

Original Article

Subgroup analysis of Japanese patients in a phase III randomized, controlled study of neoadjuvant atezolizumab or placebo, combined with *nab*-paclitaxel and anthracycline-based chemotherapy in early triple-negative breast cancer (IMpassion031)

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Abstract

Background: In the global phase III IMpassion031 study, neoadjuvant atezolizumab plus *nab*-paclitaxel/anthracycline-based chemotherapy improved pathological complete response in patients with early stage triple-negative breast cancer. Here, we report primary analysis results from a subgroup of Japanese patients.

Methods: Patients with histologically documented, previously untreated, stage cT2–cT4, cN0–cN3, cM0 triple-negative breast cancer were randomized 1:1 to receive intravenous atezolizumab 840 mg or placebo every 2 weeks in combination with chemotherapy consisting of *nab*-paclitaxel intravenous 125 mg/m² once a week, followed by doxorubicin intravenous 60 mg/m² and cyclophosphamide intravenous 600 mg/m² every 2 weeks. Patients then underwent surgery. Pathological complete response (ypT0/is ypN0) in the intention-to-treat and PD-L1-positive (≥1% PD-L1-expressing tumor-infiltrating immune cells) populations were co-primary endpoints.

Results: This subanalysis (data cutoff: 3 April 2020) included 36 patients from Japan (intention-to-treat; atezolizumab arm, $n = 17$; placebo arm, $n = 19$). Pathological complete response occurred in 41% ($n = 7$; 95% confidence interval, 18–67) of patients in the atezolizumab arm and 37% ($n = 7$; 95% confidence interval, 16–62) in the placebo arm. In the PD-L1-positive population, pathological complete response occurred in 50% ($n = 5$; 95% confidence interval, 19–81) of patients in the atezolizumab arm and 45% ($n = 5$; 95% confidence interval, 17–77) in the placebo arm. Treatment-related grade 3–4 adverse events occurred in 71% and 68% of patients in the respective arms. **Conclusion:** Atezolizumab added to neoadjuvant chemotherapy numerically improved pathological complete response versus placebo in this small exploratory analysis of Japanese patients with early stage triple-negative breast cancer, a trend directionally consistent with the global study results. No new safety signals were identified.

Key words: atezolizumab, neoadjuvant treatment, triple-negative breast cancer, Japanese

Introduction

Triple-negative breast cancer (TNBC), characterized by the absence of the estrogen and progesterone receptors and the lack of overexpression and/or amplification of the epidermal growth factor receptor HER2, is one of the most aggressive forms of breast cancer (1). TNBC accounts for ~10–20% of all breast cancers in the global as well as Asian populations (2), and it is associated with poorer clinical outcomes and a higher mortality rate than other breast cancer subtypes (3–5).

About 26–38% of patients with early stage TNBC experience local and distant relapse (6,7), despite receiving optimal treatment with standard-of-care neoadjuvant chemotherapy as well as adjuvant capecitabine for residual disease following surgery (8). The majority of recurrences occur within 3 years of diagnosis (3,6,7), with the 5-year recurrence rate of TNBC being higher than that of other breast cancer subtypes and 97% of the recurrences involving distant sites (6).

Therapeutic options for metastatic TNBC, which has poor survival rates, are limited. Therefore, therapeutic intervention at an early stage, when treatment with curative intent may still be possible, is highly recommended (9,10). Neoadjuvant or adjuvant chemotherapy, particularly with anthracycline/taxane-based regimens, is the preferred treatment for early stage TNBC globally, including in a majority of the Asian countries (11).

Combining immune checkpoint inhibitors such as anti-programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) agents with chemotherapy has emerged as a relevant therapeutic strategy in this setting (12). Atezolizumab is an engineered humanized anti-PD-L1 monoclonal antibody that reinvigorates anti-tumor immunity through the inhibition of the interactions between PD-1 and B7.1 with PD-L1 (13). The atezolizumab plus *nab*-paclitaxel combination was approved in Japan for the treatment of metastatic TNBC in patients with PD-L1 expression on tumor-infiltrating immune cells (ICs) covering $\geq 1\%$ of tumor area (PD-L1 positive) following the results of the phase III IMpassion130 study, which showed there was a statistically significant improvement in progression-free survival and clinically meaningful overall survival benefit in the PD-L1-positive population with the addition of atezolizumab (14).

The global, randomized, double-blind, placebo-controlled, phase III IMpassion031 study compared the efficacy and safety of atezolizumab in combination with neoadjuvant chemotherapy, comprising *nab*-paclitaxel, followed by doxorubicin and cyclophosphamide,

with those of placebo plus neoadjuvant chemotherapy in patients with previously untreated early stage TNBC (cT2–cT4, cN0–cN3, cM0) (15). The atezolizumab arm showed a statistically significant improvement in pathological complete response (pCR) rate in the global intention-to-treat (ITT) population and a numerically higher pCR rate in the global PD-L1-positive (PD-L1 expression on ICs covering $\geq 1\%$ of tumor area) population. In the ITT population ($n = 333$; atezolizumab arm, $n = 165$; placebo arm, $n = 168$), pCR was observed in 58% (95% confidence interval [CI], 50–65) of the patients in the atezolizumab arm, compared with 41% (95% CI, 34–49) of the patients in the placebo arm, with a statistically significant difference of 17% (95% CI, 6–27; one-sided $P = 0.0044$). In the PD-L1-positive population, pCR was observed in 69% (95% CI, 57–79) of the patients in the atezolizumab arm ($n = 77$), versus 49% (95% CI, 38–61) of the patients in the placebo arm ($n = 75$) with an absolute rate difference of 20% (95% CI, 4–35; one-sided $P = 0.021$), which did not cross the statistical significance boundary. The safety profile of neoadjuvant atezolizumab when combined with chemotherapy in this study was consistent with the known safety profile of single-agent atezolizumab (15).

Several studies have shown that Asian patients may demonstrate a different clinical response and tolerability to systemic therapy compared with those observed among non-Asian study populations across cancer types, including breast cancer (16,17). Asian patients showed better clinical efficacy but a higher risk of toxicities than non-Asian patients with chemotherapy or immunotherapy in some lung cancer studies (17–20), suggesting the need to investigate clinical benefit and safety of systemic therapies in these populations. However, subgroup analyses of Japanese patients in global lung cancer studies with atezolizumab treatment regimens have shown that clinical outcomes and safety profiles with atezolizumab treatment are broadly similar between Japanese patients and the global study populations (21–23). In the IMpassion130 study investigating the efficacy and safety of atezolizumab plus chemotherapy versus placebo in patients with advanced TNBC, Japanese patients in the atezolizumab arm demonstrated a higher response rate than the global population, while also reporting a greater incidence of some toxicities (21). Therefore, an analysis of clinical response to anti-cancer immunotherapy among Japanese patients is of interest to help tailor patient-specific treatment strategies.

Here, we describe the primary efficacy and safety results at the time of final pCR analysis from a subgroup of Japanese patients with

early stage TNBC in the global IMpassion031 study (NCT03197935, Eudra [CT2016-004734-22] and JapicCTI-173 630).

Patients and methods

Study design

IMpassion031 is a global, randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of atezolizumab plus neoadjuvant chemotherapy consisting of *nab*-paclitaxel followed by doxorubicin and cyclophosphamide in treatment-naïve patients with early stage TNBC (15). The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The institutional review board or ethics committee of each participating institution provided ethics approval to conduct the study. All patients were required to provide informed written consent.

Patients

Eligible participants were patients aged ≥ 18 years and had histologically documented TNBC (a negative HER2, estrogen receptor and progesterone receptor status based on the American Society of Clinical Oncology/College of American Pathologists guidelines, per a central laboratory assessment) (24,25). Patients had clinical stage cT2–cT4, cN0–cN3, cM0 TNBC, with a primary breast tumor size of >2 cm by at least one radiographic or clinical measurement, and an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 or 1. A confirmation of PD-L1 status by central testing was required for enrollment; PD-L1 status was assessed using the VENTANA SP142 assay (Ventana Medical Systems, Inc., Tucson, AZ, USA). Patients with tumors having PD-L1 expression on ICs covering $\geq 1\%$ of tumor area were defined as PD-L1 positive, and those with tumor PD-L1 expression on ICs covering $<1\%$ of tumor area were designated as PD-L1 negative.

Key exclusion criteria included a prior history of invasive breast cancer, bilateral breast cancer, previous systemic therapy for the treatment and prevention of breast cancer, previous treatment with anthracyclines or taxanes for any malignancy and prior treatment with CD137 agonists or immune-checkpoint blockade therapies, including anti-CD40, anti-CTLA-4, anti-PD-1 and anti-PD-L1 therapeutic antibodies. Other exclusion criteria were a history of ductal or pleomorphic lobular carcinoma in situ, unless treated surgically >5 years prior to current breast cancer diagnosis, and incisional and/or excisional biopsy of primary tumor and/or axillary lymph nodes.

Treatment

Eligible patients were randomly assigned 1:1 using a permuted-block randomization method to receive either atezolizumab intravenous (IV) 840 mg or a matching placebo once every 2 weeks combined with *nab*-paclitaxel IV 125 mg/m² once every week for 12 weeks, followed by doxorubicin IV 60 mg/m² plus cyclophosphamide IV 600 mg/m² once every 2 weeks for 8 weeks, and was supported by mandatory prophylactic pegfilgrastim. Patients then underwent surgery, after which they were evaluated for pCR status. Once each patient's final pCR status was determined based on a pathology report, the patients and site personnel were unblinded to the assigned treatment. Patients in the atezolizumab arm continued to receive adjuvant atezolizumab IV 1200 mg once every 3 weeks for an additional 11 doses and a total of ~ 12 months of atezolizumab treatment. Patients in the placebo arm underwent surgery and were

subsequently monitored for up to 1 year from the start of study treatment. Patients in both arms could receive adjuvant standard-of-care treatment per investigator decision if there was residual disease at the time of surgery.

Assessments and endpoints

The co-primary study endpoint was pCR, defined as absence of invasive tumor from both breast and lymph nodes (ypT0/is ypN0), in the ITT and PD-L1-positive populations. Stratification factors for randomization were American Joint Committee on Cancer stage at diagnosis (II vs. III) and tumor PD-L1 IC expression ($\geq 1\%$ vs. $<1\%$ of tumor area).

Safety was evaluated in the neoadjuvant treatment phase for all randomized patients who received at least one dose of study treatment. For patients who underwent surgery within the scope of the study, adverse events (AEs) were analyzed for the neoadjuvant phase from Cycle 1, Day 1 to the day before surgery. For patients without surgery within the scope of the study, AEs were analyzed if they were reported from Cycle 1, Day 1 to the day prior to the date that was earlier between either 30 days after the last dose of study treatment, or the start of a new anti-cancer therapy.

Statistical analysis

The global study was designed to enroll ~ 40 patients from Japan, constituting about 10% of the global IMpassion031 ITT population. Statistical analysis for the Japanese subpopulation followed the same methods as for the global IMpassion031 study, the details of which have been previously reported (15). The proportions of patients with pCR in the ITT and PD-L1-positive populations were calculated, and two-sided 95% CIs were estimated by the Clopper–Pearson method. The 95% CIs for the difference in pCR rate between the treatment arms were determined by the normal approximation to the binomial distribution. The analyses of the IMpassion031 study in Japanese patients were descriptive and not powered for statistical significance.

Safety was summarized by monitoring the incidence, nature and severity of all AEs graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, including treatment-emergent AEs leading to study treatment withdrawal. AEs were analyzed by SAS (version 9.4) and presented by treatment arm.

Results

Patient demographics and baseline characteristics

Thirty-six patients were enrolled from nine sites in Japan between 7 September 2017 and 20 September 2019 (Fig. 1) and constituted the ITT population, with 17 patients randomized to the atezolizumab arm and 19 patients randomized to the placebo arm. The PD-L1-positive population included 10 patients in the atezolizumab arm and 11 patients in the placebo arm.

Baseline characteristics were balanced between the two treatment arms, in both the ITT and the PD-L1-positive populations (Table 1).

Efficacy

At the data cutoff of 3 April 2020, pCR in the ITT population was observed in 41% (7 of 17; 95% CI, 18–67) of patients in the atezolizumab arm and 37% (7 of 19; 95% CI, 16–62) of patients in the placebo arm (Fig. 2A), with an absolute difference in pCR rate of 4% (95% CI, –28 to 36). In the PD-L1-positive population, pCR

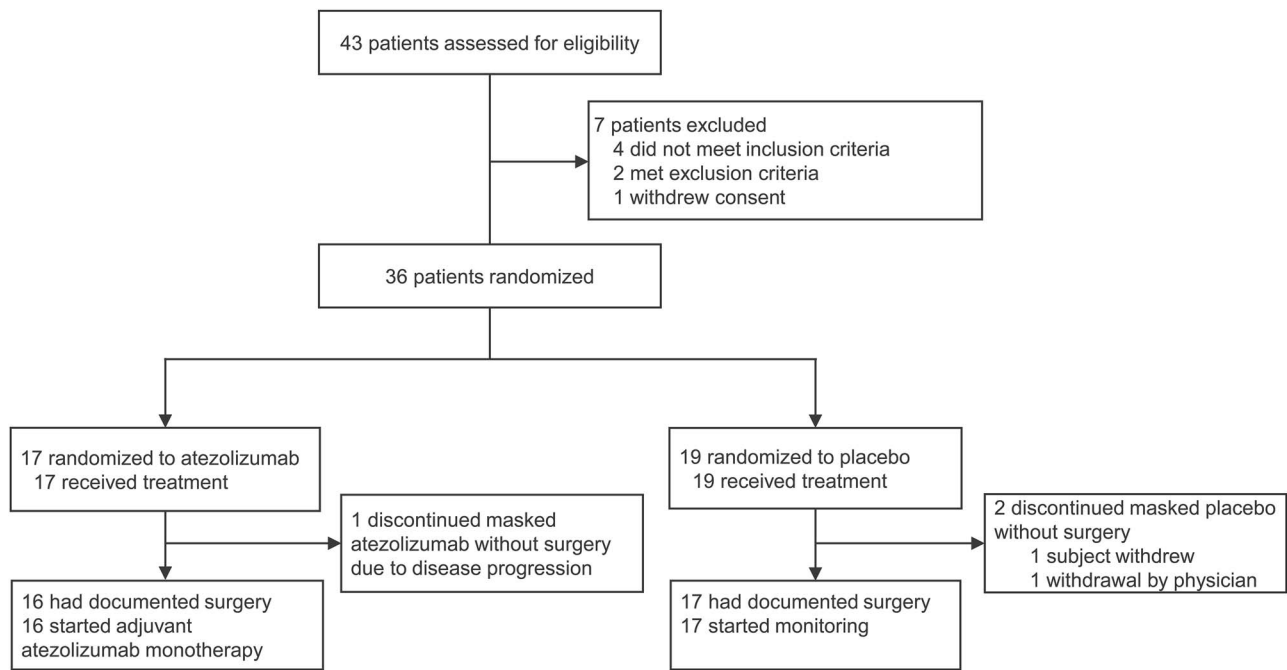


Figure 1. CONSORT diagram.

was observed in 50% (5 of 10; 95% CI, 19–81) of patients in the atezolizumab arm and 45% (5 of 11; 95% CI, 17–77) of patients in the placebo arm (Fig. 2B) at an absolute rate difference of 5% (95% CI, –38 to 47). In the PD-L1-negative population, pCR was observed in 29% (2 of 7; 95% CI, 4–71) of patients in the atezolizumab arm and 25% (2 of 8; 95% CI, 3–65) of patients in the placebo arm (Fig. 2C), with an absolute difference of 4% (95% CI, –41 to 49) in pCR rate.

The median follow-up duration in the ITT population was 22.2 months (range, 6.1–28.0) in the atezolizumab arm and 21.9 months (range, 4.5–29.2) in the placebo arm.

Safety

The median duration of atezolizumab or placebo treatment was 17.4 weeks (range, 0–25) and 19.1 weeks (range, 4–25) in the atezolizumab arm and placebo arm, respectively (Supplementary Table S1). The corresponding median duration of treatment with *nab*-paclitaxel, doxorubicin and cyclophosphamide was 12.1 weeks (range, 0–15), 6.1 weeks (range, 0–8) and 6.1 weeks (range, 0–8), respectively, in the atezolizumab arm, and 12.3 weeks (range, 4–16), 6.1 weeks (range, 0–11) and 6.1 weeks (range, 0–11) in the placebo arm. The median number of doses received of atezolizumab or placebo was 8 in the atezolizumab arm and 10 in the placebo arm. The median number of doses of *nab*-paclitaxel, doxorubicin and cyclophosphamide received in either arm was 12, 4 and 4, respectively. Average dose intensity of atezolizumab was a median of 100 (range, 60–100). Average dose intensity of *nab*-paclitaxel, doxorubicin and cyclophosphamide was a median of 97.9 (range, 60–101), 97.0 (range, 87–101) and 99.0 (range, 87–102), respectively, in the atezolizumab arm, and 98.5 (range, 72–100), 98.7 (range, 93–104) and 98.9 (range, 93–104) in the placebo arm.

In the safety-evaluable population, all patients in both treatment arms experienced at least 1 AE of any grade in the neoadjuvant

phase (Table 2). Grade 3–4 AEs occurred in 12 out of 17 (71%) and 14 out of 19 (74%) patients in the atezolizumab and placebo arms, respectively (Table 2). The six most frequent any-grade AEs occurring in patients in the atezolizumab arm were alopecia (94% [$n = 16$] vs. 95% [$n = 18$]), peripheral sensory neuropathy (82% [$n = 14$] vs. 89% [$n = 17$]), nausea (82% [$n = 14$] vs. 74% [$n = 14$]), neutrophil count decreased (59% [$n = 10$] vs. 68% [$n = 13$]), constipation (59% [$n = 10$] vs. 63% [$n = 12$]) and rash (59% [$n = 10$] vs. 42% [$n = 8$]) (Table 3).

Grade 3–4 AEs occurring in $\geq 10\%$ of patients either in the atezolizumab or placebo arm were neutrophil count decreased (24% [$n = 4$] vs. 42% [$n = 8$]), hepatic function abnormal (18% [$n = 3$] vs. 5% [$n = 1$]), peripheral sensory neuropathy (12% [$n = 2$] vs. $n = 0$), anemia (12% [$n = 2$] vs. 5% [$n = 1$]), lymphocyte count decreased (12% [$n = 2$] vs. 11% [$n = 2$]), white blood cell count decreased (12% [$n = 2$] vs. 26% [$n = 5$]), alanine aminotransferase increased (12% [$n = 2$] vs. 16% [$n = 3$]), leukopenia (12% [$n = 2$] vs. $n = 0$) and neutropenia (12% [$n = 2$] vs. 5% [$n = 1$]) (Table 3 and Supplementary Table S2).

All AEs in both treatment arms were treatment related (Table 2). Treatment-related grade 3–4 AEs were experienced by 12 (71%) and 13 (68%) patients in the atezolizumab and placebo arms, respectively. No grade 5 AEs occurred in either treatment arm.

Any-grade AEs of special interest (AESI) were reported in 15 patients (88%) in the atezolizumab arm and in 18 patients (95%) in the placebo arm, with grade 3–4 AESIs occurring in 6 (35%) and 4 patients (21%), respectively (Table 2). The two most common AESIs occurring in the atezolizumab and placebo arms were rash (82% [$n = 14$] vs. 79% [$n = 15$]) and hepatitis (laboratory abnormalities; 65% [$n = 11$] vs. 58% [$n = 11$]) (Table 4). Serious AESIs were experienced by four patients (24%) in the atezolizumab arm and one patient (5%) in the placebo arm. Systemic corticosteroid treatment for AESIs was required by four patients (24%) in the atezolizumab arm and one patient (5%) in the placebo arm. Serious AEs were experienced by five patients (29%) in the atezolizumab arm and four

Table 1. Demographics and baseline characteristics of the study populations

	ITT		PD-L1 positive	
	Atezolizumab + chemotherapy (n = 17)	Placebo + chemotherapy (n = 19)	Atezolizumab + chemotherapy (n = 10)	Placebo + chemotherapy (n = 11)
Median age (range), years	51 (30–69)	54 (32–70)	47 (41–64)	55 (32–66)
Age group, n (%)				
<40 years	1 (6)	4 (21)	0	2 (18)
41–64 years	14 (82)	11 (58)	10 (100)	7 (64)
≥65 years	2 (12)	4 (21)	0	2 (18)
Baseline ECOG PS, n (%)				
0	17 (100)	19 (100)	10 (100)	11 (100)
Tobacco use history, n (%)				
Never	15 (88)	12 (63)	8 (80)	8 (73)
Previous	1 (6)	4 (21)	1 (10)	2 (18)
Current	1 (6)	3 (16)	1 (10)	1 (9)
PD-L1 subgroups, n (%)				
PD-L1 positive	10 (59)	11 (58)	10 (100)	11 (100)
PD-L1 negative	7 (41)	8 (42)	0	0
Primary clinical tumor classification				
T2	11 (65)	15 (79)	7 (70)	8 (73)
T3	4 (24)	3 (16)	2 (20)	2 (18)
T4a	0	0	0	0
T4b	1 (6)	1 (5)	0	1 (9)
T4c	0	0	0	0
T4d	1 (6)	0	1 (10)	0
Clinical nodal involvement, n (%)				
N0	7 (41)	4 (21)	5 (50)	2 (18)
N1	4 (24)	9 (47)	2 (20)	6 (55)
N2	1 (6)	3 (16)	0	1 (9)
N3	5 (29)	3 (16)	3 (30)	2 (18)
Histological subtype, n (%)				
Ductal	15 (88)	18 (95)	8 (80)	10 (91)
Tubular	0	1 (5)	0	1 (9)
Other	2 (12)	0	2 (20)	0
Overall disease clinical stage, n (%)				
IIA	4 (24)	3 (16)	3 (30)	1 (9)
IIB	5 (29)	9 (47)	3 (30)	6 (55)
IIIA	2 (12)	4 (21)	0	2 (18)
IIIB	1 (6)	0	1 (10)	0
IIIC	5 (29)	3 (16)	3 (30)	2 (18)

ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; PD-L1, programmed death-ligand 1.

patients (21%) in the placebo arm. Serious AEs occurring in ≥1% of patients in the atezolizumab arm were hepatic function abnormal, febrile neutropenia, interstitial lung disease and peripheral sensory neuropathy (Supplementary Table S3).

Discontinuation of any study treatment due to AEs occurred in 10 patients (59%) in the atezolizumab arm and 9 patients (47%) in the placebo arm (Table 2). Seven patients in the atezolizumab arm (41%) and seven patients in the placebo arm (37%) discontinued atezolizumab or placebo. The most frequent reasons for atezolizumab or placebo treatment discontinuation were hepatic function abnormal (atezolizumab, 18% [$n = 3$]; placebo, 5% [$n = 1$]) and peripheral sensory neuropathy (atezolizumab, 12% [$n = 2$]; placebo, $n = 0$).

Supportive treatment with pegfilgrastim was administered to minimize treatment discontinuation with dose-dense anthracycline-based chemotherapy (Supplementary Table S4).

Discussion

To the best of our knowledge, no subgroup analyses have been conducted to specifically explore the efficacy and safety of neoadjuvant atezolizumab-chemotherapy combinations in Japanese patients with early stage TNBC. This subgroup analysis provides key insights into this neoadjuvant regimen in this patient population and can potentially guide treatment decisions in these patients.

This subgroup analysis of Japanese patients in the IMpassion031 study was exploratory and conducted in a small sample size ($N = 36$). Therefore, any interpretation based on the results of this analysis must be made with caution. The global IMpassion031 study population showed a statistically significant and clinically meaningful increase in pCR with neoadjuvant atezolizumab plus chemotherapy in patients with early stage TNBC in the ITT population and a numerical increase in the PD-L1-positive population (15). In the Japanese ITT population, a numerically higher pCR rate, albeit with

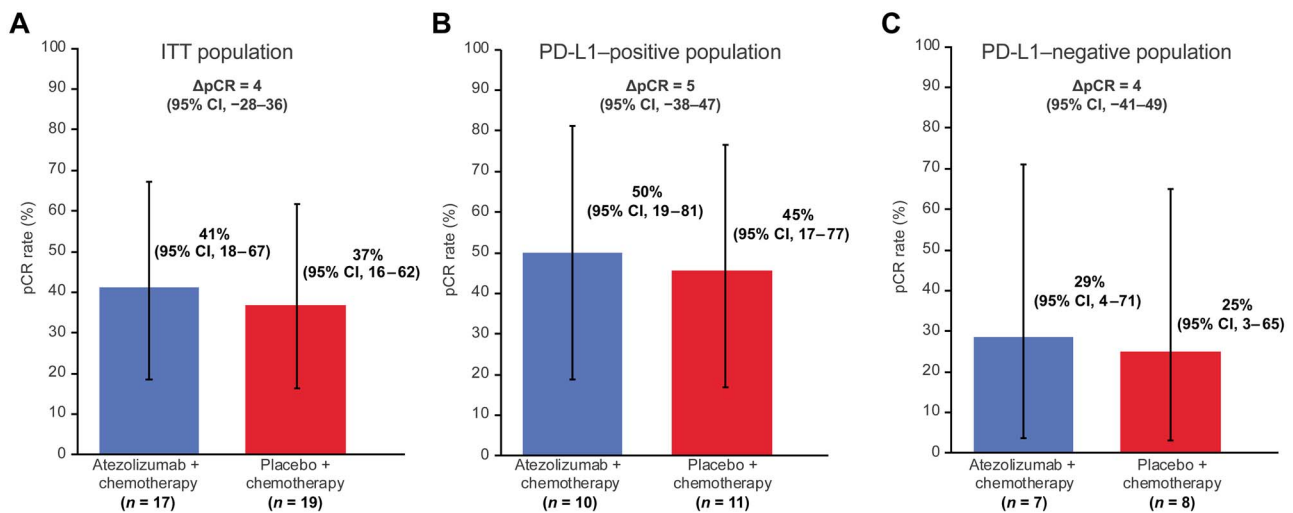


Figure 2. Pathological complete response in the (A) intention-to-treat population, (B) PD-L1-positive population and (C) PD-L1-negative population. pCR, pathological complete response; PD-L1, programmed death-ligand 1; ITT, intention-to-treat.

Table 2. Summary of adverse events in the Japanese safety-evaluable group during the neoadjuvant phase

Patients with AE, n (%)	Atezolizumab + chemotherapy (n = 17)	Placebo + chemotherapy (n = 19)
All-cause any grade AEs	17 (100)	19 (100)
Grade 3-4 AEs	12 (71)	14 (74)
Grade 5 AEs	0	0
Treatment-related AEs		
Any grade	17 (100)	19 (100)
Grade 3-4	12 (71)	13 (68)
Grade 5	0	0
Serious AEs	5 (29)	4 (21)
Treatment-related	5 (29)	4 (21)
AESIs		
Any grade	15 (88)	18 (95)
Grade 3-4	6 (35)	4 (21)
Requiring systemic corticosteroids	4 (24)	1 (5)
AEs leading to discontinuation of any study drug	10 (59)	9 (47)
Atezolizumab or placebo	7 (41)	7 (37)
nab-paclitaxel	7 (41)	6 (32)
Doxorubicin	2 (12)	3 (16)
Cyclophosphamide	2 (12)	3 (16)

AE, adverse event; AESI, AE of special interest.

largely overlapping 95% CIs, was observed in the atezolizumab arm (41%; 95% CI, 18-67) compared with that in the placebo arm (37%; 95% CI, 16-62). This trend of numerical increase in pCR was directionally consistent with what was observed in the global population (atezolizumab, 58%, 95% CI, 50-65; placebo, 41%, 95% CI, 34-49) (15).

In the Japanese PD-L1-positive population, patients who received neoadjuvant atezolizumab plus chemotherapy had a numerically higher pCR rate (50%; 95% CI, 19-81) than patients who received neoadjuvant placebo plus chemotherapy (45%; 95% CI, 17-77), consistent with the trend observed in the global study (atezolizumab, 69%, 95% CI, 57-79; placebo, 49%, 95% CI, 38-61). The proportion of patients who achieved a pCR was lower in the PD-L1-negative population than that in the ITT and the PD-L1-positive populations, with the atezolizumab arm continuing to demonstrate a numerically higher pCR rate (29%; 95% CI, 4-71) than the placebo

arm (25%; 95% CI, 3-65), consistent with what was observed in the global study population (atezolizumab, 48%; placebo, 34%). A consistent trend of increased pCR, although marginal, was observed in the atezolizumab arm among Japanese patients, regardless of PD-L1 expression status, similar to the results observed in the global IMpassion031 study.

The overall safety profile of the atezolizumab plus chemotherapy regimen in Japanese patients was similar to the safety profile observed among the global study population. No new safety signals were identified. Some differences were noted in specific AEs, which must be interpreted with caution considering the small number of patients who had these AEs. The Japanese patients in the IMpassion031 study showed similar rates of grade 3-4 AEs and treatment-related grade 3-4 AEs as the global study population. However, the incidence of some any-grade AEs appeared to be numerically higher in Japanese patients than in the global population: for example,

Table 3. Adverse events occurring in $\geq 10\%$ of patients in the safety-evaluable population during the neoadjuvant phase

Patients with AE, n (%)	Atezolizumab + chemotherapy (n = 17)		Placebo + chemotherapy (n = 19)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Alopecia	16 (94)	0	18 (95)	0
Nausea	14 (82)	0	14 (74)	0
Peripheral sensory neuropathy	14 (82)	2 (12)	17 (89)	0
Constipation	10 (59)	0	12 (63)	0
Neutrophil count decreased	10 (59)	4 (24)	13 (68)	8 (42)
Rash	10 (59)	1 (6)	8 (42)	0
Arthralgia	9 (53)	0	9 (47)	0
Malaise	9 (53)	0	8 (42)	0
White blood cell count decreased	9 (53)	2 (12)	8 (42)	5 (26)
Alanine aminotransferase increased	6 (35)	2 (12)	9 (47)	3 (16)
Myalgia	8 (47)	0	5 (26)	0
Dry skin	7 (41)	0	4 (21)	0
Insomnia	7 (41)	0	3 (16)	0
Pyrexia	7 (41)	0	4 (21)	0
Dysgeusia	6 (35)	0	7 (37)	0
Anemia	6 (35)	2 (12)	4 (21)	1 (5)
Stomatitis	6 (35)	0	4 (21)	0
Hepatic function abnormal	5 (29)	3 (18)	1 (5)	1 (5)
Aspartate aminotransferase increased	5 (29)	0	7 (37)	0
Diarrhoea	5 (29)	0	9 (47)	0
Headache	5 (29)	0	6 (32)	0
Epistaxis	4 (24)	0	2 (11)	0
Nail disorder	4 (24)	0	2 (11)	0
Nasopharyngitis	4 (24)	0	3 (16)	0
Blood alkaline phosphatase increased	3 (18)	0	0	0
Decreased appetite	3 (18)	0	5 (26)	0
Dry eye	3 (18)	0	1 (5)	0
Oedema	3 (18)	0	4 (21)	0
Fatigue	3 (18)	0	6 (32)	0
Infusion related reaction	3 (18)	0	3 (16)	0
Lymphocyte count decreased	2 (12)	2 (12)	2 (11)	2 (11)
Pain	3 (18)	0	1 (5)	0
Vomiting	3 (18)	0	3 (16)	0
Abdominal discomfort	2 (12)	0	1 (5)	0
Back pain	2 (12)	0	1 (5)	0
Blood lactate dehydrogenase increased	2 (12)	0	0	0
Dermatitis acneiform	2 (12)	0	2 (11)	0
Eczema	2 (12)	0	3 (16)	0
Keratitis	2 (12)	0	0	0
Lacrimation increased	2 (12)	0	0	0
Leukopenia	2 (12)	2 (12)	0	0
Neutropenia	2 (12)	2 (12)	1 (5)	1 (5)
Oedema peripheral	2 (12)	0	5 (26)	0
Pruritus	2 (12)	0	2 (11)	0
Skin hyperpigmentation	2 (12)	0	1 (5)	0
Thrombocytopenia	2 (12)	1 (6)	0	0
Abdominal pain upper	2 (12)	0	1 (5)	0
Vertigo	2 (12)	0	0	0
γ -glutamyltransferase increased	1 (6)	1 (6)	2 (11)	0
Hordeolum	1 (6)	0	2 (11)	0
Nail discoloration	1 (6)	0	5 (26)	0
Oropharyngeal pain	1 (6)	0	2 (11)	0
Paronychia	1 (6)	0	2 (11)	0
Peripheral motor neuropathy	1 (6)	0	2 (11)	0
Neuropathy peripheral	1 (6)	0	2 (11)	0
Red blood cell count decreased	1 (6)	0	2 (11)	0
Abdominal pain	0	0	2 (11)	0

(Continued)

Table 3. Continued

Patients with AE, <i>n</i> (%)	Atezolizumab + chemotherapy (<i>n</i> = 17)		Placebo + chemotherapy (<i>n</i> = 19)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Acne	0	0	2 (11)	0
Conjunctivitis	0	0	2 (11)	0
Macular oedema	0	0	2 (11)	0
Rash maculo-papular	0	0	2 (11)	0
Platelet count decreased	0	0	2 (11)	0
Upper respiratory tract infection	0	0	2 (11)	0

AE, adverse event.

Table 4. Adverse events of special interest in the safety-evaluable population during the neoadjuvant phase

Patients with AE, <i>n</i> (%)	Atezolizumab + chemotherapy (<i>n</i> = 17)		Placebo + chemotherapy (<i>n</i> = 19)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Rash	14 (82)	1 (6)	15 (79)	0
Hepatitis (laboratory abnormalities)	11 (65)	6 (35)	11 (58)	4 (21)
Infusion-related reactions	3 (18)	0	3 (16)	0
Ocular inflammatory toxicity	2 (12)	0	0	0
Guillain-Barré syndrome	0	0	1 (5)	0
Hypothyroidism	1 (6)	0	1 (5)	0
Pneumonitis	1 (6)	0	1 (5)	0

AE, adverse event.

alopecia (Japanese, 94% [*n* = 16]; global, 75% [*n* = 123]), nausea (Japanese, 82% [*n* = 14]; global, 65% [*n* = 106]) and peripheral sensory neuropathy (Japanese, 82% [*n* = 14]; global, 33% [*n* = 54]). A higher incidence of peripheral sensory neuropathy has been reported in Japanese patients in other breast cancer studies as well (26), including the IMpassion130 study, which reported a numerically higher frequency of alopecia and peripheral sensory neuropathy in the atezolizumab arm of the Japanese subgroup than in the overall population (21). In the placebo arm of the IMpassion130 study, numerically higher incidences of alopecia, nausea and peripheral sensory neuropathy were also seen in Japanese patients compared with the global population, which was an observation common in both the atezolizumab and placebo arms of the IMpassion031 study, as well.

The frequency of discontinuing any treatment due to AEs also appeared to be higher among Japanese patients than in the global population, in both the atezolizumab (Japanese, 59% [*n* = 10]; global, 23% [*n* = 37]) and placebo (Japanese, 47% [*n* = 9]; global, 20% [*n* = 33]) treatment arms. Atezolizumab or placebo treatment discontinuation was also higher in the Japanese population (atezolizumab, 41% [*n* = 7]; placebo, 37% [*n* = 7]) than the global population (atezolizumab, 13% [*n* = 21]; placebo, 11% [*n* = 19]) (15). The frequency of treatment discontinuation of any study drug due to AEs in the Japanese patients was similar between the treatment arms, as was also observed in the global study population. In both the placebo and atezolizumab arms, treatment discontinuation in Japanese patients was most frequently reported to be caused by AEs.

Dose-dense adjuvant chemotherapy regimens, although not approved in Japan, are recommended by Japanese treatment guidelines for breast cancers with a high relapse rate, such as TNBC (27). Among Japanese patients in the IMpassion031 study, 12 patients in the atezolizumab arm and 17 patients in the placebo

arm received dose-dense neoadjuvant chemotherapy, all of whom also received supportive treatment with pegfilgrastim to minimize treatment discontinuation with dose-dense anthracycline-based chemotherapy, in accordance with the protocol. One patient in each arm was administered only one dose of anthracycline-based chemotherapy with pegfilgrastim. Treatment interval between pegfilgrastim administration and the next chemotherapy dose was calculated for 11 patients in the atezolizumab arm and 16 patients in the placebo arm, for those who were administered at least two doses of pegfilgrastim. The minimum treatment interval between pegfilgrastim administration and the next session of chemotherapy ranged from 11 to 14 days. There was no notable increase in the incidence and severity of neutropenic events observed in either the atezolizumab or placebo arms, irrespective of the treatment interval between pegfilgrastim administration and the following chemotherapy session. Although the sample size of patients receiving supportive pegfilgrastim treatment was small, these results suggest that pegfilgrastim can be safely administered and is effective for managing neutropenia in patients receiving atezolizumab plus dose-dense anthracycline-based chemotherapy.

Study strengths include the randomized and controlled nature of the study. However, the small sample size of this exploratory subgroup analysis was a limitation of this study. As IMpassion031 study was not designed to provide a definitive interpretation in the Japanese subgroup, further investigations with immunotherapy combinations are required in this patient subgroup. The modest increase in the pCR rate in the atezolizumab arm (4–5%) must be interpreted with caution in view of the small sample size of this descriptive analysis and the wide 95% CIs for the pCR rate difference.

In conclusion, in Japanese patients with early stage TNBC, the numerical improvement in pCR observed with atezolizumab

combined with neoadjuvant *nab*-paclitaxel, followed by doxorubicin and cyclophosphamide, versus that with placebo showed a trend directionally consistent with that observed in the global IMpassion031 study population. The safety profile of the investigated treatment regimen observed in Japanese patients was similar to that observed in the overall IMpassion031 study population. Atezolizumab plus neoadjuvant chemotherapy comprising *nab*-paclitaxel, followed by doxorubicin and cyclophosphamide, was well tolerated in Japanese patients. No new safety signals were identified.

Data sharing statement

For eligible studies qualified researchers may request access to individual patient level clinical data through a data request platform. At the time of writing this request platform is Vivli. <https://vivli.org/ourmember/roche/>. For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, visit https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient reidentification.

Supplementary Material

Supplementary material can be found at *Japanese Journal of Clinical Oncology* online.

Author contributions

Substantial contributions to the conception or design of the work: S.S., K.Ki., A.H.

Acquisition of data for the work: S.S., S.O., M.I., N.H., K.Ko., N.M., N.N., T.Y., M.H.

Analysis of data for the work: S.S., S.N.

Interpretation of data for the work: S.S., N.H., N.M., K.Ki., A.H.

Revising the work critically for important intellectual content: all authors.

Final approval of the version to be published: all authors.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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Conflict of interests

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