Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial

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Summary

Background Pembrolizumab monotherapy showed durable antitumour activity and manageable safety in patients with metastatic triple-negative breast cancer. We aimed to examine whether the addition of pembrolizumab would enhance the antitumour activity of chemotherapy in patients with metastatic triple-negative breast cancer.

Methods In this randomised, placebo-controlled, double-blind, phase 3 trial, done in 209 sites in 29 countries, we randomly assigned patients 2:1 with untreated locally recurrent inoperable or metastatic triple-negative breast cancer using a block method (block size of six) and an interactive voice-response system with integrated web-response to pembrolizumab (200 mg) every 3 weeks plus chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin) or placebo plus chemotherapy. Randomisation was stratified by type of on-study chemotherapy (taxane or gemcitabine–carboplatin), PD-L1 expression at baseline (combined positive score [CPS] ≥1 or <1), and previous treatment with the same class of chemotherapy in the neoadjuvant or adjuvant setting (yes or no). Eligibility criteria included age at least 18 years, centrally confirmed triple-negative breast cancer; at least one measurable lesion; provision of a newly obtained tumour sample for determination of triple-negative breast cancer status and PD-L1 status by immunohistochemistry at a central laboratory; an Eastern Cooperative Oncology Group performance status score 0 or 1; and adequate organ function. The sponsor, investigators, other study site staff (except for the unmasked pharmacist), and patients were masked to pembrolizumab versus saline placebo administration. In addition, the sponsor, the investigators, other study site staff, and patients were masked to patient-level tumour PD-L1 biomarker results. Dual primary efficacy endpoints were progression-free survival and overall survival assessed in the PD-L1 CPS of 10 or more, CPS of 1 or more, and intention-to-treat populations. The definitive assessment of progression-free survival was done at this interim analysis; follow-up to assess overall survival is continuing. For progression-free survival, a hierarchical testing strategy was used, such that testing was done first in patients with CPS of 10 or more (prespecified statistical criterion was $\alpha=0\cdot00411$ at this interim analysis), then in patients with CPS of 1 or more ($\alpha=0\cdot00111$ at this interim analysis, with partial alpha from progression-free survival in patients with CPS of 10 or more passed over), and finally in the intention-to-treat population ($\alpha=0\cdot00111$ at this interim analysis). This study is registered with ClinicalTrials.gov, NCT02819518, and is ongoing.

Findings Between Jan 9, 2017, and June 12, 2018, of 1372 patients screened, 847 were randomly assigned to treatment, with 566 patients in the pembrolizumab–chemotherapy group and 281 patients in the placebo–chemotherapy group. At the second interim analysis (data cutoff, Dec 11, 2019), median follow-up was 25·9 months (IQR 22·8–29·9) in the pembrolizumab–chemotherapy group and 26·3 months (22·7–29·7) in the placebo–chemotherapy group. Among patients with CPS of 10 or more, median progression-free survival was 9·7 months with pembrolizumab–chemotherapy and 5·6 months with placebo–chemotherapy (hazard ratio [HR] for progression or death, 0·65, 95% CI 0·49–0·86; one-sided p=0·0012 [primary objective met]). Median progression-free survival was 7·6 and 5·6 months (HR, 0·74, 0·61–0·90; one-sided p=0·0014 [not significant]) among patients with CPS of 1 or more and 7·5 and 5·6 months (HR, 0·82, 0·69–0·97 [not tested]) among the intention-to-treat population. The pembrolizumab treatment effect increased with PD-L1 enrichment. Grade 3–5 treatment-related adverse event rates were 68% in the pembrolizumab–chemotherapy group and 67% in the placebo–chemotherapy group, including death in <1% in the pembrolizumab–chemotherapy group and 0% in the placebo–chemotherapy group.

Interpretation Pembrolizumab–chemotherapy showed a significant and clinically meaningful improvement in progression-free survival versus placebo–chemotherapy among patients with metastatic triple-negative breast cancer with CPS of 10 or more. These findings suggest a role for the addition of pembrolizumab to standard chemotherapy for the first-line treatment of metastatic triple-negative breast cancer.

Lancet 2020; 396: 1817–28

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See Online for appendix

Funding Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc.

Introduction

Treatment of triple-negative breast cancer is challenging, as these tumours lack targets for therapeutic intervention. Compared with other breast cancer subtypes, triple-negative breast cancer behaves more aggressively, with earlier relapses and poorer survival outcomes.[1,2] Cytotoxic chemotherapy, including taxane or platinum, remains the standard systemic treatment for most patients;[3] however, their tumours become rapidly resistant to chemotherapy.[2,4] These data underscore the need for improved therapeutic approaches.

Intact immune surveillance is important for controlling cancer growth.[5] The PD-1 receptor-ligand interaction is a major pathway used by tumours to suppress active T-cell-mediated immune response.[6,7] The anti-PD-1 monoclonal antibody pembrolizumab has shown promising anti-tumour activity and an acceptable safety profile as monotherapy across many tumour types, including metastatic triple-negative breast cancer.[8–11] The immunomodulatory properties of chemotherapy suggest that combining pembrolizumab with chemotherapy might enhance anti-tumour activity.[12] Several clinical trials in patients with breast cancer show that combination regimens with pembrolizumab plus chemotherapy offer promising anti-tumour activity without a substantial increase in serious toxicity.[13–15] In this phase 3 KEYNOTE-355 trial, we aimed to compare the efficacy and safety of pembrolizumab plus chemotherapy with placebo plus chemotherapy in patients with previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer.

Methods

Study design and participants

KEYNOTE-355 is a randomised, double-blind, placebo-controlled trial done in 209 sites in 29 countries in Europe, North America, Asia, Australia and New Zealand, and Latin America. Eligibility criteria included age at least 18 years, centrally confirmed triple-negative breast cancer as defined by American Society of Clinical Oncology–College of American Pathologists guidelines;[16,17] at least one measurable lesion based on Response Evaluation Criteria in Advanced Solid Tumors version 1.1 as assessed by the investigator; provision of a newly obtained tumour sample from a locally recurrent inoperable or metastatic

Research in context

Evidence before this study

We searched PubMed for clinical trials published in English between Jan 1, 2010, and Jan 1, 2020, assessing checkpoint blockade in patients with metastatic triple-negative breast cancer, using the search terms "metastatic", "triple-negative breast cancer", "checkpoint blockade", and "pembrolizumab". We found that pembrolizumab monotherapy showed durable antitumour activity and had a manageable safety profile in patients with metastatic triple-negative breast cancer in the KEYNOTE-012, KEYNOTE-086, and KEYNOTE-119 clinical trials.

Added value of this study

In KEYNOTE-355, we examined whether the addition of pembrolizumab would enhance the antitumour activity of chemotherapy, including taxanes and a non-taxane platinum-based regimen, in patients with previously untreated metastatic triple-negative breast cancer. The results show that pembrolizumab–chemotherapy resulted in a significant and clinically meaningful improvement in progression-free survival compared with chemotherapy alone in patients with a combined positive score (CPS) of 10 or more, as indicated by a median progression–free survival that was 4·1 months longer (9·7 months with pembrolizumab–chemotherapy as compared with 5·6 months with placebo–chemotherapy; hazard ratio for progression or death, 0·65). On the basis of these results, the trial met its protocol-specified primary objective. Although the boundary for declaring a significant progression-free survival benefit of pembrolizumab-chemotherapy in patients with CPS of 1 or more was not crossed, and formal testing in the intention-to-treat population was not done owing to the prespecified hierarchical testing strategy, pembrolizumab–chemotherapy showed numerical increases in median progression-free survival in both populations. Further, pembrolizumab showed improved treatment effects on progression-free survival over the chemotherapy control with PD-L1 enrichment. The safety profile of pembrolizumab was consistent with that reported in previous studies, and no new safety signals were observed.

Implications of all the available evidence

To our knowledge, KEYNOTE-355 is the first reported phase 3 study that evaluated an anti-PD-1 monoclonal antibody for the treatment of patients with previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer. The findings suggest a role for the addition of pembrolizumab to standard chemotherapy for the first-line treatment of metastatic triple-negative breast cancer. These results are consistent with those of the phase 3 IMPASSION130 trial, which showed significantly improved median progression-free survival with the PD-L1 inhibitor atezolizumab plus nab-paclitaxel versus nab-paclitaxel alone for first-line treatment of metastatic triple-negative breast cancer; however, our study extends observations with pembrolizumab to include several standard chemotherapy partners as well as patients with early recurrences, thereby offering more treatment options to a wider patient population with a high unmet medical need.

site for determination of triple-negative breast cancer status and PD-L1 status by immunohistochemistry at a central laboratory (an archival tumour sample was used with permission from the study sponsor if a new tumour biopsy was not obtainable); an Eastern Cooperative Oncology Group performance status score[18] 0 or 1 (based on a 5-point system in which higher numbers reflect greater disability); and adequate organ function. Full inclusion and exclusion criteria are included in the trial protocol. Patients with de novo metastatic triple-negative breast cancer were eligible for the study. Patients who completed treatment for stage I–III breast cancer were eligible if at least 6 months had elapsed between completion of treatment with curative intent (eg, date of primary breast tumour surgery or date of last adjuvant chemotherapy administration including capecitabine, whichever occurred last) and the first documented (by biopsy or imaging) local or distant disease recurrence; adjuvant radiation therapy was excluded from the 6-month interval requirement. Patients who received taxane, gemcitabine, or platinum agents in the neoadjuvant or adjuvant setting could be treated with the same class of chemotherapy (taxane or gemcitabine–carboplatin) if at least 12 months had elapsed between the completion of treatment with curative intent and the first documented local or distant disease recurrence.

Exclusion criteria included treatment with an investigational agent within 4 weeks before randomisation;

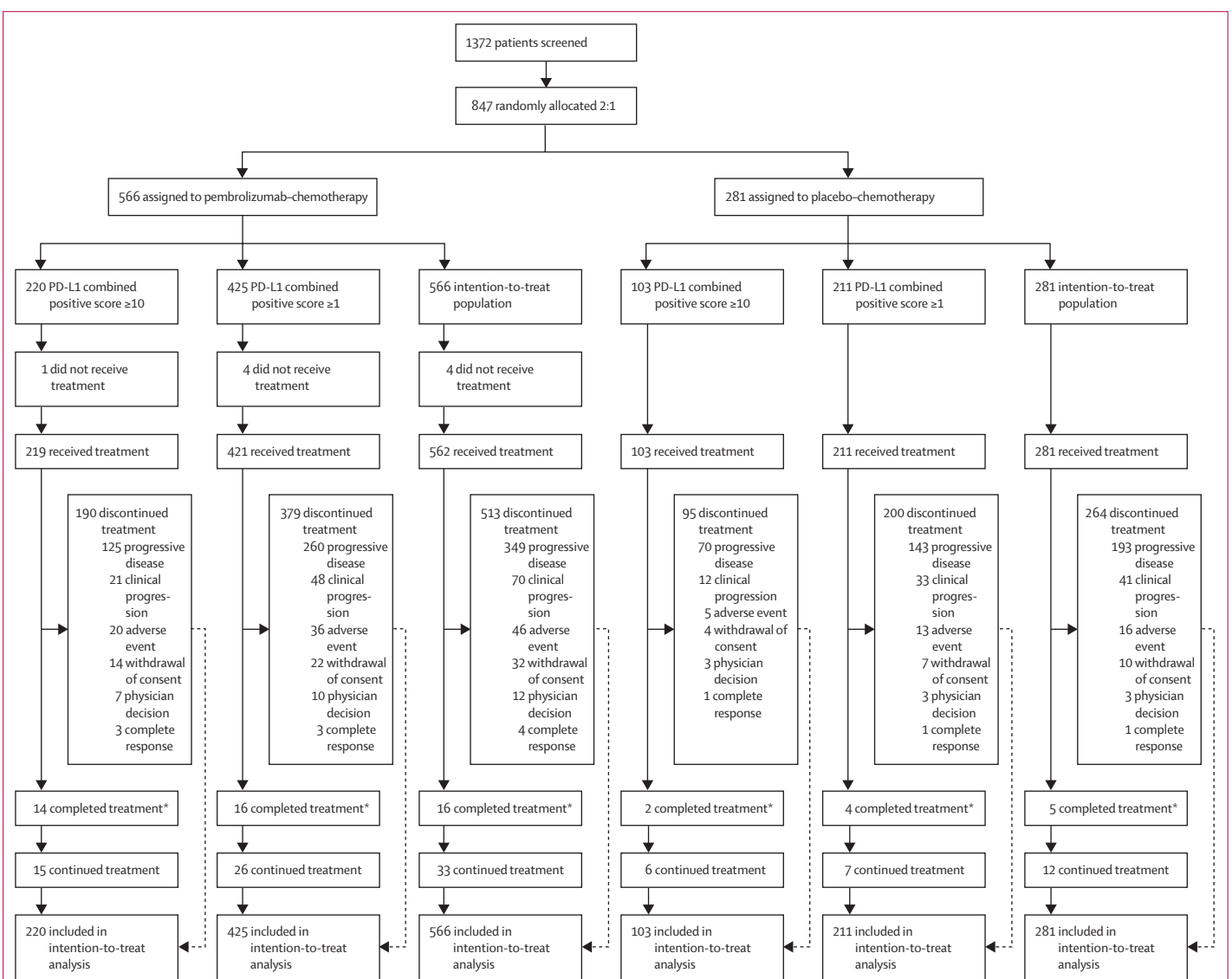


Figure 1: **Trial profile**
Numbers of patients who were screened, randomly assigned, and treated by trial population in part 2 of the trial at the second interim analysis (database cutoff date of Dec 11, 2019) are shown.
*Includes all patients who received 35 administrations of pembrolizumab or placebo and discontinued from chemotherapy.

	PD-L1 combined positive score ≥10†		PD-L1 combined positive score ≥1†		Intention-to-treat population	
	Pembrolizumab–chemotherapy group (n=220)	Placebo–chemotherapy group (n=103)	Pembrolizumab–chemotherapy group (n=425)	Placebo–chemotherapy group (n=211)	Pembrolizumab–chemotherapy group (n=566)	Placebo–chemotherapy group (n=281)
Age						
Median (IQR), years	52 (44–62)	55 (43–63)	52 (43–62)	52 (43–63)	53 (44–63)	53 (43–63)
<65 years of age	178 (81%)	79 (77%)	337 (79%)	168 (80%)	443 (78%)	224 (80%)
Race						
American Indian–Alaska Native	2 (1%)	0	7 (2%)	0	11 (2%)	1 (<1%)
Asian	44 (20%)	20 (19%)	89 (21%)	41 (19%)	123 (22%)	52 (19%)
Black–African American	9 (4%)	6 (6%)	16 (4%)	10 (5%)	20 (4%)	17 (6%)
Multiple	6 (3%)	3 (3%)	9 (2%)	7 (3%)	11 (2%)	8 (3%)
White	153 (70%)	70 (68%)	291 (68%)	146 (69%)	384 (68%)	195 (69%)
Missing	6 (3%)	4 (4%)	13 (3%)	7 (3%)	17 (3%)	8 (3%)
Menopausal status						
Premenopausal	74 (34%)	34 (33%)	146 (34%)	76 (36%)	178 (31%)	92 (33%)
Postmenopausal	146 (66%)	69 (67%)	278 (65%)	135 (64%)	387 (68%)	189 (67%)
Missing	0	0	1 (<1%)	0	1 (<1%)	0
Eastern Cooperative Oncology Group performance status						
0	134 (61%)	62 (60%)	253 (60%)	134 (64%)	332 (59%)	173 (62%)
1	86 (39%)	41 (40%)	171 (40%)	77 (36%)	232 (41%)	108 (38%)
2	0	0	0	0	1 (<1%)	0
Missing	0	0	1 (<1%)	0	1 (<1%)	0
Disease-free interval‡						
De novo metastasis	68 (31%)	35 (34%)	135 (32%)	65 (31%)	167 (30%)	84 (30%)
<12 months	49 (22%)	17 (17%)	92 (22%)	37 (18%)	126 (22%)	50 (18%)
≥12 months	102 (46%)	51 (50%)	195 (46%)	109 (52%)	270 (48%)	147 (52%)
Unknown	1 (<1%)	0	3 (1%)	0	3 (1%)	0
Disease status						
Metastatic, de novo	68 (31%)	35 (34%)	135 (32%)	65 (31%)	167 (30%)	84 (30%)
Metastatic, recurrent	144 (65%)	62 (60%)	274 (64%)	135 (64%)	383 (68%)	185 (66%)
Locally recurrent inoperable	7 (3%)	6 (6%)	13 (3%)	11 (5%)	13 (2%)	12 (4%)
Missing	1 (<1%)	0	3 (1%)	0	3 (1%)	0
Number of metastatic sites						
0–2	122 (55%)	62 (60%)	232 (55%)	130 (62%)	313 (55%)	166 (59%)
≥3	97 (44%)	41 (40%)	190 (45%)	81 (38%)	250 (44%)	115 (41%)
Missing	1 (<1%)	0	3 (1%)	0	3 (1%)	0
Site of metastatic disease§						
Any	212 (96%)	97 (94%)	409 (96%)	200 (95%)	550 (97%)	269 (96%)
Bone	52 (24%)	22 (21%)	112 (26%)	54 (26%)	169 (30%)	85 (30%)
Brain	5 (2%)	6 (6%)	14 (3%)	8 (4%)	17 (3%)	9 (3%)
Breast	17 (8%)	7 (7%)	26 (6%)	14 (7%)	35 (6%)	18 (6%)
Chest wall	56 (25%)	15 (15%)	103 (24%)	33 (16%)	132 (23%)	45 (16%)
Liver	62 (28%)	32 (31%)	131 (31%)	61 (29%)	171 (30%)	78 (28%)
Lung	120 (55%)	55 (53%)	236 (56%)	119 (56%)	324 (57%)	162 (58%)
Lymph nodes	169 (77%)	79 (77%)	318 (75%)	157 (74%)	417 (74%)	206 (73%)
Other	46 (21%)	17 (17%)	77 (18%)	34 (16%)	110 (19%)	51 (18%)
Chemotherapy on study (interactive voice-response system)						
Nab-paclitaxel	63 (29%)	36 (35%)	130 (31%)	74 (35%)	173 (31%)	95 (34%)
Paclitaxel	33 (15%)	11 (11%)	62 (15%)	22 (10%)	82 (14%)	32 (11%)
Gemcitabine–carboplatin	124 (56%)	56 (54%)	233 (55%)	115 (55%)	311 (55%)	154 (55%)

(Table 1 continues on next page)

	PD-L1 combined positive score ≥10†		PD-L1 combined positive score ≥1†		Intention-to-treat population	
	Pembrolizumab–chemotherapy group (n=220)	Placebo–chemotherapy group (n=103)	Pembrolizumab–chemotherapy group (n=425)	Placebo–chemotherapy group (n=211)	Pembrolizumab–chemotherapy group (n=566)	Placebo–chemotherapy group (n=281)
(Continued from previous page)						
Previous treatment with same class neoadjuvant or adjuvant chemotherapy (interactive voice-response system)						
Yes	46 (21%)	19 (18%)	91 (21%)	45 (21%)	124 (22%)	62 (22%)
No	174 (79%)	84 (82%)	334 (79%)	166 (79%)	442 (78%)	219 (78%)
Previous neoadjuvant or adjuvant chemotherapy						
Yes	131 (60%)	62 (60%)	256 (60%)	136 (64%)	357 (63%)	181 (64%)
Taxanes	107 (49%)	50 (49%)	213 (50%)	115 (55%)	290 (51%)	156 (56%)
Platinum	13 (6%)	6 (6%)	31 (7%)	17 (8%)	41 (7%)	24 (9%)
Anthracyclines	115 (52%)	50 (49%)	227 (53%)	115 (55%)	318 (56%)	155 (55%)
Other	118 (54%)	55 (53%)	236 (56%)	126 (60%)	329 (58%)	169 (60%)
No	89 (40%)	41 (40%)	169 (40%)	75 (36%)	209 (37%)	100 (36%)

Data are median (IQR) or n (%). CPS=combined positive score. All patients were female. *Based on data from the intention-to-treat population. Percentages might not total 100 because of rounding. †The PD-L1 CPS was defined as number of PD-L1–positive cells (tumour cells, lymphocytes, and macrophages) divided by total number of tumour cells × 100. ‡Defined as the interval from the completion of treatment with curative intent (eg, date of primary breast tumour surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence. §Breast, chest wall, and lymph node categories also include locally recurrent lesions.

Table 1: **Baseline characteristics***

previous therapy targeting PD-1, PD-L1, PD-L2, or an agent directed to another co-inhibitory T-cell receptor; failure to recover (to grade ≤1 or baseline) from adverse events owing to previously administered therapy; grade at least 2 neuropathy; active autoimmune disease requiring systemic treatment within the previous 2 years; diagnosis of immunodeficiency or immunosuppressive therapy within the previous week; active central nervous system metastases or carcinomatous meningitis (previously treated stable brain metastases was permitted); history of non-infectious pneumonitis requiring glucocorticoids or current pneumonitis; history of human immunodeficiency virus; history of interstitial lung disease; active tuberculosis; active hepatitis B or hepatitis C infection; class II–IV congestive heart failure or myocardial infarction within 6 months of randomisation; or any active infection requiring systemic therapy. Full inclusion and exclusion criteria are included in the trial protocol.

The trial was done in accordance with standards of Good Clinical Practice and the Declaration of Helsinki. The trial protocol and all amendments were approved by the appropriate ethics body at each participating institution. All patients provided written informed consent before enrolment. The trial protocol has been published online and is available with the full text of this article.

Randomisation and masking

In the safety run-in part of the trial (part 1), 35 patients were randomly assigned in a 1:1:1 ratio to pembrolizumab in combination with chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin); both pembrolizumab and chemotherapy administration were open-label. In this phase 3 trial (part 2), 847 patients were randomly assigned in a 2:1 ratio to receive pembrolizumab plus chemotherapy or placebo plus chemotherapy by means of a block method (block size of six) and a central interactive voice response system with an integrated web-response system (Oracle, Redwood City, CA, USA). Stratification factors were the type of on-study chemotherapy received (taxane or gemcitabine-carboplatin), tumour PD-L1 expression at baseline (combined positive score [CPS] ≥1 or CPS <1), and previous treatment with the same class of chemotherapy in the neoadjuvant or adjuvant setting (yes or no). Chemotherapy administration was open-label. As a double-blind study for pembrolizumab, the sponsor, investigators, other study site staff (except for the unmasked pharmacist), and patients were masked to pembrolizumab versus saline placebo administration. The unmasked pharmacist provided the masked study site staff with ready-to-use identically packaged pembrolizumab–saline infusion solutions for administration at scheduled infusion visits. In addition, the sponsor, the investigators, other study site staff, and patients were masked to patient-level tumour PD-L1 biomarker results.

Procedures

This study was done in two parts. In part 1, patients received 200 mg of pembrolizumab (Keytruda, Merck Sharp and Dohme) every 3 weeks in combination with one of three chemotherapy options (nab-paclitaxel 100 mg/m² on days 1, 8, and 15, every 28 days; paclitaxel 90 mg/m² on days 1, 8, and 15, every 28 days; or gemcitabine 1000 mg/m² plus carboplatin area under the curve 2 on days 1 and 8, every 21 days). In part 2, patients received pembrolizumab–chemotherapy (investigator's choice of nab-paclitaxel; paclitaxel; or gemcitabine-carboplatin, as described) or placebo–chemotherapy for up to

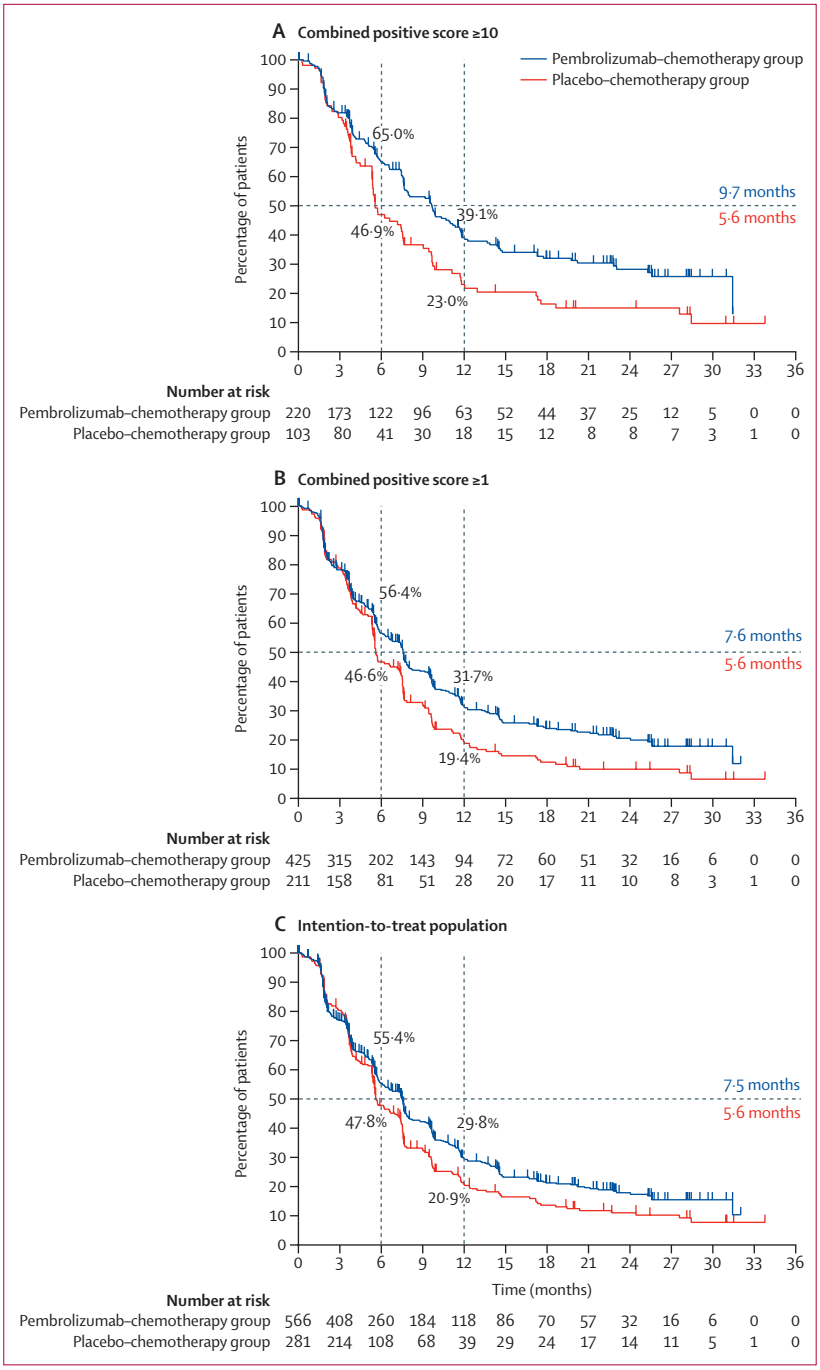


Figure 2: **Kaplan-Meier estimates of progression-free survival. (A) Patients with PD-L1-positive combined positive score ≥10 tumours. (B) Patients with PD-L1-positive CPS ≥1 tumours. (C) The intention-to-treat population**

Tick marks indicate censoring of the data at the time of the last imaging assessment.

35 administrations (pembrolizumab or placebo only; chemotherapy was continued at the investigator's discretion) or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or physician's decision. Crossover between treatment groups was not permitted.

Response was assessed by imaging every 8 weeks until week 24, then every 9 weeks during the first year, and then every 12 weeks thereafter on the basis of Response Evaluation Criteria in Advanced Solid Tumors (RECIST) version 1.1[19] as assessed by a central imaging vendor. Complete responses and partial responses must have been confirmed by a follow-up scan at least 4 weeks from the date the response was first documented. After central verification of disease progression or start of new anticancer therapy, patients were monitored for survival every 12 weeks. Baseline PD-L1 expression in archival or newly obtained formalin-fixed tumour samples was assessed at a central laboratory (Q² Solutions, Valencia, CA, USA) by means of the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) and characterised by the CPS, defined as the number of PD-L1-positive cells (tumour cells, lymphocytes, and macrophages) divided by total number of tumour cells × 100.[20] Patients were eligible for the study regardless of PD-L1 status.

Outcomes

The primary objective of part 1 was to evaluate the safety and tolerability of pembrolizumab–paclitaxel, pembrolizumab–nab-paclitaxel, and pembrolizumab–gemcitabine-carboplatin. In part 2, the dual primary efficacy endpoints were progression-free survival based on RECIST version 1.1 as assessed by a central imaging vendor and overall survival in patients with CPS of 10 or more and CPS of 1 or more and in the intention-to-treat population. The final, definitive progression-free survival analysis was done at this (the second) interim analysis; these are the efficacy results presented in this report. Prespecified secondary efficacy endpoints were the objective response rate, duration of response, and disease control rate, all based on RECIST version 1.1 as assessed by a central imaging vendor; these endpoints are planned for future reporting. The trial protocol and all amendments are available in the appendix. Of note, the primary endpoints were amended after enrolment completion and the first interim analysis to include progression-free survival and overall survival in patients with CPS of 10 or more based on data from other studies showing increased clinical benefit with PD-L1 enrichment;[8–11] the CPS at cutoff 10 was not a stratification factor. Consequently, PD-L1-positive tumours are classified as CPS of 1 or more and CPS of 10 or more, and PD-L1-negative tumours are classified as CPS less than 1.

Safety was a prespecified secondary endpoint. Adverse events were monitored throughout the study and for 30 days after treatment discontinuation (90 days for serious adverse events) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[21] Immune-mediated adverse events were programmatically established from a predefined list of Medical Dictionary for Regulatory

Activities (MedDRA) terms,[22] which was updated with each new version of MedDRA.

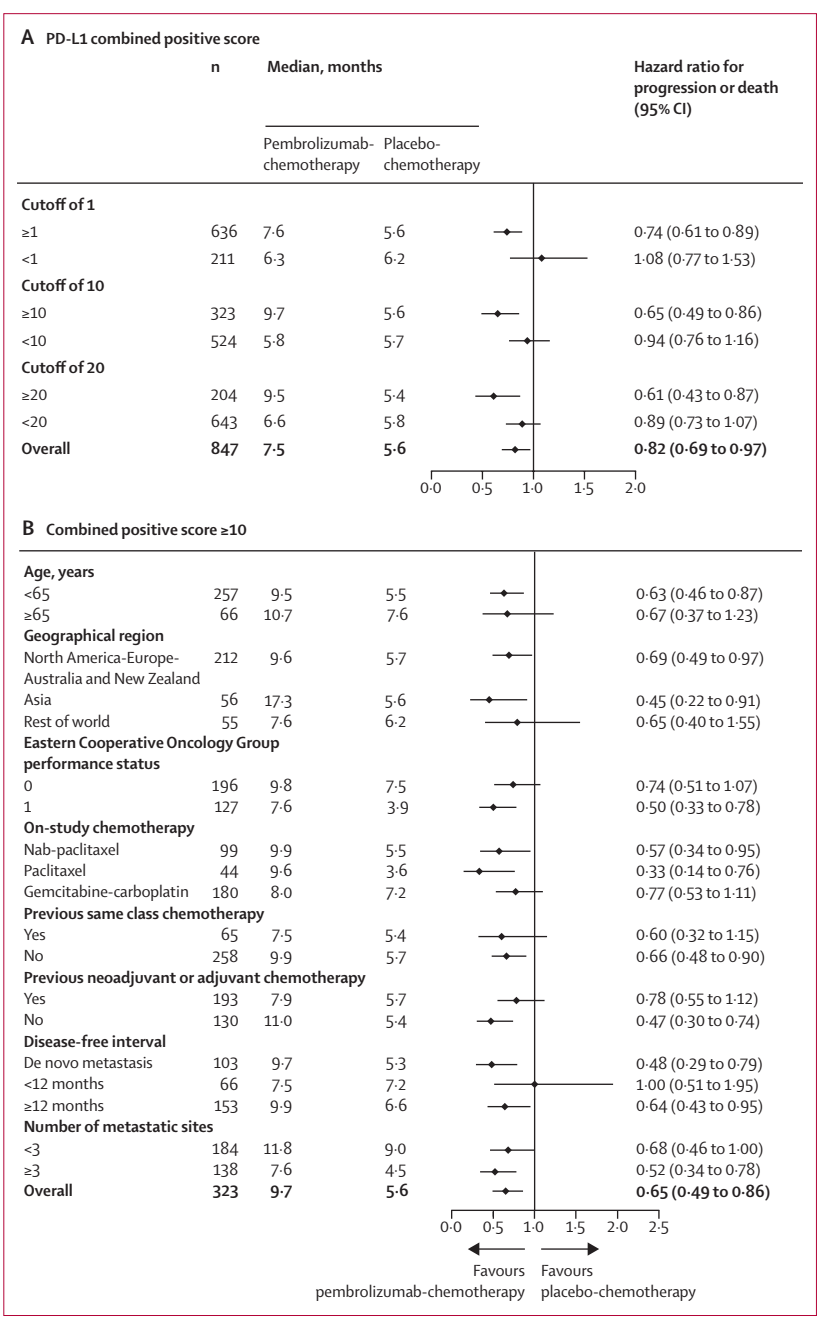
Statistical analysis

Efficacy was assessed in the intention-to-treat population, which included all patients randomly assigned to part 2 (patients in part 1 were excluded from part 2 analyses). Safety was assessed in the all-patients-as-treated population, which included all randomly assigned patients who received at least one dose of study treatment. The non-parametric Kaplan-Meier method was used to estimate progression-free survival, overall survival, and duration of response curves in each treatment group and the censoring rules were outlined in the protocol (see appendix p 115). The primary progression-free survival and overall survival hypotheses were tested by means of the stratified log-rank test; hazard ratios (HRs) and associated 95% CIs were analysed by means of a stratified Cox proportional hazard model with Efron's method of tie handling. The same stratification factors used for randomisation were used in all stratified analyses. The consistency of the progression-free survival treatment effect was assessed in subgroups (see appendix p 133) descriptively by means of HRs and 95% CIs calculated with a non-stratified Cox proportional hazards model with Efron's method of tie handling. All statistical analyses were done with SAS (version 9.4).

The family-wise type I errors across the primary and secondary hypotheses were strictly controlled at a one-sided α of 0·025, which was split between progression-free survival (0·005), overall survival (0·018), and objective response rate (0·002) endpoints. α can be re-allocated among endpoints by means of the graphic approach of Maurer and Bretz.[23] For progression-free survival, a hierarchical testing strategy was used, such that testing was done first in patients with CPS of 10 or more (prespecified statistical criterion was alpha=0·00411 at this interim analysis), then in patients with CPS of 1 or more (alpha=0·00111 at this interim analysis, with partial alpha from progression-free survival in patients with CPS of 10 or more passed over), and finally in the intention-to-treat population (alpha=0·00111 at this interim analysis). The definitive assessment of progression-free survival and an interim assessment of overall survival were done at this interim analysis; follow-up to assess overall survival is continuing and planned for future reporting. The target sample size was approximately 828 participants to ensure an adequate number of patients for progression-free survival and overall survival analyses. The trial had an overall 86% power for the analysis of progression-free survival in patients with CPS of 10 or more. The full statistical analysis plan is in the protocol. An external, independent data monitoring committee oversaw the trial, periodically assessed safety, and assessed efficacy at prespecified interim analyses. This study is registered with ClinicalTrials.gov, NCT02819518.

Role of the funding source

The funder of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report. All authors contributed to drafting the manuscript, provided final approval to publish, and agreed to be accountable for all aspects of the manuscript. All authors had full access to all the data in



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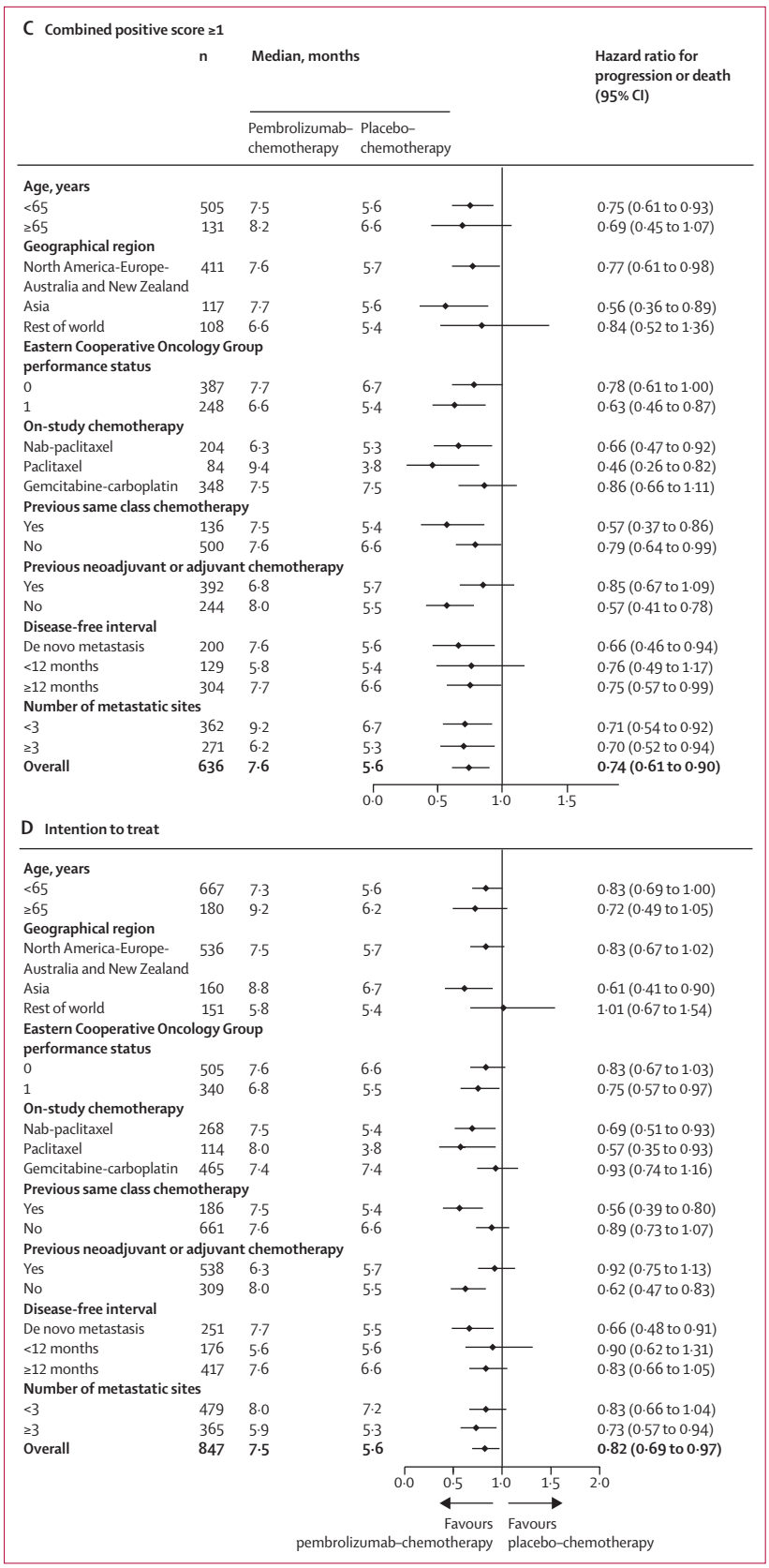

the manuscript and approved the decision to submit for publication.

Results

Following the open-label safety run-in part, of 1372 patients screened, 847 from 209 sites in 29 countries were randomly assigned to treatment with pembrolizumab–chemotherapy (n=566) or placebo–chemotherapy (n=281) from Jan 9, 2017, to June 12, 2018 (figure 1). The baseline characteristics of the patients were as expected and similar between the two treatment groups (table 1). Among the 847 allocated patients, 211 (25%) had PD-L1 CPS of less than 1, 636 (75%) had PD-L1 CPS of 1 or more, and 323 (38%) had PD-L1 CPS of 10 or more. The baseline characteristics of the PD-L1 CPS of 1 or more and PD-L1 CPS of 10 or more subgroups were generally representative of the intention-to-treat population (table 1).

At the second interim analysis (data cutoff, Dec 11, 2019), the median time from randomisation to data cutoff was 25·9 months (IQR 22·8–29·9) in the pembrolizumab–chemotherapy group and 26·3 months (22·7–29·7) in the placebo–chemotherapy group. Overall, 843 patients began treatment, 777 patients (92%) discontinued treatment, and 21 patients (2%) completed trial treatment (figure 1). Exposure data are provided in the appendix (p 10).

In patients with CPS of 10 or more (figure 2A), median progression-free survival in the pembrolizumab–chemotherapy group was 9·7 months and in the placebo–chemotherapy group was 5·6 months (HR for progression or death, 0·65, 95% CI 0·49–0·86; one-sided p=0·0012). According to the prespecified statistical criterion of alpha=0·00411, pembrolizumab–chemotherapy significantly improved progression-free survival compared with placebo–chemotherapy in patients with CPS of 10 or more. The rate of progression-free survival in patients with CPS of 10 or more was higher in the pembrolizumab–chemotherapy group than in the placebo–chemotherapy

Figure 3: **Analysis of difference in progression-free survival in subgroups**
Forest-plot analyses of progression-free survival are shown. (A) By PD-L1 combined positive score status at baseline. (B) In patients with PD-L1–positive CPS ≥10 tumours. (C) In patients with PD-L1–positive CPS ≥1 tumours. (D) In the intention-to-treat population. Hazard ratios for progression or death are shown. Analysis (hazard ratio and 95% CI) in the overall population is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane or gemcitabine–carboplatin), tumour PD-L1 status (CPS ≥1 or CPS <1), and previous treatment with same class of chemotherapy in the (neo)adjuvant setting (yes or no); analysis in the subgroups is based on the unstratified Cox model. The analyses in the subgroups of disease-free interval at baseline and number of metastatic sites excluded patients with missing values for the indicated categories. Eastern Cooperative Oncology Group performance-status scores are assessed on a 5-point scale, with higher numbers indicating greater disability; data are not shown for one patient with a missing value and one patient with an Eastern Cooperative Oncology Group performance-status score of 2 (a score of 2 indicates that the patient was ambulatory, awake and active >50% of waking hours, and capable of all self-care but unable to work).

group at 6 months (65·0% *vs* 46·9%) and at 12 months (39·1% *vs* 23·0%).

In patients with CPS of 1 or more (figure 2B), median progression-free survival in the pembrolizumab–chemotherapy group was 7·6 months and in the placebo–chemotherapy group was 5·6 months (HR 0·74, 95% CI 0·61–0·90; one-sided p=0·0014). There was no significant between-treatment group difference in progression-free survival in patients with CPS of 1 or more according to the prespecified statistical criterion of alpha=0·00111. The rate of progression-free survival in patients with CPS of 1 or more was higher in the pembrolizumab–chemotherapy group than in the placebo–chemotherapy group at 6 months (56·4% *vs* 46·6%) and at 12 months (31·7% *vs* 19·4%).

In the intention-to-treat population (figure 2C), median progression-free survival in the pembrolizumab–chemotherapy group was 7·5 months versus 5·6 months in the placebo–chemotherapy group (HR 0·82, 95% CI 0·69–0·97). Significance was not tested in the intention-to-treat population owing to the prespecified hierarchical testing strategy for progression-free survival. The rate of progression-free survival in the intention-to-treat population was higher in the pembrolizumab–chemotherapy group than in the placebo–chemotherapy group at 6 months (55·4% *vs* 47·8%) and at 12 months (29·8% *vs* 20·9%).

In patients with PD-L1 CPS of less than 1, median progression-free survival was 6·3 months in the pembrolizumab–chemotherapy group and 6·2 months in the placebo–chemotherapy group (HR, 1·08, 95% CI 0·77–1·53). The pembrolizumab treatment effect increased with PD-L1 enrichment (figure 3A). The benefits of pembrolizumab–chemotherapy on progression-free survival were generally consistent across predefined subgroups, including those that were defined on the basis of choice of chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine–carboplatin) and disease-free interval (de novo metastasis; <12 months; or ≥12 months; figure 3B–3D). Although the HR was 1·00 in patients with CPS of 10 or more who had a disease-free interval of less than 12 months, these results should be interpreted with caution because of the small sample size and widely overlapping CI. In the larger patient population with CPS of 1 or more, a similar benefit of pembrolizumab–chemotherapy was observed across disease-free interval subgroups.

Adverse events of any grade that were considered related to study treatment by the investigator occurred in 96% of the 562 patients treated in the pembrolizumab–chemotherapy group and 95% of the 281 patients treated in the placebo–chemotherapy group, with anaemia (49% *vs* 46%), neutropenia (41% *vs* 38%), and nausea (39% *vs* 41%) being the most common (table 2). These treatment-related adverse events were of grade 3 or higher in 68% of patients in the pembrolizumab–chemotherapy group and 67% of patients in the placebo–chemotherapy group. Treatment-related adverse events led to death in two (<1%) patients in the pembrolizumab–chemotherapy group (one from acute kidney injury and one from pneumonia) and no patients in the placebo–chemotherapy group.

	Pembrolizumab–chemotherapy group (n=562)		Placebo–chemotherapy group (n=281)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event*	554 (99%)	438 (78%)	276 (98%)	207 (74%)
Treatment-related adverse event†				
Total	541 (96%)	383 (68%)	267 (95%)	188 (67%)
Anaemia	275 (49%)	92 (16%)	129 (46%)	41 (15%)
Neutropenia	231 (41%)	167 (30%)	107 (38%)	84 (30%)
Nausea	221 (39%)	9 (2%)	115 (41%)	4 (1%)
Alopecia	186 (33%)	5 (1%)	94 (33%)	3 (1%)
Fatigue	160 (28%)	16 (3%)	83 (30%)	7 (2%)
Neutrophil count decreased	125 (22%)	98 (17%)	74 (26%)	57 (20%)
Alanine aminotransferase increased	115 (20%)	33 (6%)	46 (16%)	13 (5%)
Immune-mediated adverse event‡				
Total	144 (26%)	29 (5%)	17 (6%)	0
Hypothyroidism	87 (15%)	2 (<1%)	9 (3%)	0
Hyperthyroidism	27 (5%)	1 (<1%)	3 (1%)	0
Pneumonitis	14 (2%)	6 (1%)	0	0
Colitis	10 (2%)	2 (<1%)	4 (1%)	0
Severe skin reactions	10 (2%)	10 (2%)	1 (<1%)	0

Data are n (%). *Listed are all adverse events that occurred during randomly allocated study treatment or within the 30 days thereafter (within 90 days for serious events). The as-treated population included all patients who underwent randomisation and received ≥1 dose of study treatment. Events are listed in descending order of frequency in the pembrolizumab–chemotherapy group. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. †Adverse events that were attributed to study treatment by the investigator. Treatment-related adverse events that occurred in at least 20% of patients are reported. Patients might have had more than one event. ‡Adverse events based on a list of terms specified by the sponsor and considered regardless of treatment attribution by the investigator that occurred in at least ten patients in the pembrolizumab–chemotherapy group are reported.

Table 2: **Adverse events**

Immune-mediated adverse events occurred in 26% of patients in the pembrolizumab–chemotherapy group and 6% of patients in the placebo–chemotherapy group (table 2); these events were of grade 3 or higher in 5% of patients in the pembrolizumab–chemotherapy group and 0% of patients in the placebo–chemotherapy group. The only immune-mediated adverse event of grade 3 or higher that occurred in at least ten patients was severe skin reaction (2%) in the pembrolizumab–chemotherapy group; there were no such events in the placebo–chemotherapy group. Infusion reactions occurred in 4% of the pembrolizumab–chemotherapy group and 5% of the placebo–chemotherapy group; these reactions were of grade 3 or higher in 1% in the pembrolizumab–chemotherapy group and 0% in the placebo–chemotherapy group. Thyroiditis was infrequent, occurring in 1% of the patients in the pembrolizumab–chemotherapy group and in 0% of those in the placebo–chemotherapy group. No patients died because of immune-mediated adverse events.

Discussion

We describe the primary progression-free survival results from the global phase 3 KEYNOTE-355 clinical trial of first-line treatment with pembrolizumab–chemotherapy, as compared with placebo–chemotherapy, in patients with locally recurrent inoperable or metastatic triple-negative breast cancer. Pembrolizumab–chemotherapy resulted in a significant and clinically meaningful improvement in progression-free survival compared with chemotherapy alone in patients with CPS of 10 or more, as indicated by a median progression-free survival that was 4·1 months longer (9·7 months with pembrolizumab–chemotherapy as compared with 5·6 months with placebo–chemotherapy; HR for progression or death, 0·65). On the basis of these results, the trial met one of its protocol-specified primary objectives. Although the boundary for declaring a significant benefit of pembrolizumab–chemotherapy in progression-free survival in patients with CPS 1 or more was not crossed and formal testing in the intention-to-treat population was not done, pembrolizumab–chemotherapy showed numerical increases in median progression-free survival in both populations and improved treatment effects over the chemotherapy control group with PD-L1 enrichment. The benefit of pembrolizumab–chemotherapy was generally consistent across predefined subgroups.

Our results extend observations from earlier trials of pembrolizumab that showed improved outcomes with PD-L1 enrichment in patients with triple-negative breast cancer. After initial efficacy was shown in the phase 1b KEYNOTE-012 trial in patients with heavily pretreated PD-L1–positive metastatic triple-negative breast cancer,[11] the phase 2 KEYNOTE-086 trial showed that pembrolizumab had robust antitumour activity in the cohort of patients with previously untreated PD-L1–positive (CPS ≥1) metastatic triple-negative breast cancer.[8] Although the response rate in KEYNOTE-086 was lower in the cohort of PD-L1 unselected patients with previously treated disease, a trend toward a greater response with pembrolizumab was observed in patients with PD-L1-positive tumours than those with PD-L1-negative tumours.[9] In the phase 3 KEYNOTE-119 trial,[10] pembrolizumab did not produce a significant survival benefit relative to single-agent chemotherapy in patients with previously treated metastatic triple-negative breast cancer, but a clear trend toward improved efficacy with PD-L1 enrichment was observed, particularly in the exploratory subgroup of patients with CPS of 20 or more. The present results are also consistent with findings from phase 1 trials of the immune checkpoint inhibitors atezolizumab[24] and avelumab[25] for the treatment of metastatic triple-negative breast cancer, showing improved clinical response in patients with higher PD-L1 expression.

Our results complement those from trials that show a clinical benefit with pembrolizumab plus chemotherapy versus chemotherapy alone as neoadjuvant therapy for triple-negative breast cancer.[13–15] Our findings are also consistent with the results of the phase 3 IMPASSION130 trial, which showed significantly improved progression-free survival with atezolizumab plus nab-paclitaxel versus nab-paclitaxel alone for first-line treatment of metastatic triple-negative breast cancer (7·2 *vs* 5·5 months, HR for progression or death, 0·80 [p=0·0025] in the intention-to-treat population; 7·5 *vs* 5·0 months, HR, 0·62 [p<0·001] in the PD-L1-positive subgroup).[26] It is important to note that a different PD-L1 assay was used in IMPASSION130 (positivity was defined by immune cell staining ≥1% according to VENTANA PD-L1 SP142 immunohistochemical testing[27]). Although there was approximately 80% concordance in patients captured by immune cell 1% and above (SP142) and CPS of 10 or more,[28] and both assays identified approximately 40% of the intention-to-treat populations that benefited from immunotherapy plus chemotherapy, these two assays should not be considered as interchangeable.[29]

The safety profile of pembrolizumab in combination with chemotherapy was generally consistent with the known toxic effects of each single agent and with those observed in other pembrolizumab–chemotherapy combination trials. The most common treatment-related adverse events of grade 3 or higher in both treatment groups were consistent with toxicities commonly observed with chemotherapy, and the addition of pembrolizumab did not increase the rates of these adverse events. As expected, the incidence of grade 3 or 4 immune-mediated adverse events was higher in the pembrolizumab–chemotherapy group than in the placebo–chemotherapy group (5% *vs* 0%), primarily owing to severe skin reactions (2%).

A key strength of our study is the inclusion of taxanes (solvent-based paclitaxel and nab-paclitaxel) and a non-taxane platinum-based regimen (gemcitabine–carboplatin), which permits assessment of the clinical benefit of pembrolizumab in combination with several routinely used chemotherapy partners. The subgroup analyses show a generally consistent benefit of pembrolizumab–chemotherapy versus chemotherapy alone on progression-free survival irrespective of chemotherapy partner. However, these results should be interpreted with caution as these subgroups are underpowered, and the only objective of subgroup analyses is to explore convergent validity. Another strength of our study is that in addition to patients with at least a 12-month disease-free interval, our study included patients with early recurrences (between 6 months and 12 months following completion of definitive treatment for early disease), which are common in triple-negative breast cancer. Follow-up to assess overall survival and long-term safety is ongoing.

In summary, first-line treatment with pembrolizumab–chemotherapy showed a significant and clinically meaningful improvement in progression-free survival as compared with chemotherapy alone in patients with metastatic triple-negative breast cancer with CPS of 10 or more. A clear trend towards improved efficacy with PD-L1 enrichment was observed in patients treated with

pembrolizumab–chemotherapy. Safety was consistent with the known profiles of each regimen and no new safety signals were observed. These findings suggest a role for the addition of pembrolizumab to standard chemotherapy for the first-line treatment of metastatic triple-negative breast cancer.

Contributors

JC, HSR, HI, SL, ZG, JZ, GA, and VK contributed to the conception, design, or planning of the study; DWC, HSR, ZN, S-AI, MMY, CG, OL, CHB, EH, HI, NM, MTO, EG, SL, ZG, GA, and VK contributed to the acquisition of the data; HSR, ZN, S-AI, CG, OL, CHB, EH, EG, SL, ZG, JZ, GA, VK, and PS contributed to the analysis of the data; DWC, HSR, ZN, S-AI, MMY, CHB, EH, HI, NM, EG, SL, ZG, JZ, GA, VK, and PS contributed to the interpretation of the results; CHB contributed to the recruitment and treatment of patients; ZG and JZ contributed statistical expertise; MMY, MTO, EG, SL, ZG, GA, and PS contributed to the drafting of the manuscript; JC, DWC, HSR, ZN, S-AI, MMY, CG, OL, CHB, EH, HI, NM, EG, SL, ZG, JZ, GA, VK, and PS contributed to the critical review or revision of the manuscript; all authors approved the final version to be published, and agree to be accountable for all aspects of the final report.

Declaration of interests

JC reports personal fees and research funding paid to his institution from Roche, AstraZeneca, Merck Sharp & Dohme, and Eisai; personal fees from Celgene, Cellestia, Biothera Pharmaceutical, Merus, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Servier, GlaxoSmithKline, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Kyowa Kirin, Novartis, Pfizer, Samsung Bioepis; research funding paid to his institution from Ariad Pharmaceuticals, Bayer Healthcare, F Hoffman-La Roche, Guardanth Health, Piqur Therapeutics, Puma C, and Queen Mary University of London, outside the submitted work. In addition, JC has a MedSIR patent pending. DWC reports research support from Merck during the conduct of the study; research support paid to his institution from Merck, Pfizer, and GlaxoSmithKline; personal fees from Merck, Roche–Genentech, AstraZeneca, GlaxoSmithKline, Novartis, Pfizer, Puma, Agenda, Exact Sciences, and Dynamo Therapeutics, outside the submitted work. In addition, DWC has a Biomarkers of TTK inhibitors patent pending. HSR reports funding for sponsored studies paid to the University of California San Francisco from Pfizer, Novartis, Lilly, Roche–Genentech, Macrogenics, OBI, Merck, Eisai, Immunomedics, Daiichi Sankyo, Seattle Genetics, and Odonate; travel support for educational meetings from Daiichi Sankyo, Mylan, Pfizer, Merck, AstraZeneca, Novartis, and Macrogenics; and consulting fees from Samsung and Puma, outside the submitted work. S-AI reports grants from AstraZeneca, Eisai, Pfizer, Roche, and Daewoong; an advisory role for AstraZeneca, Amgen, Eisai, Hanmi, Novartis, Lily, MedPacto, Pfizer, and Roche; and travel expenses for presentation from Novartis, outside the submitted work. CG reports Advisory Board fees from Merck Sharp & Dohme and Roche; and speaker's bureau fees from Bristol Myers Squibb and AstraZeneca, outside the submitted work. CHB reports grants and fees from Merck Sharp & Dohme for clinical research consulting during the conduct of the study; consulting–advisory role fees from Boehringer Ingelheim, GlaxoSmithKline, and Bayer; consulting–advisory role fees and grants for clinical research from Novartis, Pfizer, Roche–Genentech, Eisai, Merck Sharp & Dohme, and AstraZeneca; grants for clinical research from Abbvie, Amgen, Astellas Pharma, Bristol Myers Squibb, Celgene, Covance, Lilly, Medication, Merck Serono, and PharmaMar; grants for academic research projects from CPO, Pontifícia Universidade Católica do Rio Grande do Sul, Latin American Cooperative Oncology Group, Grupo Brasileiro Estudos Câncer Mama, and Instituto Nacional de Câncer-Brazil, outside the submitted work. HI reports a grant from Merck Sharp & Dohme during the conduct of the study; honoraria and consulting fees from Novartis, AstraZeneca, Pfizer, Lilly, Daiichi Sankyo, Eisai, and Chugai; and a grant from Chugai, outside the submitted work. NM reports honoraria and research funding paid to his institution from Chugai, AstraZeneca, Pfizer, Eli-Lilly, Eisai, Takeda, Kyowa-Kirin, Merck Sharp & Dohme, Novartis, and Daiichi Sankyo, outside the submitted work. EG reports non-financial support from Merck Sharp & Dohme during the conduct of the study; honoraria, consulting–advisory fees and meeting support from Novartis, Roche, Bristol Myers Squibb, and Pfizer; and honoraria from AstraZeneca and Astellas, outside the submitted work. SL reports research funding or consulting fees paid to her institution from Bristol Myers Squibb, Roche–Genentech, Puma Biotechnology, Pfizer, Seattle Genetics, Novartis, Merck Sharp & Dohme, Eli Lilly, Aduro Biotech, GI Therapeutics, AstraZeneca, and GlaxoSmithKline; and non-remunerated consultancy for Bristol Myers Squibb, Roche–Genentech, Pfizer, Seattle Genetics, Novartis, Merck Sharp & Dohme, and AstraZeneca, outside the submitted work. In addition, SL is supported by the National Breast Cancer Foundation of Australia Endowed Chair and the Breast Cancer Research Foundation, New York. ZG, JZ, GA, and VK are employees of Merck Sharp & Dohme and own stock or stock options in Merck. PS reports consultancy fees from Pfizer, AstraZeneca, Novartis, Roche, Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Eisai, Celgene, and Puma; consultancy fees to his spouse from Genentech and Roche; and grants or funding to his institution from Roche, Genentech, Oncogenex, Novartis, Astellas, and AstraZeneca, outside the submitted work. All other authors declare no competing interests.

Data sharing

Merck Sharp & Dohme's data sharing policy, including restrictions, is available at EngageZone. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

For more on **EngageZone** see http://engagezone.msd.com/ds_documentation.php

Acknowledgments

The authors thank the patients, their families and caregivers for participating in this trial, all of the investigators and site personnel, and the following employees of Merck Sharp & Dohme: Wilbur Pan, Deborah Card, Eleanor Readinger, Shana Hamm, Roger Maxwell, and Krystal Bourdon, for collection of data, supervision of research, provision of study materials or patients or administrative or logistical support; Aline Galvao, for collection of data, supervision of research, administrative or logistical support, and review of imaging data related to the primary end point; Donna Letizia, for collection of data and imaging expertise; Jennifer Kimmel, for study management; Mercedes Bustamante, for data collection and management; Xuan Zhou and Madhusudhan Reddy Papasani, for statistical expertise; Christine McCrary Sisk, for medical writing and editorial assistance; and Joseph C Naggar and Michele McColgan, for administrative or logistical support.

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