication bias [**Figure 5, Figure 6, Figure 7, s Figure 2**].

4. Discussion

We performed a systematic review and meta-analysis to evaluate the activity of anti-PD-1/PD-L1 in pre-treated asMM in terms of ORR and DCR. Notably, as higher efficacy is observed in tumours whose aetiology is associated to carcinogens exposure, ICIs evaluation in asMM finds a rational as most cases are related to asbestos exposure.[31–33] Unfortunately, most of the studies about ICIs in asMM do not report this information. MM is somehow resistant to cytotoxic chemotherapy, especially non-epithelioid subtypes. The recent demonstration that the combination of the anti-CTLA-4 monoclonal antibody ipilimumab with nivolumab could significantly increase OS as compared to platinum plus pemetrexed in the first-line setting, is predicted to change the treatment landscape of this aggressive disease.[5] However, while the superiority of ICIs combination appeared to be clear in non-epithelioid tumors, patients with epithelioid MM showed less benefit and chemotherapy may be still regarded as a treatment option, while waiting for the results of chemo-immunotherapy combination from ongoing clinical trials.[34] Unfortunately, due to the lack of specific data, we could not evaluate the activity of ICIs in pre-treated patients according to histology. Following platinum-based chemotherapy, second-line treatments have only modest efficacy, with ORR of 8.63%, a DCR of 54.8%, and a median PFS and OS of 3.4 and 7.86 months, respectively.[35]Only recently a formal demonstration of vinorelbine efficacy has been provided by a phase 2 trial.[36] Moreover, another randomised phase 2 trial showed that the addition of the anti-vascular endothelial growth factor receptor 2 (VEGFR-2) monoclonal antibody ramucirumab to gemcitabine could increase OS as compared to gemcitabine and placebo in second-line setting.[37] Our meta-analysis indicates that ICIs provide an ORR and DCR of 18.1% and 55.4%, respectively, without significant differences between agents. Overall, the heterogeneity between the studies was moderate, both in the entire

population and in patients whose tumours expressed PD-L1,. No significant evidence of publication bias was found.

However, the results of the phase 3 PROMISE-meso trial showed that, despite the higher ORR with pembrolizumab, no survival differences were observed as compared to single agent chemotherapy in pre-treated asMM.[25] Notably, this trial was designed with PFS as primary end-point. OS events were 92 at the time of the analysis, leading to a 19% statistical power for a HR of 0.8, meaning that the study was not powered to allow meaningful conclusion about OS.[25] Indeed, the interpretation of these results is challenging. Since most of the studies included in our meta-analysis lack of a comparison arm, we were not able to compare ICIs with single-agent chemotherapy. However, to our knowledge, ORR has never been demonstrated to be a surrogate marker of survival in MM. Moreover, 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. For this latter reason, as most studies were single-arm trials, observer bias could not be ruled out.

The present meta-analysis suggests that PD-L1+ tumours might better respond to single-agent immunotherapy. However, trials are highly heterogeneous when accounting for PD-L1 evaluation because different IHC clones and cut-offs were used, so that these data should be taken with caution. Indeed, available data suggest that PD-L1 expression in malignant pleural mesothelioma is prognostic, with high levels associated with poorer outcomes even after accounting for other variables such as histology and performance status.[38–40]

A recent publication reported that the antigenic potential of mesothelioma could be better predicted by other factors, including chromosomal rearrangements (chromoplexy and chromothripsis).[41] Such interesting data deserve more studies in the context of ICIs therapy for MM. Adoptive immunotherapy as well as vaccines, alone or in combination with ICIs, are another active field of investigation. Preliminary results of a phase I study of intrapleural injection of mesothelin-targeted chimeric antigen receptor T-cell (CAR-T) therapy, with or without anti PD-1 agents, showed 63% RR in 18 asMM patients, 37% of which already treated with 3 or more lines of therapy.[42] The treatment landscape of asMM is therefore expected to change, and immunotherapy may have a pivotal role both in treatment-naïve and pre-treated patients. Along with those from Checkmate 743, results of ongoing studies on chemo-immunotherapy combinations are expected to change the treatment landscape of untreated unresectable MPM. While waiting for these data, , our meta-analysis suggests that anti-PD-(L)1

agents might be useful in some chemotherapy pre-treated patients, even if reliable predictive factors are still lacking.

Figure legends

Figure 1. PRISMA flowchart of selected trials

Figure 2. Objective response rate of trials selected for the meta-analysis and aggregate data

Figure 3. Disease control rate of trials selected for the meta-analysis and aggregate data

Figure 4. Objective response rate of trials reporting activity according to PD-L1 expression and aggregate data.

Caption: PD-L1 clone SP-263 in Scherpereel et al.

Figure 5. Funnel plot for objective response rate

Figure 6. Funnel plot for disease control rate

Figure 7. Funnel plot for objective response rate in PD-L1 positive patients (Scherpereel SP-263)

sFigure 1. Objective response rate of trials reporting activity according to PD-L1 expression and aggregate data (Scherpereel 28-8)

sFigure 2. Funnel plot for objective response rate in PD-L1 positive patients (Scherpereel 28-8)

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A systematic review and meta-analysis of trials assessing PD-1/PD-L1 immune checkpoint inhibitors activity in pre-treated advanced stage malignant mesothelioma

Abstract

Introduction

Advanced stage malignant mesothelioma (asMM) patients have poor prognosis. Several trials investigated the role of programmed cell death protein-1 (PD-1) and its ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) in pre-treated asMM.

Methods

A systematic review of the literature of clinical trials testing single-agent anti PD-1/PD-L1 ICIs in pre-treated asMM was performed. Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) data were extracted. The predictive role of PD-L1 was assessed.

Results

We selected 130 studies including ~~497~~ 888 patients. ORR and DCR were ~~20~~18.1% (95% confidence interval [CI] 13.9~~6.8~~-22.8~~23.9~~%) and 55.4~~.6~~% (95% CI: ~~50.2~~48.1-~~59.0~~62.5%), respectively. Median PFS and OS ranged from 2.1~~5~~ to ~~6.1~~5.9 and from 6.7~~36~~ to 20.9 months, respectively. ORR according to PD-L1 ~~expression ranged from 19% to 55.5~~was 27.0% (95% CI: 18.7-36.2%)~~%~~.

Conclusions

Anti-PD-(L)1 ICIs might be considered a treatment option for chemotherapy-resistant asMM, even if reliable predictive factors are still lacking.

Keywords

Mesothelioma; immune checkpoint inhibitors; nivolumab; pembrolizumab; avelumab

Abbreviations

MM: malignant mesothelioma

OS: overall survival

PFS: progression-free survival

ICIs: immune checkpoint inhibitors

CTLA-4: cytotoxic T-lymphocyte antigen-4

PD-1: programmed cell death protein-1

PD-L1: programmed death-ligand 1

asMM: advanced stage malignant mesothelioma

mAbs: monoclonal antibodies

ASCO: American Society of Clinical Oncology

ESMO: European Society of Medical Oncology

IASLC: International Association for the Study of Lung Cancer

ELCC: European Lung Cancer Congress

HR: hazard ratio

CI: confidence interval

ORR: objective response rare

FDA: Food and Drug Administration

EMA: European Medicines Agency

q2w: every two weeks

q3w: every three weeks

ECOG: Eastern Cooperative Oncology Group

PS: performance status

IHC: immunohistochemistry

DoT: duration of treatment

RECIST: Response Evaluation Criteria in Solid Tumours

PD-L1+: PD-L1 positive

PD-L1-: PD-L1 negative

MPM: malignant pleural mesothelioma

mRECIST: modified RECIST

iRECIST: immune RECIST

DoR: duration of response

RR: response rate

PR: partial response

SD: stable disease

BAP1: BRCA1 associated protein 1

CAR-T: chimeric antigen receptor T-cell

1. Introduction

Malignant mesothelioma (MM) is a rare and aggressive tumour of mesothelial surfaces. Asbestos exposure is the main risk factor, even if this neoplasm can occur in non-exposed subjects and rarely can be due to germline mutations.[1] The combination of platinum and pemetrexed has been for decades~~is~~ the standard systemic first-line treatment, providing a small although significant survival benefit as compared to platinum alone, and better symptom control.[2] ~~Recently, in o~~One randomized study the addition of bevacizumab improved progression-free and overall survival (PFS and OS) as compared to chemotherapy alone.[3] Overall clinical results are still modest, claiming for novel approaches to ~~significantly ameliorate the~~significantly increase survival of MM patients. In the last few years, immune checkpoint inhibitors (ICIs) radically changed treatment paradigm of many solid tumours. While cytotoxic T-lymphocyte antigen-4 (CTLA-4) directed agents alone did not confer any benefit in advanced MM,[4] their combination with a programmed cell death protein-1 (PD-1) inhibitor recently demonstrated to be superior to platinum plus pemetrexed in a phase 3 randomized trial in treatment naïve advanced pleural MM patients.[5] However, the magnitude of benefit seems superior in non-epithelioid MM, while at best modest in epithelioid tumors.[6] S~~s~~everal trials and case-series suggest that ~~programmed cell death protein-1 (~~PD-1) and programmed death-ligand 1 (PD-L1) antagonists may increase survival in chemotherapy pre-treated advanced stage MM (asMM) patients too.[7] However, such results are still debated because the only randomized trial with active control did not show survival differences between pembrolizumab and single agent chemotherapy, while another placebo-controlled study showed the superiority of nivolumab as compared to best supportive care.[8] To this end, we performed a systematic review and meta-analysis to define the activity and efficacy of PD-1/PD-L1 monoclonal antibodies (mAbs) in chemotherapy pre-treated asMM patients.

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2. Material and Methods

2.1 Trial identification criteria

We identified all clinical trials testing ICIs in pre-treated asMM as single-agent in single-arm as well as multi-arm studies. The following Mesh terms were used: "mesothelioma", "malignant mesothelioma~~, malignant~~", "atezolizumab", "avelumab", "durvalumab", "nivolumab", "pembrolizumab", "immunotherapy", "PD-1", "PD-L1". Search was made on Pubmed/Medline and Cochrane library on ~~September~~ January ~~13~~20th, 202~~0~~2. Papers published in peer-reviewed journals and in English language were selected. We also searched proceedings of major International

meetings such as American Society of Clinical Oncology- ASCO annual meetings, European Society of Medical Oncology- ESMO annual meetings, International Association for the Study of Lung Cancer- IASLC World Conferences on Lung Cancer, European Lung Cancer Congress- ELCC from 2014 onwards for relevant abstracts. When more than one report of the same study was available, the most recent data (with longer follow-up and/or higher number of patients) were considered (**Figure 1**).

2.2 Aims of the meta-analysis

- (i) To evaluate the activity of single-agent PD-1/PD-L1 directed ICIs in chemotherapy pre-treated asMM in terms of objective response rare (ORR) and disease control rate (DCR);
- (ii) To evaluate the efficacy of single-agent PD-1/PD-L1 directed ICIs in chemotherapy pre-treated asMM in terms of PFS and OS;
- (iii) To explore the potential role of PD-L1 expression as a predictive marker of activity. For this aim, the ORR and DCR analyses were repeated in the subgroup of patients included, within each trial, in the highest category of PD-L1 expression (even if with heterogeneous methods and cut-offs).

2.3 Data extraction for the meta-analysis

The following data were extracted from each study: (a) first author, phase of the study, and year of publication; (b) type of ICIs agent and number of patients assigned to the experimental treatment; (c) percentage of patients treated in second-line; (d) site of MM (pleural *vs* peritoneal *vs* others) and histology; (e) median follow-up and range; (f) ORR (number of patients obtaining objective response) in the whole study population and in the "PD-L1 high" subpopulation; in the randomized trial, ORR was collected for both treatment arms in order to calculate odds ratio; (g) DCR (number of patients obtaining objective response or disease stabilization) in the study population and in the "PD-L1 high" subpopulation; in the randomized trial, DCR was collected for both treatment arms in order to calculate odds ratio; (g) median PFS and median OS; in the randomized trial, hazard ratio (HR) and 95% confidence interval (CI) of experimental treatment compared to control arm, in the intention to treat population, were collected. Outcome results by histologic subtypes were also collected to provide a descriptive analysis.

2.4 Data analysis

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Meta-analysis on response/disease control rates was performed with MedCalc Statistical Software version 20.015 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). Freeman-Tukey transformation (arcsine square root transformation) was used to calculate the weighted summary proportion under the fixed and random effects model.

Heterogeneity was measured by Cochran's Q, calculated as the weighted sum of squared differences between individual study proportion and the pooled proportion across studies. The I^2 statistic was used to describes the percentage of variation across studies that is due to heterogeneity ~~To obtain a quantitative measure of the degree of heterogeneity among studies included in the analysis, the Higgins I^2 index was computed.~~ The likelihood of publication bias was assessed by both Egger's and Begg's tests and by visual inspection of funnel plots. ~~The MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used for statistical analyses.~~

3. Results

3.1 Systematic review of the literature

3.1.1 Atezolizumab

No results from clinical trials evaluating the anti PD-L1 mAb atezolizumab in pre-treated asMM were found. A randomized phase 3 trial comparing carboplatin plus pemetrexed– plus bevacizumab with or without atezolizumab is ongoing in treatment-naive asMM [NCT03762018]~~However, a single-arm phase trial with atezolizumab in this population is ongoing [NCT 03786419].~~

3.1.2 Avelumab

Avelumab~~, a humanized anti-PD-L1 IgG1 mAb,~~ has been evaluated in MM within the phase Ib JAVELIN trial.[9] Fifty-three patients with unresectable pre-treated MM received avelumab 10 mg/Kg every two weeks (q2w). Median age was 67 years (range 32-84), and median number of previous lines was 2 (range 1-8). Thirty-two patients (60%) were male, and 39 (74%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1. Most patients had epithelioid histology (n:43, 81%). PD-L1 expression, evaluated with Dako PD-L1 immunohistochemistry (IHC) 73-10 pharmDx, was ≥1% in 21 patients (40%), negative in 22 patients (42%), not evaluable in 10 (19%). High PD-L1 expression (≥5% of positive tumour cells)

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was reported in 16 patients (30%), while 27 (51%) had a low/negative expression. The median duration of treatment (DoT) was 2.8 months (range 0.9-28.1), with a median of 6 delivered doses (range 2-59). At a median follow-up of 24.8 months (range 16.8-27.8), the ORR (by Response Evaluation Criteria in Solid Tumours- RECIST 1.1) was 9% (95% CI: 3.1-20.7) and the DCR was 58% (n:31). Median PFS and OS were 4.1 (95% CI: 1.4-6.2) and 10.7 (95% CI: 6.4-20.2) months, respectively. ORR was higher in PD-L1 high (19%, 3 out of 16 patients; 95% CI: 4.0-45.6) than in low/negative patients (7%, 2 out of 27 patients; 95% CI: 0.9-24.3) (p=0.34). Median PFS for PD-L1 high and PD-L1 low/negative patients was 5.3 (95% CI: 1.4-17.8) and 1.7 (95% CI: 1.4-8.3) months, respectively, while median OS was 20.2 (95% CI: 4.9-not estimable) and 10.2 (95% CI: 3.8-21.0) months, respectively. Using a 1% cut-off for PD-L1 positive (PD-L1+) and negative (PD-L1-) definition, ORR was 14% (3 patients; 95% CI: 2.9-34.9) and 10% (2 patients; 95% CI: 1.2-30.4), respectively (p= 1.00). In PD-L1+, the median PFS was 5.3 months (95% CI: 1.4-12.0) as compared to 1.6 months in PD-L1- patients (95% CI: 1.4-6.8). The median OS was 20.2 months (95% CI: 6.1- not estimable) and 7.5 months (95% CI: 3.8-21.0) in PD-L1+ and PD-L1-, respectively.

3.1.3 Durvalumab

No results from clinical trials evaluating the anti PD-L1 mAb durvalumab in pre-treated asMM were found. This agent has been studied in 2 single-arm phase 2 trials combined with chemotherapy in treatment-naïve, unresectable malignant pleural mesothelioma (MPM) patients.[10,11] A phase 3 randomized trial comparing cisplatin plus pemetrexed plus durvalumab versus cisplatin plus pemetrexed is ~~initiating enrolment~~ongoing [NCT-04334759].

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3.1.4 Nivolumab

~~The fully human anti-PD-1 Ig G4 mAb n~~Nivolumab has been studied in MM alone or in combination with anti-CTLA-4 mAbs. Nivolumab was administered at 3 mg/kg q2w in a single-arm, single-centre, phase II trial in advanced stage MPM patients progressing to at least one prior chemotherapy, with ECOG-PS 0-1.[12] Tumour assessment was performed by RECIST modified for MM (mRECIST) and immune RECIST (iRECIST). The DCR at 12 weeks was the primary end-point. The study enrolled 38 patients, 34 received nivolumab. Median age was 67 years (range 50-81), 82% (n:28) were male, 47% (n:16) had ECOG-PS 1, 82% (n:28) had epithelioid histology, and most had stage I to III disease (n:24, 71%). All but one patient received second-

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line nivolumab. The median number of administered doses was 7, the median DoT was 2.8 months. The 12 weeks DCR was 47% (95% CI: 30-65), with 8 partial responses (PR) (24%; 95% CI: 11-42) and another patient PR after 18 weeks, leading to 26% ORR. Three pseudo-progressions were observed. At a median follow-up of 27.5 months (95% CI: 19.3-not reached), median duration of response (DoR) was 7.0 months, while median PFS and OS were 2.6 (95% CI: 2.23-5.49) and 11.8 (95% CI: 9.7-15.7) months, respectively. Nine cases (27%) were PD-L1+ (cut-off 1% by 28-8 antibody), mostly epithelioid. Among them, clinical benefit (PR or long-term stable disease- SD) was observed in 5 (55%), with 4 experiencing PR. Overall, 8 out of 23 (34.8%) evaluable PD-L1- patients had clinical benefit.

The single-arm phase 2 trial MERIT had a similar design differing for the nivolumab dose (240 mg q2w) and the number of previous chemotherapy lines (no more than 2, including platinum-pemetrexed combination).[13,14] The primary end-point ORR was centrally assessed by mRECIST. Thirty-four patients were enrolled, the median age was 68 years, 79% (n:27) had epithelioid histology. Median DoT was 6.8 months (median number of doses: 12.5). ~~At a median follow-up of 12.8 months,~~ ORR was 29% (95% CI: 16.8-46.2) and DCR was 68% (95% CI: 50.8-80.9). At a median follow-up of 17.3 months, ~~M~~median OS and PFS were 17.3 (95% CI: 11.5-~~not reached~~26.6) and ~~6.1~~5.9 (95% CI: ~~2.9-9.9~~not reported) months, respectively. 59% of patients (n:20) was PD-L1+ (cut-off 1% by 28-8 antibody), ~~12~~35% (n:~~12~~4) PD-L1-, in 6% (n:2) not evaluable. ORR was higher in PD-L1+ patients as compared to PD-L1- (40% *vs* 8%, respectively)~~, with similar trends using higher cut-offs (5% and 10%)~~. At the same time, PD-L1+ patients ~~had~~ did not have longer OS (HR 0.98~~542~~; 95% CI: 0.~~208~~43-~~1~~2.23~~415~~, p=0.969~~2021~~) and PFS (HR 0.82~~725~~; 95% CI: 0.37~~16~~-1.82~~668~~, p=0.629~~4490~~) as compared to PD-L1-.

Single agent nivolumab was also investigated in a randomized phase II, non-comparative, multicentre trial (MAPS-2).[15] This study enrolled patients with MPM, already treated with one or two lines of chemotherapy. Patients were randomized 1:1 to nivolumab or nivolumab plus ipilimumab. Nivolumab was administered at 3 mg/Kg dose q2w. ~~Disease assessment was performed every 12 weeks (mRECIST criteria), with central revision.~~ PD-L1 expression was assessed using 28-8 pharmDx (n:99) and SP-263 clones (n:104), with high expression defined as ≥25% or ≥50% tumour cells expressing PD-L1. ~~An exploratory cut-off threshold was defined on results from a post-hoc analysis.~~ The primary end-point was DCR at 12 weeks, ~~secondary objectives included~~ OS and PFS were secondary objectives~~.~~ ~~Among the 132 recruited patients,~~ Overall, 68 out of 132 patients were randomized to single agent nivolumab and 63 received the

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treatment. The median age was 72.3 years, most of the patients were male (75%), had stage III or IV disease (89%), and while only 30% had ECOG-PS 0. Fifty-two patients (83%) had epithelioid histology, 44 (70%) had received one previous line. After a median follow-up of 20.1 months, the 12 weeks DCR was 44% (95% CI: 31-58), while the ORR was 19% (95% CI: 8-29). In the intention-to-treat population, the response rate (RR) was 17.5% (95% CI: 8-1-26.8), while the DCR at 12 weeks was 40% (95% CI: 28-52). The median DoR was 7.4 months (95% CI: 4.1-11.9), while median PFS and OS were 4.0 (95% CI: 2.8-5.7) and 11.9 (95% CI: 6.7-17.7) months, respectively. The subgroup analysis of ORR and DCR by PD-L1 expression were not reported separately by treatment. Overall, the ORR was significantly higher in PD-L1+ patients (using 1% cut-off with both clones) in both arms, while the 12 weeks DCR was not. Using a 25% cut-off for high expressors, both RR and DCR were significantly higher in patients with high PD-L1 expression as assessed by both clones.

Domoulin et al. reported rReal-world data about 59 107 patients affected by MPM treated with nivolumab 3 mg/Kg q2w within the Dutch expanded access program were reported.[16,17] All patients were pre-treated with at least one prior platinum-antifolate regimen (54 97 treated in second-line). Median age was 72 69 years (range 5034-843), 9087% of patients were male, 9583% with ECOG-PS 0-1, 78. Forty-one patients had epithelioid histology. Median PFS and OS were 2.3 (95% CI 1.6-2.9)64 and 6.736 (95% CI 6.2-10.0) months, respectively, and ORR and DCR by mRECIST was were 102% and 37%, respectivelyby mRECIST.

Another series reported 27 patients with asMM treated with nivolumab 3mg/Kg q2w. The median age of 25 evaluable patients was 67 years (range 38-89), 72% were male, 56% had ECOG-PS ≥2, 76% had epithelioid histology.[18] Median PFS was 5 months, the ORR was 24% by RECIST 1.1 with a DCR of 60% in the whole group. Patients with PD-L1 ≥1% and <1% had a DCR of 63% and 55%, respectively.

Early results of a retrospective single-centre Japanese series including 79 patients (78.7% males, n:63) with MPM and treated with nivolumab as second- (63.2%), third- (19%) or ≥fourth-line (17.8%) were presented.[19] 21.5% (n=17) had an ECOG-PS ≥2, 81% (n:=64) had epithelioid histology. Among 71 patients considered for efficacy, the ORR (by mRECIST) and DCR by mRECIST were 26.8% and 66.2%, respectively. ORR were 22.8%, 55.6%, and 20% for epithelioid, sarcomatoid, and biphasic MPM, respectively. At a median follow-up of 13.3 months (range 4.2-18.9), median PFS and OS were 4.1 and 14.3 months, respectively. At multivariate analysis, PS

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≥2 was an independent negative factor for both PFS (HR 2.6; 95% CI: 1.46-4.62) and OS (HR 2.33; 95% CI: 1.30-4.15).

TheA randomized, double-blind, placebo-controlled CONFIRM ~~clinical~~ trial compareding nivolumab with placebo in previously treated MM with a 2:1 allocation proportion.[8] ~~is currently ongoing (CONFIRM Study, NCT 03063450).~~ Overall, 221 patients were assigned to the nivolumab arm. Their median age was 74 years (IQR 65-74), 76% (n:167) were male, 95% (n:211) had MPM, 88% (95%) had epithelioid histology. The ORR with nivolumab compared with placebo was significantly higher: 11% *vs* 1% (25 vs 1 partial responses, odds ratio 14.0, p=0.00086), while the DCR was 64% *vs* 55%. Tumors from 161 ~~Among~~ patients treated with immunotherapy~~, 161 tumours~~ were evaluable for PD-L1 expression and 60 resulted to be positive (defined as 1% threshold 1% with clone 22-C3 clone). Median OS was 10.2 months (95% CI 8.5-12.1) in the nivolumab group and 6.9 months (95% CI: 5.0-8.0;) in the placebo group (HR 0.69, 95% CI: 0.52-0.91, p=0·0090). Median PFS by investigators was 3.0 (95% CI: 2.8-4.1) and 1.8 months (1.4-2.6) months in the nivolumab and placebo group, respectively (HR 0.67, 95% CI: 0.53-0.85, p=0·0012). Seven out of 60 patients (12%) with PD-L1 positive MM achieved a partial response with nivolumab.

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3.1.5 Pembrolizumab

~~Pembrolizumab is a humanised Ig G4 mAb directed against PD-1.~~ The phase IB KEYNOTE-028 study was a multicentre, non-randomised, open-label, multicohort trial of pembrolizumab in patients with advanced solid tumours with PD-L1 expression (≥1%, tested with 22C3 clone).[20,21] Among 38 MPM patients, 25 received pembrolizumab 10 mg/Kg q2w for a maximum of 24 months. The primary end-points were safety, tolerability and ORR (by RECIST based on investigator review); PFS, OS and DoR were secondary end-points. Eighteen (72%) patients had epithelioid MPM. At a median follow-up of 18.7 months, ORR was 280% ~~(95% CI: 6.8-40.7)~~ and the ~~clinical benefit rate~~DCR (~~defined as complete response plus PR plus SD for 6 months or more)~~ was 4076% ~~(95% CI: 21.1-61.3). The DCR was 72%. Of note, two additional patients had a reduction in tumour size of more than 30% but were not included in the confirmed ORR as they did not have a subsequent confirmatory imaging.~~ Median PFS and OS were 5.84 (95% CI: 3.4-8.27~~.5~~) and 18 (95% CI: 9.4-not reached) months, respectively.

A registry study enrolled 93 patients with unresectable MPM, both untreated and previously treated with chemotherapy.[22] Data collection was retrospective, with PD-L1 evaluation by SP263

clone or by E1L3N clone. Pembrolizumab was administered at different doses (200 mg q3w or q2w, 10 mg/Kg q2w, 2 mg/Kg q2w or q3w). Sixty-six patients (71%) had ECOG-PS 0-1, the median age was 68 years (range 25-94), most patients were male (91%, n:85), 67 (73%) had epithelioid histology. Four patients received pembrolizumab as first-line, 48 as second-line (52%), and 41 (48%) as third-line or subsequent. At a median follow-up of 9 months, the ORR was 18% and the DCR was 48% in the whole cohort. Median PFS and OS were 3.1 (95% CI: 2.6-6.4) and 7.2 (95% CI: 4.9-10.0) months, respectively. PD-L1 expression was associated with ORR and DCR at the univariate analysis but not at the multivariate analysis.

Desai et al. conducted a two-part, phase II, single-centre, non-randomised trial enrolling patients with MM.[23] The part A enrolled 35 unselected patients to determine the ORR to pembrolizumab (200 mg q3w) and to find the optimal PD-L1 cut-off for positivity (22C3 clone). The part B was initiated when 7 responses were reported in part A, ~~–~~and intended to use a biomarker enrichment strategy for PD-L1. However, as no PD-L1 cut-off was established in part A, part B enrolled 30 patients irrespective of PD-L1 level. All enrolled patients previously received at least one previous line of therapy, including platinum and pemetrexed, but no more than 2 systemic regimens. eTh median age was 68 years (range 26-85), 77% were male, and 53% had ECOG-PS 0. 77% had epithelioid histology, 88% had pleural mesothelioma while 12% had peritoneal, and 61% had already received one previous systemic treatment. Disease assessment was performed by mRECIST. ORR was 22% and DCR was 63%. Median PFS and OS were 4.1 and 11.5 months, respectively. PD-L1 expression ≥50% was associated with higher RR and longer median PFS.

The cohort study by Cengel et al enrolled ~~82~~ 74 patients receiving pembrolizumab after disease progression to chemotherapy and evaluated ORR (by mRECIST), PFS and OS.[24] Median age was 7~~3~~2 years (range 52-92), and 5~~9~~9 (74%) were male. Three patients received immunotherapy as first-line. ~~Sixty three~~Fifty-eight (78%) patients had epithelioid histology~~, 42 treated in second line~~. ~~PD-L1 expression was not determined in 45 patients, <1% in 16, and ≥1% in 21.~~ Median OS of the entire population was ~~8.5~~7.9 months, median PFS 7.9~~4.2~~ months, ORR 2~~5~~6%~~, and DCR 71%~~.

The PROMISE-meso ~~In 2019, the results of~~was a phase III, open-label, ~~randomized~~ trial ~~PROMISE-meso trial have been presented.[19] This trial~~that randomized 1:1 MPM patients, who progressed to platinum-based chemotherapy, to receive either pembrolizumab 200 mg q3w or chemotherapy based on investigator choice (gemcitabine or vinorelbine).[25] Histological subtype (epithelioid *vs* non-epithelioid) was the only stratification factor, while PD-L1 expression was

exploratory. The primary end-point was PFS (assessed by blinded independent central review), and secondary end-points were ORR (by RECIST 1.1), time to treatment failure, OS, investigator-assessed PFS and adverse events. PD-L1 immunohistochemistry was assessed by using clone SP263. The study enrolled 144 patients (73 treated with pembrolizumab, 50.7%), ~~90~~89% with epithelioid histology, 82~~80~~% males. After a median follow-up of 11.8 months, pembrolizumab arm showed a median PFS of 2.5 months as compared to 3.4 months of the control (HR 1.06, 95% CI: 0.73-1.53, p=0.76 stratified by histological subtype). Pembrolizumab led to a superior ORR (22% *vs* 6%, p=0.004), while the median DoR was higher with chemotherapy (~~11~~7.2 months *vs* 4.6 months). Median OS was not statistically different between study arms, being 10.7 and ~~11~~12.~~4~~7 months in the experimental and control arm, respectively (HR 1.~~04~~12, 95% CI: 0.~~66~~74-1.6~~9~~7, p=0.59~~85~~), without differences even after adjusting for cross-over. The DCR in the pembrolizumab group was 45%, with 16 patients achieving PR and 17 SD. No differences were observed neither in median PFS nor in OS according to PD-L1 expression (TPS <1% *vs* ≥1%).

A retrospective single-centre cohort study of pembrolizumab in MPM included 13 non-papillary peritoneal tumours, all pre-treated with chemotherapy.[26] Median age of enrolled patients was 65.6 years, 62% had known asbestos exposure. Histology was epithelioid in 70% of cases. ORR was 18%, while DCR was 81%. Median PFS and OS were 5.7 and 20.9 months, respectively. No differences in PFS were observed comparing epithelioid histology *vs* others, or by PD-L1 status (positive *vs* negative, median PFS 5.1 *vs* 5.7 months respectively, p=0.73).

Another retrospective real-world study included 98 patients with MM (95 pleural, 3 peritoneal) treated with pembrolizumab.[27] Median age was 70 years (range 46-91), most patients were male (92%) and with ECOG-PS of 0-1 (78%), 76% had epithelioid histology. Four patients received pembrolizumab as first-line because unfit for chemotherapy, while the others were chemotherapy pre-treated (64% one previous line). Pembrolizumab was administered at 200 mg q3w (73%) or at 2 mg/Kg q3w (27%), the median number of cycles was 6 (range 1-35). PD-L1 was assessed with. Using a 1% cut-off, PD-L1 expression (E1L3N clone) resulted negative in 46%, positive in 32%, while for remaining data was missing. ORR was 18% (95% CI: 12-28%) as per investigator-assessed mRECIST, and DCR 56% (95% CI: 47-66). The median PFS and OS were 4.8 (95% CI: 3.6-6.2) and 9.5 (6.6-13.7) months, respectively. PD-L1 expression and BRCA1 associated protein 1 (BAP1) loss were not associated with objective response, although ORR was numerically higher in PD-L1+ patients (23% *vs* 11%) and those with BAP1 loss (20% *vs* 13%).

Kim et al evaluated 115 patients treated with pembrolizumab, nivolumab, or nivolumab in combination with ipilimumab after disease progression to first-line platinum-based chemotherapy.[28] The median age was 75 years (IQR 69-79.5), most were male (74%), and had epithelioid histology (67%). The median OS of the entire cohort was 8.7 months (95% CI: 7.7-10-9).

Finally, 1184 patients with ECOG PS 0 to 1 who had disease progression on or intolerance to standard therapy ~~affected by asMM~~ were enrolled into the MPM cohort of Keynote-158 trial, a phase 2 single-arm study assessing the efficacy of pembrolizumab ~~in patients with non-colorectal high microsatellite instability/mismatch repair deficient tumours~~.[29] The median age was 68 years (IQR 61-64), 69% (n:82) had epithelioid histology, 48% (n:57) received immunotherapy as second-line; 77 out of 108 assessable tumours had positive PD-L1 expression (≥ 1 by 22C3 clone). ~~Among 233 enrolled patients,~~ ORR was ~~34.38~~% (95% CI: ~~28.34-40.8~~15), median DoR was 14.3 months, and the median PFS and OS were ~~4.1~~2.1 (95% CI: 2.1~~4-4~~3.9) and ~~23.5~~10 (95% CI: ~~13.5~~7.6 ~~not reached~~13.4) months, respectively. ~~However, data about patients with asMM are not available.~~ ORR in PD-L1 positive patients was 12%.

3.2 Meta-analysis

We selected 1~~3~~0 studies including ~~497~~ 888 patients, most with pleural MM.[8,9,12,14,15,17,19,20,23,25,26,29,30] **Table 1** summarizes the main characteristics of the selected trials. Four studies were excluded due to the inclusion of treatment naïve patients,[18,22,24,27] ~~while one study because no data on asMM patients were available.~~[22], and one due to the inclusion of patients treated with dual ICIs combination.[28] The analysis of patients from the phase III PROMISE-meso and CONFIRM trials ~~and was were~~was restricted to those assigned to ~~pembrolizumab (n:73)~~immunotherapy.[8,25] Data on responses were available for ~~487~~ 888 patients, irrespective of PD-L1 levels. A total of ~~434~~ 835 patients (~~89.1~~94%) received anti-PD-1 inhibitors (nivolumab ~~[N]~~ or pembrolizumab [~~P~~]), while 53 (~~10.9~~6%) were treated with avelumab ~~(A)~~ [**Table 1**]. In aggregate, ORR was ~~20.1~~18.1% (95% CI: ~~16.8~~13.9-~~23.9~~22.8%; Cochran's Q p=0.0011, I^2=63.35%) ~~with no significant differences between drugs (N:21.5%, P:21.4%, A:9.4%; p=0.121. I^2=26.18%, p=0.2027~~) [**Figure 2**]. DCR was ~~54~~55.46% (95% CI: ~~50.2~~48.1-~~59~~62.50%; ~~without significant differences between agents (N:51.7%, P:57.8%, A:58.5%; p=0.385. I^2=68.14%,~~ Cochran's Q p<=0.00019, I^2=76.57%) [**Figure 3~~2~~**]. In unselected patients, the median PFS ranged from 2.1~~5~~ to ~~6.1~~5.8 months, while the median OS from 6.7~~36~~ to 20.9 months.

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Tumour response according to PD-L1 expression were reported in 10~~6~~ out of ~~10~~13 studies, with PD-L1 positivity defined using heterogeneous cut-offs depending of each different trial (ranging from 1% to 50%).[9,12,13,15,20,23] This subgroup included ~~125~~304 and ~~131~~310 patients, depending on the clone adopted in the study by Scherpereel et al. (~~n: 125 fo~~ther~~r~~ 28-8~~, n: 131 for~~and SP-263, respectively) [**Table 2**].[15] ORR was ~~34.4~~28.0% (95% CI: ~~26.7~~19.0-~~43.1~~38.0%;~~, I²=28.52%,~~ Cochran's Q p=0.0006~~2210~~, I^2=69.03%) and ~~32.1~~27.0% (95% CI: ~~24~~18.7~~.7~~-36.2~~40.5~~%;~~-~~ Cochran's Q p=0.0021, I^2=65~~22~~.2~~23~~%~~, p=0.2667~~), respectively, although it ranged from 12~~9~~% to 56% in different studies [**Figure ~~43;~~** forest plot of the analysis with the largest sample, accounting for the use of SP-263 clone in [15]; **sFigure 1** accounting for the use of 28-8 clone]. ~~No publication biases were found at a significance level < 0.05~~The funnel plots showed no evidence of publication bias [**Figure 5, Figure 6, Figure 7, s Figure 2**]. ~~[**Figure 4, Figure 5**].~~

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4. Discussion

~~The present study~~We performed a systematic review and meta-analysis to evaluate the activity of anti-PD-1/PD-L1 in pre-treated asMM in terms of ORR and DCR. Notably, as higher efficacy is observed in tumours whose aetiology is associated to carcinogens exposure, ICIs evaluation in asMM finds a rational as most cases are related to asbestos exposure.[31–33] ~~Therefore, the assessment of the efficacy of ICIs in asMM finds a rationale as most of the cases are related to asbestos exposure.~~ Unfortunately, most of the studies about ICIs in asMM do not report this information. ~~At the same time,~~ MM is ~~partially~~ somehow resistant to cytotoxic chemotherapy, especially non-epithelioid subtypes. The recent demonstration that the combination of the anti-CTLA-4 monoclonal antibody ipilimumab with nivolumab could significantly increase OS as compared to platinum plus pemetrexed in the first-line setting, is predicted to change the treatment landscape of this aggressive disease.[5] However, while the superiority of ICIs combination appeared to be clear in non-epithelioid tumors, patients with epithelioid MM showed less benefit and chemotherapy may be still regarded as a treatment option, while waiting for the results of chemo-immunotherapy combination from ongoing clinical trials.[34] Unfortunately, due to the lack of specific data, we could not evaluate the activity of ICIs in pre-treated patients according to histology. ~~and s~~Following platinum-based chemotherapy, ~~second~~second-line treatments ~~have never formally demonstrated to increase survival as compared to best supportive care~~have only modest efficacy~~.~~ ~~Indeed, international guidelines suggest the treatment with vinorelbine or gemcitabine in pre-treated patients, reporting~~with

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ORR- of 8.63%, a DCR of 54.8%, -and a median PFS and OS of 3.4 and 7.86 months, respectively.[35] Only recently a formal demonstration of vinorelbine efficacy has been provided by a phase 2 trial.[36] Moreover, another randomised phase 2 trial showed that the addition of the anti-vascular endothelial growth factor receptor 2 (VEGFR-2) monoclonal antibody ramucirumab to gemcitabine could increase OS as compared to gemcitabine and placebo in second-line setting.[37] Our~~The present~~ meta-analysis indicates that ICIs provide an ORR and DCR of ~~20~~18.1% and ~~a DCR of~~ 5~~5~~4.~~6~~%, respectively, without significant differences between agents~~drugs~~. Overall, the heterogeneity between the studies was ~~low~~ moderate~~when evaluating the ORR~~, both in the entire population and in patients whose tumours expressed PD-L1, ~~while the heterogeneity was significant for the evaluation of thein terms of DCR~~. ~~We did not found~~No significant evidence of publication bias was found.

However, the results of the phase 3 PROMISE-meso trial showed that, despite the higher ORR with pembrolizumab, no survival differences were observed as compared to single agent chemotherapy in pre-treated ~~advanced stage MPM~~asMM.[25] Notably, this trial was designed with PFS as primary end-point. OS events were ~~71~~ 92 at the time of the analysis, leading to a 1~~9~~6% statistical power for a HR of 0.8, meaning that the study was not powered to allow meaningful conclusion about OS.[25] -Indeed, the interpretation of these results is challenging. Since most of the studies included in our meta-analysis lack of a comparison arm, we were not ~~cap~~able to compare ICIs with single-agent chemotherapy. However, to our knowledge, ORR has never been demonstrated to be a surrogate marker of survival in MM. Moreover, 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. For this latter reason, as most studies were single-arm trials, observer bias could not be ruled out.

The present meta-analysis suggests that PD-L1+ tumours might better respond to single-agent immunotherapy. However, trials are highly heterogeneous when accounting for PD-L1 evaluation because different IHC clones and cut-offs were used, so that these data should be taken with caution. Indeed, available data suggest that PD-L1 expression in malignant pleural mesothelioma is prognostic, with high levels associated with poorer outcomes even after accounting for other variables such as histology and performance status.[38–40] ~~Moreover, a~~A recent publication reported that the antigenic potential of mesothelioma could be better predicted by other factors, including chromosomal rearrangements (chromoplexy and chromothripsis).[41] Such interesting data deserve more studies in the context of ICIs therapy for

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MM. Adoptive immunotherapy as well as vaccines, alone or in combination with ICIs, are another active field of investigation. Preliminary results of a phase I study of intrapleural injection of mesothelin-targeted chimeric antigen receptor T-cell (CAR-T) therapy, with or without anti PD-1 agents, showed 63% RR in 18 asMM patients, 37% of which already treated with 3 or more lines of therapy.[42] The treatment landscape of asMM is therefore expected to change, and immunotherapy may have a pivotal role both in treatment-naïve and pre-treated patients. Along with those from Checkmate 743, results of ongoing studies on chemo-immunotherapy combinations ~~are .~~ ~~The recent results of the Checkmate 743 trial, showing that nivolumab plus ipilimumab led to significantly longer OS as compared to platinum plus pemetrexed in untreated unresectable MPM, are starting this paradigm shift~~are expected to change the treatment landscape of untreated unresectable MPM.[5] While waiting for these data, ~~Non-epithelioid tumours seem to derive the most benefit. Unfortunately, due to the lack of specific data, we could not evaluate the activity of single-agent ICIs in different histologies. As results of other ongoing studies are eagerly awaited~~, our meta-analysis suggests that anti-PD-(L)1 agents might be useful in some chemotherapy pre-treated patients, even if reliable predictive factors are still lacking.

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Figure legends

Figure 1. PRISMA flowchart of selected trials

Figure 2. Objective response rate of trials selected for the meta-analysis and aggregate data

~~*Abbreviations.* ORR: objective response rate.~~

Figure 3. Disease control rate of trials selected for the meta-analysis and aggregate data

Figure 4~~3~~. Objective response rate of trials reporting activity according to PD-L1 expression and aggregate data.

~~*Abbreviations.* ORR: objective response rate.~~*Caption*: PD-L1 clone SP-263 in Scherpereel et al.

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Figure 5~~4~~. Funnel plot for objective response rate

Figure 6~~5~~. Funnel plot for disease control rate

Figure 7. Funnel plot for objective response rate in PD-L1 positive patients (Scherpereel SP-263)

sFigure 1. Objective response rate of trials reporting activity according to PD-L1 expression and aggregate data (Scherpereel 28-8)

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sFigure 2. Funnel plot for objective response rate in PD-L1 positive patients (Scherpereel 28-8)

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Table 1. Main characteristics of trials selected for the meta-analysis

Study	**Phase**	**Setting**	**Population (subtypes)**	**Drug**	**ORR** [a] % (n)	**DCR** [a] % (n)	**Median OS** [a] months (95% CI)	**Median PFS** [a] months (95% CI)
Hassan et al. JAMA Oncol 2019	Ib	Pts progressed after platinum and pemetrexed	53 Epithelioid 43 Sarcomatoid 2 mixed or Unknown 8	Avelumab 10 mg/kg every two weeks	9 (5/53)	58 (31/53)	10.7 (6.4-20.2)	4.1 (1.4-6.2)
Quispel-Janssen et al. JTO 2018	II	Pts progressed after at least one CT regimen	34 Epithelioid 28 Sarcomatoid 2 Mixed 4	Nivolumab 3 mg/kg every two weeks	26 (9/34)	47 (16/34)	11.8 (9.7-15.7)	2.6 (2.23-5.49)
Okada et al. Clin Cancer Res 2019	II	Pts resistant to maximum 2 regimens of CT including platinum-pemetrexed	34 Epithelioid 27 Biphasic 4 Sarcomatoid 3	Nivolumab 240 mg every two weeks	29 (10/34)	68 (23/34)	17.3 (11.5-NR)	6.1 (2.9-9.9)
Scherpereel et al. Lancet Oncol 2019	II	Pts progressed after first- or second-line platinum-pemetrexed CT	63 Epithelioid 52 Sarcomatoid or biphasic 11	Nivolumab 3 mg/kg every two weeks	17 (11/63)	40 [b] (25/63)	11.9 (6.7-17.7)	4 (2.8-5.7)
Dumoulin et al. JTO 2019	Real-world	Pts progressed after at least one cycle of platinum-folate CT	59 Epithelioid 41 Sarcomatoid or mixed 13 Unknown 5	Nivolumab 3 mg/kg every two weeks	12 (7/59)	41 (24/59)	6.36 (4.92-9.12)	2.64 (1.56-4.20)
Mikami et al. JCO 2020	Retrospective single-centre	Pts pretreated with at least one line of therapy	79 Epithelioid 64 Sarcomatoid 9 Biphasic 6	Nivolumab	27 (19/71)	66 (47/71)	14.3	4.1
Alley et al.	Ib	Pts for whom standard	25	Pembrolizumab 10 mg/kg every 2 weeks	20 (5/25)	72 (18/25)	18 (9.4-NR)	5.4 (3.4-7-5)

Lancet Oncol 2017		therapy failed	Epithelioid 18 Sarcomatoid 2 Biphasic 2 Unknown 3					
Desai et al. JTO 2018	II	Pts progressed after platinum-pemetrexed, who received no more than two lines of therapy	64 Epithelioid 49 Sarcomatoid 5 Biphasic 10	Pembrolizumab 200 mg every 3 weeks	22 (14/64)	63 (40/64)	11.5 (na)	4.1 (na)
Popat et al. Ann Oncol 2019	III	Pts progressed after previous platinum-based CT	73 [c] Epithelioid 66 Other 7	Pembrolizumab 200 mg every 3 weeks	22 (16/73) [e]	45 (33/73)	10.7 (7.6-ne)	2.5 (2.1-4.2)
Marmarelis et al. JCO 2020	Retrospective single-centre	Pts progressed to a previous CT	13 Epithelioid 9 Sarcomatoid 2 Biphasic 1 Despoplastic 1	Pembrolizumab	18 (2/11)	81 (9/11)	20.9 (na)	5.7 (na)

Abbreviations. ORR: objective response rate; DCR: disease control rate; OS: overall survival; PFS: progression-free-survival; Pts: patients; CI: interval confidence; CT: chemotherapy; NR: not reached; ne: not estimable; na: not available

a Calculated among patients evaluable for disease response or outcomes
b DCR at 12 weeks from randomization
c Pembrolizumab cohort

Table 2. Main characteristic of trials reporting activity according to PD-L1 expression

Study	**PD-L1 threshold**	**IHC PD-L1 antibody clone**	**Population evaluable for PD-L1** (PD-L1 positive pts)	**ORR in PD-L1 positive pts** % (n)	**Median OS in PD-L1 positive pts** months (95% CI)	**Median PFS in PD-L1 positive pts** months (95% CI
Hassan et al. JAMA Oncol 2019	5%	73-10	43 (16)	19 (3/16)	20.2 (4.9-ne)	5.3 (1.4-17.8)
Quispel-Janssen et al. JTO 2018	1%	28-8	33 (9)	56 (5/9)	na	na
Okada et al. Clin Cancer Res 2019	1%	28-8	32 (20)	40 (8/20)	ne (HR OS 0.542; 95% CI 0.208-1.415)	ne (HR 0.725; 95% CI 0.316-1.668)
Scherpereel et al. Lancet Oncol 2019	1%	28-8	99	39 (16/41)	na	na
		SP-263	104	32 (15/47)		
Alley et al. Lancet Oncol 2017	1%	22C3	25	20 (5/25)	18 (9.4-NR)	5.4 (3.4-7-5)
Desai et al. JTO 2019	50%	22C3	62 (14)	43 (6/14)	12.5	4.9
Popat et al. Ann Oncol 2019	1%	E1l3N	51 (32)	na	10.7 (6.8-ne)	3.2 (1.9-4.2)

Abbreviations. IHC: immunohistochemistry; PD-L1: programmed death-ligand 1; ORR: objective response rate; OS: overall survival; PFS: progression-free-survival; CI: interval confidence; HR: hazard ratio; ne: not estimable, na: not available.

Table 1. Main characteristics of trials selected for the meta-analysis

Study	**Phase**	**Setting**	**Population (subtypes)**	**Drug**	**ORR** [a] % (n)	**DCR** [a] % (n)	**Median OS** [a] months (95% CI)	**Median PFS** [a] months (95% CI)	**Median PFS and OS by histology**
Hassan et al. JAMA Oncol 2019	Phase Ib	Pts progressed after platinum and pemetrexed	53 Epithelioid 43 Sarcomatoid 2 mixed or Unknown 8	Avelumab 10 mg/kg every two weeks	9 (5/53)	58 (31/53)	10.7 (6.4-20.2)	4.1 (1.4-6.2)	na
Quispel-Janssen et al. JTO 2018	Phase II	Pts progressed after at least one CT regimen	34 Epithelioid 28 Sarcomatoid 2 Mixed 4	Nivolumab 3 mg/kg every two weeks	26 (9/34)	47 (16/34)	11.8 (9.7-15.7)	2.6 (2.23-5.49)	na
Fujimoto et al. JTO Clin and Research Reports 2021	Phase II	Pts resistant to maximum 2 regimens of CT including platinum-pemetrexed	34 Epithelioid 27 Biphasic 4 Sarcomatoid 3	Nivolumab 240 mg every two weeks	29 (10/34)	68 (23/34)	17.3 (11.5-26.6)	5.9 (na)	**Ep vs non-Ep** mOS 15.7 vs 26.6 months (HR 2.10, 95% CI 0.73-6.11) mPFS 3.9 vs 18.2 months (HR 2.79, 95% CI 1.03-7.56)
Scherpereel et al.	Phase II	Pts progressed after first- or second-line	63 [b] Epithelioid 52	Nivolumab 3 mg/kg every two weeks	17 (11/63)	40 [c] (25/63)	11.9 (6.7-17.7)	4 (2.8-5.7)	ne

Lancet Oncol 2019		platinum-pemetrexed CT	Sarcomatoid or biphasic 11						
Cantini et al. TLCR 2020	Real-world (expanded access program)	Pts progressed after at least one cycle of platinum-folate CT	107 Epithelioid 78 Sarcomatoid or mixed 22 Unknown 7	Nivolumab 3 mg/kg every two weeks	10 (11/107)	37 (40/107)	6.7 (6.2-10.0)	2.3 (1.6-2.9)	**Non-Ep vs Ep** mOS 4.8 vs 7.4 months (HR 1.71, 95% CI 0.92–3.16)
Mikami et al. JCO 2020	Retrospective single-centre	Pts pretreated with at least one line of therapy	79 Epithelioid 64 Sarcomatoid 9 Biphasic 6	Nivolumab	27 (19/71)	66 (47/71)	14.3	4.1	na
Fennell et al. Lancet Oncol 2021	Phase III	Pts progressed after/on platinum-based CT	221 [b] Epithelioid 195 Non-Epithelioid 26	Nivolumab 240 mg every two weeks (vs placebo)	11 (25/221)	64 (142/221)	10.2 (8.5–12.1)	3.0 (2.8-4.1)	ne
Alley et al. JTO 2017	Phase Ib	Pts for whom standard therapy failed	25 Epithelioid 18 Sarcomatoid 2 Biphasic 2 Unknown 3	Pembrolizumab 10 mg/kg every 2 weeks	28 (7/25)	76 (19/25)	18 (9.4-NR)	5.8 (3.4-8.2)	na
Desai et al. JTO 2018	Phase II	Pts progressed after platinum-pemetrexed, who received no more than	64 Epithelioid 49 Sarcomatoid 5 Biphasic 10	Pembrolizumab 200 mg every 3 weeks	22 (14/64)	63 (40/64)	11.5 (na)	4.1 (na)	na

		two lines of therapy							
Marmarelis et al. JCO 2020	Retrospective single-centre	Pts progressed to a previous CT	13 Epithelioid 9 Sarcomatoid 2 Biphasic 1 Despoplastic 1	Pembrolizumab	18 (2/11)	81 (9/11)	20.9 (na)	5.7 (na)	**Ep vs non-Ep** mOS 17.5 vs NR, log rank p=0.31 mPFS 5 vs 39 months, log rank p=0.14
Popat et al. Ann Oncol 2020	Phase III	Pts progressed after/on platinum-based CT	73 [d] Epithelioid 66 Non-Epithelioid 7	Pembrolizumab 200 mg every 3 weeks (vs mono-chemotherapy)	22 (16/73)	45 (33/73)	10.7 (7.6–15.0)	2.5 (2.1-4-2)	ne
Yap et al. Lancet Respir Med 2021	Phase II	Pts progressed or ineligible to standard therapies	118 Epithelioid 82 Sarcomatoid 9 Biphasic 10 na 17	Pembrolizumab 200 mg every 3 weeks	8 (10/118)	46 (54/118)	10.0 (7.6-13.4	2.1 (2.1-3.9)	na
Zhou et al. Clinical Lung Cancer 2021	Retrospective, single-centre	Pts pretreated with at least one line of therapy	14 Epithelioid 13 Mixed 1	Pembrolizumab (n=12), nivolumab (n=2)	21 (3/14)	43 (6/14)	na	na	na

Abbreviations. ORR: objective response rate; DCR: disease control rate; OS: overall survival; PFS: progression-free-survival; Pts: patients; CI: interval confidence; CT: chemotherapy; NR: not reached; ne: not estimable; na: not available; Ep: epithelioid; non-Ep: non epithelioid; iv: intravenous.

a Calculated among patients evaluable for disease response or outcomes
b Nivolumab cohort
c DCR at 12 weeks from randomization
d Pembrolizumab cohort

Table 2. Main characteristic of trials reporting activity according to PD-L1 expression

Study	**PD-L1 threshold**	**IHC PD-L1 antibody clone**	**Population evaluable for PD-L1** (PD-L1 positive pts)	**ORR in PD-L1 positive pts** % (n)	**Median OS in PD-L1 positive pts** months (95% CI)	**Median PFS in PD-L1 positive pts** months (95% CI)
Hassan et al. JAMA Oncol 2019	5%	73-10	43 (16)	19 (3/16)	20.2 (4.9-ne)	5.3 (1.4-17.8)
Quispel-Janssen et al. JTO 2018	1%	28-8	33 (9)	56 (5/9)	na	na
Fujimoto et al. JTO Clin and Res Reports	1%	28-8	32 (20)	40 (8/20)	19.1 (ne)	7.2 (ne)
Scherpereel et al. Lancet Oncol 2019	1%	28-8	99	39 (16/41)	na	na
		SP-263	104	32 (15/47)		
Cantini et al. TLCR 2020	1%	SP263 or 22C3	33 (11)	36 (4/11)	5.4 (ne)	4.2 (ne)
Fennel et al. Lancet Oncol 2021	1%	22C3	161 (60) [a]	12 (7/60) [b]	na	na
Alley et al. Lancet Oncol 2017	1%	22C3	25	20 (5/25)	18 (9.4-NR)	5.4 (3.4-7-5)
Desai et al. JTO 2019	50%	22C3	62 (14)	43 (6/14)	12.5	4.9
Popat et al. Ann Oncol 2020	1%	E1L3N	69 (31) [b]	29 (9/31) [a]	13.8 [a] (7.5-NR)	4.1 [a] (1.9-4.3)
Yap et al. Lancet Respir Med 2021	1%	22C3	108 (77)	12 (9/77)	na	na

Abbreviations. IHC: immunohistochemistry; PD-L1: programmed death-ligand 1; ORR: objective response rate; OS: overall survival; PFS: progression-free-survival; CI: interval confidence; HR: hazard ratio; ne: not estimable; na: not available; NR: not reached.

a Pembrolizumab cohort
b Nivolumab cohort

Figure 1

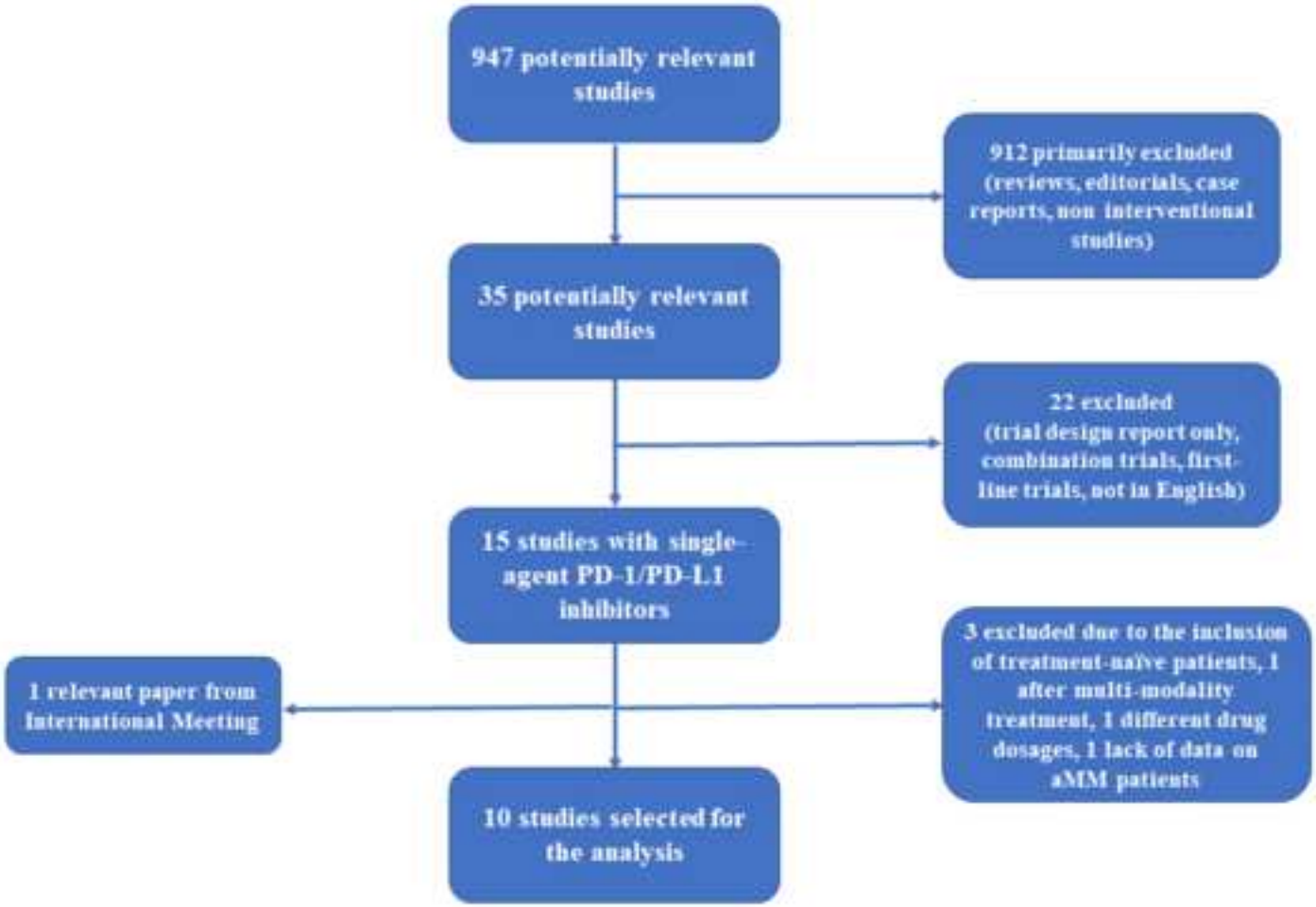
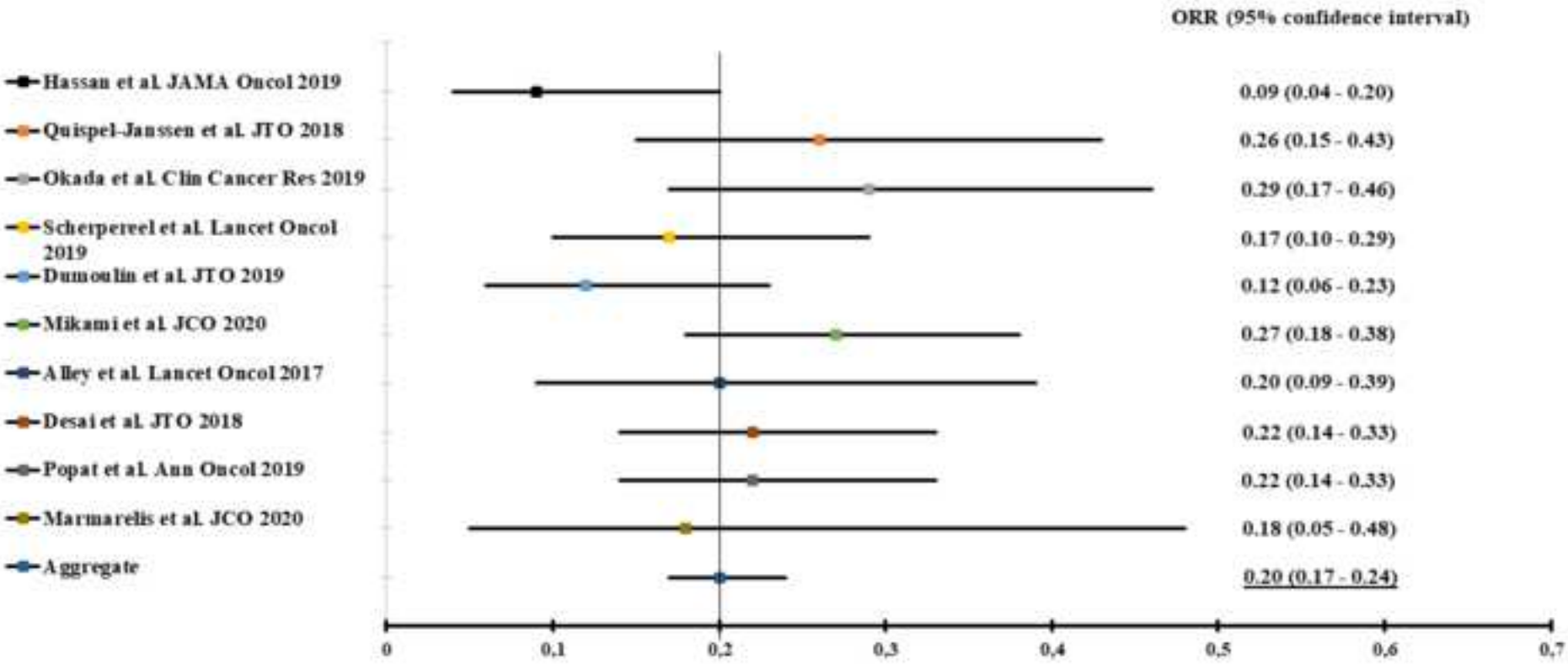


Figure 2



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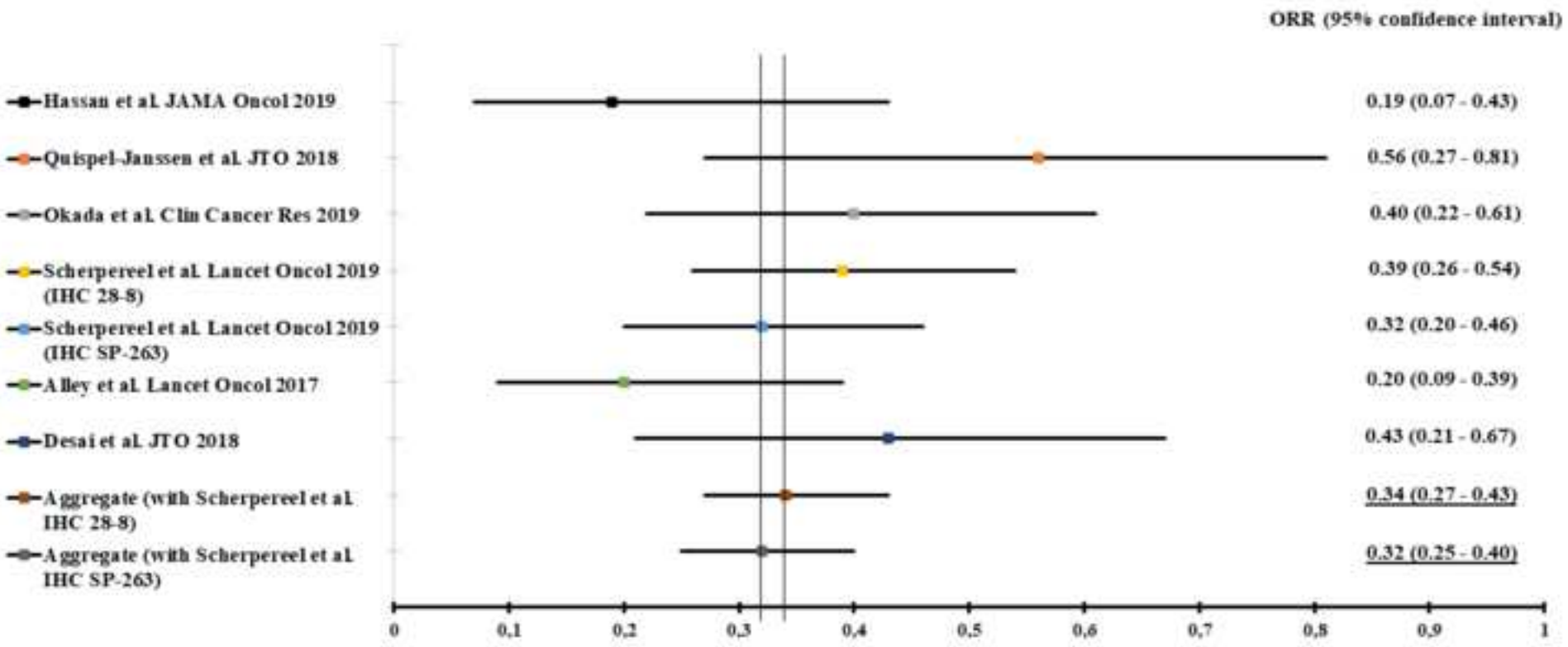

Figure 4

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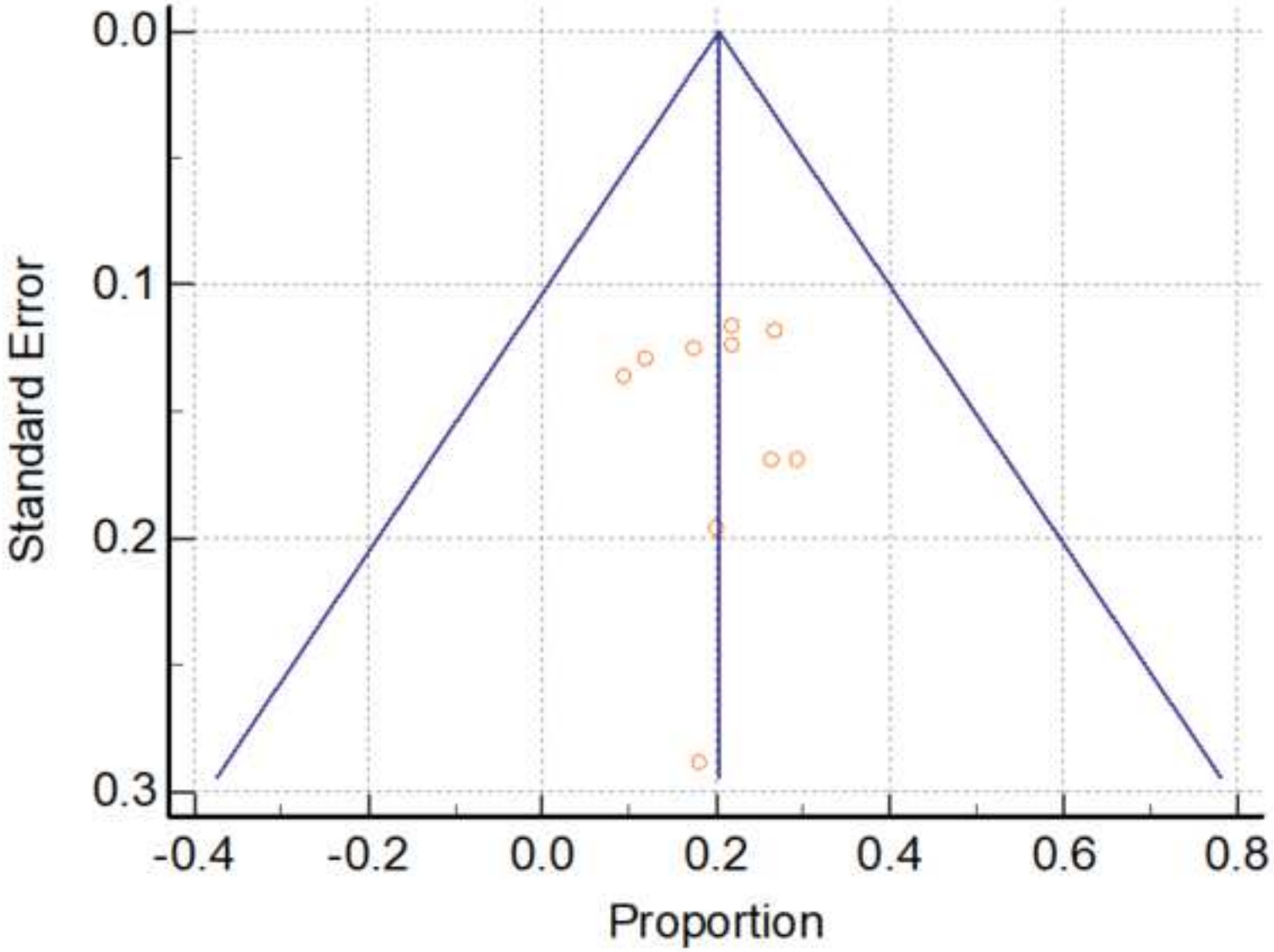

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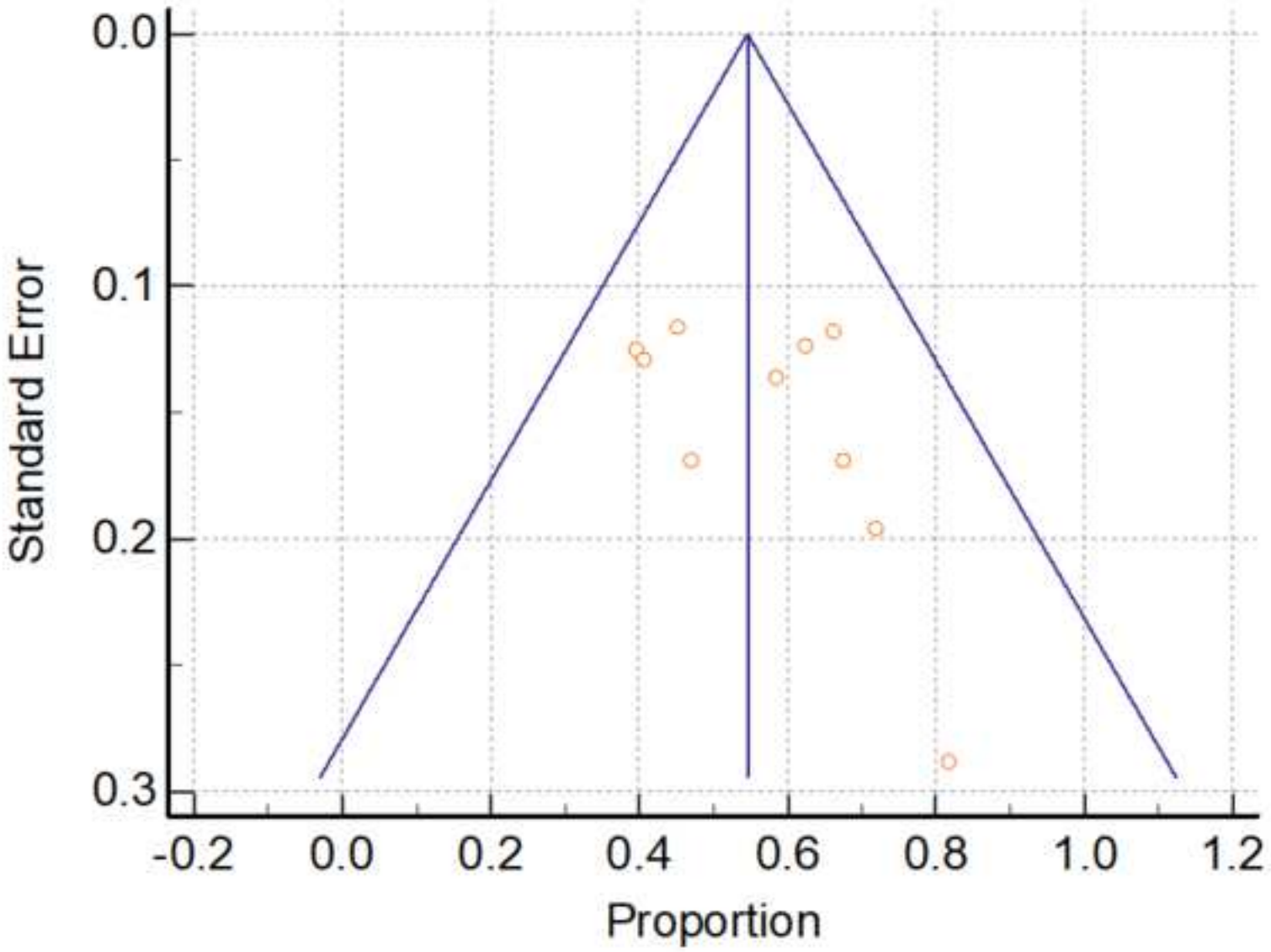

Figure 7

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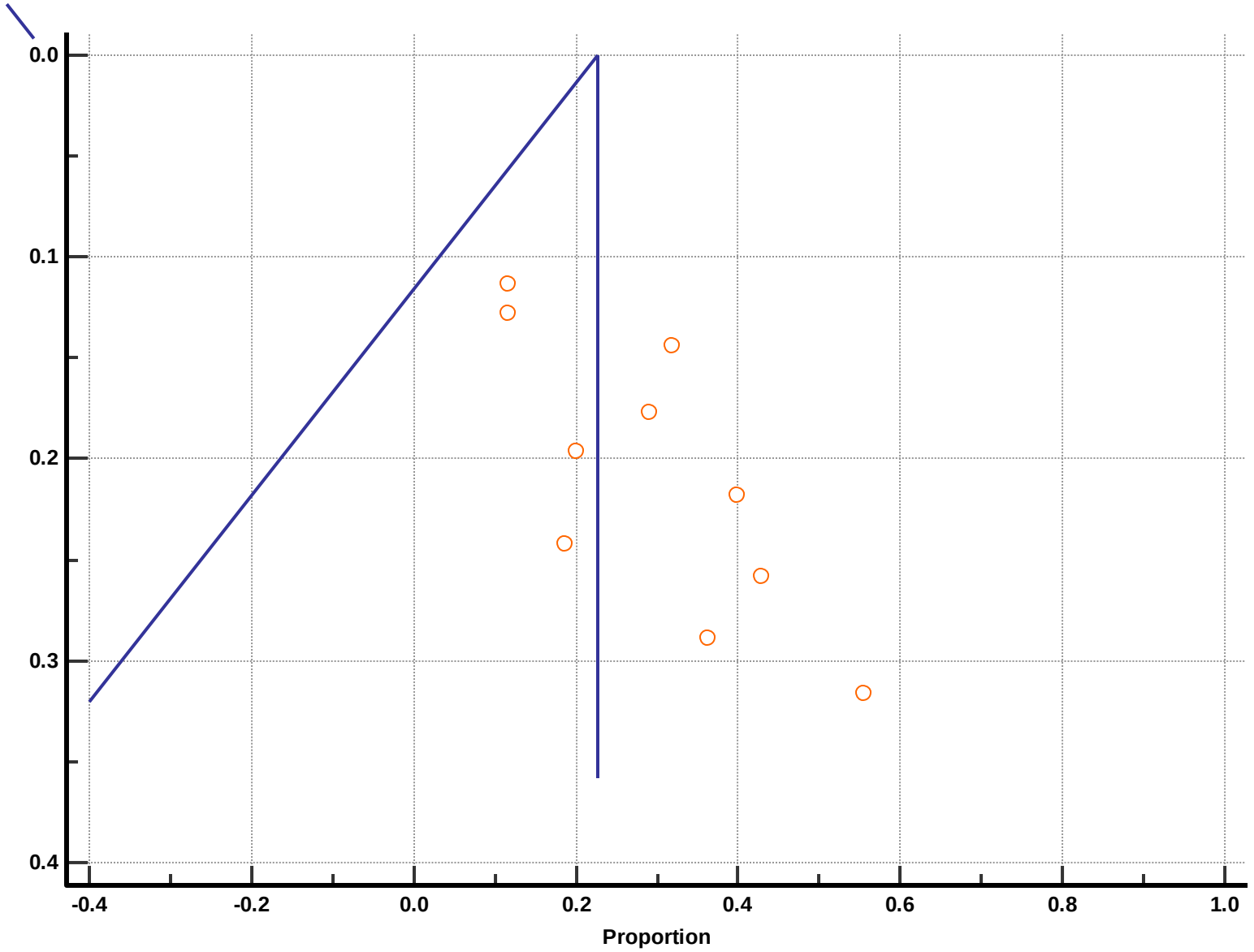

Figure 1

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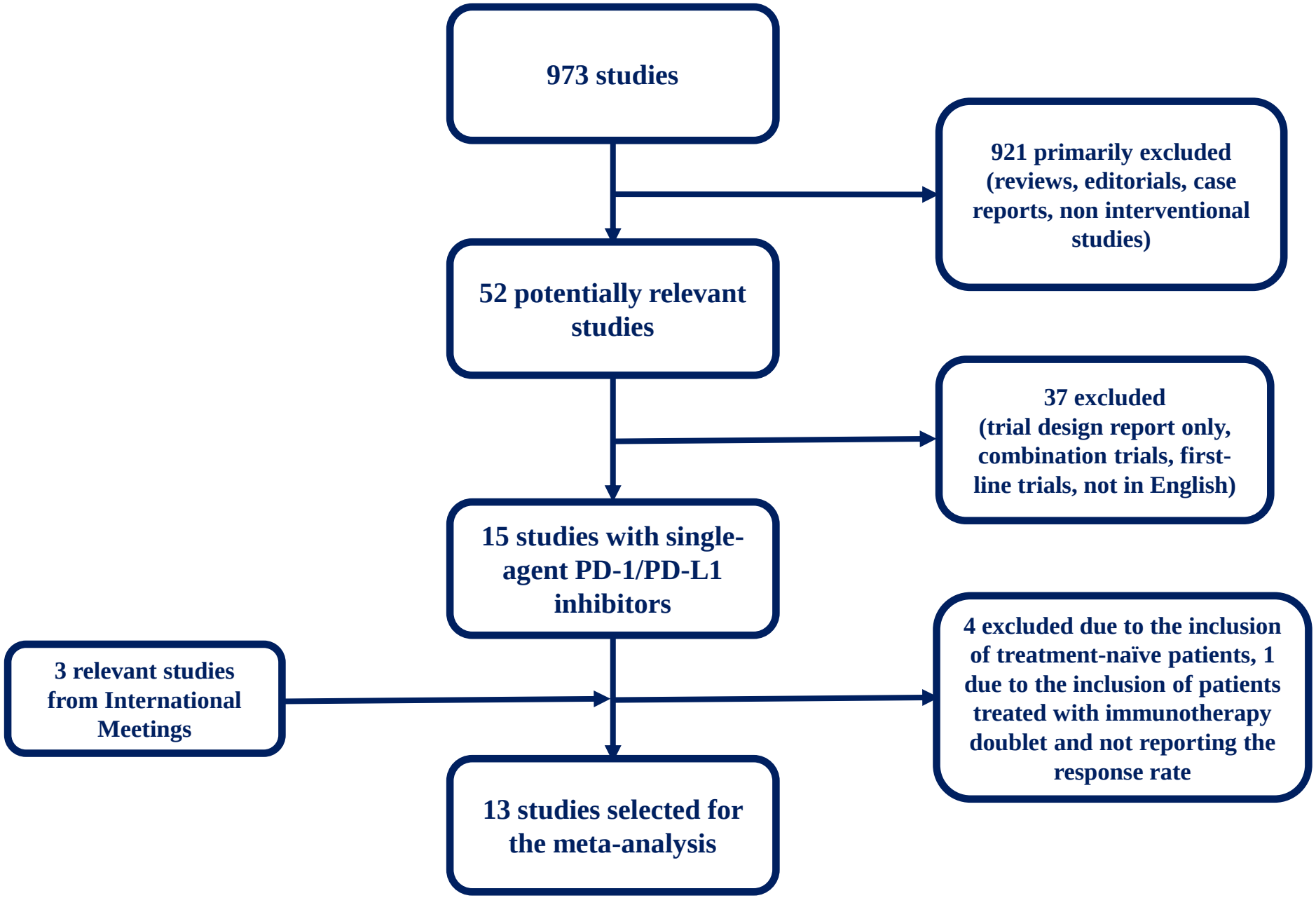
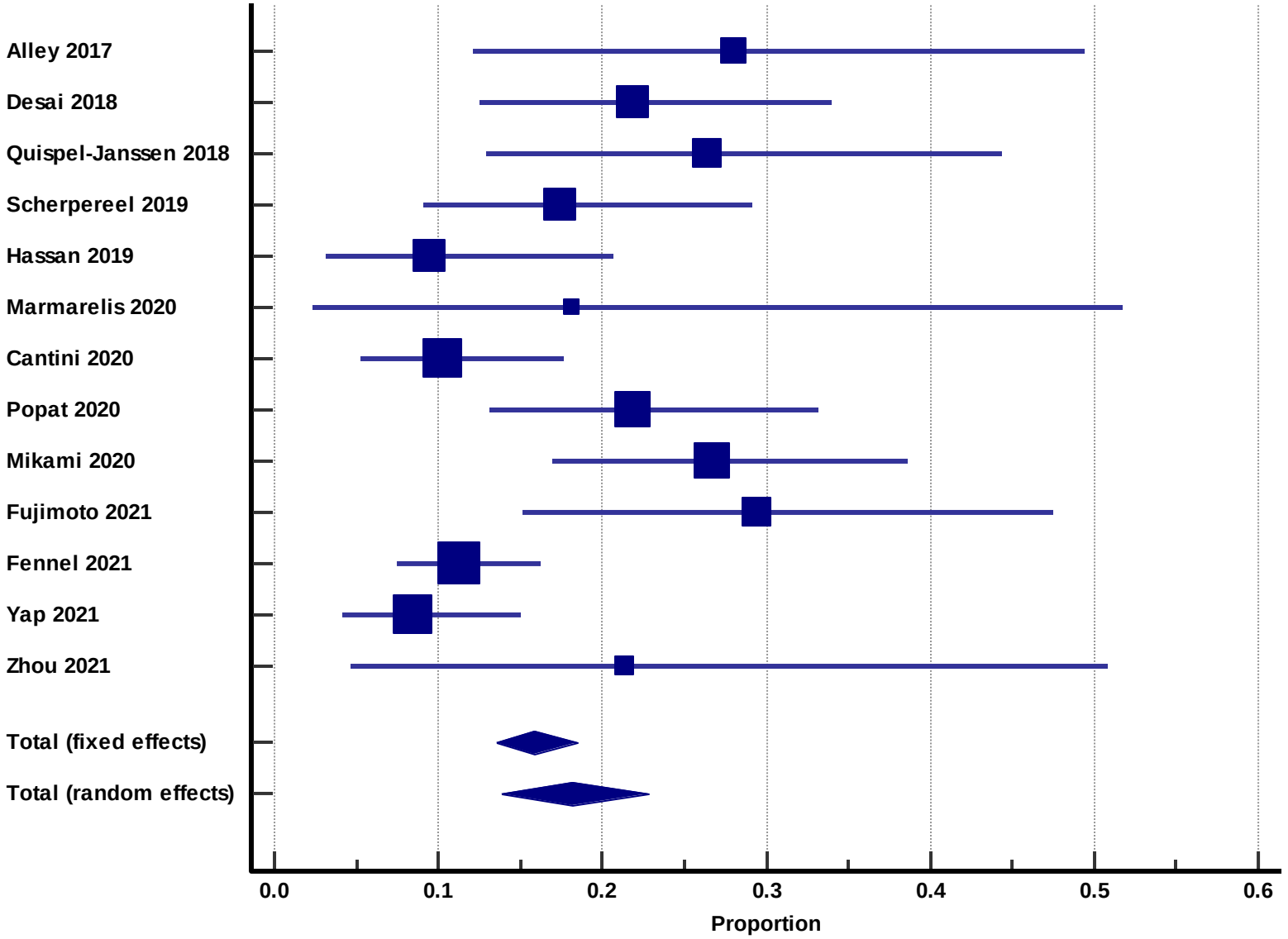


Figure 2

Click here to access/download;Figure;Figure 2_ORR forest plot.pptx



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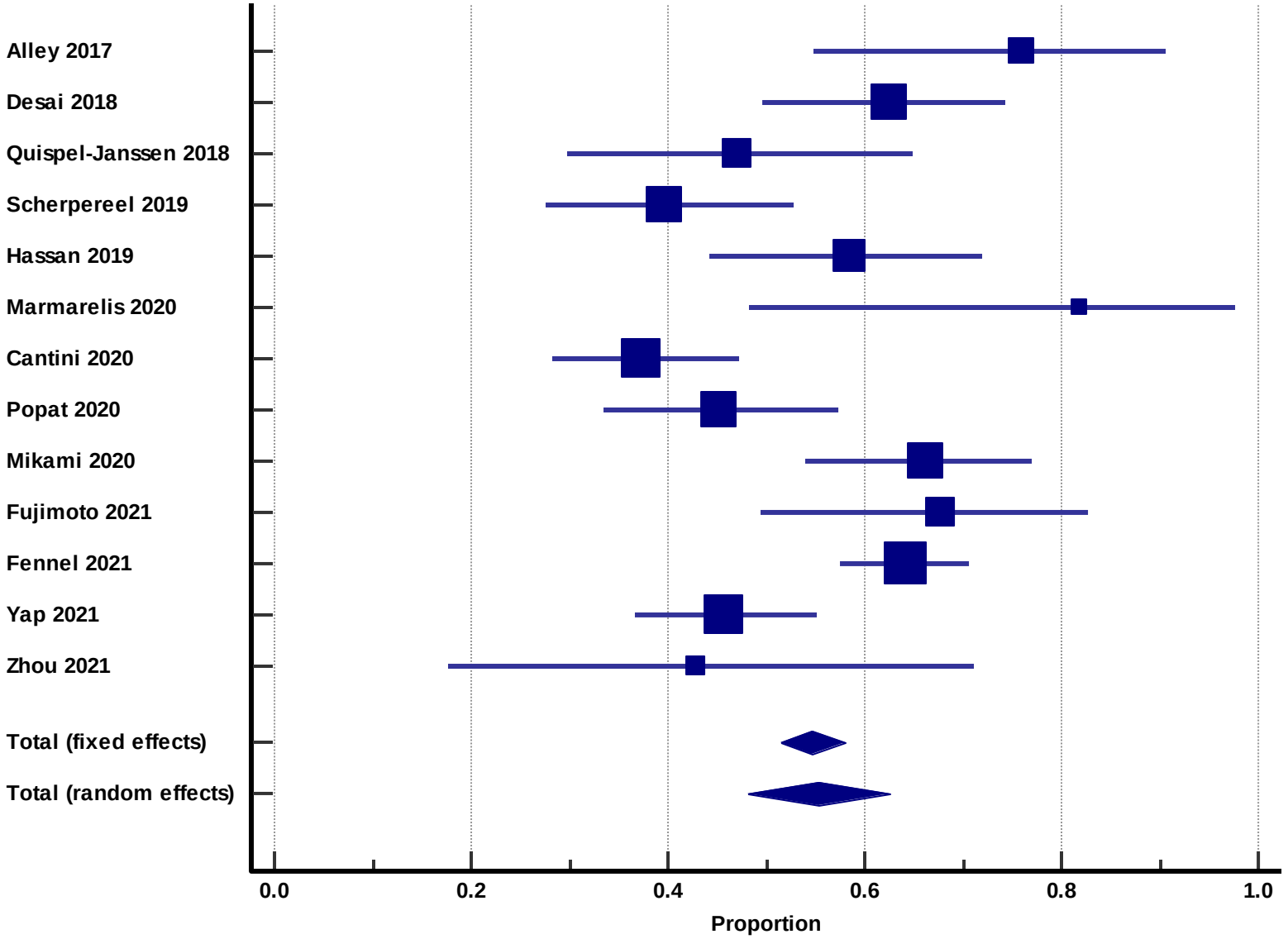

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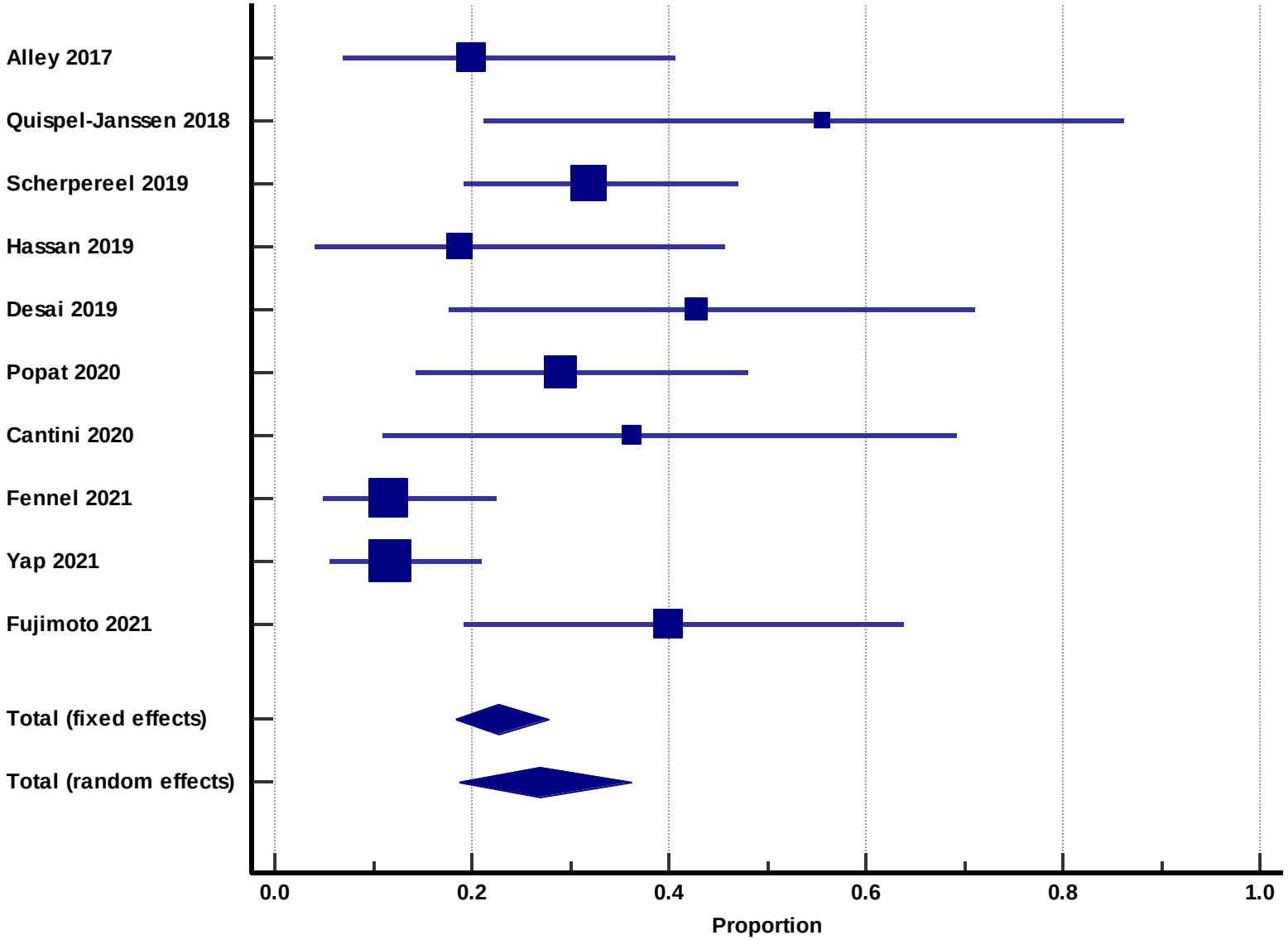

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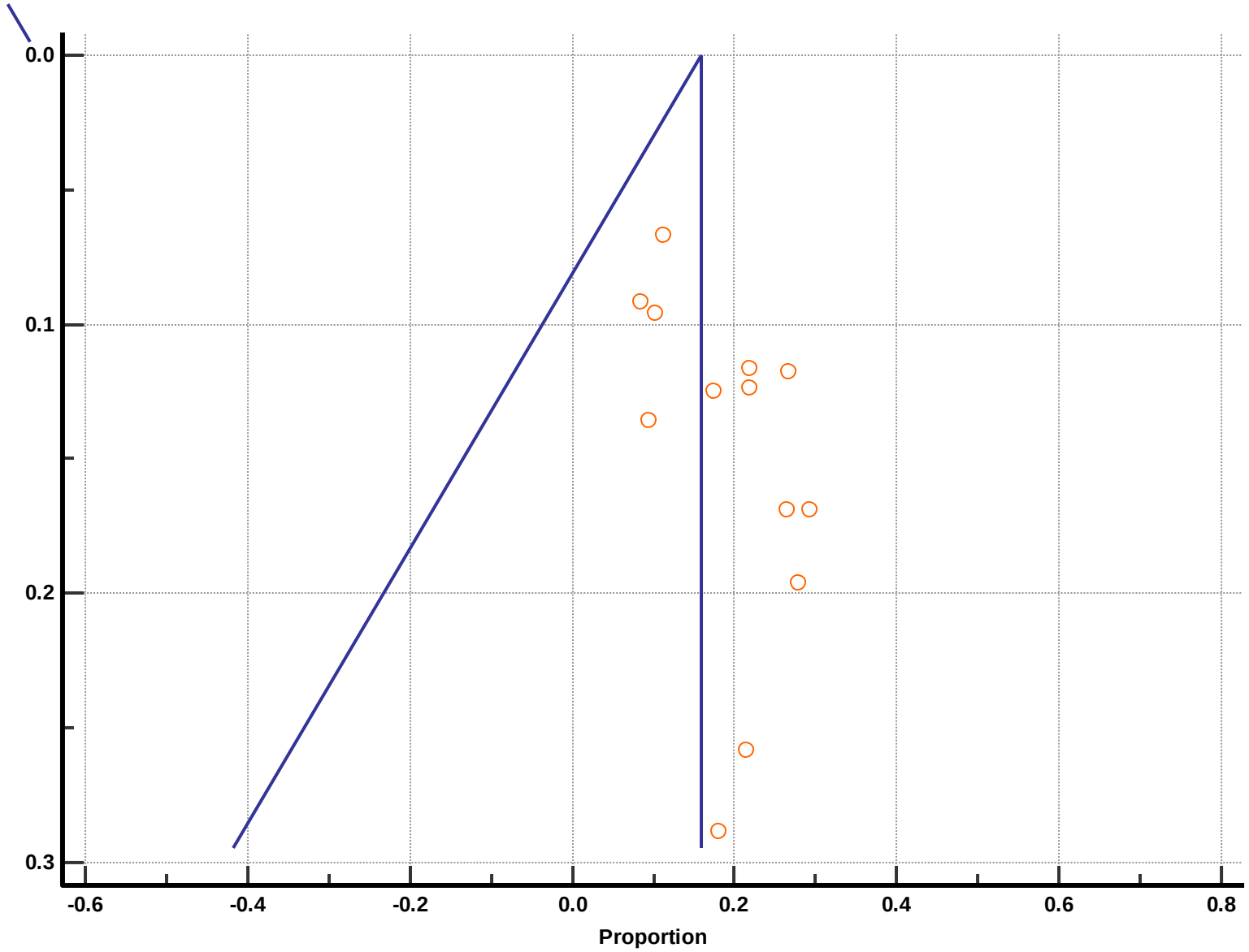

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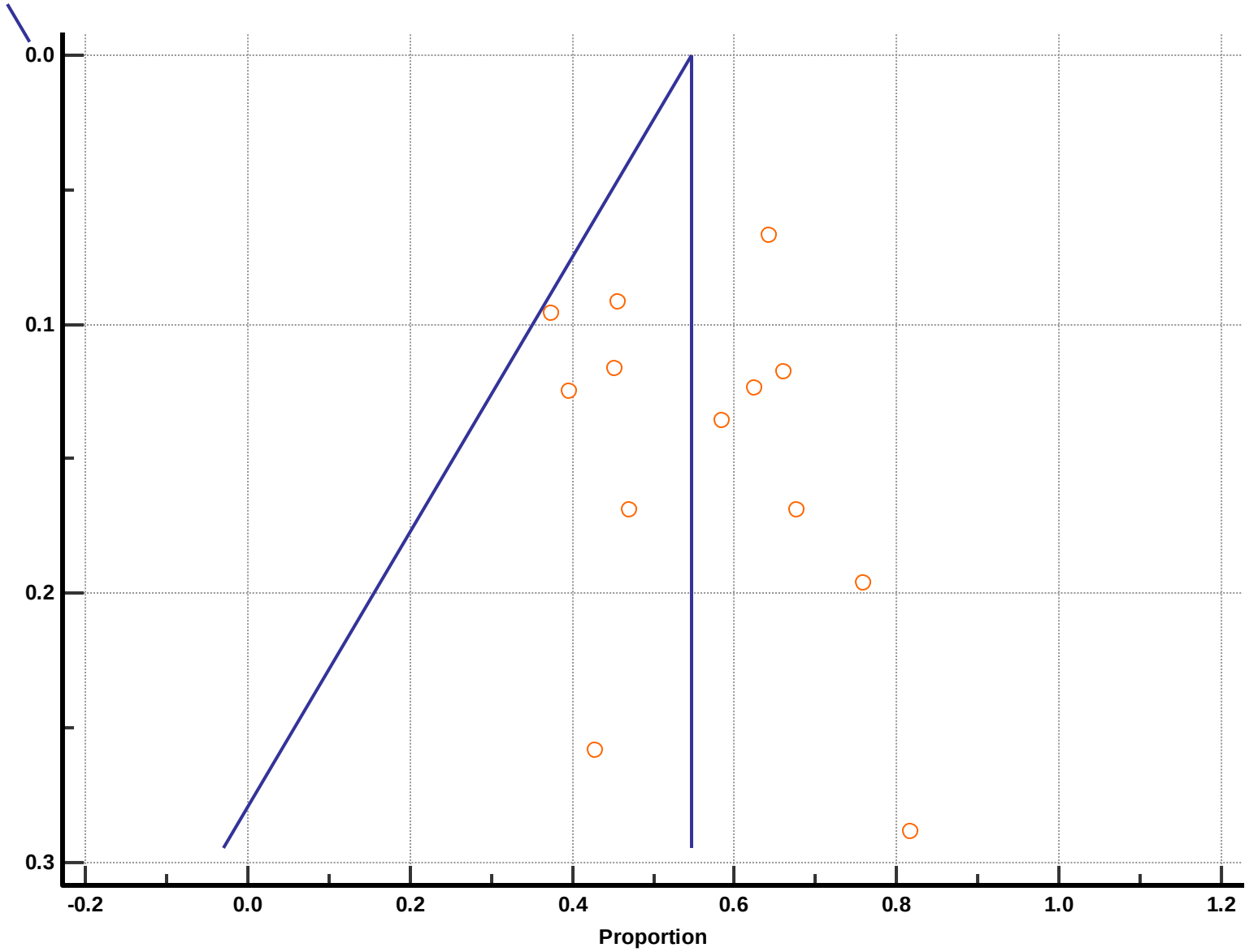
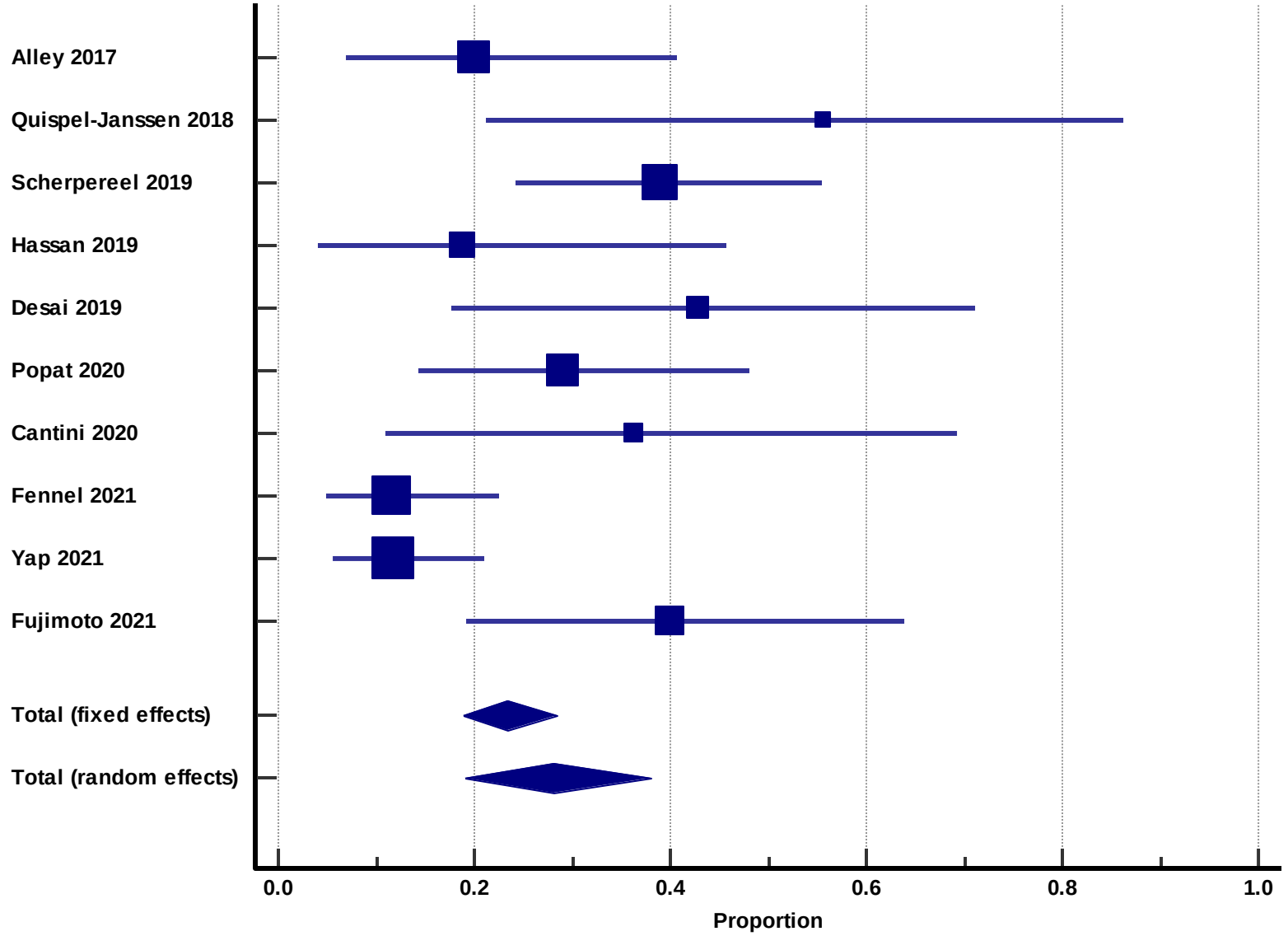
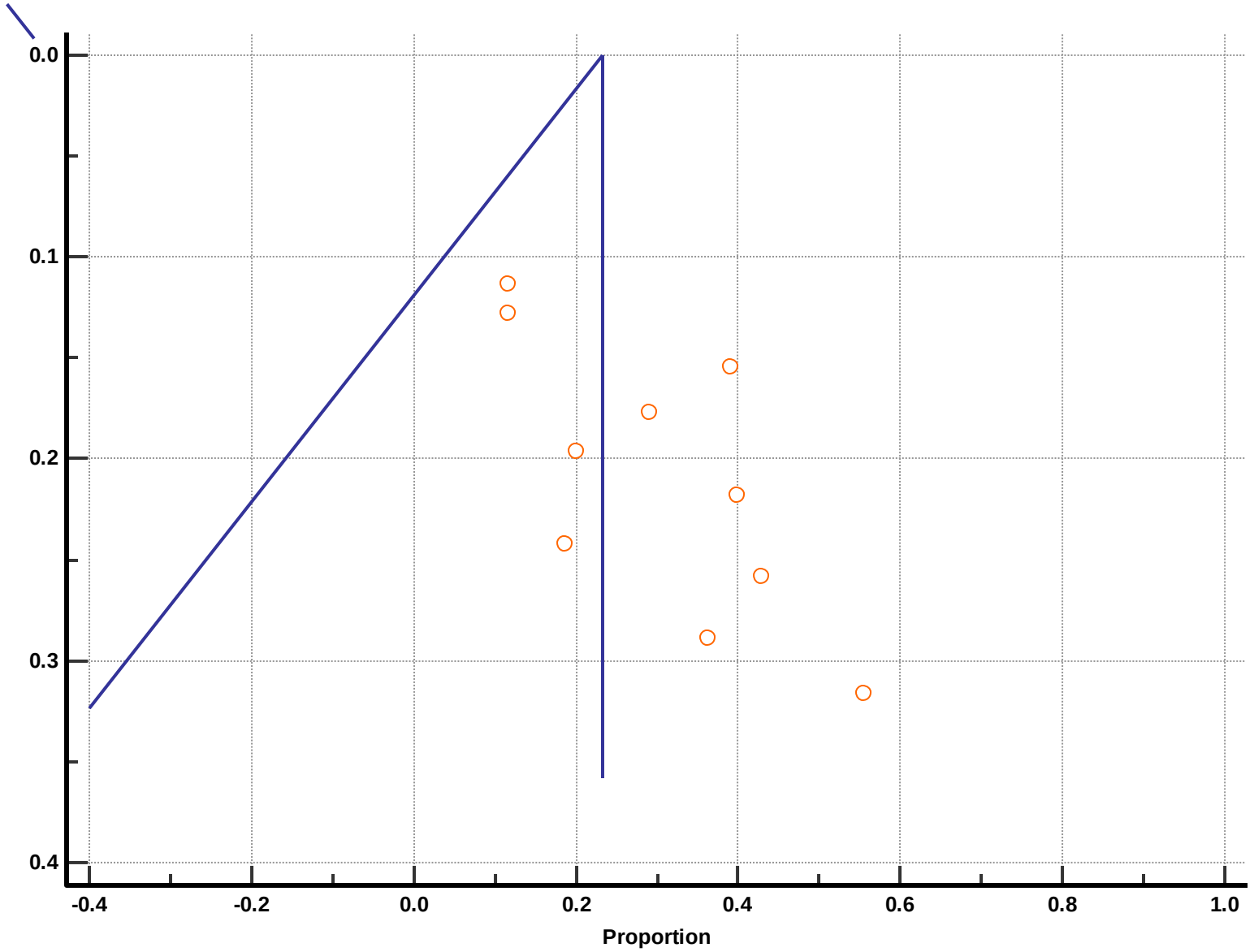


Supplementary figure 1



Supplementary figure 2



Highlights:

- First systematic review on single-agent immune checkpoint inhibitors (ICIs) against PD-1/PD-L1 in pre-treated advanced malignant mesothelioma
- Single-agent ICIs could lead to 18.1% response rate and 55.4% disease-control rate in pre-treated advanced malignant mesothelioma
- This result compares favourably with historical data with single-agent chemotherapy
- Predictive factors of immunotherapy efficacy are still lacking

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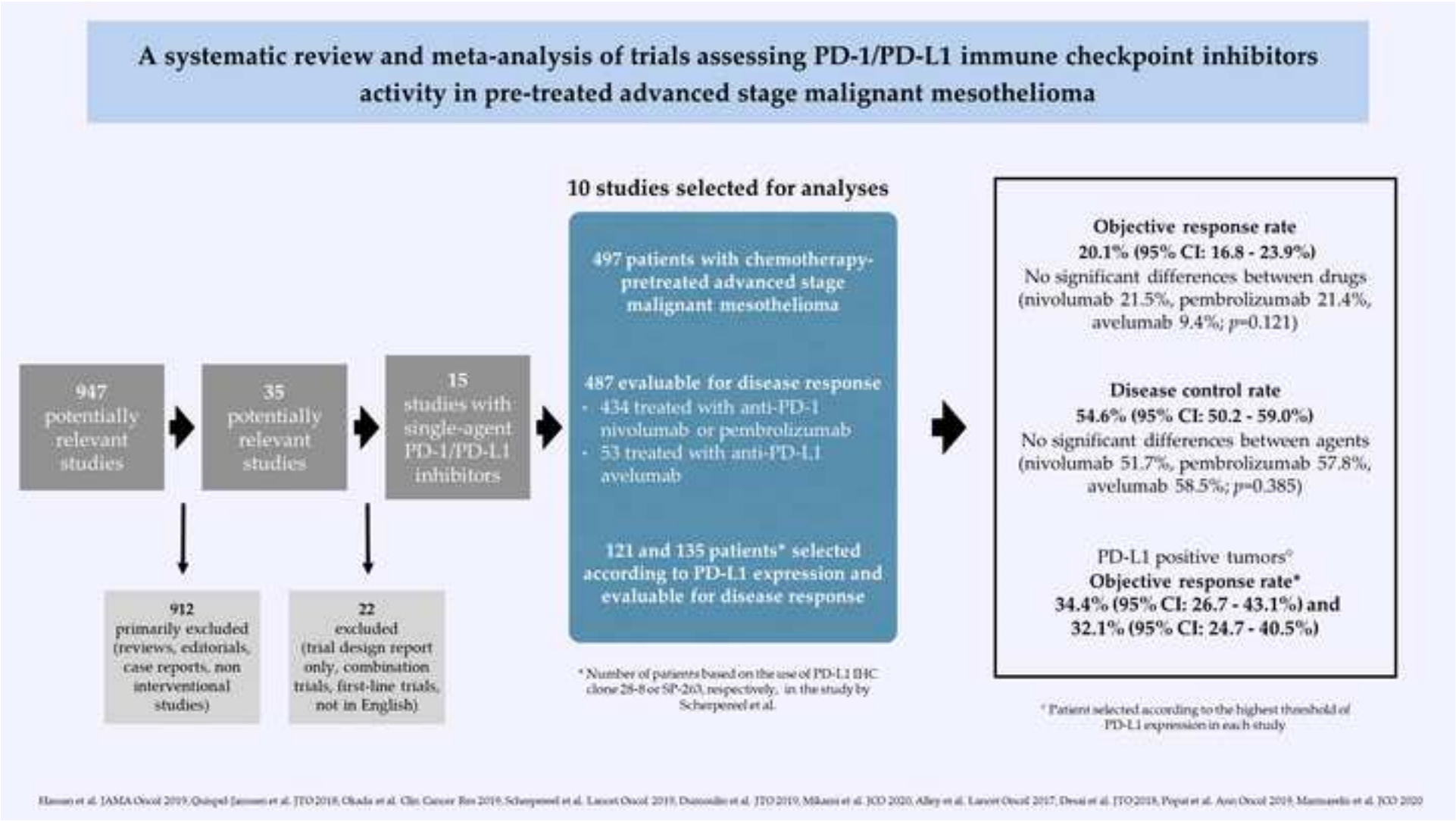
Graphical Abstract



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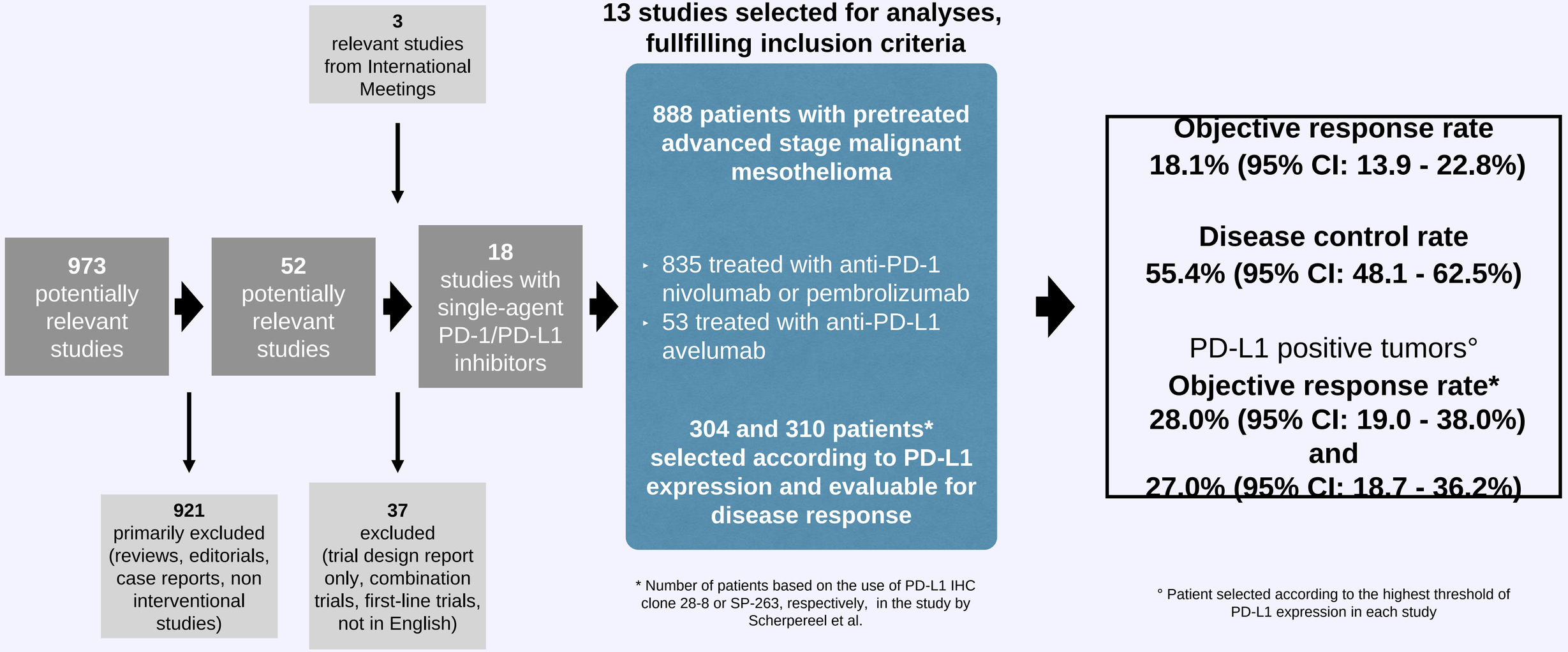

* Number of patients based on the use of PD-L1 IHC clone 28-8 or SP-263, respectively, in the study by Scherpereel et al.

° Patient selected according to the highest threshold of PD-L1 expression in each study

Alley et al. Lancet Oncol 2017, Desai et al. JTO 2018, Quispel-Janssen et al. JTO 2018, Scherpereel et al. Lancet Oncol 2019, Hassan et al. JAMA Oncol 2019, Marmarelis et al. JCO 2020, Cantini et al. TLCR 2020, Popat et al. Ann Oncol 2020, Mikami et al. JCO 2020, Fujimoto 2021 JTO Clinical and Research Reports, Fennell et al. Lancet Oncol 2021, Yap et al. Lancet Respiratory Medicine 2021, Zhou et al. Clinical Lung Cancer 2021

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Conflict of interest statement

Marco Tagliamento declares travel, accommodations, expenses supported by Roche, Bristol-Myers Squibb, Astra Zeneca, Takeda, and activity as medical writer supported by Novartis, Amgen outside the submitted work.

Paolo Bironzo declares honoraria as speaker bureau by Roche, Bristol-Myers Squibb, Astra Zeneca, Takeda, Merck Sharp and Dohme, Beigene, outside the submitted work. He declares expenses by Amgen and Daiichi Sankyo.

Massimo Di Maio acted as consultant for Eisai, Takeda, Janssen, Astellas, Pfizer and AstraZeneca, outside the submitted work.

Giorgio Vittorio Scagliotti received honoraria from AstraZeneca, Eli Lilly, MSD, Pfizer,Roche; acts as a consultant or advisor for AstraZeneca, Beigene and Verastem; received research funding from Eli Lilly (institutional), MSD (institutional) and Tesaro (institutional); Travel, Accommodations, Expenses from Bayer.

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