Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France: a phase 3, open-label, randomised controlled trial

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Summary

Background Pleural mesothelioma usually presents at an advanced, incurable stage. Chemotherapy with platinum–pemetrexed is a standard treatment. We hypothesised that the addition of pembrolizumab to platinum–pemetrexed would improve overall survival in patients with pleural mesothelioma.

Methods We did this open-label, international, randomised phase 3 trial at 51 hospitals in Canada, Italy, and France. Eligible participants were aged 18 years or older, with previously untreated advanced pleural mesothelioma, with an Eastern Cooperative Oncology Group performance status score of 0 or 1. Patients were randomly assigned (1:1) to intravenous chemotherapy (cisplatin [75 mg/m²] or carboplatin [area under the concentration-time curve 5–6 mg/mL per min] with pemetrexed 500 mg/m², every 3 weeks for up to 6 cycles), with or without intravenous pembrolizumab 200 mg every 3 weeks (up to 2 years). The primary endpoint was overall survival in all randomly assigned patients; safety was assessed in all randomly assigned patients who received at least one dose of study therapy. This trial is registered with ClinicalTrials.gov, NCT02784171, and is closed to accrual.

Findings Between Jan 31, 2017, and Sept 4, 2020, 440 patients were enrolled and randomly assigned to chemotherapy alone (n=218) or chemotherapy with pembrolizumab (n=222). 333 (76 %) of patients were male, 347 (79%) were White, and median age was 71 years (IQR 66–75). At final analysis (database lock Dec 15, 2022), with a median follow-up of 16·2 months (IQR 8·3–27·8), overall survival was significantly longer with pembrolizumab (median overall survival 17·3 months [95% CI 14·4–21·3] with pembrolizumab *vs* 16·1 months [13·1–18·2] with chemotherapy alone, hazard ratio for death 0·79; 95% CI 0·64–0·98, two-sided p=0·0324). 3-year overall survival rate was 25% (95% CI 20–33%) with pembrolizumab and 17% (13–24%) with chemotherapy alone. Adverse events related to study treatment of grade 3 or 4 occurred in 60 (27%) of 222 patients in the pembrolizumab group and 32 (15%) of 211 patients in the chemotherapy alone group. Hospital admissions for serious adverse events related to one or more study drugs were reported in 40 (18%) of 222 patients in the pembrolizumab group and 12 (6%) of 211 patients in the chemotherapy alone group. Grade 5 adverse events related to one or more drugs occurred in two patients on the pembrolizumab group and one patient in the chemotherapy alone group.

Interpretation In patients with advanced pleural mesothelioma, the addition of pembrolizumab to standard platinum–pemetrexed chemotherapy was tolerable and resulted in a significant improvement in overall survival. This regimen is a new treatment option for previously untreated advanced pleural mesothelioma.

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Introduction

Despite bans and workplace measures to decrease exposure to asbestos, the incidence of pleural mesothelioma will increase due to the long latency for development and continued asbestos use in the developing world.[1] Pleural mesothelioma usually presents at an advanced, unresectable stage. Chemotherapy with platinum–pemetrexed is standard, with median survival of 12–16 months.[2–4] The immunotherapies nivolumab and ipilimumab improved survival compared with platinum-pemetrexed, particularly in non-epithelioid histology.[4]

Pembrolizumab, an inhibitor of programmed cell death protein-1 (PD-1), is approved for the treatment of multiple malignancies[5–8] and combination therapy with pembrolizumab, platinum, and pemetrexed is well tolerated and used routinely in the treatment of non-small-cell lung cancer.[5] In the three-arm, randomised phase 2 component of the Canadian Cancer Trials Group (CCTG) trial IND227,[9] a pembrolizumab, platinum, and

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Research in context

Evidence before this study

We searched PubMed from database inception until May 24, 2023, for phase 3 randomised trials evaluating immunotherapy agents in the first-line treatment of unresectable, advanced pleural mesothelioma, using search terms that included "mesothelioma", "immunotherapy", "randomised", "pembrolizumab", "nivolumab", "atezolizumab", "durvalumab" "ipilimumab", "tremelimumab", and "phase 3". Platinum–pemetrexed was the standard regimen used in the treatment of pleural mesothelioma for two decades, with modest improvements in outcomes. When we started this trial, there were no randomised phase 3 data available that evaluated the role of immunotherapy in the first-line treatment of pleural mesothelioma. During the conduct of this trial, results became available that the combination of the immunotherapies nivolumab and ipilimumab improved survival compared with platinum–pemetrexed, and that nivolumab as a single agent improved survival in pleural mesothelioma that had been previously treated with chemotherapy. Pembrolizumab, an inhibitor of programmed cell death protein 1 (PD-1), is approved for the treatment of multiple malignancies and, when combined with platinum–pemetrexed, is a well-tolerated regimen used routinely in the treatment of non-small-cell lung cancer. In the three-arm, randomised phase 2 component of the Canadian Cancer Trials Group trial IND227, pembrolizumab–platinum–pemetrexed led to a significantly higher response rate than chemotherapy (47% *vs* 19%), with improved survival (19·8 months *vs* 8·9 months) in previously untreated pleural mesothelioma. The phase 3 component of IND227 was designed to test the efficacy and safety of pembrolizumab given with standard platinum-pemetrexed chemotherapy versus standard platinum-pemetrexed chemotherapy alone.

Added value of this study

Adding the PD-1 inhibitor pembrolizumab to standard platinum–pemetrexed chemotherapy significantly improved outcomes compared with treatment with chemotherapy alone in patients with advanced pleural mesothelioma, with a 21% reduction in the risk of death. The benefit was seen in most subgroups and was regardless of PD-L1 status and was despite the higher rate of use of salvage immunotherapy with the chemotherapy alone. Overall survival outcomes with this regimen were similar to those reported with nivolumab-ipilimumab, while progression-free survival and objective response rates were higher. The tolerability of this regimen in patients with pleural mesothelioma was similar to that observed with this regimen in advanced non-small-cell lung cancer and, despite a higher incidence of adverse events with the addition of pembrolizumab, there was no detrimental effect on patient-reported quality of life.

Implications of all the available evidence

The addition of pembrolizumab to platinum-pemetrexed was a tolerable regimen that resulted in improved overall survival, progression-free survival, and objective response rates compared with platinum–pemetrexed alone, regardless of PD-L1 expression. This regimen, already familiar to thoracic medical oncologists for the treatment of non-small cell lung cancer, represents a new treatment option for patients with advanced pleural mesothelioma especially for patients at risk of adverse outcomes due to early or rapid progression.

pemetrexed combination led to a significantly higher response rate than did chemotherapy (47% *vs* 19%), with improved survival (19·8 *vs* 8·9 months). We present the final results of the phase 3 component of IND227, designed to compare the efficacy and safety of platinum, pemetrexed, and pembrolizumab versus platinum and pemetrexed in patients with previously untreated, advanced, unresectable pleural mesothelioma.

Methods

Study design and participants

IND227 was an open-label, randomised, phase 3 trial done at 51 CCTG, National Cancer Institute – Naples and Intergroupe Francophone de Cancérologie Thoracique sites. Eligible adult patients had advanced pleural mesothelioma unsuitable for surgery; no previous systemic therapy for advanced disease ([neo] adjuvant chemotherapy permitted more than 1 year before treatment); an Eastern Cooperative Oncology Group performance status score of 0 or 1;[10] measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1·1[11] modified (mRECIST) for use in pleural mesothelioma;[12] and provided a tumour sample for correlative analysis. Patients were excluded if they had untreated CNS metastases, pneumonitis, glucocorticoids equivalent to more than 10 mg daily of prednisone (within 7 days before the first dose of study treatment), or with concurrent serious illness or cancer. Full eligibility criteria are listed in the trial protocol.

The trial protocol and all amendments were approved by national health authorities and the ethics boards of record for each participating institution. All patients provided written informed consent before enrolment. All authors attest that the trial was done according to the protocol and its amendments and in accordance with the principles of Good Clinical Practice.

Randomisation and masking

Patients were randomly assigned (1:1) to receive platinum-pemetrexed chemotherapy with or without pembrolizumab using minimisation stratified by histology (epithelioid versus other) and study centre. Patients and investigators were not masked to treatment assignment.

Procedures

Pemetrexed premedication with folic acid, vitamin B12 and glucocorticoids was given. All participants were treated with intravenous cisplatin 75 mg/m² (carboplatin [area under the concentration-time curve 5–6 mg/mL per min] could be substituted) and pemetrexed 500 mg/m² every 3 weeks for up to 6 cycles. Patients randomly assigned to the pembrolizumab group also received intravenous pembrolizumab 200 mg every 3 weeks for up to 2 years.

Treatment was continued until disease progression, unacceptable toxic effects, investigator or patient decision, or until planned treatment was complete. Patients could continue treatment until confirmed progression by iRECIST.[13] Platinum-pemetrexed doses were held or reduced for toxic effects as recommended in product monographs. Doses of pembrolizumab were held (but not reduced) for toxic effects on the basis of protocol guidance.

Adverse events were monitored continuously throughout the study and during follow-up. Patients were evaluated before each cycle, 4 weeks after discontinuation, every 12 weeks until progression, and then every 24 weeks until death. Adverse events and laboratory abnormalities were graded by use of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4·0 (appendix p 4) Imaging was scheduled every 6 weeks for 3 assessments, then every 12 weeks for both groups; unscheduled imaging was collected and assessed. Quality of life questionnaires were completed at each visit until disease progression. PD-L1 expression was assessed by Discovery Life Sciences (formerly Qualtek Laboratories, Ocean, NJ, USA). Partial central pathology review (done by SL and M-ST) was preplanned (appendix p 2).

Outcomes

The primary endpoint was overall survival defined as the time from random assignment to death from any cause. Median and mean overall survival were also calculated. Patients alive at data cutoff were censored at the last day known alive. Secondary endpoints were progression-free survival (time from the day of random assignment until the first observation of progression or death due to any cause; patients who were alive without progression were censored at their last date of disease assessment unless definitive therapy had been initiated or two or more consecutive assessments were missed), response rate (complete or partial response; confirmation was not required; duration of response used the censoring rules described above), quality of life (European Organisation for Research and Treatment of Cancer Quality of Life questionnaire C30[14] and lung cancer module LC13[15]), and health economics. Response-based outcomes were based on blinded independent central review (BICR) and mRECIST; exploratory analyses also used CCTG standard central review and iRECIST standards. Health economics analyses will be reported separately.

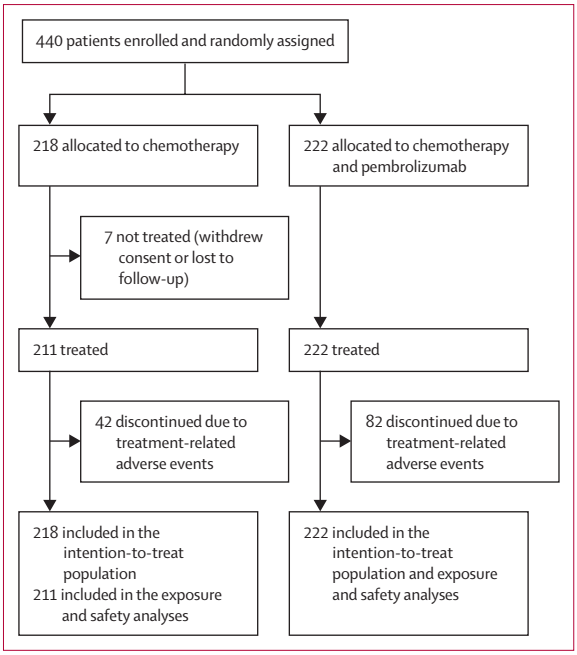

Figure 1: **Trial profile**

Statistical analysis

IND227 was redesigned in April, 2018, (phase 2 reported separately; all analysed patients were excluded from the phase 3 trial[9]) to a phase 3 design; a further amendment in April, 2020, refined the planned interim analysis and adjusted the hazard ratio from 0·65 to 0·7. Efficacy was assessed in all randomly assigned patients and safety and drug exposure were assessed in patients receiving at least one dose of any protocol therapy. The Kaplan-Meier method was used to generate overall and progression-free survival curves; statistical significance was tested by the stratified log-rank test, adjusting for histology provided at random assignment (appendix p 2). For primary estimates of treatment differences stratified Cox regression models were used to estimate hazard ratios and 95% CIs. For objective response rate, the stratified Cochran-Mantel-Haenszel test was used to compare the two treatment groups.[16] Overall survival was to be tested first; if the success criterion was met, 70 % of its alpha would be allocated to progression-free survival, and 30% of the alpha to objective response rates. All statistical analyses were done using Statistical Analysis System software Version 9.4 (SAS Institute, Cary, NC, USA). Subgroup analyses were prespecified in the statistical analysis plan; if exploratory analyses were done, they were clearly defined as exploratory.

With an assumed median survival of 16 months with chemotherapy and 334 events, the trial would have a power of 90% to show a hazard ratio for death of 0·70 with a two-sided alpha level of 0·05 at the final analysis. The required number of events would be observed by accruing 430 patients (440 after assuming ten patients

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See **Online** for appendix

	Chemotherapy only (n=218)	Chemotherapy plus pembrolizumab (n=222)
Sex		
Female	50 (23%)	57 (26%)
Male	168 (77%)	165 (74%)
Ethnicity		
White	172 (79%)	175 (79%)
Other	1 (1%)	1 (1%)
Unknown or not reported	45 (21%)	46 (21%)
Median age, years (range)	70·9 (28·0–88·0)	70·9 (33·2–86·7)
Eastern Cooperative Oncology Group performance status score		
0	105 (48%)	101 (46%)
1	113 (52%)	121 (55%)
Previous asbestos exposure*		
No	87 (40%)	98 (44%)
Yes	130 (60%)	124 (56%)
Histological subtypes†		
Epithelioid	168 (77%)	174 (78%)
Mixed or biphasic	27 (12%)	35 (16%)
Sarcomatoid	21 (10%)	10 (5%)
Other	2 (1%)	3 (1%)
European Organisation for Research and Treatment of Cancer prognostic score[19]		
≤1·27	76 (35%)	77 (35%)
>1·27	141 (65%)	145 (65%)
Unknown	1 (0%)	0
Programmed cell death ligand 1‡ ≥1 cutoff		
Positive	132 (61%)	131 (59%)
Negative	63 (29%)	70 (32%)
Unknown	6 (3%)	7 (3%)
Not done	17 (8%)	14 (6%)
Median months from first histological diagnosis to random assignment, (range); (IQR)	1·8 (0·49–169·0); (1·3–2·8)	1·8 (0·26–73·4); (1·4–2·5)
Previous smoking history	116 (53%)	129 (58%)
Previous major surgery	24 (11%)	17 (8%)
Previous radiation	16 (7%)	9 (4%)
Previous adjuvant or neoadjuvant chemotherapy	9 (4%)	3 (1%)

Data are n (%) unless otherwise specified. *As reported by the investigator. †Baseline information provided by site; does not include revision after central pathology review. ‡Estimated using Combined Positive Score method.

Table 1: **Patient characteristics**

dropped out early) over 34 months with 31 months of follow-up. With an estimated progression-free survival of 7 months in the chemotherapy alone arm, the trial would have a power of 90% to show a hazard ratio for progression or death of 0·70, based on a minimum of 376 events. The power for objective response rate testing at a two-sided 0·015 level is approximately 88% to detect a 17% difference between an underlying objective response rate of 43% with chemotherapy alone and 60% with chemotherapy plus pembrolizumab.

One interim analysis for overall survival was planned 11 months after the last patient was randomly assigned, with early termination considered if the two-sided p value of the stratified log-rank test was significant using the methods of Lan-DeMets with O'Brien-Fleming type boundaries. To control for multiplicity, the graphical method of Maurer and Bretz[17] was used to strictly control the type 1 error at a two-sided 0·05. Full details of the statistical analyses plan can be found in the protocol. All reported p values are two-sided.

The interim analysis was done in November, 2021, when 279 deaths had occurred. The data monitoring committee recommended the study continue to its planned final analysis. Based on a generalisation of the Lan-DeMets error spending function approach using an O'Brien-Fleming stopping boundary to reject the null hypothesis, controlling for a two-sided alpha of 5% at the end of the study when 334 events were observed, the nominal significance level to reject the null hypothesis was 0·02838 at the interim analysis and 0·04188 at the final analysis for overall survival for a two-sided stratified log-rank test among all randomly assigned patients. The actual boundary used for the final analysis of overall survival was two-sided 0·0409 because there were 342 events at the data cutoff for final analysis.

An exploratory analysis of restricted mean survival time (RMST) was done as the effect in overall survival appeared to be delayed as noted in previous publications of immunotherapy.[18] RMST is defined as the area under the survival curve up to a specific timepoint and is considered a descriptive measure as an alternative to median overall survival, and can provide an accurate measure of trial-based survival capturing tail or delayed treatment effect.

Patients who had had at least one follow-up quality of life assessment after baseline were included in the analysis of quality of life. Times to deterioration (a 10-point increase from the baseline score) for cough, dyspnoea, and chest pain were the primary endpoints for the analysis and were compared between two treatment groups by the log-rank test, with adjustment by the Hochberg method for the comparison of multiple endpoints. Cross-sectional analysis was also done by calculating the mean of change scores from baseline at each timepoint for each treatment group with comparisons by Wilcoxon test.

Role of the funding source

CCTG collected the data, controlled the database, performed all analyses presented in this paper, and was responsible for writing the paper. Merck provided pembrolizumab and partial funding for the trial, reviewed the protocol, independently confirmed the results after CCTG completed the final analysis, and reviewed and provided comments on this paper.

Results

Between Jan 31, 2017, and Sept 4, 2020, 440 patients were enrolled and randomly assigned to chemotherapy (218 patients) or chemotherapy plus pembrolizumab (222 patients; figure 1). 137 patients were enrolled in

Canada, 212 were enrolled in Italy, and 91 were enrolled in France. Details of any patients who were assessed but not enrolled are maintained only at the centre on screening logs and are not included here. Baseline characteristics were balanced between the groups (table 1) although the proportion of patients older than 65 years was higher in the pembrolizumab group than in the chemotherapy only group (81% versus 72%). 333 (76 %) of 440 patients were male, 347 (79%) were White, and median age was 71 years (IQR 66–75). Seven patients were enrolled to the chemotherapy group and immediately withdrew consent or were lost to follow-up and were never treated; 433 patients (211 in the chemotherapy arm, and 222 in the pembrolizumab arm) were included in the safety analyses. Data cutoff was Sept 16, 2022; 342 patients had died; the median follow-up was 16·16 months (0·033–60·19 months, IQR 8·3–27·8). At data cutoff, 98 patients were still alive (55 in the pembrolizumab group and 43 in the chemotherapy group). Central pathology review was done for 120 patients. After random assignment, histology was revised in only 14 patients (88% concordance). The median number of chemotherapy cycles was 6 for both groups (IQR 4–6, range 1–6 for the pembrolizumab group; IQR 5–6, range 1–8 for the chemotherapy group) while the median number of cycles of pembrolizumab was 10 (IQR 5–18, range 1–36; table 2). Dose modifications and median dose-intensity of chemotherapy drugs was similar in both groups; 162 (73%) of 222 patients receiving pembrolizumab had a delay in administration of pembrolizumab (most common reason administrative or scheduling). The most common reason for pembrolizumab discontinuation was disease progression. The most common reason for chemotherapy discontinuation in both groups was completion of treatment. 116 (55%) of 211 patients in the chemotherapy group and 115 (52%) of 222 patients in the pembrolizumab group received post-protocol chemotherapy. 59 (28%) of 211 patients in the chemotherapy group and 17 (8%) of 222 patients in the pembrolizumab group received subsequent immunotherapy (appendix p 6).

With 342 deaths (175 in the chemotherapy group and 167 in the pembrolizumab group), the hazard ratio for death was 0·79 (95 % CI 0·64–0·98, stratified log-rank p=0·0324). Median survival was 17·3 months (95% CI 14·4–21·3) in the pembrolizumab group and 16·1 months (13·1–18·2) in the chemotherapy group (figure 2A). The proportion of patients alive at 2 years and 3 years was 39% (95% CI 33–46%) at 2 years and 25% (20–33%) at 3 years in the pembrolizumab group and 33% (27–40%) at 2 years and 17% (13–24%) at 3 years in the chemotherapy group. The effect on overall survival appeared to be delayed (figure 2A). 54-month restricted mean overall survival was 20 months (95% CI 17·9–22·0) for the chemotherapy group and 23·4 months (21·0–25·8) for the pembrolizumab group in exploratory analyses.

	Chemotherapy (n=211)	Chemotherapy plus pembrolizumab (n=222)
Median number of cycles (range)		
Chemotherapy	6 (1–8*); IQR (5–6)	6 (1–6); IQR (4–6)
Pembrolizumab	NA	10 (1–36); IQR (5–18)
Platinum used		
Cisplatin only	100 (47%)	94 (42%)
Carboplatin only	84 (40%)	96 (43%)
Cisplatin then carboplatin	27 (13%)†	32 (14%)†
Dose delays		
Cisplatin	61 (29%)	60 (27%)
Carboplatin	73 (35%)	78 (35%)
Pemetrexed	129 (61%)	135 (61%)
Pembrolizumab	NA	163 (73%)‡
Dose reductions		
Cisplatin	32 (15%)	37 (17%)
Carboplatin	35 (17%)	44 (20%)
Pemetrexed	51 (24%)	63 (28%)
Discontinuation due to adverse events		
Cisplatin	35 (17%)	36 (16%)
Carboplatin	8 (4%)	29 (13%)
Either platinum	42 (20%)	58 (26%)
Pemetrexed	14 (7%)	36 (16%)
Pembrolizumab	NA	36 (16%)

Data are n (%). NA=not applicable. *One patient had 8 cycles due to patient and investigator request. †The most common reason for switch was adverse event related to cisplatin. ‡Most common were administrative, COVID-19, neutropenia, and patient request.

Table 2: **Treatment delivery and dose modifications**

Hazard ratios favoured the pembrolizumab group in most prespecified subgroups including PD-L1 status (figure 2B). Median survival in patients with non-epithelioid histology was 12·3 months (95% CI 8·7–21·2) in the pembrolizumab group versus 8·2 months (5·9–10·8) in the chemotherapy group (hazard ratio 0·57, 95% CI 0·36–0·89). Median survival in the epithelioid subtype was 19·8 months (95% CI 16·0–22·2) in the pembrolizumab group versus 18·2 months (16·0–20·4) in the chemotherapy group (hazard ratio 0·89, 95% CI 0·70–1·13; figure 2C, D; appendix p 18). Estimated survival rate for those with epithelioid histology was 40% (95 % CI 33–48%) at 2 years and 26% (19–34%) at 3 years in the pembrolizumab group, and 37% (30–45%) at 2 years and 20% (14–28%) at 3 years in the chemotherapy group. For patients with non-epithelioid histology, estimated survival rate was 35% (95% CI 23–52%) at 2 years and 23% (13–40%) at 3 years in the pembrolizumab group versus 19% (11–35%) at 2 years and 7% (2–21%) at 3 years in the chemotherapy group. Post-hoc exploratory analyses were done to generate hypotheses in the subset of patients with epithelioid histology. Objective response rate per BICR and mRECIST was 67% (117 of 175 patients)

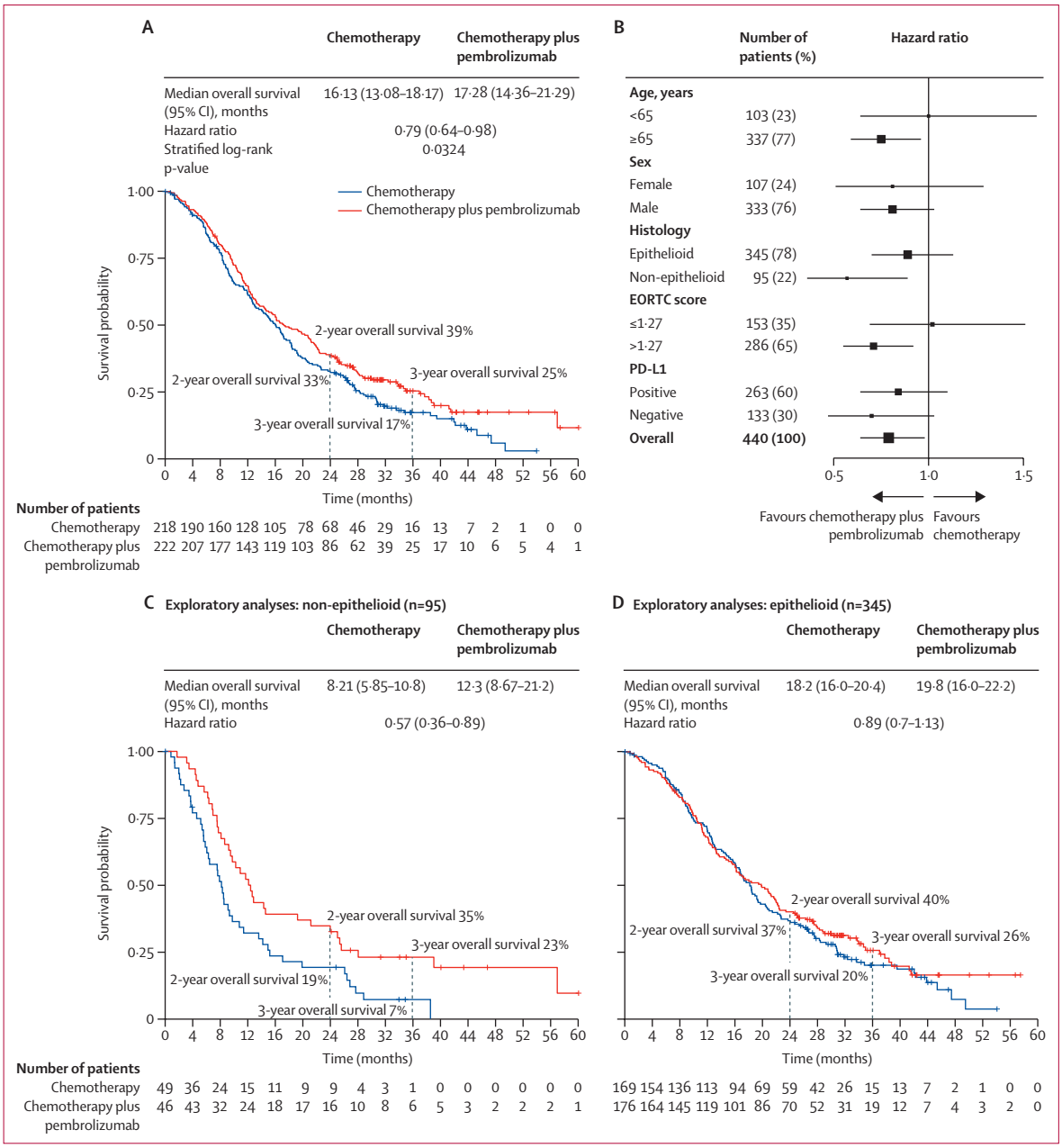

Figure 2: **Overall survival**

(A) All patients. Stratified log-rank uses histology reported at random assignment. (B) Major subgroups. (C) Exploratory analysis in non-epithelioid histology. Central histology was used when available. (D) Exploratory analysis in epithelioid histology. Central histology was used when available. EORTC=European Organisation for Research and Treatment of Cancer. PD-L1=programmed cell death ligand 1.

in the pembrolizumab group and 47% (77 of 164 patients) in the chemotherapy group (two-sample proportion test p value 0·0003). In addition, trends for better survival outcomes with pembrolizumab were observed for younger patients and those that had PD-L1-negative pleural mesothelioma (appendix pp 20–21).

With 363 events of disease progression or death (171 [78·4%] of 218 patients in the chemotherapy group and 192 [86·5%] of 222 patients in the pembrolizumab group), the hazard ratio for progression or death was 0·80 (95% CI 0·65–0·99, stratified log rank p=0·0372). Median progression-free survival was 7·13 months (95% CI 6·9–8·1) in the pembrolizumab group and 7·16 months (6·8–7·7) with chemotherapy alone. 1-year progression-free survival rate was 26% (95% CI 21–33%) in the pembrolizumab group and 17% (95% CI 12–23%) in the chemotherapy group (figure 3A). Results for progression-free survival were similar when investigator-determined by

mRECIST or iRECIST (data not shown). Hazard ratios favoured the pembrolizumab group in most prespecified subgroups (figure 3B). In the subgroup with non-epithelioid histology, median progression-free survival was 6·9 months (95% CI 4·5–9·7) in the pembrolizumab arm and 4·5 months (4·0–6·4) in the chemotherapy group with a hazard ratio of 0·48 (95% CI 0·3–0·8; figure 3C). In patients with epithelioid histology, median progression-free survival was 7·13 months (95% CI 6·9–8·1) in the pembrolizumab group and 7·39 months (7·0–8·4) in the chemotherapy group (hazard ratio for progression or death 0·93, 95% CI 0·7–1·2; figure 3D).

Objective response rate was 62% (95% CI 55–68%) in the pembrolizumab arm and 38% (32–45%) for chemotherapy alone (odds ratio for response 2·70, 95% CI 1·8–4·0; stratified p<0·0001, table 3, appendix p 19). Median duration was 5·8 months (95% CI 5·5–7·0, range 0·03–38·9; IQR 3·6–10·7) for the pembrolizumab group

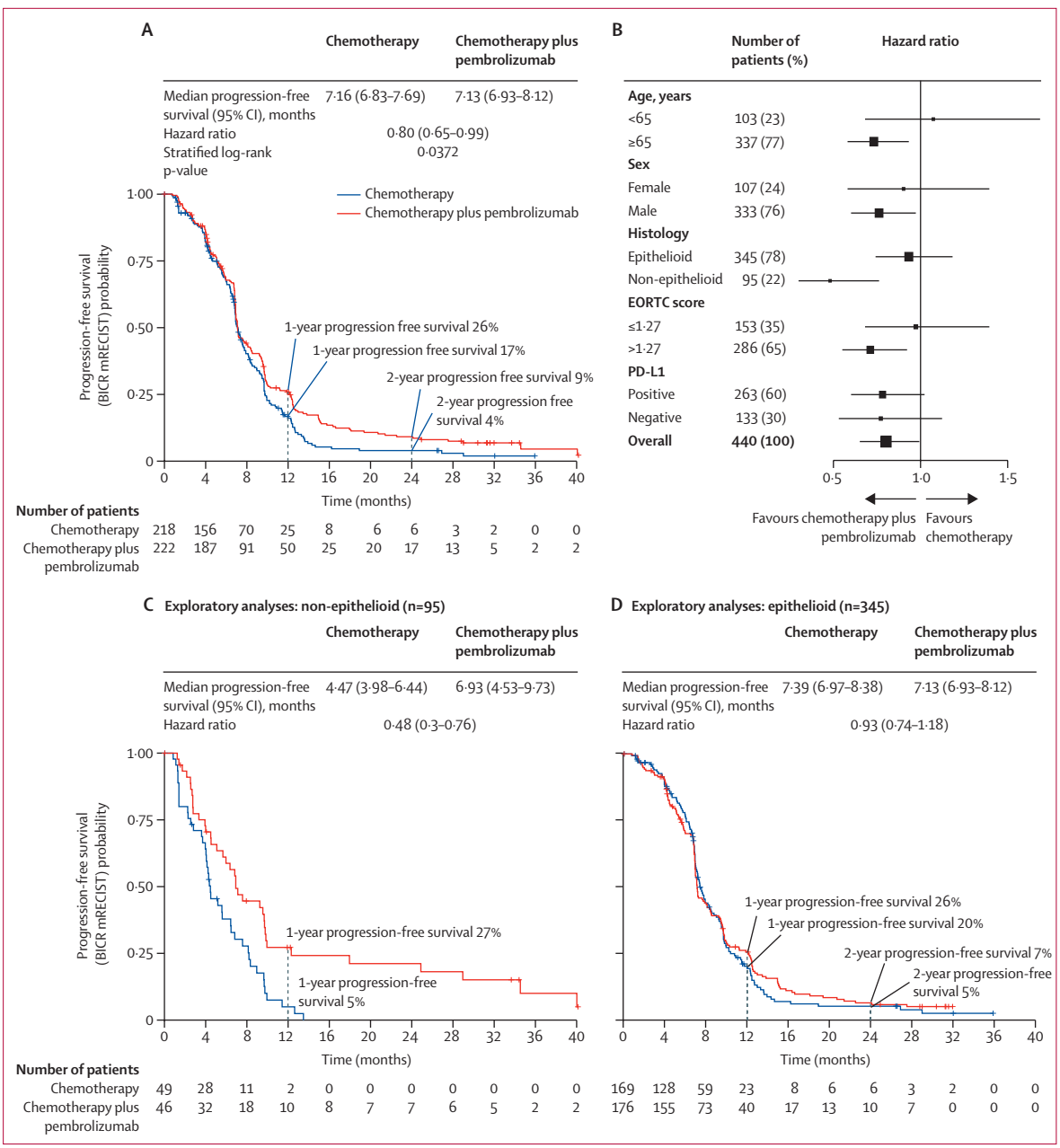

Figure 3: **Progression-free survival**
(A) All patients. (B) Major subgroups. (C) Exploratory analysis in non-epithelioid histology. Central histology was used when available. (D) Exploratory analysis in epithelioid histology. Central histology was used when available. BICR mRECIST=blinded independent central review modified Response Evaluation Criteria in Solid Tumours. EORTC=European Organisation for Research and Treatment of Cancer. PD-L1=programmed cell death ligand 1.

	Chemotherapy alone (n=218)	Chemotherapy plus pembrolizumab (n=222)	p value
Complete response	0	2 (1%)	p<0·0001*; odds ratio 2·7 (95% CI 1·8–4·0)
Partial response	83 (38%)	136 (61%)	..
Stable disease or neither complete response nor progressive disease	103 (47%)	70 (32%)	..
Disease progression	11 (5%)	9 (4%)	..
Inevaluable			
Not assessed	13 (6%)	3 (1%)	..
Baseline images not available	8 (4%)	2 (1%)	..
Duration of complete or partial response, months			
Median (95% CI)	5·5 (4·2–6·0)	5·8 (5·5–7·0)	p=0·185
IQR	3·2–9·4	3·6–10·7	..
Range	0·03–25·1	0·03–38·9	..

Data are n (%) unless otherwise specified. *p value based on comparison of proportions of patients with either complete response or partial response as best response.

Table 3: **Best overall response as assessed by blinded independent central review, using mRECIST 1.1**

	Chemotherapy alone (n=211)			Chemotherapy plus pembrolizumab (n=222)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any	141 (67%)	31 (15%)	1 (<1%)	138 (65%)	50 (23%)	10 (5%)
Anaemia	0	0	0	0	4 (2%)	1 (<1%)
Anorexia	36 (17%)	2 (1%)	0	38 (17%)	0	0
Constipation	27 (13%)	0	0	36 (16%)	0	0
Diarrhoea	18 (9%)	3 (1%)	0	48 (22%)	3 (1%)	0
Dysgeusia	27 (13%)	0	0	26 (12%)	0	0
Fatigue	100 (47%)	12 (6%)	0	97 (44%)	15 (7%)	0
Febrile neutropenia	0	2 (1%)	0	0	8 (4%)	3 (1%)
Mucositis oral	32 (15%)	2 (1%)	0	42 (19%)	0	0
Nausea	93 (44%)	2 (1%)	0	99 (45%)	10 (5%)	0
Peripheral sensory neuropathy	17 (8%)	0	0	24 (11%)	0	0
Pruritus	7 (3%)	0	0	33 (15%)	0	0
Rash (maculo-papular)	14 (7%)	1 (<1%)	0	28 (13%)	2 (1%)	0
Vomiting	29 (14%)	2 (1%)	0	40 (18%)	3 (1%)	0
Watering eyes	14 (7%)	0	0	26 (12%)	0	0

Data are n (%). Deaths more than 24 h after onset of adverse event are captured as the worst previous grade.

Table 4: **Adverse events related to at least one study drug occurring in 10% or more of patients in either group (or in 2% or more if grade 3 or higher grade) within 30 days of the last dose of study drug**

and 5·5 months (4·2–6·0, range 0·03–25·1; 3·2–9·4) with chemotherapy alone. The median time to onset of response was 2·6 months (IQR 1·3–2·8) in the pembrolizumab group and 2·6 months (1·3–2·9) in the chemotherapy group. In the pembrolizumab group, the response rate in PD-L1 was 64% (95% CI 55–72%) in PD-L1-postive patients and 59% (46–70%) in PD-L1-negative patients (data not shown; prespecified analysis). Investigator-determined response rates were similar to those determined by masked independent central review (data not shown).

Quality of life questionnaire compliance was 97% at baseline and greater than 88% during protocol treatment in both groups but was lower in the pembrolizumab group during follow-up (55% *vs* 86% in the chemotherapy alone group at week 16) because of a longer duration of treatment (up to 2 years every 3 weeks for the pembrolizumab group and then every 12 weeks until progression, compared with 18 weeks for the chemotherapy group then every 12 weeks until progression). A total of 3297 quality of life questionnaires were completed in the pembrolizumab group compared with 1419 in the chemotherapy group. At baseline, quality of life scores were generally balanced, although patients in the pembrolizumab group had worse scores for dyspnoea.

Medians were not reached for any of three quality of life primary endpoints with no statistically significant difference for the time to deterioration with regards to cough (hazard ratio 1·02, 95% CI 0·68–1·55; p=0·91 with Hochberg adjustment), dyspnoea (1·02, 0·69–1·53; p=0·91), or chest pain (1·07, 0·68–1·7; p=0·91).

In cross-sectional analysis, pembrolizumab was associated with less deterioration from baseline in global health status at cycle 6 than was chemotherapy alone (mean change score –1·5 *vs* –5·5, p=0·04) and larger improvement from baseline in pain at cycle 3 (–7·5 *vs* –3·7, p=0·04) and cycle 5 (–9·2 *vs* –3·5, p=0·009) and pain in chest at cycle 4 (–8·7 *vs* 0·63, p<0·001). At week 4 of follow-up, pembrolizumab-containing treatment was associated with larger worsening from baseline in haemoptysis (mean change score 1·1 *vs* 0·5, p=0·04) but less worsening from baseline in hair loss (mean change score 5·5 *vs* 15·0, p<0·001).

217 (98%) of 222 patients in the pembrolizumab group and 200 (95%) of 211 patients in the chemotherapy group reported at least one adverse event, with grade 3 or 4 related events reported in 60 (27%) of 222 patients in the pembrolizumab group and 32 (15%) of 211 patients in the chemotherapy group (table 4; appendix pp 7–10). The most frequently occurring adverse events in both groups were fatigue and nausea. Diarrhoea and skin effects were more common in the pembrolizumab group (table 4). The most frequent potentially immune-mediated toxic effects were skin effects, diarrhoea or colitis, hypothyroidism, joint pain, and pneumonitis (appendix p 7). Myelosuppression was more frequent in the pembrolizumab group with greater need for blood transfusions (25% *vs* 16%), platelet transfusions (5% *vs* 1%) and episodes of febrile neutropenia (5% *vs* 1%; appendix p 10). Adverse events leading to discontinuation of one or more trial therapies occurred in 82 (37%) of 222 patients in the pembrolizumab group (in 16% of patients considered related to pembrolizumab), and in 42 (20%) of 211 in the chemotherapy group (table 5; appendix p 9). Adverse events leading to discontinuation in at least 5% of patients in the pembrolizumab group were increased creatinine or acute kidney injury, fatigue, and anaemia. Only increased creatinine or acute kidney injury was reported in at least 5% of patients in the chemotherapy group. Most of these events were grade 1 or 2; neutropenia (2% in the

chemotherapy group and 3% in the pembrolizumab group); anaemia (3% in the pembrolizumab group), and sepsis (2% in the pembrolizumab group) were the only grade 3 or worse events leading to discontinuation in more than 1% of patients. Hospital admissions occurred in 36% of patients in the pembrolizumab group and 18% of patients in the chemotherapy group but were considered related to at least one protocol drug in only 18% of patients in the pembrolizumab group and 6% of patients in the chemotherapy group and were predominantly during the first 5–6 cycles of protocol treatment in both groups (appendix p 8). There were nine deaths that were considered by the investigator to be related to one or more protocol therapy drugs (appendix p 4). Rates of adverse events reported in an expedited manner, which included serious adverse events, were higher with pembrolizumab (92 [41%] patients in the pembrolizumab group *vs* 38 [18%] patients in the chemotherapy group) but for nine (4%) patients with pembrolizumab these events did not meet the criteria for a serious adverse event (appendix p 8).

	Chemotherapy alone (n=211)		Chemotherapy plus pembrolizumab (n=222)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Discontinued any protocol therapy due to adverse event	42 (20%)	13 (6%)	82 (37%)	37 (17%)
Discontinued any protocol treatment due to adverse event (excluding platinum)	14 (7%)	7 (3%)	62 (28%)	33 (15%)
Discontinued platinum for adverse event	42 (20%)	13 (6%)	58 (26%)	21 (9%)
Death due to adverse event (all causes)	11 (5%)	..	14 (6%)	..
Death due to related adverse event	2 (1%)	..	7 (3%)	..
Death within 24 h of onset of a related adverse event	1 (<1%)	..	2 (1%)	..

Data are n (%).

Table 5: **Adverse events leading to treatment discontinuation or death**

Discussion

In this academic cooperative group designed and conducted phase 3 trial, pembrolizumab added to platinum and pemetrexed chemotherapy significantly improved the primary endpoint of overall survival and other key efficacy outcomes in patients with advanced pleural mesothelioma, with a 21% reduction in the risk of death. The benefit was seen in most prespecified subgroups and was regardless of PD-L1 status. The Kaplan-Meier curve remained above that of chemotherapy alone for its entirety.

Although overall survival was significantly longer with pembrolizumab, median survival improvement was only slightly longer than 1 month. Delayed efficacy outcomes with immunotherapy have been observed in other trials and are biologically plausible. In such instances, others have recommended the use of methods such as RMST, which can capture tail or delayed treatment effect. In exploratory analyses, the mean difference in overall survival was 3·4 months (54-month restricted mean overall survival 20 months [95% CI 17·9–22·0] with chemotherapy and 23·4 months [21·0–25·8) with pembrolizumab).[4,18,20]

Benefit appeared more pronounced in patients with non-epithelioid histology, confirming that immunotherapy is an important component of treatment for these patients, as chemotherapy alone is ineffective. The underlying reason for this differential effect is unclear. One study found high tumour infiltrating lymphocytes to be associated with improved outcomes in sarcomatoid pleural mesothelioma[21] and another study documented differences in expression of immune-related genes in sarcomatoid compared with epithelioid pleural mesothelioma.[22] A four-gene inflammatory score appeared to predict outcomes to immunotherapy in CheckMate 743.[20] The hazard ratios for overall and progression-free survival in the epithelioid group favoured pembrolizumab despite the 95% CIs overlapping one, with an estimated 3-year overall survival of 26%, an absolute increase of 6%, similar to that with nivolumab–ipilimumab (24% and 5% respectively in CheckMate-743).[20] Furthermore, response rates were significantly higher with pembrolizumab in the epithelioid subset (67% *vs* 47%), suggesting that there is a true treatment effect with its addition. We were not able to define a subset of epithelioid patients who did not benefit in exploratory analyses, although trends to better outcomes were observed for younger patients (younger than 70 years) and patients who were PD-L1-negative (appendix pp 20–21). These analyses were not preplanned and are underpowered to detect differences and should be interpreted with caution. Tumour, blood, and images were banked for all patients, and further correlative studies are planned to delineate these observations.

Importantly, the rate of progressive disease as a best response to platinum–pemetrexed–pembrolizumab was only 4%, substantially lower than the 18% reported for nivolumab–ipilimumab. This reduction in early progression events is reflected in the shape of the Kaplan-Meier curve for progression-free-survival: the curve for the pembrolizumab group is almost always above that for the chemotherapy group, with a greater separation of the curves at approximately 9 months and a statistically significant hazard ratio of 0·80. This lower rate of early progression was also reflected in the significantly improved objective response rate seen with the addition of pembrolizumab, regardless of histological results. Responses occurred rapidly, an important consideration in patients with a heavy tumour burden or disease-related symptoms. This might be particularly relevant if used in a [neo]adjuvant approach.

During the conduct of IND227, the results of other trials of immunotherapy in pleural mesothelioma were published, and this might have influenced patient and investigator decision making in this open-label trial, including whether to participate once randomly assigned

and choice of second-line treatments. Immunotherapy agents have activity in the post-chemotherapy setting in pleural mesothelioma[23,24] and, while a similar proportion of patients in both groups went on to receive subsequent chemotherapy, 28% of patients in the chemotherapy alone group (*vs* 8% in the pembrolizumab group) went on to receive immunotherapy, higher than the 20% reported for the chemotherapy group in CheckMate-743, and higher than in our phase 2 study (19% in the chemotherapy group *vs* 11% in the pembrolizumab group).[9] The chemotherapy group in our trial had a median survival of 16·1 months, higher than that seen in other phase 3 trials in patients with mesothelioma,[2,4] despite similar baseline characteristics.

In CheckMate-743, a larger proportion of patients were PD-L1-positive than in our trial, possibly reflecting differences in the testing and scoring of PD-L1 status. Combined Positive Score is used with pembrolizumab for all tumour types except non-small-cell lung cancer. The benefit of immunotherapy in both trials was seen regardless of PD-L1 status, although the magnitude was greater in our trial in the PD-L1-negative subgroup, while the PD-L1-positive and PD-L1-negative subgroups had similar outcomes to nivolumab–ipilimumab. As in CheckMate-743, patients in the chemotherapy group who were PD-L1-negative had numerically better survival than those who were PD-L1-positive, suggesting a possible prognostic role; others have also noted the possibility of worse survival in patients with epithelioid pleural mesothelioma that had high PD-L1 staining.[25] The prognostic and predictive role of PD-L1 expression in pleural mesothelioma requires further investigation[26] and consideration should be given to stratifying for PD-L1 status in future studies in pleural mesothelioma.

The addition of pembrolizumab increased both treatment duration (up to 104 weeks *vs* 18 weeks) and adverse events. Related grade 3 or 4 adverse events occurred at a similar rate to that reported in KEYNOTE-189, the phase 3 trial of this regimen in non-small-cell lung cancer,[5] despite the higher median age of patients enrolled to the current trial (71 *vs* 65 years). Rates of hospital admission were also higher. Consistent with what was observed in KEYNOTE-189, the addition of pembrolizumab to platinum-pemetrexed chemotherapy increased the incidence of febrile neutropenia and grade 3 or greater diarrhoea or colitis and acute kidney injury. The rate of grade 3 or greater pneumonitis was only 2% in the pembrolizumab group. Rates of grade 3 or greater toxic effects leading to discontinuation of any component of study therapy in both groups were similar to those reported in CheckMate-743 and in KEYNOTE-189. The rate of an adverse event of any causality leading to death in the pembrolizumab group was similar to that seen in KEYNOTE-189. Overall, the pembrolizumab containing regimen was tolerable in this patient population and no new safety signals were observed.

Quality of life analyses did not reveal a delay in the time to deterioration in symptoms such as cough and dyspnoea or chest pain. However, the addition of pembrolizumab was associated with improvement in pain and less deterioration in global health status. Quality of life analyses did not demonstrate a detriment to the addition of pembrolizumab despite the increased toxic effects. More detailed analyses of quality of life data will be the subject of a separate report.

Our study had limitations. The absence of masking might impact adverse event attribution and patient and investigator decision making regarding continuation of therapy. Patients enrolled to the pembrolizumab group were seen more frequently, had more laboratory tests, and completed quality of life questionnaires more frequently than those in the chemotherapy group. Patients in the pembrolizumab group also had many laboratory abnormalities reported as adverse events if felt immune-mediated, and adverse events requiring steroid treatment were reported in an expedited fashion; all these factors would favour the chemotherapy group for adverse event reporting, early unscheduled imaging assessment, and early detection of disease progression.

There are two ongoing phase 3 trials that will add to the data on the role of immunotherapy in first-line chemotherapy in advanced pleural mesothelioma: DREAM3R (NCT04334759) is investigating the addition of durvalumab to standard platinum-pemetrexed chemotherapy and has nivolumab–ipilimumab as a choice in the control group, and BEAT-MESO (NCT03762018) is assessing the addition of the PD-L1 inhibitor atezolizumab to platinum, pemetrexed, and bevacizumab. Moving forward, more understanding is required to determine which patients with epithelioid histology derive benefit from immunotherapy before embarking on additional phase 3 trials, and thus the correlative exploratory endpoints are underway. However, we believe that prevention of pleural mesothelioma through international measures to ban all asbestos use is preferable to treating established disease and strongly support such initiatives.

In conclusion, the addition of pembrolizumab to platinum-pemetrexed was a tolerable regimen that did not lead to a detriment in quality of life despite increased toxicity and that resulted in improved overall survival, progression-free survival, and objective response rates compared with platinum and pemetrexed chemotherapy, regardless of PD-L1 expression. This familiar regimen represents a new treatment option for patients with advanced pleural mesothelioma.

Contributors

QC, FP, PB, GZ, DT, SAL, LS, CWL, and NL designed the study. MCP, PG, JS, PB-W, and LS were responsible for conduct and data management. QC, LG, FG, GLR, MF, MM, PB, AM, FLC, GLC, DED, PAZ, MP, JRG, MLS, CG, GZ, XQ, VW, PG, SD, CWL, NL, AS, and SAL were responsible for patient enrolment. WT, DT, PB-W, and LS analysed the data. SAL and LS wrote the manuscript. QC, FP, LG, WT, MCP, FG, GLR, MF, MM, PB, AM, FLC, GLC, DED, PAZ, MP, JRG, MLS, CG, GZ, XQ, VW, PG, SD, DT, CWL, NL, JS, PB-W, YL, SL, M-ST, and AS reviewed the article. All authors had access to the Statistical

Analysis Report. WT, DT, LS, PB-W, and YL had access to and verified the underlying data. QC, FP, LG, WT, PB, SL, and LS had responsibility for the decision to submit for publication.

Declaration of interests

MP has received grants for research to institution from AstraZeneca and Roche; payment for educational events from Astellas, Pfizer, and AstraZeneca; and received drugs for research from Roche and AstraZeneca. GLR received consulting fees from MSD, BMS, AstraZeneca, Roche, Novartis, Lilly, Amgen, Sanofi, Pfizer, Takeda, GSK, and Italfarmaco; received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from MSD, BMS, AstraZeneca, Roche, Novartis, Lilly, Amgen, Sanofi, Pfizer, Takeda, GSK, and Italfarmaco; received support for attending meetings or travel from Roche, MSD, BMS, and Amgen; has participated on a Data Safety Monitoring Board or Advisory Board for MSD, BMS, AstraZeneca, Roche, Novartis, Lilly, Amgen, Sanofi, Pfizer, Takeda, GSK, and Italfarmaco; and has other financial or non-financial interests from MSD, BMS, AstraZeneca, Roche, Novartis, Amgen, Sanofi, Pfizer, Takeda, and GSK. YL holds stock or stock options from Merck. SL received consulting fees from Lilly, MSD, Sanofi, and AbbVie and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AstraZeneca. AS received grants or contracts (payments to institution) from MSD, BMS, AstraZeneca, Roche, and Amphera; received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AstraZeneca, BMS, MSD, and Roche; received support for attending meetings or travel from AstraZeneca, BMS, MSD, and Roche; and participated on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, BMS, MSD, and Roche. MF received consulting fees from AstraZeneca, BMS, and Takeda and received honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AstraZeneca, BMS, and Takeda. 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DED has received research grants from CIHR, CancerCare Manitoba Foundation, and AstraZeneca; received research grants and salary awards from Manitoba Medical Services Foundation; received payment for educational events from Roche, Boehringer Ingelheim, and BMS; served on an advisory board for Merck, AstraZeneca, Pfizer, Jazz Pharmaceuticals, and Novartis; has acted in a leadership or fiduciary role in a board, society, committee or advocacy group, paid or unpaid for Lung Cancer Canada (Medical Advisory Committee), Canadian Association of Medical Oncologists (Chair, Fellowship Committee), and Canadian Cancer Trials Group (Chair, Small Cell Lung Cancer Working Group); and received equipment, materials, drugs, medical writing, gifts, or other services from AstraZeneca (Medical writing assistance on a small-cell lung cancer paper). QC has received grants to institution from Alkermes, Amgen, Apollomics, Astellas, AstraZeneca, Bicycle, BMS, Conjupro, Decipher, Eli Lilly, Esperas, Exactis, GSK, iTEOS, Kelun, Merck, Mirati, Nuvalent, Ocellaris, Pfizer, Rvolution Medicines, Roche, SeaGen, Spectrum, and Treadwell; received consulting fees from Amgen, AnHeart, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, GSK, Jazz Pharmaceuticals, Janssen, Merck and Co, Novartis, Pfizer, Roche, and Takeda; received payment for speaking or presentations from AstraZeneca; acted on an advisory board for Amgen, AnHeart, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, GSK, Jazz Pharmaceuticals, Janssen, Merck and Co, Novartis, Pfizer, Roche, and Takeda; acted on a Data Safety Monitoring Committee for Merck and KGaA; and occupied a leadership or fiduciary role in a board, society, committee, or advocacy group, paid or unpaid for Lung Cancer Canada and Canadian Mesothelioma Foundation. CWL has served as a member of the Board of Directors for Canadian Mesothelioma Foundation. LG received grants or contracts to institution from BMS, MSD, Takeda, Pfizer, Roche, Amgen, Sanofi, Janssen, Lilly, and Novartis; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from BMS, MSD, Takeda, Pfizer, Roche, Amgen, Sanofi, Janssen, Lilly, and Novartis; received support for attending meetings or travel from Pfizer, MSD, AstraZeneca, and Takeda; and participated on a Data Safety Monitoring Board or Advisory Board for Inhatarget Therapeutics. XQ received support for attending meetings or travel from Pfizer (ESMO 2022), Janssen (ASCO 2022), and Sanofi (ASCO 2023). 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Amgen, Sanofi, Eli Lilly, GSK, Roche, Takeda, Boehringer Ingelheim, AstraZeneca, and Pfizer. FP received partial funding to institution and experimental study drug from Pfizer; received financial support to institution from Roche, Bayer, AstraZeneca, Pfizer, Incyte, Tesaro/GSK, and Merck; and received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Bayer, Pierre Fabre, AstraZeneca, Incyte, Ipsen, Clovis, Astellas, Sanofi, Roche, and Pfizer. All other authors declare no competing interests.

Data sharing

CCTG has a formal data sharing policy and process found at www.ctg.queensu.ca/docs/public/policies/DataSharingandAccessPolicy.pdf. Protocol, analysis plan, and informed consent documents will be made available with publication.

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