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Results from the randomized KEYNOTE-355 study of pembrolizumab plus chemotherapy for Asian patients with advanced TNBC

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In the phase 3 KEYNOTE-355 study (NCT02819518), pembrolizumab plus chemotherapy demonstrated statistically significant and clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS) versus placebo plus chemotherapy among patients with previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) and programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥ 10 tumors. We analyzed outcomes for the subgroup of patients enrolled in Asia in KEYNOTE-355. Patients received pembrolizumab 200 mg or placebo (2:1 randomization) every 3 weeks for 35 cycles plus investigator's choice chemotherapy. Primary endpoints were PFS per Response Evaluation Criteria in Solid Tumors version 1.1 and OS. Among patients enrolled in Hong Kong, Japan, Korea, Malaysia and Taiwan (pembrolizumab plus chemotherapy, $n = 113$; placebo plus chemotherapy, $n = 47$), 117 (73.1%) had PD-L1 CPS ≥ 1 and 56 (35.0%) had PD-L1 CPS ≥ 10. Median time from randomization to data cutoff (June 15, 2021) was 43.8 (range, 36.8–53.2) months (intent-to-treat [ITT] population). Hazard ratios (HRs [95% CI]) for PFS in the CPS ≥ 10, CPS ≥ 1, and ITT populations were 0.48 (0.24–0.98), 0.58 (0.37–0.91), and 0.66 (0.44–0.99), respectively. Corresponding HRs (95% CI) for OS were 0.54 (0.28–1.04), 0.62 (0.40–0.97), and 0.57 (0.39–0.84). Grade 3/4 treatment-related adverse events (AEs) occurred in 77.9% versus 78.7% of patients with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. No grade 5 AEs occurred. Clinically meaningful improvement in PFS and OS with manageable toxicity were observed with pembrolizumab plus chemotherapy versus placebo plus chemotherapy in patients enrolled in Asia with previously untreated, inoperable or metastatic TNBC. Trial registration: ClinicalTrials.gov, NCT02819518.

Metastatic triple-negative breast cancer (TNBC) accounts for ~10% of all breast cancers globally and appears to have a similar incidence in Asia, albeit with considerable regional variability[1–4]. Programmed cell death ligand 1 (PD-L1) expression and high levels of tumor-infiltrating lymphocytes (TIL) were found to be prognostic for survival[5–9]. Immunotherapies targeting the programmed cell death 1 (PD-1) signaling pathway, such as the anti–PD-1 monoclonal antibody pembrolizumab, have demonstrated modest response rates in patients with metastatic TNBC as monotherapy[10–14].

In the global KEYNOTE-355 study, patients with locally recurrent inoperable or metastatic TNBC received first-line treatment with either pembrolizumab or placebo plus paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin. Pembrolizumab plus chemotherapy significantly improved progression-free survival (PFS) and overall survival (OS)

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compared with placebo plus chemotherapy in patients with PD-L1–positive tumors (combined positive score [CPS] ≥10)[15,16]. Median PFS was 9.7 months in the pembrolizumab plus chemotherapy group and 5.6 months in the placebo plus chemotherapy group (hazard ratio [HR], 0.65 [95% CI, 0.49–0.86]; $P = 0.0012$). Median OS was 23.0 months and 16.1 months, respectively (HR, 0.73 [95% CI, 0.55–0.95]; $P = 0.0093$). Based on PFS results from KEYNOTE-355, pembrolizumab plus chemotherapy was approved by regulatory agencies in several countries[17,18] for patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10).

Evidence suggests that there are important epidemiologic and biologic differences between Asian and non-Asian patients with TNBC that may affect response to treatment. For example, the probability of being diagnosed with TNBC decreases with age for White women in the United States but not for Asian American or East Asian women[4]. Additionally, driver mutations in the *MYC* and *PTK2* genes have been reported to occur less frequently among patients from Japan than in a non-Asian patient population[19], and patients from Korea with breast cancer have been reported to have increased TIL gene signatures compared with a non-Asian patient population[20]. Furthermore, certain patient characteristics (e.g., body mass index) have been reported to contribute towards difference in the toxicity profile among patients from Japan and Hong Kong versus patients from United States/Canada[21], and polymorphisms in genes associated with drug clearance have been reported to contribute to chemotherapy pharmacokinetics among Asian versus non-Asian patients with breast cancer[22].

Taken together, the available evidence highlights a need to evaluate the efficacy and safety of a broad range of anticancer therapies among Asian women with TNBC. The current analysis was conducted to better understand treatment outcomes with pembrolizumab among patients with TNBC enrolled in Asia in KEYNOTE-355.

Results

Patient population

The subgroup of patients enrolled in Asia included 160 patients randomized (pembrolizumab plus chemotherapy, $n = 113$; placebo plus chemotherapy, $n = 47$) between January 10, 2017 and May 23, 2018, in Hong Kong ($n = 7$), Japan ($n = 87$), Korea ($n = 27$), Malaysia ($n = 21$) and Taiwan ($n = 18$) (Fig. 1). Patient demographics and baseline disease characteristics were generally similar between the treatment groups (Table 1). At data cutoff for this analysis (June 15, 2021), median follow-up was 43.8 (range, 36.8–53.2) months in the intention-to-treat (ITT) population.

Patients received a median of 10 (range, 1–35) doses of pembrolizumab and 10 (range, 2–35) doses of placebo. The median number of chemotherapy administrations in the pembrolizumab and placebo groups, respectively, were 22 (range, 2–108) and 18 (range, 3–109) for nab-paclitaxel; 18 (range, 12–30) and 26 (range, 14–33) for paclitaxel; 16 (range, 1–83) and 16 (range, 2–51) for gemcitabine; and 16 (range, 1–83) and 16 (range, 2–51) for carboplatin. Patients could discontinue chemotherapy without discontinuing pembrolizumab/placebo and vice versa. Median duration of exposure was 32 (range, 0–199) weeks in the pembrolizumab plus chemotherapy group and 30 (range, 3–146) weeks in the placebo plus chemotherapy group.

Efficacy

At data cutoff, 23/38 patients (60.5%) with PD-L1 CPS ≥ 10 in the pembrolizumab plus chemotherapy group and 14/18 patients (77.8%) in the placebo plus chemotherapy group had experienced progressive disease or died. Among patients with PD-L1 CPS ≥ 10, median PFS was 17.3 (95% CI, 7.6–31.1) months with pembrolizumab plus chemotherapy and 5.6 (95% CI, 5.3–9.0) months with placebo plus chemotherapy (HR, 0.48 [95% CI, 0.24–0.98]; Fig. 2A), with 6-month PFS rates of 73.0% and 39.1%, respectively. Among patients with PD-L1 CPS ≥ 1, 56/81 patients (69.1%) and 32/36 patients (88.9%), respectively, had experienced progressive disease or died. Median PFS was 7.7 (95% CI, 6.3–14.8) months versus 5.6 (95% CI, 5.3–7.7) months (HR, 0.58 [95% CI, 0.37–0.91]; Fig. 2B), with 6-month PFS rates of 64.2% and 48.3%, respectively. In the ITT population, 80/113 patients (70.8%) and 39/47 patients (83.0%), respectively, had experienced progressive disease or died. Median PFS was 8.8 (95% CI, 7.4–10.3) months versus 6.7 (95% CI, 5.3–7.7) months (HR, 0.66 [95% CI, 0.44–0.99]; Fig. 2C), with 6-month PFS rates of 64.2% and 51.9%, respectively.

At data cutoff, 24/38 patients (63.2%) with PD-L1 CPS ≥ 10 in the pembrolizumab plus chemotherapy group and 16/18 patients (88.9%) in the placebo plus chemotherapy group had died. Among patients with PD-L1 CPS ≥ 10, median OS was 26.7 (95% CI, 18.7–44.0) months versus 17.4 (95% CI, 11.5–22.6) months (HR, 0.54 [95% CI, 0.28–1.04]; Fig. 3A), with 12-month OS rates of 78.9% and 66.7% respectively. Among patients with PD-L1 CPS ≥ 1, 61/81 patients (75.3%) and 31/36 patients (86.1%), respectively, had died. Median OS was 22.0 (95% CI, 18.7–26.7) months versus 16.9 (95% CI, 11.5–19.2) months (HR, 0.62 [95% CI, 0.40–0.97]; Fig. 3B), with 12-month OS rates of 79.0% and 63.9%, respectively. In the ITT population, 85/113 patients (75.2%) and 42/47 patients (89.4%), respectively, had died. Median OS was 24.1 (95% CI, 20.2–27.5) months versus 17.2 (95% CI, 11.8–19.2) months (HR, 0.57 [95% CI, 0.39–0.84]; Fig. 3C), with 12-month OS rates of 79.6% and 63.8%, respectively.

The objective response rate (ORR) was 57.9% (95% CI, 40.8–73.7%) in the pembrolizumab plus chemotherapy group and 38.9% (95% CI, 17.3–64.3%) in the placebo plus chemotherapy group in patients with PD-L1 CPS ≥ 10, 53.1% (95% CI, 41.7–64.3%) and 47.2% (95% CI, 30.4–64.5%) in patients with PD-L1 CPS ≥ 1, and 49.6% (95% CI, 40.0–59.1%) and 44.7% (95% CI, 30.2–59.9%) in the ITT population, respectively (Supplementary Table 1). Results for PFS, OS, and ORR in patients with PD-L1 CPS < 10 are provided in Supplementary Table 2.

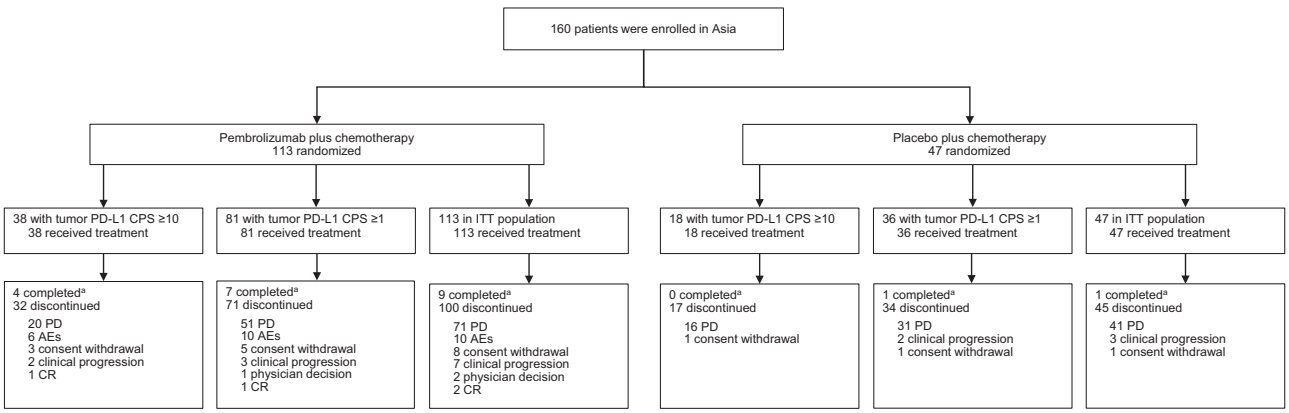

Fig. 1 | Patient disposition. [a]Includes all patients who received 35 administrations of pembrolizumab or placebo and discontinued from chemotherapy. AE adverse event, CPS combined positive score, CR complete response, ITT intention-to-treat, PD progressive disease, PD-L1 programmed cell death ligand 1.

Table 1 | Patient demographics and baseline disease characteristics in the Asian subgroup

	Pembrolizumab plus chemotherapy *N* = 113	Placebo plus chemotherapy *N* = 47
Age, years, median (range)	55.0 (29–79)	50.0 (24–74)
Age < 65 years	90 (79.6)	38 (80.9)
Menopausal status		
Premenopausal	37 (32.7)	17 (36.2)
Postmenopausal	76 (67.3)	30 (63.8)
ECOG PS		
0	79 (69.9)	36 (76.6)
1	34 (30.1)	11 (23.4)
HER2 status		
0–1+ by IHC	80 (70.8)	34 (72.3)
2+ by IHC	33 (29.2)	13 (27.7)
Tumor PD-L1 status		
CPS < 1	32 (28.3)	11 (23.4)
CPS ≥ 1	81 (71.7)	36 (76.6)
CPS ≥ 10	38 (33.6)	18 (38.3)
Disease status		
De novo metastatic	38 (33.6)	15 (31.9)
Recurrent metastatic	72 (63.7)	31 (66.0)
Locally recurrent inoperable	3 (2.7)	1 (2.1)
Disease-free interval		
De novo metastasis	38 (33.6)	15 (31.9)
< 12 months	19 (16.8)	7 (14.9)
≥ 12 months	56 (49.6)	25 (53.2)
On-study chemotherapy		
Nab-paclitaxel	32 (28.3)	15 (31.9)
Paclitaxel	7 (6.2)	3 (6.4)
Gemcitabine-carboplatin	74 (65.5)	29 (61.7)
Prior same-class chemotherapy		
Yes	11 (9.7)	10 (21.3)
No	102 (90.3)	37 (78.7)
Enrollment location		
Hong Kong	7 (6.2)	0
Japan	61 (54.0)	26 (55.3)
Korea	17 (15.0)	10 (21.3)
Malaysia	15 (13.3)	6 (12.8)
Taiwan	13 (11.5)	5 (10.6)

CPS combined positive score, *ECOG PS* Eastern Cooperative Oncology Group performance status, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *PD-L1* programmed cell death ligand 1.
Except where indicated, data are no. (%) of patients.

Safety

Treatment-related adverse events (AEs) of any grade occurred in 110/113 patients (97.3%) who received pembrolizumab plus chemotherapy and 46/47 patients (97.9%) who received placebo plus chemotherapy (Table 2). Decreased neutrophil count, decreased white blood cell count and anemia were the most common treatment-related AEs in both treatment groups. Grade 3 or 4 treatment-related AEs were reported for 88 patients (77.9%) who received pembrolizumab plus chemotherapy and 37 patients (78.7%) who received placebo plus chemotherapy. No deaths were attributed to treatment-related AEs. Twenty-six patients (23.0%) and 5 patients (10.6%), respectively, discontinued ≥1 components of study treatment because of a treatment-related AE.

Immune-mediated AEs and infusion reactions were reported for 36/113 patients (31.9%) receiving pembrolizumab plus chemotherapy and 5/47 patients (10.6%) receiving placebo plus chemotherapy. The most common immune-mediated AEs in the pembrolizumab plus chemotherapy group were hypothyroidism, adrenal insufficiency, and hyperthyroidism (Table 2). Immune-mediated AEs and infusion reactions were mostly grade 1 or 2; grade 3 or 4 immune-mediated AEs and infusion reactions occurred in 7 patients (6.2%) in the pembrolizumab plus chemotherapy group (adrenal insufficiency, $n = 2$; severe skin reaction, $n = 2$; hepatitis $n = 1$; infusion reaction, $n = 1$; pneumonitis, $n = 1$). No patient in the placebo plus chemotherapy group had a grade 3 or 4 immune-mediated AE or infusion reaction. No deaths were attributed to immune-mediated AEs or infusion reactions in either treatment group.

Discussion

Clinically meaningful improvements in PFS and OS were observed among patients with locally recurrent inoperable or metastatic TNBC who were enrolled in Asia in the KEYNOTE-355 trial who received first-line treatment with pembrolizumab plus chemotherapy compared with patients who received placebo plus chemotherapy. HRs for both PFS and OS favored the pembrolizumab plus chemotherapy group in patients enrolled in Asia overall and among patients with PD-L1 CPS ≥ 10 and CPS ≥ 1 tumors.

We did not separately analyze results in the subgroup of patients who were enrolled outside of Asia for comparison with our findings because that was not the objective of the current analysis. Comparison of our findings with those of the global population from KEYNOTE-355 is therefore limited as the subgroup of patients enrolled in Asia was included in both populations. Recognizing the limitations, the results suggest that benefit with pembrolizumab plus chemotherapy in patients enrolled in Asia with PD-L1 CPS ≥ 10 TNBC was at least as favorable as seen in the global population, with some evidence suggesting that the magnitude of benefit may be greater. However, it must be noted that the 95% CIs in these groups were wider than, and overlapped with, those for the global population. The current results also showed HRs for PFS and OS that favored pembrolizumab plus chemotherapy among patients with PD-L1 CPS ≥ 1 tumors and in the ITT population. Any such potential differences between the global population and the subgroup of patients enrolled in Asia might be driven by differences in driver gene mutations[19], genetic polymorphisms[22], and/or immunological factors (such as TILs) between these groups[23]. The finding that benefit was greater among patients enrolled in Asia with higher tumor PD-L1 expression was consistent with the overall study results and with an exploratory subgroup analysis of the KEYNOTE-119 study, which reported a numeric improvement in OS with pembrolizumab monotherapy versus chemotherapy in previously treated patients with CPS ≥ 20 with metastatic TNBC who were enrolled in the Asia-Pacific region[24].

Results from the current analysis and the global population of KEYNOTE-355 are supported by earlier findings from the phase 1 KEYNOTE-173 and phase 3 KEYNOTE-522 trials, which demonstrated clinical benefit associated with addition of pembrolizumab to chemotherapy as neoadjuvant treatment for early-stage TNBC[25–27]. In KEYNOTE-522, the pathological complete response rate at the time of definitive surgery for patients with previously untreated stage II or III TNBC was 64.8% with pembrolizumab plus chemotherapy and 51.2% with placebo plus chemotherapy[25]. The HR for event-free survival (EFS) was 0.63 (95% CI, 0.48–0.82)[26]. Median EFS was not reached in either treatment group, with 18-month EFS rates of 91.3% and 85.3%, respectively.

Consistent with our findings, the results from a subgroup analysis of patients enrolled at Japanese centers in the phase 3 IMpassion130 study also demonstrated improved outcomes with atezolizumab in advanced TNBC. Median PFS was 7.4 months with atezolizumab plus chemotherapy and 4.6 months with placebo plus chemotherapy (HR, 0.47 [95% CI, 0.25–0.90])

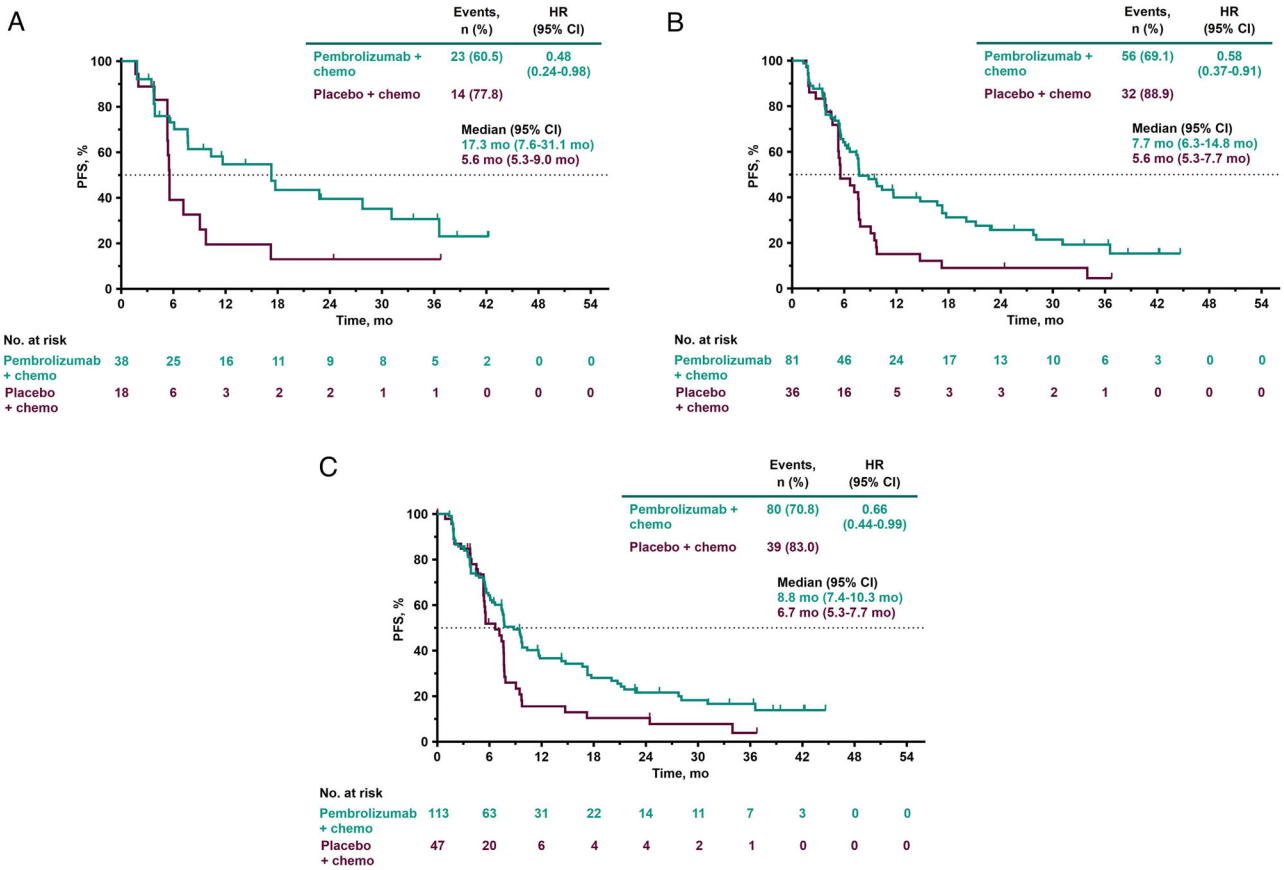

Fig. 2 | Progression-free survival. Results in (**A**) patients with tumor PD-L1 CPS ≥ 10, (**B**) patients with tumor PD-L1 CPS ≥ 1, and (**C**) the ITT population. CPS combined positive score, HR hazard ratio, PD-L1 programmed cell death ligand 1, ITT intention-to-treat.

in the ITT population[28]. Among patients with PD-L1–positive TNBC (assessed using a different assay to that used in the current study), median PFS was 10.8 and 3.8 months, respectively (HR, 0.04 [95% CI, <0.01 to 0.35]). Median OS in the ITT population was not estimable with atezolizumab plus chemotherapy and 16.8 months with placebo plus chemotherapy (HR, 0.44 [95% CI, 0.16–1.24]). In the PD-L1–positive subgroup, median OS was not estimable and 13.3 months, respectively (HR, 0.12 [95% CI, 0.01–0.99]). In the global population of IMpassion130, a statistically significant improvement was demonstrated for PFS (HR, 0.80 [95% CI, 0.69–0.92]; $P = 0.002$) but not for OS (HR, 0.84 [95% CI, 0.69–1.02]; $P = 0.08$) with the addition of atezolizumab to chemotherapy[29].

Our results show that pembrolizumab plus chemotherapy has a manageable safety profile among patients enrolled in Asia with TNBC. Consistent with the global population[15], treatment-related AEs of any grade were reported for 97% of patients who received pembrolizumab plus chemotherapy and 98% who received placebo plus chemotherapy. In the subgroup of patients enrolled in Asia, grade 3 or 4 treatment-related AEs occurred at slightly higher rates (78% and 79% of patients, respectively) than were seen in the global population (68% and 67%, respectively). This is not unexpected as prior evidence has reported differences in hematological toxicities between Asian patients and non-Asian patients, including a higher incidence of neutropenia due to taxane-based therapy compared with non-Asian patients[30]. In the subgroup of patients enrolled in Asia, immune-mediated AEs were reported for 32% of patients receiving pembrolizumab plus chemotherapy and 11% receiving placebo plus chemotherapy. The corresponding rates were 26% and 6%, respectively, in the global population. Median duration of treatment was similar among patients enrolled in Asia versus that in the global population (pembrolizumab plus chemotherapy group: 32 weeks vs 26 weeks; placebo plus chemotherapy, 30 weeks vs 23 weeks)[15].

This analysis provides important information describing the activity of pembrolizumab plus chemotherapy in patients enrolled in Asia with locally recurrent inoperable or metastatic TNBC[31]. However, given that KEYNOTE-355 was not powered to detect statistically significant differences among the subgroup of patients enrolled in Asia, caution is warranted in interpreting the results. The global analysis found a statistically significant and clinically meaningful treatment difference for PFS and OS among patients with tumor PD-L1 CPS ≥ 10 but not for those with CPS ≥ 1[15,16]. Consequently, statistical significance was not assessed for the global ITT population. Numeric differences in PFS and OS outcomes were observed between treatment groups for all subgroups (CPS ≥ 10, CPS ≥ 1, and ITT) in both the current subgroup analyses in patients enrolled in Asia and in the global analyses, with the greatest differences observed among the CPS ≥ 10 subgroup. Additionally, in patients enrolled in Asia with PD-L1 CPS < 10, median PFS and 6-month PFS rates were similar between the two treatment groups and the median OS and 6-month OS rate was higher in the pembrolizumab plus chemotherapy group. However, no formal statistical testing was performed in this subgroup in either the global population or in the patients enrolled in Asia. Our results also highlight a critical need for a more ethnically diverse population in future immunotherapy trials as the majority of patients (~70%) enrolled in the global population of KEYNOTE-355 were of White race[15].

In summary, the present results show clinically meaningful improvements in PFS and OS with pembrolizumab plus chemotherapy in the subgroup of patients enrolled in Asia with locally recurrent inoperable or metastatic TNBC. These findings support the use of pembrolizumab plus chemotherapy as a standard-of-care treatment regimen for Asian patients with PD-L1–positive (CPS ≥ 10), locally recurrent inoperable or metastatic TNBC, consistent with the global population from KEYNOTE-355.

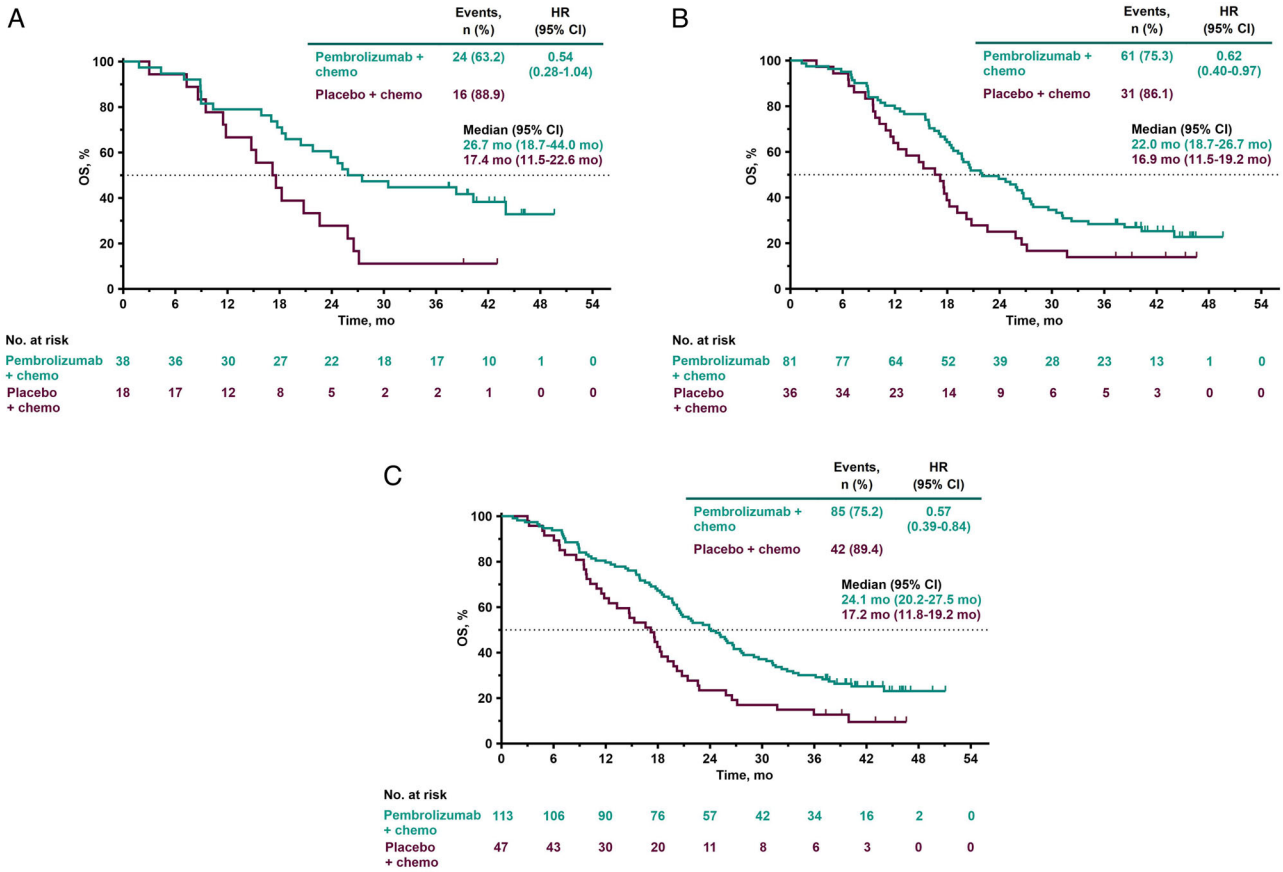

Fig. 3 | Overall survival. Results in (**A**) patients with tumor PD-L1 CPS ≥ 10, (**B**) patients with tumor PD-L1 CPS ≥ 1, and (**C**) the ITT population. CPS combined positive score, HR hazard ratio, PD-L1 programmed cell death ligand 1, ITT intention-to-treat.

Methods

Study design and participants

KEYNOTE-355 (ClinicalTrials.gov, NCT02819518) was a phase 3, randomized, placebo-controlled, multicenter, international trial. Detailed methods were previously published[15,16]. Briefly, eligible patients (≥18 years) had previously untreated, locally recurrent inoperable or metastatic, centrally confirmed TNBC as defined by the American Society of Clinical Oncology College of American Pathologists guidelines[32,33]; ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by the investigator; de novo metastasis or completion of treatment with curative intent ≥6 months before the first disease recurrence; Eastern Cooperative Oncology Group performance status of 0–1; and adequate organ function. Patients were ineligible if they were receiving systemic steroids; had active central nervous system metastases; had a diagnosis of immunodeficiency or received immunosuppressive therapy in the previous week; had class II to IV congestive heart failure or myocardial infarction within 6 months of randomization; had active autoimmune disease in the previous 2 years; had any active infection requiring systemic therapy; history of noninfectious pneumonitis requiring glucocorticoids or current pneumonitis; or history of interstitial lung disease. All patients provided a new tumor sample for immunohistochemistry determination of TNBC and PD-L1 status; however, patients were eligible to enroll regardless of tumor PD-L1 status.

The study was conducted in accordance with the Declaration of Helsinki and the International Council on Harmonisation Good Clinical Practice guidelines. An institutional review board or independent ethics committee at each site approved the protocol (Supplementary Table 3). Patients provided written informed consent.

Randomization and study treatment

Patients were randomized 2:1 to receive pembrolizumab 200 mg or placebo intravenously (IV) every 3 weeks plus the investigator's choice of open-label chemotherapy. Chemotherapy dosing regimens consisted of nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days; paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days; or gemcitabine 1000 mg/m^2 with carboplatin AUC 2 on days 1 and 8 every 21 days. Pembrolizumab was continued for up to 35 administrations (~2 years) or until confirmation of progressive disease, unacceptable toxicity, consent withdrawal, or physician decision. Chemotherapy was continued at the investigator's discretion.

Randomization was done using a central interactive voice response system with an integrated web-response system (Oracle; Redwood City, CA). Randomization used a block method (block size of 6) and was stratified according to chemotherapy received (taxane or gemcitabine-carboplatin), tumor PD-L1 expression (CPS ≥ 1 or < 1), and prior treatment with the same class of chemotherapy in the neoadjuvant or adjuvant setting (yes or no). Patients, investigators, the sponsor, and other study site staff were blinded to treatment assignment and tumor PD-L1 status.

Endpoints

The dual primary endpoints were PFS (per RECIST version 1.1) by blinded independent central review (BICR) and OS among the ITT population (all randomized patients) and among patients with PD-L1–positive tumors (CPS ≥ 10 and ≥ 1). After enrollment and the first interim analysis were complete, the primary endpoints were amended to include assessments of PFS and OS in patients with tumor CPS ≥ 10. This decision was based on data from other clinical studies that showed greater clinical benefit in patients with higher PD-L1 expression[12,15,16]. Secondary endpoints included ORR per RECIST version 1.1 by BICR in the ITT population and in those with PD-L1–positive tumors (CPS ≥ 10 and ≥ 1), and safety.

Table 2 | Adverse events

	Pembrolizumab plus chemotherapy *N* = 113		Placebo plus chemotherapy *N* = 47	
Treatment-related AEs				
Any	110 (97.3)		46 (97.9)	
Grade ¾	88 (77.9)		37 (78.7)	
Serious	22 (19.5)		6 (12.8)	
Led to death	0		0	
Led to treatment discontinuation	26 (23.0)		5 (10.6)	
Any AE leading to dose modification[a]				
Pembrolizumab or placebo	74 (65.5)		24 (51.1)	
Nab-paclitaxel	26 (23.0)		9 (19.1)	
Paclitaxel	6 (5.3)		2 (4.3)	
Gemcitabine	67 (59.3)		28 (59.6)	
Carboplatin	68 (60.2)		28 (59.6)	
	Any grade	**Grade 3–4**	**Any grade**	**Grade 3–4**
Hematologic treatment-related AEs reported for ≥20% of patients in either group				
Blood and lymphatic system disorders				
Anemia	59 (52.2)	24 (21.2)	24 (51.1)	8 (17.0)
Neutropenia	23 (20.4)	19 (16.8)	9 (19.1)	7 (14.9)
Investigations				
Decreased neutrophil count	65 (57.5)	53 (46.9)	29 (61.7)	23 (48.9)
Decreased white blood cell count	57 (50.4)	36 (31.9)	27 (57.4)	19 (40.4)
Decreased platelet count	31 (27.4)	12 (10.6)	11 (23.4)	7 (14.9)
Non-hematologic treatment-related AEs reported for ≥20% of patients in either group				
Gastrointestinal disorders				
Nausea	51 (45.1)	3 (2.7)	21 (44.7)	1 (2.1)
Vomiting	20 (17.7)	3 (2.7)	10 (21.3)	1 (2.1)
Constipation	31 (27.4)	1 (0.9)	11 (23.4)	0
Stomatitis	25 (22.1)	2 (1.8)	6 (12.8)	0
General disorders and administration site conditions				
Fatigue	25 (22.1)	3 (2.7)	11 (23.4)	2 (4.3)
Malaise	22 (19.5)	2 (1.8)	12 (25.5)	0
Metabolism and nutrition disorders				
Decreased appetite	31 (27.4)	2 (1.8)	8 (17.0)	1 (2.1)
Nervous system disorders				
Peripheral sensory neuropathy	23 (20.4)	3 (2.7)	7 (14.9)	0
Skin and subcutaneous tissue disorders				
Alopecia	48 (42.5)	0	18 (38.3)	0
Rash	28 (24.8)	1 (0.9)	6 (12.8)	0
Immune-mediated AEs and infusion reactions	36 (31.9)	7 (6.2)	5 (10.6)	0
Hypothyroidism	19 (16.8)	0	0	0
Hyperthyroidism	5 (4.4)	0	1 (2.1)	0
Thyroiditis	3 (2.7)	0	0	0
Adrenal insufficiency	5 (4.4)	2 (1.8)	0	0
Severe skin reactions	2 (1.8)	2 (1.8)	0	0
Pneumonitis	2 (1.8)	1 (0.9)	0	0
Hepatitis	1 (0.9)	1 (0.9)	0	0
Vasculitis	1 (0.9)	0	1 (2.1)	0
Colitis	0	0	1 (2.1)	0
Infusion reactions	10 (8.8)	1 (0.9)	2 (4.3)	0

AEs adverse events.
Data represent no. (%) of patients.
[a]Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Assessments

Baseline tumor PD-L1 status was assessed at a central laboratory (Q^2 Solutions; Valencia, CA) using PD-L1 IHC 22C3 PharmDx (Agilent Technologies, Inc.; Carpinteria, CA). PD-L1 status was determined according to the CPS, calculated as the number of PD-L1–positive tumor cells, lymphocytes, and macrophages, divided by the total number of tumor cells, multiplied by 100[34].

Tumor imaging was done every 8 weeks through week 24, then every 9 weeks through week 52, and every 12 weeks thereafter. Response was assessed per RECIST version 1.1 by BICR. Patients who had progressive disease or who began new anticancer therapy were contacted every 12 weeks to monitor survival.

Adverse events were monitored throughout the study and for 30 days after treatment had ended (90 days for serious AEs). AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Immune-mediated AEs were based on a predefined list of MedDRA terms.

Statistical analyses

The study was powered to test hypotheses in the global population; no alpha was assigned to the exploratory analyses of patients enrolled in Asia; therefore, the results reported herein are considered descriptive only. PFS and OS were estimated using the nonparametric Kaplan-Meier method. An unstratified Cox proportional hazard model with the Efron method of tie handling was used to calculate HRs with 95% CIs. The randomization stratification factors were also used for all stratified analyses. Statistical analyses were done using SAS version 9.4 (Cary, NC). A full description of statistical analyses for the primary and secondary hypotheses have been previously published[15,16].

Data availability

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a

detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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Competing interests

Seock-Ah Im: reports advisory role for AstraZeneca, Daiichi-Sankyo, GSK, Hanmi, Idience, Lilly, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), Novartis, Pfizer, Bertis and Roche; and grants for AstraZeneca, Boryung Pharm, Daewoong Pharm, Daiichi-Sankyo, Eisai, Pfizer, and Roche. Javier Cortes: Consulting/Advisor: Roche, Celgene, Cellestia, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, MSD, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, and Expres2ion Biotechnologies. Honoraria: Roche, Novartis, Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, MSD, Daiichi Sankyo, and AstraZeneca. Research funding to institution: Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer Healthcare, Eisai, F. 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Additional information

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