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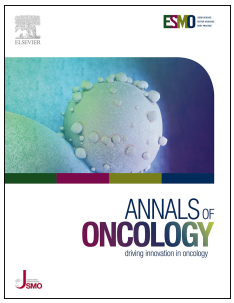

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A multicentre randomised phase III trial comparing pembrolizumab vs single-agent chemotherapy for advanced pre-treated malignant pleural mesothelioma: the European Thoracic Oncology Platform (ETOP 9-15) PROMISE-meso trial

Authors:

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Highlights

- First RCT evaluating efficacy of an anti-PD1 agent versus chemotherapy in relapsed MPM, with immunotherapy crossover allowed
- Objective response rate was significantly improved for pembrolizumab (22% vs 6%, p=0.004)
- No improvement for independently reviewed PFS for pembrolizumab over chemotherapy (HR=1.06, 95% CI: 0.73-1.53, p=0.76)
- No overall survival improvement for pembrolizumab over chemotherapy (HR=1.04, 95% CI: 0.66-1.67, p=0.85)

Abstract

Background

Malignant pleural mesothelioma (MPM) is an aggressive malignancy characterized by limited treatment options and a poor prognosis. At relapse after platinum-based chemotherapy, single-agent chemotherapy is commonly used and single-arm trials of immune-checkpoint inhibitors have demonstrated encouraging activity.

Patients and methods

PROMISE-meso is an open-label 1:1 randomised phase III trial investigating the efficacy of pembrolizumab (200mg/Q3W) vs institutional choice single-agent chemotherapy (gemcitabine or vinorelbine) in relapsed MPM patients with progression after/on previous platinum-based chemotherapy. Patients were performance status 0-1 and unselected for PD-L1 status. At progression, patients randomised to chemotherapy were allowed to crossover to pembrolizumab. The primary endpoint was progression-free survival (PFS), assessed by blinded independent central review (BICR). Secondary endpoints were overall survival (OS), investigator assessed (IA)-PFS, objective response rate (ORR), and safety. Efficacy by PD-L1 status was investigated in exploratory analyses.

Results

Between September 2017 and August 2018, 144 patients were randomised, (pembrolizumab: 73; chemotherapy: 71). At data cut-off [20/02/2019, median follow-up of 11.8 months (IQR: 9.9-14.5)], 118 BICR-PFS events were observed. No difference in BICR-PFS was detected (HR=1.06, 95%CI:0.73-1.53; p=0.76), and median BICR-PFS (95% CI) for pembrolizumab was 2.5(2.1-4.2), compared with 3.4(2.2-4.3) months for chemotherapy. A difference in ORR for pembrolizumab was identified (22%, 95%CI:13%-33%), over chemotherapy (6%,95%CI:2%-14%; p=0.004). Forty-five patients (63%) assigned to chemotherapy, received pembrolizumab at progression. With follow-up to 21 August 2019 [17.5 months: 14.8-19.7)], no difference in OS was detected between groups (HR=1.12,95%CI:0.74-1.69; p=0.59), even after adjusting for cross-over. Pembrolizumab safety was consistent with previous observations. Exploratory efficacy analyses by PD-L1 status demonstrated no improvements in ORR/PFS/OS.

Conclusion

This is the first randomised trial evaluating the efficacy of pembrolizumab in MPM patients progressing after/on previous platinum-based chemotherapy. In biologically unselected patients, although associated with an improved ORR, pembrolizumab improves neither PFS nor OS over single-agent chemotherapy.

Key words

Malignant pleural mesothelioma; Pembrolizumab; Immune-checkpoint inhibition; Randomized clinical trial

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive malignancy caused in most cases by asbestos exposure. The disease is invariably fatal, with median survival up to 16 months in most recent trials.

The only treatment proven to improve MPM survival to date is cisplatin-anti-folate combination first-line chemotherapy[1,2] and this benefit is modestly but significantly augmented with the addition of bevacizumab.[3] At relapse, no anti-cancer therapies have demonstrated a survival advantage and single-agent chemotherapy with either vinorelbine or gemcitabine is commonly used in practice, supported by International Guidelines,[4] with modest activity shown in single-arm trials and institutional series reporting a progression-free survival (PFS) of around 3 months.[5]

Immune-checkpoint inhibitors have demonstrated significant activity in other malignancies in some cases with efficacy related to extent of PD-L1 tumour expression. Mesothelioma carcinogenesis is underpinned by the chronic inflammatory response to asbestos fibres through multiple pathways.[6] Moreover, PD-L1 is strongly expressed on a proportion of mesotheliomas where it defines a poorer prognosis.[7] Pembrolizumab is a humanized monoclonal antibody, designed to directly block the interaction between PD-1 and its ligands. At time of PROMISE-meso design, the KEYNOTE-028 MPM expansion cohort had reported an encouraging 28% ORR and a median 6 month PFS in 25 PD-L1 expressing MPM patients.[8] We designed this trial to formally evaluate whether pembrolizumab improves PFS, assessed by blinded independent radiological review (BIRC), compared to standard, institutional-choice single-agent chemotherapy with either gemcitabine or vinorelbine.

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Methods

Patients

Eligible patients had histologically confirmed MPM (all histologies), progressed on/after platinum-based chemotherapy, ECOG performance status (PS) 0-1, measurable/evaluable disease according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1, pleural rind being measured perpendicular to the chest wall), adequate haematological/renal/liver function and tumour tissue available for translational research. All trial participants provided written informed consent.

Trial design and treatment administration

Patients were randomly assigned (1:1) to receive either institutional choice chemotherapy, gemcitabine: 1000mg/m^2 intravenous (i.v.) day one and eight of three-week cycles (Q3W), vinorelbine: 30mg/m^2 i.v. or 60/80mg/m^2 orally day one and eight Q3W, or pembrolizumab at a fixed dose i.v. 200mg/Q3W until disease progression (PD), toxicity or patient refusal for a maximum of two years. Pembrolizumab administration was allowed beyond RECIST-defined PD in case of clinical benefit, upon physician and patient agreement. Patients in the chemotherapy arm were allowed to crossover to pembrolizumab at PD identified locally. Tumour assessments for all patients were performed by CT-scan of the thorax and upper abdomen at baseline, every 9 weeks for the first 6 months and every 12 weeks thereafter up to two years until tumour progression determined according to RECIST v1.1. Confirmation of response by additional imaging was not required. For both arms, radiology outcomes according to local sites was retrospectively independently evaluated by BICR performed by an external vendor. PD-L1 immunohistochemistry (IHC) was performed using clone SP263 (Supplement part II).

Ethics committees and relevant health authorities approved the trial protocol. This trial was registered with ClinicalTrials.gov, number NCT02991482.

Randomisation and masking

Computer assisted centralized block stratified randomisation balanced by institution, with histological subtype stratum (epithelioid vs non-epithelioid) was implemented to allocate patients treatments. Participants, physicians and investigators were not blinded to treatment assignment.

Endpoints

The primary endpoint was BICR-PFS, defined as time from randomisation to PD according to RECIST v1.1 or death from any cause. Secondary endpoints included: investigator-assessed PFS (IA-PFS); Overall Survival (OS; time from randomisation to death from any cause); ORR according to RECIST v1.1, based on BICR (percentage of patients that achieved complete (CR)/partial response (PR)); time-to-treatment failure (TTF; time from randomisation to treatment failure for any reason, including treatment discontinuation due to toxicity or refusal/withdrawal, progression of disease or death, even after treatment completion); and safety according to the common terminology criteria for adverse events (AEs) version 4.0 (CTCAE V4.0). Exploratory endpoints included duration of response (DOR; BICR/IA), defined as the time from documented objective response to PD or death from any cause, and efficacy by tumour PD-L1 status.

Statistical Analysis

The study was designed to detect an increase in median BICR-PFS, from 3.5 months for chemotherapy to 6.0 months for pembrolizumab, corresponding to a 6-month PFS of 30% versus 50% for chemotherapy and pembrolizumab arms, respectively (Hazard Ratio (HR) of 0.58, assuming exponential survival). Using 80% power and a one-sided type I error of 2.5%, 110 events were required to achieve the trial goal. No formal interim analysis was planned. Interim safety analyses were performed in six-month intervals and reviewed by the European Thoracic Oncology Platform (ETOP) independent data monitoring committee (IDMC).

Balance of baseline characteristics between the two treatment groups was tested by Fisher's exact and Mann-Whitney tests, for categorical and continuous variables correspondingly. All time-to-event endpoints were estimated by the Kaplan-Meier method and modelled via stratified Cox proportional hazards models adjusted for clinicopathological variables of interest: sex, age, ECOG PS, PD-L1 status and the European Organization for Research and Treatment of Cancer (EORTC) score for malignant mesothelioma.[9] The backward elimination

method, with a removal criterion at 10% was implemented to select the statistically significant predictors and subsequently obtain HRs and corresponding 95% confidence intervals (CIs). The proportional hazards assumption was tested, using the Schoenfeld residuals. All p-values reported for time-to-event endpoints correspond to Wald test from stratified by histologic subtype Cox models except for the primary analysis of BICR-PFS where we also report the stratified log-rank test, as set by the protocol. Difference in ORR was assessed by the stratified Miettinen and Nurminen's method.

Efficacy outcomes were assessed separately, in subgroups defined by PD-L1 levels (cut-offs considered: 1% and 20%).

Analysis populations

Efficacy was assessed in the intent-to-treat (ITT) cohort: all patients randomised, analysed upon their initial treatment assignment. Evaluation of treatment compliance and safety were assessed in the as-treated (AT) population: all patients randomised that received at least one dose of trial treatment, with treatment assignments designated according to actual study treatment received. Finally, the crossover (CO) cohort included all patients randomised to chemotherapy that switched to pembrolizumab at PD.

OS analysis taking into account crossover

Censored and inverse probability weighted (IPW)[10] analyses were performed for OS, to account for a possible cross-over effect. In the censored analysis, all chemotherapy patients who switched to receive pembrolizumab were censored at time of crossover. In the IPW approach, patients randomised to chemotherapy were censored at the time of crossover. Simultaneously, inverse weights were assigned to the remainder of the chemotherapy patients, according to compatibility of characteristics (both baseline characteristics and post-randomisation factors).

Results

Patient and treatment characteristics

From September 2017 to August 2018, 151 patients, from 14 centres in three countries (United Kingdom, Switzerland and Spain) were screened. 144 were randomised: 73 to pembrolizumab and 71 chemotherapy, most receiving vinorelbine (83%). Two patients did not receive at least one dose of the assigned trial treatment: one randomised to chemotherapy withdrew consent, and one to pembrolizumab died before treatment initiation (Figure-1).

Arms were generally well-balanced with no significant demographic differences (Table-1). Patients' median age was 70 (52-83), were mostly male (81.9%), mostly epithelioid histological subtype (88.9%), either former or never smokers (93.1%), with ECOG PS1 (75.0%), and good prognosis EORTC score (68.8%).[9] PD-L1 (SP263 clone) scoring was available for 135 patients. Six cases (4.4%) were non-evaluable and of the remaining cases, 66 (51.2%) were PD-L1<1%, and 63 (48.8%) PD-L1 positive (1-20%: 38, ≥20%: 25 patients). All patients had received prior platinum-pemetrexed chemotherapy and around 20% had received additional treatments, usually an antiangiogenic agent. Five patients had undergone prior pleurectomy (not otherwise specified). Data on best response to prior chemotherapy or previous radical surgery was not captured.

Median treatment cycles in the pembrolizumab and chemotherapy arms were 4 and 3, respectively (range: 1-24, 1-20). In the chemotherapy arm, no patients received chemotherapy beyond progression, one patient received radiotherapy and 45 (63%) patients who progressed crossed over to receive pembrolizumab. In the pembrolizumab arm, 27 patients (46.6% of 58 progressing patients) received pembrolizumab beyond progression, 9 (15.5%) received chemotherapy only and one (1.7%) received combination chemotherapy and radiotherapy (Figure-1).

Efficacy

Progression-free Survival

At data cut-off for the primary endpoint analysis of BICR-PFS (20 February 2019), median follow-up was 11.8 months, Interquartile Range (IQR): 9.9-14.5. Sixty-four (88.9%) patients in the pembrolizumab arm and 65 (92.9%) in the chemotherapy arm had discontinued treatment, mostly due to progression (87.5% and 72.3%, for

pembrolizumab and chemotherapy, respectively; Figure-1). A total of 118 (81.9%) PFS events were observed in the ITT cohort by BICR (pembrolizumab: 62, chemotherapy: 56). No difference in BICR-PFS was identified (HR=1.06,95%CI:0.73-1.53;p=0.76, Figure-2A), median BICR-PFS 2.5 months (95%CI:2.1-4.2) for pembrolizumab versus 3.4 (95%CI:2.2-4.3) for chemotherapy, respectively (stratified log-rank test p=0.76). No benefit of pembrolizumab over chemotherapy for BICR-PFS was detected in all subgroups examined (Figure-2B), with a non-significant poorer BICR-PFS HR point estimate for pembrolizumab in non-epithelioid tumours. PFS was significantly worse for those with "poor" EORTC prognostic score (HR=1.85(95%CI:1.21-2.84; p=0.0049 Table-S1).

PFS results by investigator assessment (IA) were similar to BICR-PFS (Figure-S1, Table-S2). Agreement between BICR and investigator assessment was 92%.

Overall Survival

OS was updated as of 21 August 2019, with a median follow-up of 17.5 months IQR: 14.8-19.7), similar between the two arms (p=0.36, Figure-1). Total of 92 deaths were recorded, 48(65.8%) in the pembrolizumab and 44 (62.0%) in the chemotherapy arm. The main cause of death was mesothelioma (81 cases, 88.0%). No significant difference in OS was observed between the pembrolizumab and chemotherapy arms: median 10.7 months (95%CI:7.6-15.0) and 12.4 months (95%CI:7.4-16.1), respectively (HR=1.12,95%CI: 0.74-1.69; p=0.59, Figure-3A/3B). Similarly, no OS benefit of pembrolizumab over chemotherapy was observed for all subgroups (Figure-3C), again with a non-significant poorer OS point estimate for pembrolizumab in the non-epithelioid subgroup. No apparent effect of crossover was detected, with censored and IPW analyses yielding similar results (Figure-3B; Table-S3).

A significant effect of "poor" EORTC score was detected, in all three analyses performed (ITT, Censored, IPW: all $p<0.001$), (Table-S3).

Objective Response Rate

By BICR, the ORR for pembrolizumab was significantly improved: 22% (95%CI:13%-33%) with 16 objective responses (all PR), and 6% (95%CI:2%-14%) for chemotherapy with 4 responses (all PRs) (p=0.004; accounting for histological subtype). Median DOR (95%CI), for pembrolizumab was 4.6 months (2.1, Not Estimable (NE)),

with 10 of the 16 patients with PR subsequently progressing. For chemotherapy, median DOR was 7.2 months (NE, NE) with one of the 4 patients with PR progressing. Additional details including the waterfall plot are summarised in Table-S4 and Figure-S2. By IA, a similar significant ORR improvement for pembrolizumab (19%,95%CI:11%-30%) vs chemotherapy (3%,95%CI:0%-10%) was observed, (p=0.001; adjusting for histological subtype; Table-S5).

Time to treatment failure

The overall median TTF time was 2.4 months (95%CI:2.1-4.0; p=0.17), with no difference between arms (pembrolizumab: 2.8 months; 95%CI:2.1-4.2, chemotherapy: 2.3 months; 95%CI:2.1-3.9; Figure-S3).

Efficacy outcomes by PD-L1 status

PD-L1 expression results are described in Table-S6. Of the evaluable patients, 48.8% were PD-L1 positive (1%-cut-off), and expression was balanced between arms (pembrolizumab: 46.3% vs. chemotherapy: 51.6%, p=0.59). Balance in expression was also achieved at the 20%-cut-off (pembrolizumab: 16.4% vs. chemotherapy: 22.6%, p=0.50). No benefit of pembrolizumab on BICR-PFS was detected in subgroups defined by PD-L1 status (at 1% or 20% cut-offs, Figures-S4/S5). Similar results were seen for OS (Figures-S6/S7). An excess of PD-L1 positive patients was observed among the 16 patients randomized to pembrolizumab with PR (9 PD-L1 ≥1% and 7 <1%, Figure-S8). Of the four patients randomized to chemotherapy with response, all but one were PD-L1≥1% (Figure-S8). Further results (Figures-S9/S10), demonstrate no relationship between best change (%) in tumour size and TTF by PD-L1 status. Additional analyses using the clone E1L3N are also reported (Supplement part II), with similar conclusions.

Efficacy outcomes of crossover cohort

No difference with respect to baseline characteristics was detected between the crossover cohort (45 patients) and the trial population (Table-S7). Progression for this cohort was assessed only by investigators. With 32 treatment failures, mainly due to PD (30; 2 deaths, 1 patient decision, 1 other reason), median TTF was 2.1 months (95%CI:2.0-4.1). Median PFS measured from date of cross-over was 2.1 months (95%CI:1.8-4.1, 31

PFS events). Four partial responses were observed, corresponding to an ORR of 9%; 95%CI:2%-21% (Table-S8). Median OS for this cohort (from date of cross-over) was 9.1 months (95%CI:4.7-12.1).

Safety

AEs of any grade and irrespective of relation to treatment were experienced by 97.2% of patients for pembrolizumab and 92.9% for chemotherapy, while related to treatment were experienced by 69.4% and 74.3% respectively. Immune-related attribution for AEs was not specifically recorded. The percent of patients with a grade ≥3 treatment-related AE was 19.4% in the pembrolizumab arm, including a case of grade 3 hypophysitis and 25.7% in the chemotherapy arm. Five patients in each arm experienced a treatment-related AE resulting in treatment discontinuation. There was one treatment-related death in each arm (pembrolizumab: pneumonia, chemotherapy: dyspnoea, with PD being the primary cause).

The commonest treatment-related AEs were fatigue and diarrhoea, experienced by 26.1% and 18.3% of all patients, respectively, with no difference observed between the two treatment arms. Treatment related dry skin, maculopapular rash and pruritus were more frequently observed for pembrolizumab (relative risk compared to chemotherapy arm: 12%, 11% and 10%, respectively), while treatment-related nausea, constipation and oral mucositis were more frequently observed for chemotherapy (relative risk compared to pembrolizumab: 20%, 14% and 10%; Table-2). All treatment-related neutropenia events were observed in the chemotherapy arm. Immune-related adverse events, along with treatment association are presented in Table-S9.

Discussion

Our results unequivocally demonstrate that in biologically unselected pre-treated MPM patients, there is neither improvement in PFS nor OS for pembrolizumab over vinorelbine or gemcitabine chemotherapy. Whilst an improved ORR was observed for pembrolizumab, responses were generally transient. The majority of patients randomised to chemotherapy (63%) crossed-over on progression to pembrolizumab. Despite adjusting for this, no improvement in OS was identified. Inspection of the Kaplan Meier curves for PFS and OS demonstrates neither early crossover nor detrimental event rate for pembrolizumab with maintenance of proportional hazards, and no emerging plateau. Forest plots of PFS and OS demonstrated no clinical or pathological characteristic associated with significant pembrolizumab benefit. However, the non-epithelioid histological subtype was

suggestive of poorest outcomes from pembrolizumab with HR point estimates of 1.76 for PFS and 1.54 for OS (non-significant) likely due to the small subgroup size. Importantly, PD-L1 expression did not correlate with any signal of predictive utility for pembrolizumab, or prognostic impact. We could not comment on rates of hyperprogression or pseudoprogression as these progression patterns were not specifically collected.

Toxicities identified were typical for each agent with the most discriminant toxicities in each arm typical for their drug class. Rates of grade ≥3 treatment-related adverse events were similar for pembrolizumab and chemotherapy (19.4% vs 25.7%, respectively) and similar to that seen in other trials, for example, 18% for pembrolizumab in KEYNOTE-042[11] and 20% for the mesothelioma cohort of KEYNOTE-028[8] and for chemotherapy, considerably less than that reported for vinorelbine in the randomized anetumab ravtansine/vinorelbine trial (25.7% vs 57%).[12] Our results therefore do not identify any new safety concerns for pembrolizumab in MPM.

Several factors should be considered in interpreting the lack of PFS or OS benefit for pembrolizumab despite an improved ORR. Patients recruited were typical for a MPM trial population, (predominantly elderly, male, epithelioid histological subtype, good performance status, mostly relapsed after platinum-based chemotherapy) in line with the VANTAGE-014 trial. Patients with good EORTC prognostic score were slightly overrepresented in the chemotherapy arm. Nevertheless, we confirmed the EORTC prognostic score utility (Tables-S1/S2) giving additional validation to our trial population. We did not, however, capture data on best response to prior chemotherapy and can therefore not exclude over representation of chemo-refractory patients. Nevertheless, such patients would likely be randomly distributed, and control arm outcomes argue against this being a significant bias. We did not use an artificially inadequate control arm, such as best supportive care, designing the control arm reflecting routine clinical care. Indeed, control arm performance was as expected, recapitulating the null hypothesis, 3.5 months PFS, similar to that observed for vinorelbine control in the anetumab ravtansine phase II trial (4.3 months).[12] Of note, PFS for pembrolizumab was numerically inferior to 5.4 months observed in KEYNOTE-028, possibly reflecting the highly selected nature of the latter Phase I trial cases. Additionally, enrollment criteria for KEYNOTE-028 included PD-L1 positive tumours which might represent an additional selection factor.[8] Whilst our study was powered to identify a large PFS benefit, (HR=0.58) we cannot exclude pembrolizumab causing a smaller but significant difference, although inspection of the Kaplan Meier PFS curve argues against any meaningful difference. We chose PFS as the primary endpoint rather than OS to allow an

early analysis of efficacy in case of a strong efficacy signal and since a PFS benefit has also been observed for pembrolizumab trials in other malignancies with an OS benefit. However, we observe that PFS may be difficult to accurately capture in mesothelioma, given the reliance on confidently calling disease progression using CT and RECIST-based criteria. For this reason, and also noting open label treatment allocation, we ensured BICR radiology review to minimize this risk of bias. We included cross-over to make the trial ethically appropriate, given the high-rate of off-label pembrolizumab usage for relapsed MPM.[13] To our knowledge, no patients randomised to chemotherapy received anti-PD-1/L1 therapy outside the trial. Whilst mesothelioma progression may be difficult to reliably classify,[14] we accounted for this potential bias by making BICR-PFS the primary endpoint noting high concordance between BICR-assessed and IA-assessed PFS. Moreover, others have argued that PFS rate at 9 and 18 weeks is predictive of OS, giving an earlier endpoint readout, uncontaminated by uncontrolled post-progression therapies.[15] Pembrolizumab cross-over was accounted for by two well-defined methods, both demonstrating no significant OS benefit, although, we cannot fully exclude a small OS benefit that this methodology did not detect. Visual inspection of the Kaplan Meier OS curve would not allow this to be easily identified given the high rate of crossover. Nevertheless, given that the majority of control arm patients crossed-over to receive pembrolizumab and that the similarity of median OS observed for both arms (10.7 and 12.4 months for pembrolizumab and chemotherapy, respectively) is comparative to the vinorelbine control arm of the anetumab ravtansine randomised phase II trial (11.6 months),[12] arguing against over-performance of the control arm. Moreover, we cannot exclude a modest OS benefit for sequential chemotherapy-pembrolizumab (or vice versa).

A potential benefit for immune-checkpoint inhibitor therapy in MPM is biologically attractive, given the pathogenic inflammatory microenvironment and PD-L1 expression in 14-59% of tumours.[16,17] However, with the exception of rare cases with microsatellite instability, this plausibility is balanced by a tumour type of low neoantigenic potential, low tumour mutation burden, mainly driven by genomic losses.[18] During the recruitment of PROMISE-meso, one randomised phase III trial of tremelimumab monotherapy (DETERMINE) has reported, identifying no OS benefit, after two small, uncontrolled single-arm phase II trials suggested prolonged disease control.[19,20]

Similarly, four single-arm small cohorts of anti-PD1/L-1 agents[16,17,21,22] and three cohorts of combination anti-PD1/L-1 with anti-CTLA4 combination have been published.[22-24] Across-trial comparisons are limiting, with

marked potential for hidden biases, including that from differing inclusion criteria such as requiring measurable disease, requiring a mandatory new biopsy, endpoints, imaging frequency, independent assessment of progression, or limited numbers of sites. ORRs observed in these studies of nivolumab were 10-29%,[21,24] and with median PFSs 2.6-6.1 months, median OS 10.7-17.3 months, and one-year survival rates between 43-59%,[16,21] compared with a one-year survival rate of 47.8% for PROMISE-meso. Nevertheless, the median PFS of 2.5 months we identified was at the lower end of the variation of PFS identified in previous trials, and is more likely to have been impacted on by clinical prognostic variables than discrepancies in measuring disease progression. Similarly, median DOR for pembrolizumab in PROMISE-meso was shorter for pembrolizumab at 4.6 months (based on 16 responders, with 10 of them progressing) compared to 7.2 months for chemotherapy, which should be interpreted with caution since it was based on only 4 responders with 1 progressing. Again, whilst DOR may have been impacted by ability to confidently call progression by radiological criteria, utilization of BICR will have ameliorated this bias as best as possible. Finally, pembrolizumab DOR was considerably shorter than that reported by other single arm trials of anti-PD-1/L1 monotherapy which ranged from 7.4 to 12.0. The impact of patient selection by different enrolment criteria in these trials on DOR is unknown. The three trials of anti-PD-1/L1-CTLA4 combination demonstrated ORRs of 25-29%, similar to anti-PD1/L-1 monotherapy, median PFSs of 5.6-6.2 months, median OS (where reported) of 11.2-15.9 months, with one-year survival rates of 58-64%, again comparable with 47.8% we observed.[22-24]

We evaluated the predictive utility of tumour PD-L1 expression using both the SP263 and E1L3N clones and demonstrated similar expression rates at the 1% cut-off to that previously reported, with a high concordance between clones, and excess expression in non-epithelioid subtypes. We detected no associations between PD-L1 status and efficacy, although we utilized surplus diagnostic specimens, which may be non-representative at enrolment time. Nevertheless, a lack of predictive PD-L1 expression utility has also been independently identified by most trials[8,17] but not all.[22]

Ultimately, we did not demonstrate superior PFS or OS for pembrolizumab, despite a higher ORR, and on this basis, pembrolizumab cannot be considered a new standard for relapsed MPM. Whilst OS was not improved with pembrolizumab, PROMISE-meso was not designed for non-inferiority and therefore OS equivalence between arms cannot be claimed. We have, however, been able to demonstrate meaningful activity for pembrolizumab in individual cases. A better biological understanding for the basis of this benefit is therefore

required and additional translational analyses from PROMISE-meso are on-going to this end. We also await the results of the CONFIRM trial (NCT03063450) a blinded randomised-controlled phase III trial of nivolumab versus placebo in second and third-line relapsed MPM with the co-primary endpoints of PFS and OS.

As seen for other diseases with poor prognosis immune-checkpoint inhibitors may have the greatest efficacy in the first-line setting. The very recent results of the CHECKMATE-743 trial (NCT02899299), evaluating nivolumab-ipilimumab versus platinum-pemetrexed chemotherapy, refer to a statistically significant OS improvement (Press-release BMS, 20 April 2020). Combinations with chemotherapy may also be effective, the feasibility of cisplatin-pemetrexed-durvalumab has been explored in a single arm trial (ACTRN12616001170415), and three international, multicentre randomised phase III trials are ongoing, evaluating the combination of pembrolizumab-cisplatin-pemetrexed (NCT02784171), the combination of durvalumab-cisplatin-pemetrexed (DREAM3R, NCT04334759) and the combination of carboplatin-pemetrexed-bevacizumab-atezolizumab (ETOP BEAT-meso, NCT03762018).

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Dr. Shah has attended advisory boards for MSD.

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All other authors declare no competing interests.

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Table-1. Baseline characteristics, overall and by treatment arm

Characteristic	All patients (N=144)	Pembrolizumab (N=73)	Chemotherapy (N=71)	p-value*
Age (yrs at randomization)				
N	144	73	71	0.020
Mean (95% CI)	68.9 (67.8, 70.1)	67.7 (66.1, 69.4)	70.2 (68.6, 71.7)	
Median (Min-Max)	70.0 (52.0 – 83.0)	69.0 (52.0-83.0)	71.0 (53.0-83.0)	
Age cat. -n(%)				
<70 yrs	71 (49.3)	42 (57.5)	29(40.8)	0.048
≥70 yrs	73 (50.7)	31 (42.5)	42 (59.2)	
Sex - n(%)				
Male	118 (81.9)	58 (79.4)	60 (84.5)	0.52
Female	26 (18.1)	15 (20.6)	11 (15.5)	
Histological Subtype - n(%)				
Epithelioid	128 (88.9)	66(90.4)	62 (87.3)	0.60
Non-epithelioid	16 (11.1)	7(9.6)	9 (12.7)	
Smoking history - n(%)				
Current	9 (6.3)	5 (6.8)	4 (5.6)	0.56[¥]
Former (≥100 cigarettes in the past during the whole life)	62 (43.1)	34 (46.6)	28 (39.4)	0.32[¥,§]
Never (0-99 cigarettes during the whole life)	72 (50.0)	33 (45.2)	39 (54.9)	
Unknown/missing	1 (0.7)	1 (1.4)	0 (0.0)	
ECOG performance status - n(%)				
0	35 (24.3)	21 (28.8)	14 (19.7)	0.24
1	108 (75.0)	51 (69.9)	57 (80.3)	
2[¶]	1 (0.7)	1 (1.4)	0 (0.0)	

Characteristic	All patients (N=144)	Pembrolizumab (N=73)	Chemotherapy (N=71)	p-value*
EORTC Score- n (%)				
Good prognosis	99 (68.8)	45 (61.6)	54 (76.1)	0.07
Poor prognosis	45 (31.2)	28 (38.4)	17 (23.9)	
Prior treatment- n (%)				
Carboplatin/pemetrexed[€,‡]	54 (37.5)	27 (37.0)	27 (38.0)	0.18
Cisplatin/pemetrexed[€,‡]	46 (31.9)	24 (32.9)	22 (31.0)	
Platinum ±pemetrexed ±other[€]	30 (20.8)	13 (17.8)	17 (23.9)	
Cisplatin/pemetrexed&carboplatin/pemetrexed[€]	8 (5.5)	7 (9.6)	1 (1.4)	
Missing[‡]	6 (4.2)	2 (2.7)	4 (5.6)	
PD-L1- n(%) (N=135 samples scored)				
<1%	66 (48.9)	36 (52.2)	30 (45.5)	0.67[¥]
1-20%	38 (28.2)	20 (29.0)	18 (27.3)	0.69**
≥20%	25 (18.5)	11 (15.9)	14 (21.1)	
Not Evaluable	6 (4.4)	2 (2.9)	(6.1)	

*Fisher's exact categorical, Mann-Whitney U test for continuous variables
[¥]Category "Unknown/Missing" or 'Missing' excluded
[§]Categories "Current" & "Former" combined
[€]Among these patients, 13 have also received radiotherapy
[‡]Among these patients there are 5 that underwent pleurectomy
[¶]ECOG performance status 2 due to leg braces, confirmed by ETOP
**Excluding categories "Missing" & "Not Evaluable"

Table-2. Safety information of the as-treated cohort

Event	**Pembrolizumab**	**Chemotherapy**	
	n(%) patients		
Safety cohort	72	70	
Any AE	70 (97.2)	65 (92.9)	
Treatment related AE	50 (69.4)	52(74.3)	
Treatment related AEs Grade: 3-5	14 (19.4)	18 (25.7)	
Treatment related AEs leading to death	1 (1.4)	1 (1.4)	
Treatment related AEs leading to treatment discontinuation	5 (6.9)	5 (7.1)	
Treatment related AEs occurring in ≥10% of the patients in either arm	n(%) patients		**Risk Difference (95% CI)**
Fatigue	14 (19.4%)	23 (32.9)	-0.13 (-0.28, 0.01)
Diarrhea	11 (15.3%)	15 (21.4)	-0.06 (-0.19, 0.07)
Nausea	5 (6.9%)	19 (27.1)	-0.20 (-0.32, -0.08)[¥]
Anorexia	6 (8.3%)	11 (15.7)	-0.07 (-0.18, 0.03)
Constipation	3 (4.2%)	13 (18.6)	-0.14 (-0.25, -0.04)[¥]
Pruritus	9 (12.5%)	2 (2.9)	0.10 (0.01, 0.18)[¥]
Mucositis oral	2 (2.8%)	9 (12.9)	-0.10 (-0.19, -0.01)[¥]
Dry skin	10 (13.9%)	1 (1.4)	0.12 (0.04, 0.21)[¥]
Vomiting	4 (5.6%)	7 (10.0)	-0.04 (-0.13, 0.04)
Rash maculo-papular	9 (12.5%)	1 (1.4)	0.11 (0.03, 0.19)[¥]
Neutrophil count decreased	0 (0.0%)	9 (12.9)	-0.13(-0.21, -0.05)[¥]

[¥] Statistically significant result

Key eligibility criteria

- Malignant pleural mesothelioma (all histologies)
- Progression after previous platinum-based chemotherapy
- ECOG PS 0-1
- Measurable/evaluable disease as per RECIST v1.1 criteria
- Adequate haematological, renal and liver function
- Availability of tumor tissue for translational research

151 patients registered in ETOP database

7 ineligible for inclusion

144 randomly assigned
accrual period: Sep.2017-Aug.2018

73 allocated to Pembrolizumab (ITT)
200mg fixed dose i.v. day 1 of each 3-week cycle (Q3W)

71 allocated to Chemotherapy (ITT)
12 Gemcitabine 1000mg/m^2 d1 Q3W i.v. or
58 Vinorelbine 30mg/m^2 d1/8 Q3W i.v. or 60/80mg/m^2 d1/8 Q3W p.o.

72 received treatment (1 death prior initiation)
64 discontinued treatment
56 progressive disease
4 death
1 toxicity
1 patient decision
0 investigator decision
2 other

As of 20 Feb. 2019
Median FU (IQR):
11.8 months (9.9, 14.5)

70 received treatment (1 withdrawal prior initiation)
65 discontinued treatment
47 progressive disease
4 death
6 toxicity
1 patient decision
6 investigator decision
1 other

45 patients switched to
pembrolizumab at progression

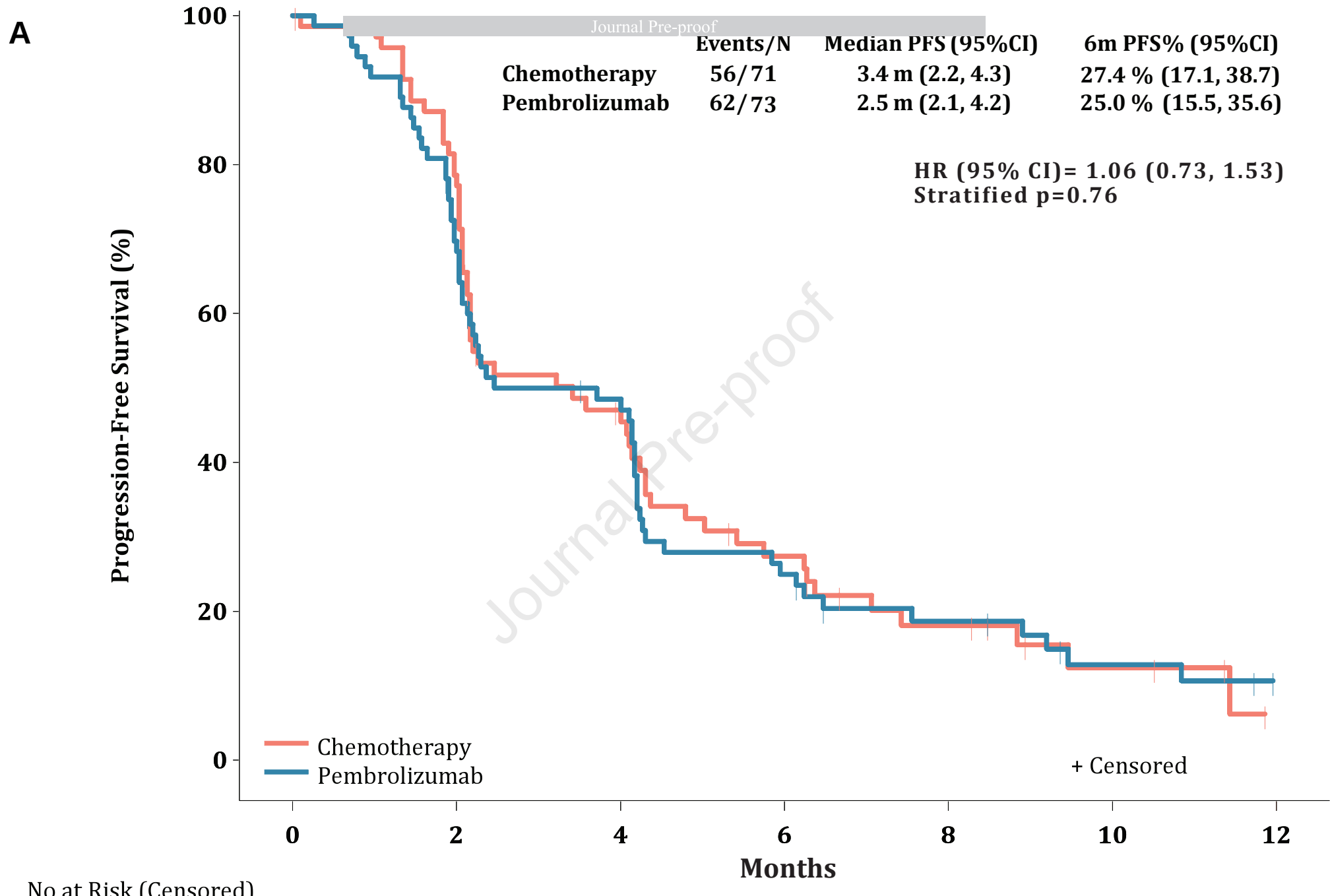
23 patients still on follow-up
2 withdrawals
Median FU (IQR): 18.2 months (15.7, 20.2)

As of 21 Aug. 2019
Median FU (IQR):
17.5 months (14.8, 19.7)

26 patients still on follow-up
1 withdrawal
Median FU (IQR): 17.2 months (14.8, 19.1)

27 received further cycles of pembrolizumab
beyond progression

A

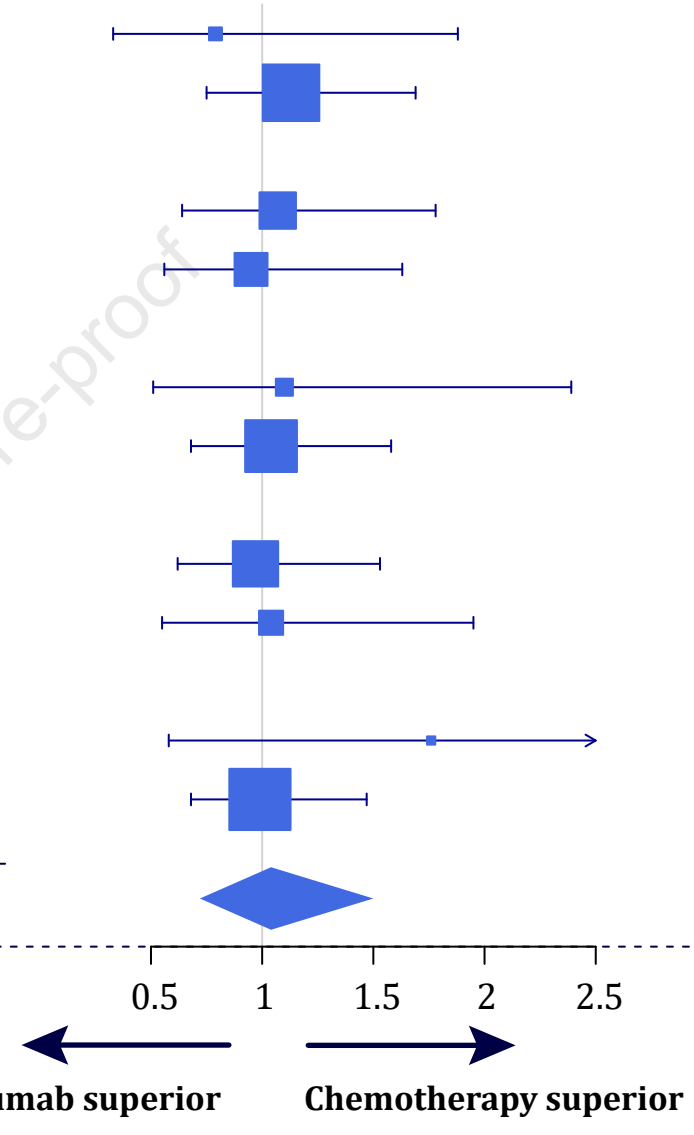


No at Risk (Censored)

Chemotherapy	71(0)	55(1)	29(6)	16(7)	9(9)	4(12)	0(15)
Pembrolizumab	73(0)	50(1)	33(3)	17(3)	11(5)	6(7)	3(9)

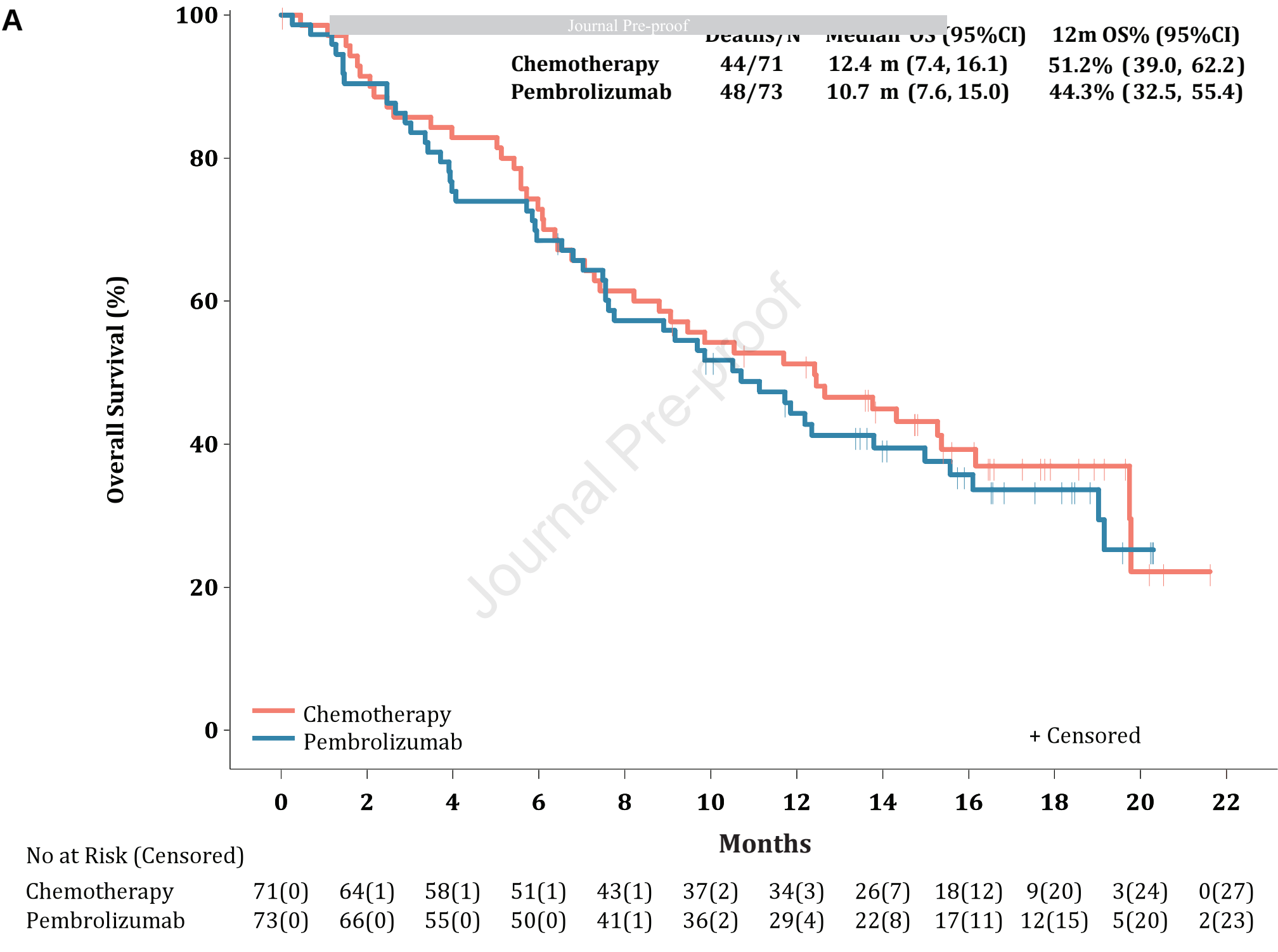
B

	Events/ N	Median PFS (months)	HR* (95% CI)
Gender			
Female	22/ 26	4.2	0.79 (0.33, 1.88)
Male	96/ 118	2.5	1.13 (0.75, 1.69)
Age			
<70	62/ 71	2.3	1.07 (0.64, 1.78)
≥70	56/ 73	4.1	0.95 (0.56, 1.63)
ECOG PS			
0	29/ 35	3.7	1.10 (0.51, 2.39)
1	88/ 108	3.4	1.04 (0.68, 1.58)
EORTC score			
Good prognosis	77/ 99	4.1	0.97 (0.62, 1.53)
Poor prognosis	41/ 45	2.0	1.04 (0.55, 1.95)
Histological Subtype			
Non – epithelioid	14/ 16	3.4	1.76 (0.58, 5.33)
Epithelioid	104/ 128	3.2	0.99 (0.68, 1.47)
All patients	118/ 144	3.4	1.04 (0.72, 1.50)



* Unadjusted/unstratified HRs

A

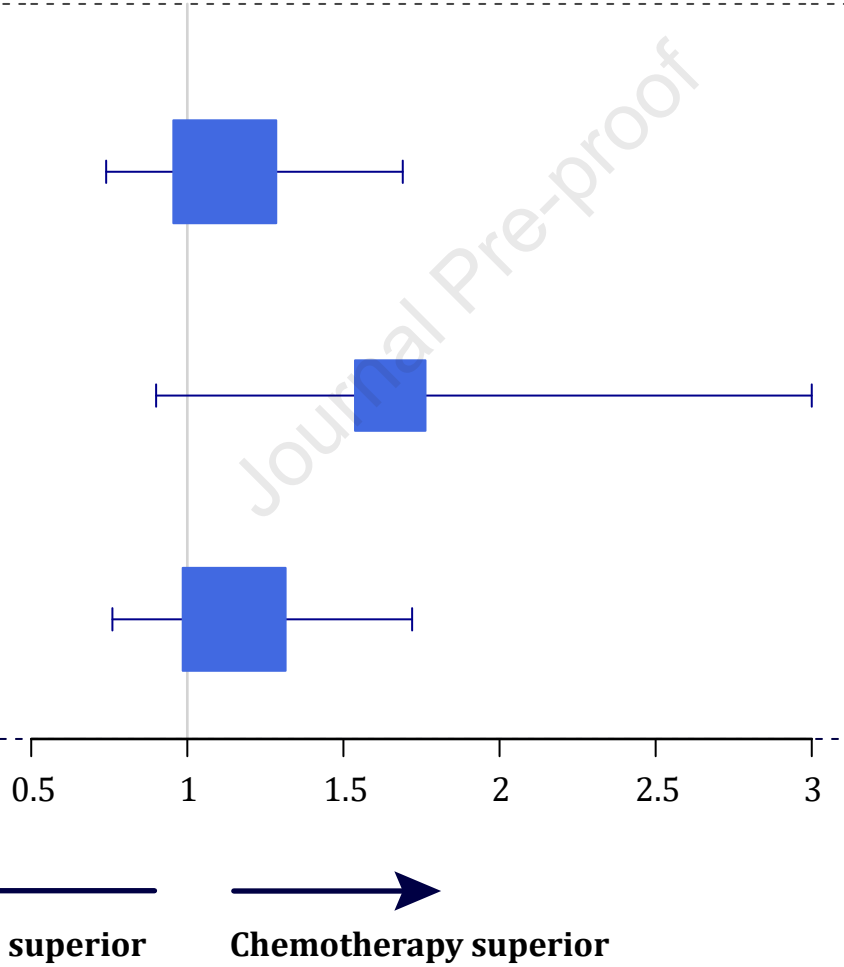


No at Risk (Censored)

Chemotherapy	71(0)	64(1)	58(1)	51(1)	43(1)	37(2)	34(3)	26(7)	18(12)	9(20)	3(24)	0(27)
Pembrolizumab	73(0)	66(0)	55(0)	50(0)	41(1)	36(2)	29(4)	22(8)	17(11)	12(15)	5(20)	2(23)

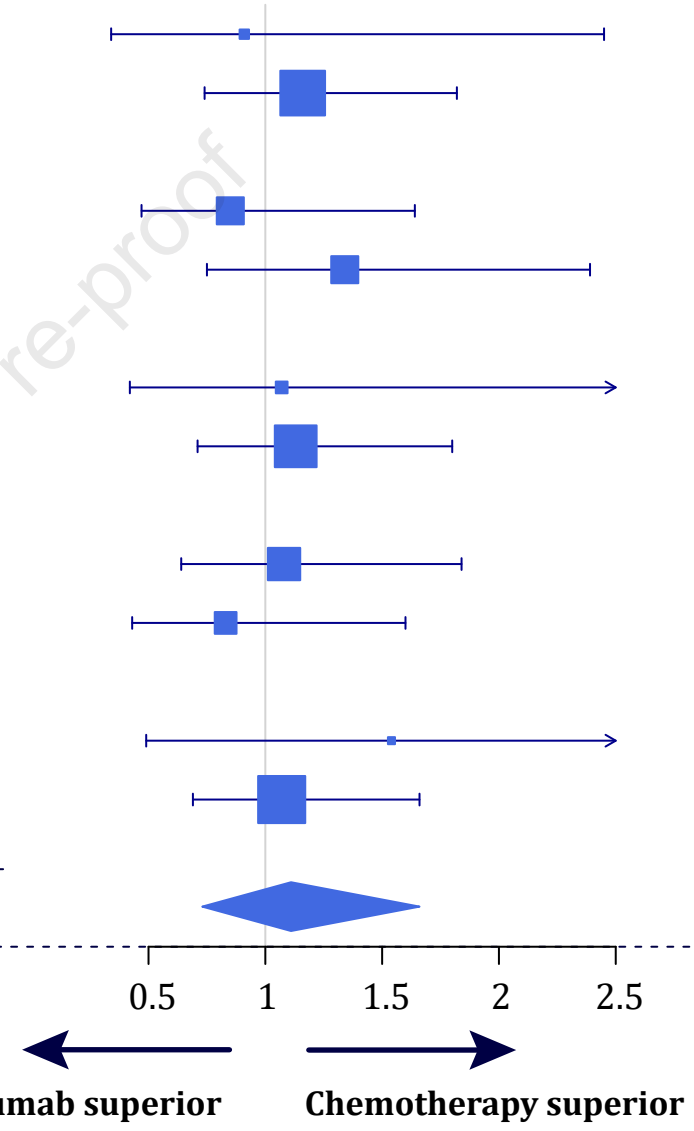
B

Method	Deaths / N	HR (95% CI)	p-value
ITT	92 / 144	1.12 (0.74, 1.69)	0.59
Censored	63 / 144	1.65 (0.90, 3.00)	0.10
IPW	92 / 144	1.15 (0.76, 1.72)	0.52



C

	Deaths/ N	Median OS (months)	HR* (95% CI)
Gender			
Female	16/ 26	9.9	0.91 (0.34, 2.45)
Male	76/ 118	11.7	1.16 (0.74, 1.82)
Age			
< 70	46/ 71	10.5	0.85 (0.47, 1.54)
≥ 70	46/ 73	11.7	1.34 (0.75, 2.39)
ECOG PS			
0	20/ 35	16.1	1.07 (0.42, 2.69)
1	71/ 108	10.5	1.13 (0.71, 1.80)
EORTC score			
Good prognosis	55/ 99	15.4	1.08 (0.64, 1.84)
Poor prognosis	37/ 45	7.0	0.83 (0.43, 1.60)
Histological Subtype			
Non – epithelioid	12/ 16	8.6	1.54 (0.49, 4.83)
Epithelioid	80/ 128	11.9	1.07 (0.69, 1.66)
All patients	**92/ 144**	**11.1**	**1.11 (0.73, 1.66)**



* Unadjusted/unstratified HRs