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ORIGINAL ARTICLE

First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis

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Background: Guidelines recommend atezolizumab plus nab-paclitaxel (A + nP) for first-line treatment of unresectable, locally advanced, or metastatic triple-negative breast cancer expressing programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells (IC), based on IMpassion130. We report the final overall survival (OS) and safety of that study as per the prespecified analysis plan.

Patients and methods: Patients were randomized to nP 100 mg/m^2 (days 1, 8, and 15 of a 28-day cycle) with atezolizumab 840 mg (A + nP) or placebo (P + nP; days 1 and 15), until progression or unacceptable toxicity. Coprimary endpoints were progression-free survival [intention-to-treat (ITT) and PD-L1 IC-positive populations] and OS (tested hierarchically in the ITT population and, if significant, in the PD-L1 IC-positive population).

Results: Each arm comprised 451 patients; 666 (73.8%) had died by the final OS analysis cut-off (median follow-up, 18.8 months; interquartile range, 8.9-34.7 months). Median OS in the ITT population was 21.0 months [95% confidence interval (CI), 19.0-23.4 months] with A + nP, and 18.7 months (95% CI, 16.9-20.8 months) with P + nP [stratified hazard ratio (HR), 0.87; 95% CI, 0.75-1.02; $P = 0.077$]. Exploratory analysis in the PD-L1 IC-positive population showed a median OS of 25.4 months (95% CI, 19.6-30.7 months) with A + nP ($n = 185$) and 17.9 months (95% CI, 13.6-20.3 months) with P + nP ($n = 184$; stratified HR, 0.67; 95% CI, 0.53-0.86). Safety outcomes were consistent with previous analyses and the known toxicity profiles of each agent. Immune-mediated adverse events of special interest were reported in 58.7% and 41.6% of patients treated with A + nP and P + nP, respectively.

Conclusion: Although the OS benefit in the ITT population was not statistically significant, precluding formal testing, clinically meaningful OS benefit was observed with A + nP in PD-L1 IC-positive patients, consistent with prior interim analyses. This combination remained safe and tolerable with longer follow-up.

Key words: triple-negative breast cancer, atezolizumab, nab-paclitaxel, first-line treatment, immune checkpoint inhibitor, metastatic

INTRODUCTION

Triple-negative breast cancer (TNBC), lacking estrogen or progesterone receptors on the cell surface and without overexpression or amplification of human epidermal growth factor receptor 2 (HER2), is associated with poor prognosis.[1,2] Until recently, systemic treatment for metastatic TNBC comprised chemotherapy alone[3] or, in some countries, combined with bevacizumab, and single-agent poly

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(ADP-ribose) polymerase (PARP) inhibitors in patients with germline *BRCA* mutations.[4-6] Expression of programmed death-ligand 1 (PD-L1) suppresses immune responses against tumors.[7,8] PD-L1 expression occurs in TNBC and is seen more frequently on tumor-infiltrating immune cells (IC) than on tumor cells.[9,10] We hypothesized that PD-L1 inhibition might be effective in treating TNBC and that combination treatment strategies may act synergistically since standard chemotherapy agents may elicit immune responses.[11]

The global, randomized, double-blind phase III IMpassion130 trial compared atezolizumab combined with nab-paclitaxel (A + nP) versus placebo plus nab-paclitaxel (P + nP) in patients with previously untreated, inoperable, locally advanced, or metastatic TNBC.[12,13] The study had four prespecified coprimary endpoints: progression-free survival (PFS) tested in parallel in both the intention-to-treat (ITT) population and in patients with PD-L1-expressing IC covering $\geq$1% of the tumor area (IC positive), and overall survival (OS) tested hierarchically in the ITT population and then, if significant, in the PD-L1 IC-positive population. The primary, and final, PFS analysis demonstrated significant benefit with A + nP in the PD-L1 IC-positive population. PFS improvement in the ITT population was driven by the PD-L1 IC-positive population.[12,14] In patients with PD-L1 IC-positive disease, a statistically and clinically meaningful 2.5-month PFS improvement was observed with A + nP [hazard ratio (HR), 0.62; 95% confidence interval (CI), 0.49-0.78; $P < 0.0001$].

The first interim OS analysis in IMpassion130 was carried out alongside the primary PFS analysis,[12] later followed by a second prespecified interim analysis.[13] As neither analysis detected statistically significant OS improvement in the ITT population, OS was not formally tested in the PD-L1 IC-positive population as per the prespecified testing hierarchy. However, exploratory analyses in the PD-L1 IC-positive population at both time points revealed clinically meaningful OS benefit with A + nP (HR, 0.62; 95% CI, 0.45-0.86 and HR, 0.71; 95% CI, 0.54-0.93, respectively), providing additional evidence for efficacy benefit with A + nP in this group.[12,13]

Based on primary results from IMpassion130, A + nP is approved by global health authorities for use in patients with unresectable, locally advanced, or metastatic TNBC and tumors that express PD-L1[15,16] and recommended in international treatment guidelines for this group.[17-19] The safety profile of A + nP was in line with the individual drug profiles, and coadministration did not appear to impact exposure to nP.[12,13] No new safety issues emerged with longer follow-up.[13] We report the prespecified final OS analysis of the pivotal IMpassion130 study and long-term safety results for A + nP in treatment-naïve, unresectable, locally advanced, or metastatic TNBC.

PATIENTS AND METHODS

Study design and conduct

The randomized, double-blind, placebo-controlled phase III IMpassion130 (NCT02425891) trial was conducted at 246 centers in 41 countries across Europe, North America, Asia, and Latin America. The complete study design was published previously,[12] and the study protocol is provided in the Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2021.05.355. The study was carried out in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki; all patients provided written informed consent. The protocol was approved by independent review boards or ethics committees at each center. Patients underwent 1 : 1 randomization using a permuted block design and an interactive voice—web response system to receive A + nP or P + nP. Randomization was stratified by the presence of liver metastases (yes versus no), previous neoadjuvant or adjuvant taxane therapy (yes versus no), and PD-L1 expression on IC as a percentage of tumor area [<1% (PD-L1 IC negative) versus $\geq$1% (PD-L1 IC positive) using the VENTANA SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems, Oro Valley, AZ)]. All investigators, study site personnel, and patients were blinded to treatment assignment.

Patients

Eligible patients were aged $\geq$18 years, with an Eastern Cooperative Oncology Group performance status of 0-1. A diagnosis of unresectable, locally advanced, or metastatic TNBC was required, with negative HER2, estrogen receptor, and progesterone receptor status determined locally as per the American Society of Clinical Oncology and College of American Pathologists guidelines.[20,21] Representative tumor specimens evaluable for prospective PD-L1 testing by immunohistochemistry (VENTANA SP142 PD-L1 assay) were required from all patients. Patients had to be eligible for taxane monotherapy, have had no previous chemotherapy or targeted therapy for metastatic TNBC, and have measurable disease as per RECIST version 1.1 (v1.1).

Procedures

Patients were given nP 100 mg/m^2 of body surface area on days 1, 8, and 15 of every 28-day cycle, and either atezolizumab 840 mg or placebo on days 1 and 15 of each cycle. Study treatments were administered intravenously, until disease progression (PD; investigator assessed as per RECIST v1.1) or unacceptable toxicity. Following a protocol amendment, placebo-arm patients who had not experienced PD or received any non-study anticancer therapy at the time of unblinding could cross over to receive atezolizumab. Temporary suspension of atezolizumab or placebo was permitted at the investigator's discretion for adverse event (AE) management, but dose reduction was not allowed. In the case of toxicity, nP dose reduction followed by discontinuation could occur if necessary. AEs and laboratory values were assessed on days 1, 8, and 15 of every cycle, as per the National Cancer Institute Common Terminology Criteria for AEs version 4.0. Tumor imaging by computed tomography or magnetic resonance imaging was carried out at baseline, every 8 weeks for 12 months, and then every 12 weeks until PD. Survival follow-up took place every 3 months from treatment discontinuation until death.

Endpoints

The coprimary endpoints were PFS (as per RECIST 1.1, tested in parallel in the ITT and PD-L1 IC-positive populations) and OS (tested initially in the ITT population and then, if significant, in the PD-L1 IC-positive population). Secondary efficacy endpoints included objective response rate, duration of response, and time to deterioration (TTD) in health-related quality of life (HRQoL; see Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2021.05.355).[22] Exploratory endpoints included additional patient-reported outcomes (PROs).

Statistical analysis

During the study, the protocol was amended from a single primary PFS endpoint to the coprimary endpoints of PFS and OS, requiring an increase in the sample size from ~350 to ~900 patients. Two interim OS analyses carried out after 59% and 80% of the total expected OS events had occurred and a final OS analysis were planned. The definitive, final PFS analysis occurred concurrently with the first interim OS analysis. Based on the outcomes of the primary PFS analysis, the final OS analysis was planned when 74% of patients had experienced mortality events.

A stepwise testing procedure was used to control the type I error for the study for treatment comparisons of the coprimary endpoints and for the secondary efficacy endpoint of objective response rate in the ITT and PD-L1 IC-positive populations. The significance boundary at the final OS analysis was determined based on the Lan—DeMets implementation of the O'Brien—Fleming use function. The null hypothesis of no difference in OS between treatment arms was tested with an allocated type I error at an α level of 0.0407. OS was tested hierarchically, first in the ITT population and then, if positive, in the PD-L1 IC-positive population, reusing the type I error used for ITT.

Comparison of OS between treatment groups was carried out using a stratified log-rank test, with HRs estimated using a stratified Cox proportional hazards model (with the same stratification factors used in randomization). OS analyses used the Kaplan—Meier method, with 95% CI estimated with the Brookmeyer—Crowley method. Exploratory analyses of OS in subgroups defined by demographic and baseline characteristics were prespecified in the statistical analysis plan to assess the consistency of study results. Safety was evaluated in all patients who received any amount of any study drug, grouped by whether any doses of atezolizumab were received. A post hoc analysis using a cure-rate model[23] is further detailed in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2021.05.355. Statistical analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients

In total, 902 patients were enrolled between 23 June 2015 and 24 May 2017. The ITT population comprised 451 patients each assigned to the A + nP and P + nP arms. The PD-L1 IC-positive population included 369 (41%) patients, 185 in the A + nP arm and 184 in the P + nP arm. The safety-evaluable population comprised 460 A + nP patients and 430 P + nP patients. Six patients per group received no treatment, six P + nP-arm patients received atezolizumab in error, and nine patients crossed over from P + nP to A + nP after unblinding for the primary analysis and were evaluated for safety with the atezolizumab group (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.05.355). Baseline characteristics, described previously,[12] were generally well balanced between treatment groups and between the ITT and PD-L1 IC-positive populations (Table 1).

Final OS

At the current data cut-off (14 April 2020), the median follow-up was 18.8 months (interquartile range, 8.9-34.7 months), and 27 (6.0%) patients in the A + nP group and 8 (1.8%) patients in the P + nP group remained on any treatment. In the A + nP arm, 322 (71.4%) patients had died, compared with 344 (76.3%) in the P + nP arm. Median OS in the ITT population was 21.0 months (95% CI, 19.0-23.4 months) with A + nP and 18.7 months (95% CI, 16.9-20.8 months) with P + nP (stratified HR, 0.87; 95% CI, 0.75-1.02; $P = 0.077$) (Figure 1A). The OS outcome in the ITT population did not cross the boundary for statistical significance. Thus, as per the hierarchical testing procedure, OS was not formally tested in the PD-L1 IC-positive population. However, exploratory analyses were carried out in this population, of whom 120 (65%) patients in the A + nP arm and 139 (76%) patients in the P + nP arm had died at the time of data cut-off. Median OS in the PD-L1 IC-positive population was 25.4 months (95% CI, 19.6-30.7 months) with A + nP and 17.9 months (95% CI, 13.6-20.3 months) with P + nP (stratified HR, 0.67; 95% CI, 0.53-0.86) (Figure 1B). Median OS in PD-L1 IC-negative patients was 19.7 months in each treatment arm (stratified HR, 1.02; 95% CI, 0.84-1.24) (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2021.05.355). OS analyses in prespecified subgroups of the ITT and PD-L1 IC-positive populations are presented (Figure 2).

At the time of analysis, subsequent non-protocol anticancer therapy received during study follow-up was generally balanced between arms. In the ITT population, 288 (63.9%) patients in the A + nP arm and 311 (69.0%) patients in the P + nP arm had received ≥1 therapy. Nineteen (4.2%) patients in the A + nP arm and 36 (8.0%) patients in the P + nP arm received checkpoint inhibitors (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.05.355). This includes nine (2.0%) patients from the P + nP arm who had not experienced PD at the time of the primary analysis and crossed over to receive atezolizumab after unblinding.

Long-term survival

Post hoc analyses were carried out to assess the potential for long-term survival in patients from IMpassion130. The 36-month OS rates for ITT patients were 28.1% (95% CI,

Table 1. Baseline patient characteristics

Characteristic	ITT population		PD-L1 IC-positive population	
	A + nP (n = 451)	P + nP (n = 451)	A + nP (n = 185)	P + nP (n = 184)
Age, median, range, (IQR), years	55.0, 20-82, (46-64)	56.0, 26-86, (47-65)	53.0, 26-82, (44-63)	53.0, 28-85, (44-63)
Age, years				
18-40	63 (14.0)	51 (11.3)	31 (16.8)	24 (13.0)
41-64	284 (63.0)	285 (63.2)	111 (60.0)	117 (63.6)
≥65	104 (23.1)	115 (25.5)	43 (23.2)	43 (23.4)
Female sex	448 (99.3)	450 (99.8)	184 (99.5)	184 (100.0)
Race				
White	308 (68.3)	301 (66.7)	125 (67.6)	129 (70.1)
Asian	85 (18.8)	76 (16.9)	38 (20.5)	28 (15.2)
Black or African American	26 (5.8)	33 (7.3)	9 (4.9)	14 (7.6)
American Indian or Alaska Native	17 (3.8)	23 (5.1)	8 (4.3)	9 (4.9)
Native Hawaiian or other Pacific Islander	1 (0.2)	0	0	0
Multiple	2 (0.4)	3 (0.7)	0	0
Unknown	12 (2.7)	15 (3.3)	5 (2.7)	4 (2.2)
ECOG PS, n/n (%)				
0	256/450 (56.9)	270/450 (60.0)	107/185 (57.8)	112/184 (60.9)
1	193/450 (42.9)	179/450 (39.8)	77/185 (41.6)	72/184 (39.1)
2[a]	1/450 (0.2)	1/450 (0.2)	1/185 (0.5)	0
Metastatic disease, n/n (%)	404/450 (89.8)	408/450 (90.7)	162/185 (87.6)	159/183 (86.9)
Number of metastatic sites, n/n (%)				
0-3	332/450 (73.8)	341/449 (75.9)	149/185 (80.5)	140/183 (76.5)
≥4	118/450 (26.2)	108/449 (24.1)	36/185 (19.5)	43/183 (23.5)
Site of metastatic disease				
Liver[b]	126 (27.9)	118 (26.2)	44 (23.8)	39 (21.2)
Bone	145 (32.2)	141 (31.3)	54 (29.2)	49 (26.6)
Brain	30 (6.7)	31 (6.9)	15 (8.1)	11 (6.0)
Lung	226 (50.1)	242 (53.7)	86 (46.5)	98 (53.3)
Lymph node only, n/n (%)	33/450 (7.3)	23/449 (5.1)	18/185 (9.7)	13/183 (7.1)
Prior neoadjuvant or adjuvant treatment	284 (63.0)	286 (63.4)	125 (67.6)	117 (63.6)
Prior taxane use[b]	231 (51.2)	230 (51.0)	96 (51.9)	94 (51.1)
Prior anthracycline use	243 (53.9)	242 (53.7)	109 (58.9)	101 (54.9)
Prior radiotherapy	268 (59.4)	280 (62.1)	119 (64.3)	112 (60.9)
Radiotherapy of the brain	25 (5.5)	27 (6.0)	14 (7.6)	11 (6.0)
Time from last surgery until diagnosis with unresectable locally advanced or metastatic disease, median, range, (IQR), months	24.5, 0.0-251.2, (15.9-38.9)	24.8, 0.0-254.0, (17.0-44.6)	21.5, 0.0-161.9, (15.0-36.2)	22.1, 0.3-156.3, (14.1-39.3)

Data are presented as n (%), unless specified otherwise, based on the full population indicated in the column header. If the baseline characteristic was not available for all patients, the denominator provided is the total number of patients assessable for this characteristic.

A + nP, atezolizumab plus nab-paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, tumor-infiltrating immune cell; IQR, interquartile range; ITT, intention to treat; PD-L1, programmed death-ligand 1; P + nP, placebo plus nab-paclitaxel.

[a] Two patients had ECOG PS 2 before start of treatment.

[b] As recorded in the case report form.

23.8% to 32.4%) in the A + nP group and 24.9% (95% CI, 20.8% to 29.0%) in the P + nP group. In the PD-L1 IC-positive population, 36-month OS rates were 35.8% (95% CI, 28.8% to 42.9%) and 22.2% (95% CI, 15.9% to 28.5%), respectively. When assessing long-term survival in the PD-L1 IC-positive population using a cure-rate model to account for patients who do not die of TNBC, estimated final survival rates (95% CI) were 17.6% (6.8% to 38.3%) and 9.1% (2.5% to 28.1%) in the A + nP and P + nP arms, respectively. These data are also supported by long-term PFS results (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2021.05.355). Among patients alive at 3 years, 12 (41.2%) patients in the A + nP arm and 4 (29.8%) patients in the P + nP arm had not experienced PD.

PROs

PRO endpoints measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30) demonstrated no difference between treatment arms with respect to TTD in global health status or HRQoL in either the PRO-evaluable ITT (HR, 0.98; 95% CI, 0.81-1.18; median, 8.2 months with A + nP and 8.0 months with P + nP) or PD-L1 IC-positive (HR, 0.98; 95% CI, 0.73-1.31; median, 7.6 and 6.4 months, respectively) populations (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.05.355). Similarly, no difference between arms was observed in TTD of role, physical, and cognitive functioning in either the ITT or PD-L1-positive populations (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.05.355). Collectively, these data indicate that patients in both arms maintained baseline HRQoL and functioning for similar durations of time.

Safety

In total, 22 (4.8%) safety-evaluable patients in the A + nP arm and 6 (1.4%) in the P + nP arm were treated with nP

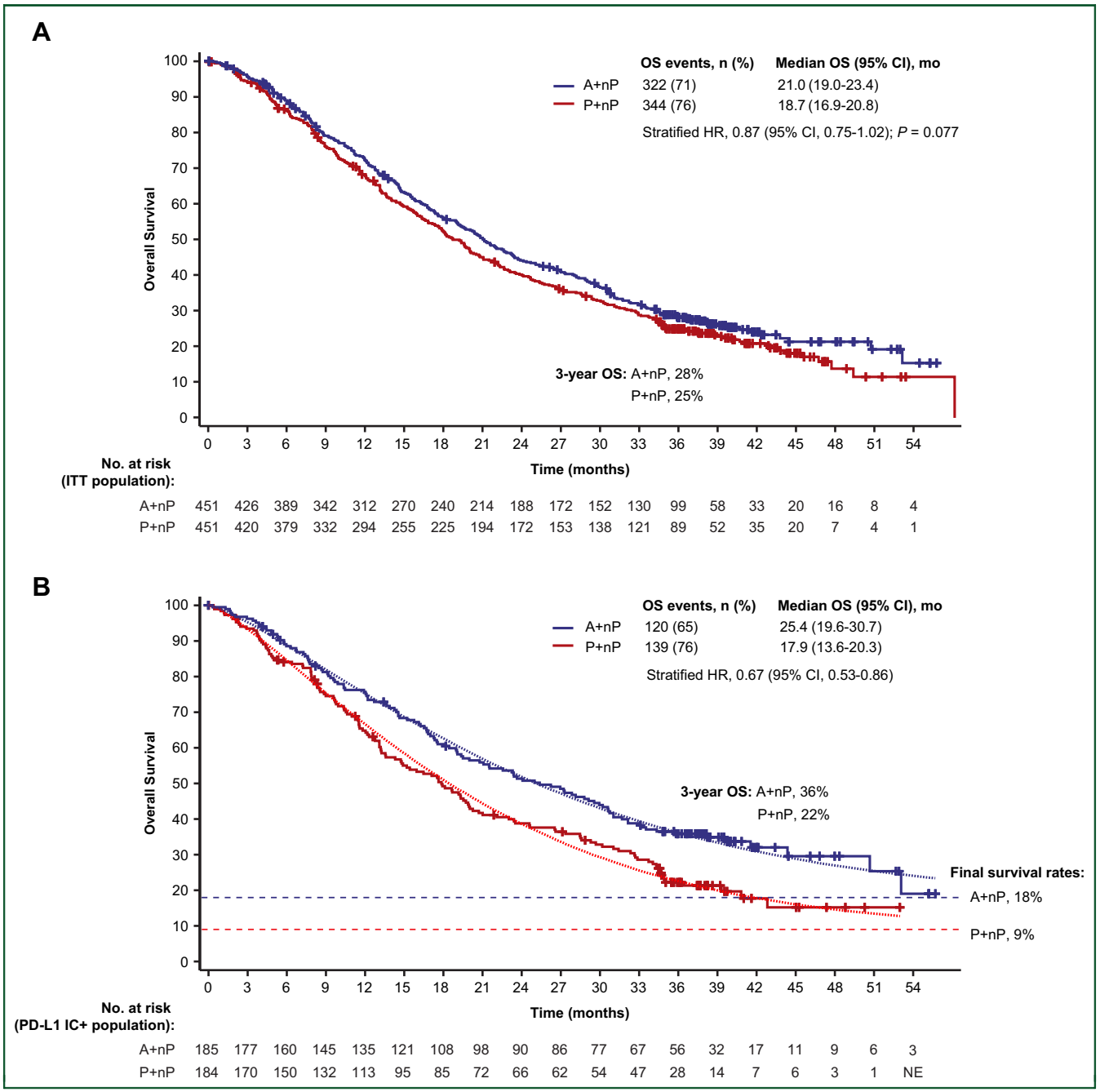

Figure 1. Kaplan–Meier curves of OS in the (A) ITT and (B) PD-L1 IC-positive populations.
A + nP, atezolizumab plus nab-paclitaxel. In panel B, modeled survival curves (thin dotted lines) and final rates (dashed lines) are additionally displayed.
CI, confidence interval; HR, hazard ratio; IC, tumor-infiltrating immune cell; ITT, intention to treat; NE, not estimable; OS, overall survival; P + nP, placebo plus nab-paclitaxel; PD-L1, programmed death-ligand 1.

for >24 months; 13 (2.8%) and 8 (1.9%), respectively, received nP for 18-24 months. Thirty-eight (8.3%) patients in the A + nP arm received atezolizumab for >24 months (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.05.355).

Any-grade AEs were reported in 457 (99%) patients in the A + nP arm and 421 (98%) patients in the P + nP arm (Table 2), the most frequent of which in both arms were alopecia, fatigue, and nausea (Table 3). No confirmed or suspected coronavirus disease-2019-related AEs were reported. AEs resulted in treatment discontinuation in 88 (19%) A + nP-arm patients and 36 (8%) P + nP-arm patients, most commonly due to neuropathy (Table 2).

Grade 3-4 AEs were observed in 233 (51%) and 183 (43%) patients, respectively (Table 2); AE frequencies were generally balanced across treatment groups (Table 3; Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.05.355), with exceptions including grade 3 peripheral neuropathy [in 26 (5.7%) patients in the A + nP group versus 12 (2.8%) patients in the P + nP group], which was considered taxane-related. No additional grade 5 AEs were reported since the previous analysis, with

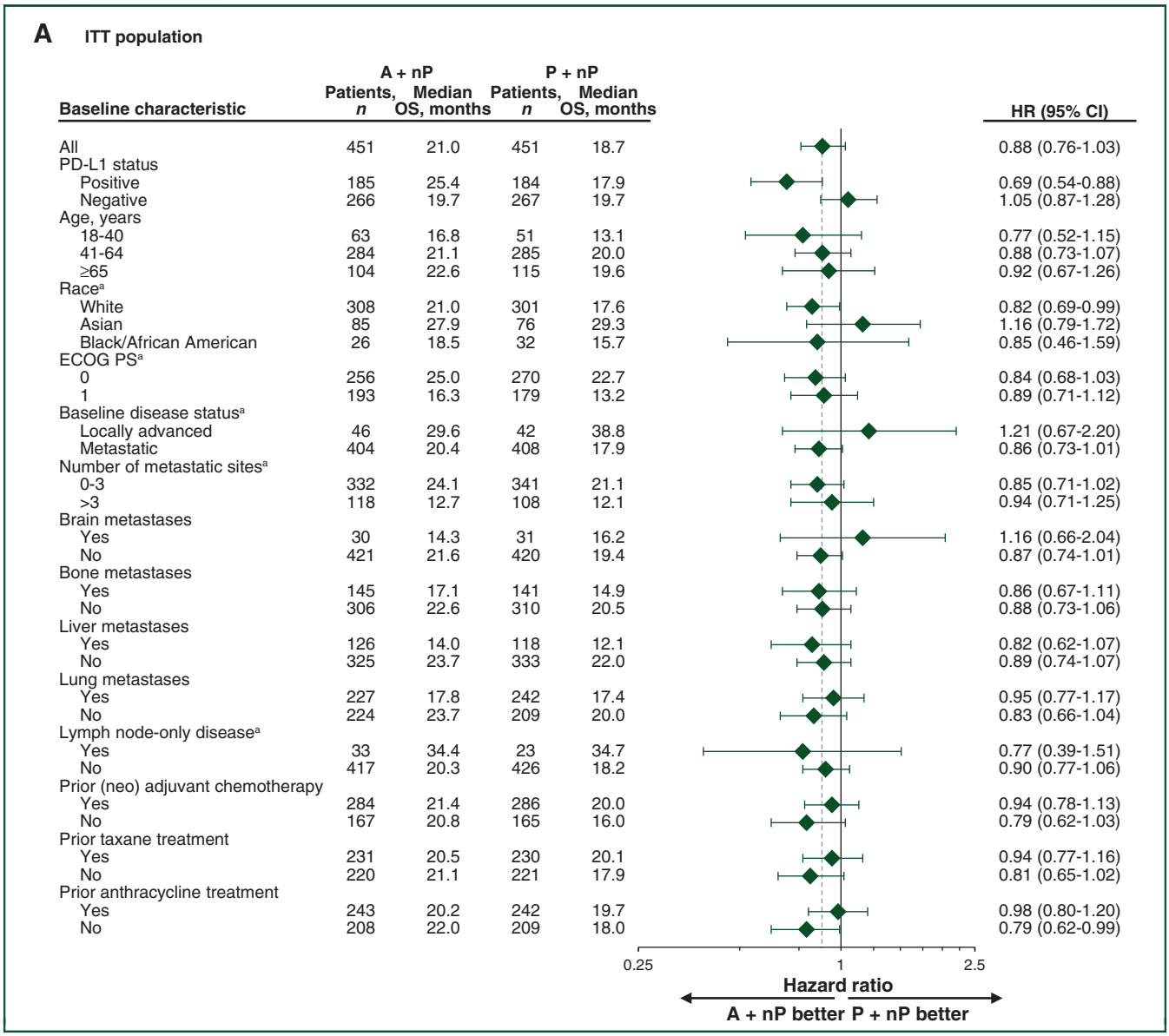

Figure 2. Forest plot of OS in patient subgroups in the (A) ITT and (B) PD-L1 IC-positive populations.
A + nP, atezolizumab plus nab-paclitaxel; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio (unstratified analysis); IC, tumor-infiltrating immune cell; ITT, intention to treat; OS, overall survival; P + nP, placebo plus nab-paclitaxel.
[a] Excludes patients with unknown or other values for indicated categories.

the incidence remaining at ~1% in each arm. Serious AEs were reported in 110 (24%) patients in the A + nP group and 80 (19%) in the P + nP group (Table 2).

AEs of special interest (AESIs), defined by the trial sponsor based on the immune-mediated risks of atezolizumab and similar agents, were observed in 270 (59%) and 179 (42%) patients treated with A + nP and P + nP, respectively. These were grades 3/4 in 39 (9%) and 20 (5%) patients, respectively (Table 2). The only new AESI category reported since the previous analysis was hypophysitis, with one A + nP-arm patient experiencing a grade 3 event. AESIs with the greatest difference in incidence between treatment groups were any-grade rash, hypothyroidism, hyperthyroidism, pneumonitis, and adrenal insufficiency (Table 4).

DISCUSSION

This final OS analysis from IMpassion130, carried out after >70% of deaths had occurred, was consistent with outcomes of the two previous interim OS analyses.[12,13] A clinically meaningful OS improvement was observed with A + nP versus P + nP in the PD-L1 IC-positive population, with an HR of 0.67 and a median increase of 7.5 months. This could not be formally tested because the clinical benefit of A + nP in the ITT population did not cross the boundary for statistical significance. Overall, the OS benefit of this regimen is most pronounced in patients with PD-L1 IC-positive tumors, consistent with PFS results.[12,14] Similar to data from other immunotherapy studies across tumor types,[24-30] the absolute magnitude of OS improvement was

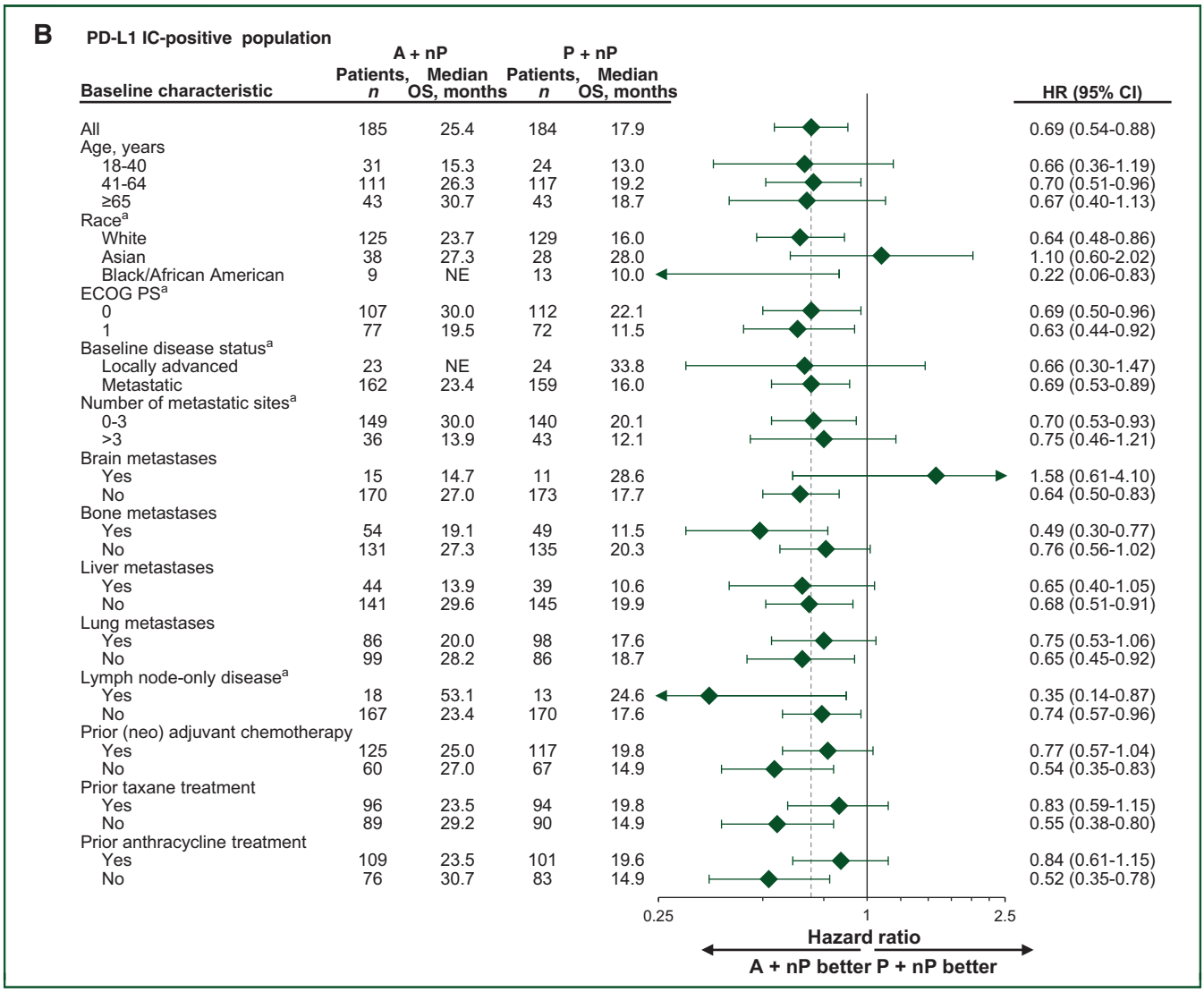

Figure 2. Continued.

greater than the magnitude of PFS improvement. Subsequent therapies remained balanced between treatment arms, mostly dominated by salvage chemotherapy agents, including capecitabine, gemcitabine, and carboplatin. Use of post-protocol checkpoint inhibitors was low in both arms, and nine patients crossed over from the placebo to the immunotherapy arm. The OS benefit observed in the PD-L1 IC-positive population was therefore unlikely to have been impacted by post-progression therapies, suggesting that it is a genuine indication of the first-line treatment impact of A + nP.

With longer follow-up, safety data remained consistent with the previous two analyses, with no evidence of late-onset or cumulative toxicity, and no new safety signals. Atezolizumab did not compromise exposure to nP. Many of the common toxicities reported reflect those typically associated with nP.[31,32] The spectrum of AESIs reported is consistent with those seen previously with atezolizumab and the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab across TNBC treatment settings.[33,34] Times to onset of AESIs were comparable with those in the previous analyses and in atezolizumab monotherapy trials.[12,13,16,35,36] Overall, AESIs were manageable; most resolved and did not lead to treatment withdrawal in the majority of patients. Consistent with earlier data,[22] updated PRO analyses indicate that adding atezolizumab to nP does not compromise patients' HRQoL or day-to-day functioning or increase patients' toxicity burden in either the ITT or PD-L1 IC-positive populations.

Importantly, this analysis documents long-term PFS and OS in PD-L1 IC-positive A + nP-arm patients, with 3-year survival now reported. Further, although OS in this population was not formally tested as per the prespecified study design, the 7.5-month improvement is clinically meaningful, underscoring that PD-L1 acts as a predictive biomarker for clinical benefit from A + nP in metastatic TNBC. In contrast, no treatment effect was seen with A + nP in PD-L1-negative patients. A similar trial investigating the PD-1 inhibitor pembrolizumab with chemotherapy was also positive for PFS in the subgroup with high PD-L1 expression (combined

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Table 2. Safety summary (safety-evaluable population)

	A + nP (n = 460)	P + nP (n = 430)
All-cause AEs[a]		
Any grade	457 (99.3)	421 (97.9)
Grade 3 or 4	233 (50.7)	183 (42.6)
Grade 5	6 (1.3)	3 (0.7)
Serious AEs	110 (23.9)	80 (18.6)
AE leading to any treatment withdrawal[b]	88 (19.1)	36 (8.4)
AE leading to A or P withdrawal	37 (8.0)	4 (0.9)
AE leading to nP withdrawal	85 (18.5)	36 (8.4)
Treatment-related AEs		
Any grade	444 (96.5)	403 (93.7)
Grade 3 or 4	191 (41.5)	129 (30.0)
Grade 5[c]	2 (0.4)	1 (0.2)
Serious AEs	58 (12.6)	31 (7.2)
AEs of special interest[d]		
Any grade	270 (58.7)	179 (41.6)
Grade 3 or 4	39 (8.5)	20 (4.7)
Grade 5	1 (0.2)	1 (0.2)
AEs of special interest leading to A or P withdrawal	11 (2.4)	2 (0.5)
Requiring treatment with systemic corticosteroids ≤30 days from onset	73 (15.9)	30 (7.0)

Data are presented as *n* (%).
A + nP, atezolizumab plus nab-paclitaxel; AE, adverse event; P + nP, placebo nab-paclitaxel.
[a] No confirmed or suspected coronavirus disease-19 AEs were reported.
[b] Most commonly due to neuropathy.
[c] Grade 5 AEs included autoimmune hepatitis (A), septic shock, (A + nP), and hepatic failure (P + nP).
[d] Defined by sponsor based on immune-mediated risks of atezolizumab and other in-class agents.

positive score ≥10 detected using 22C3 immunohistochemistry assay),[37] leading to regulatory approval in this population. However, PFS benefit was not seen in patients with PD-L1-positive metastatic TNBC in the randomized IMpassion131 study, which investigated the benefit—risk of another chemotherapy agent, paclitaxel, plus atezolizumab versus paclitaxel plus placebo.[38] The data from IMpassion131 and IMpassion130 indicate that atezolizumab should be paired with nP specifically in the treatment of metastatic TNBC.

BRCA mutation status is also used as a biomarker in HER2-negative metastatic breast cancer, including TNBC, and can predict PFS benefit from PARP inhibitors.[39,40] However, final OS analyses from phase III trials have failed to demonstrate OS benefit with either olaparib or talazoparib.[41,42] These findings coupled with data from the IMpassion130 study indicating that patients with PD-L1 IC-positive tumors obtain clinical benefit from A + nP independent of *BRCA* mutation status[14] may help guide the sequencing of immunotherapy combinations and PARP inhibitors in patients with both PD-L1 IC-positive tumors and germline *BRCA* mutations.

In conclusion, outcomes of this final OS analysis continue to support the PD-L1 testing of newly diagnosed metastatic TNBC to identify patients with PD-L1 IC-positive tumors who will benefit from standard-of-care use of A + nP.

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Table 3. Adverse events (safety-evaluable population)[a]

	A + nP (*n* = 460)			P + nP (*n* = 430)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any AE	457 (99.3)	204 (44.3)	26 (5.7)	421 (97.9)	151 (35.1)	30 (7.0)
Alopecia	263 (57.2)	2 (0.4)	0	247 (57.4)	1 (0.2)	0
Fatigue	216 (47.0)	18 (3.9)	0	194 (45.1)	15 (3.5)	0
Nausea	215 (46.7)	5 (1.1)	0	165 (38.4)	8 (1.9)	0
Diarrhea	151 (32.8)	8 (1.7)	0	149 (34.7)	9 (2.1)	0
Anemia	130 (28.3)	16 (3.5)	0	116 (27.0)	12 (2.8)	0
Cough	126 (27.4)	0	0	80 (18.6)	0	0
Constipation	117 (25.4)	3 (0.7)	0	108 (25.1)	1 (0.2)	0
Headache	116 (25.2)	3 (0.7)	0	93 (21.6)	4 (0.9)	0
Neutropenia	102 (22.2)	29 (6.3)	10 (2.2)	65 (15.1)	22 (5.1)	13 (3.0)
Neuropathy peripheral	100 (21.7)	26 (5.7)	0	97 (22.6)	12 (2.8)	0
Pyrexia	93 (20.2)	3 (0.7)	0	46 (10.7)	0	0
Vomiting	92 (20.0)	5 (1.1)	0	75 (17.4)	5 (1.2)	0
Decreased appetite	92 (20.0)	3 (0.7)	0	80 (18.6)	3 (0.7)	0
Arthralgia	89 (19.3)	1 (0.2)	0	70 (16.3)	1 (0.2)	0
Rash	84 (18.3)	2 (0.4)	0	71 (16.5)	2 (0.5)	0
Peripheral sensory neuropathy	75 (16.3)	9 (2.0)	0	52 (12.1)	8 (1.9)	0
Dyspnea	75 (16.3)	3 (0.7)	0	62 (14.4)	3 (0.7)	0
Back pain	74 (16.1)	6 (1.3)	0	58 (13.5)	2 (0.5)	0
Edema peripheral	73 (15.9)	1 (0.2)	0	68 (15.8)	6 (1.4)	0
Pruritus	73 (15.9)	0	0	45 (10.5)	0	0
Myalgia	71 (15.4)	2 (0.4)	0	67 (15.6)	3 (0.7)	0
Dizziness	69 (15.0)	0	0	43 (10.0)	0	0
Hypothyroidism	66 (14.3)	0	0	15 (3.5)	0	0
Urinary tract infection	60 (13.0)	4 (0.9)	0	43 (10.0)	3 (0.7)	0
Asthenia	60 (13.0)	3 (0.7)	0	51 (11.9)	5 (1.2)	0
Neutrophil count decreased	57 (12.4)	17 (3.7)	5 (1.1)	49 (11.4)	13 (3.0)	3 (0.7)
Upper respiratory tract infection	55 (12.0)	5 (1.1)	0	38 (8.8)	0	0
Pain in extremity	55 (12.0)	2 (0.4)	0	42 (9.8)	1 (0.2)	0
Alanine aminotransferase increased	54 (11.7)	10 (2.2)	0	38 (8.8)	5 (1.2)	0
Insomnia	54 (11.7)	0	0	52 (12.1)	3 (0.7)	0
Abdominal pain	53 (11.5)	2 (0.4)	0	53 (12.3)	1 (0.2)	0
Dysgeusia	52 (11.3)	0	0	44 (10.2)	0	0
Nasopharyngitis	52 (11.3)	0	0	36 (8.4)	0	0
Aspartate aminotransferase increased	50 (10.9)	8 (1.7)	1 (0.2)	42 (9.8)	8 (1.9)	1 (0.2)
Stomatitis	49 (10.7)	1 (0.2)	0	21 (4.9)	1 (0.2)	0
Pneumonia	32 (7.0)	12 (2.6)	0	10 (2.3)	3 (0.7)	0
Hypokalemia	30 (6.5)	7 (1.5)	4 (0.9)	10 (2.3)	4 (0.9)	0
Hypertension	25 (5.4)	5 (1.1)	0	23 (5.3)	8 (1.9)	1 (0.2)

Data are presented as *n* (%). [a] Includes any-grade AEs that occurred in ≥10% of patients in either arm and grade 3-4 AEs that occurred in ≥2% of patients in either arm.
A + nP, atezolizumab plus nab-paclitaxel; AE, adverse event; P + nP, placebo plus nab-paclitaxel.

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Table 4. Adverse events of special interest (safety-evaluable population)

AE (medical concept)[a]	A + nP (n = 460)						P + nP (n = 430)					
	AESI		Resolved AESI	First AESI (any grade)		AESI leading to A withdrawal	AESI		Resolved AESI	First AESI (any grade)		AESI leading to P withdrawal
	Any grade	Grade 3 or 4	Any grade	Median time to onset, months	Median duration, months	Any grade	Any grade	Grade 3 or 4	Any grade	Median time to onset, months	Median duration, months	Any grade
Rash	165 (35.9)	5 (1.1)	138 (30.0)	1.4 (0.0-37.5)	1.0 (0.0-38.1+)	2 (0.4)	112 (26.0)	2 (0.5)	87 (20.2)	1.0 (0.0-29.0)	0.9 (0.0-47.6+)	0
Hypothyroidism	84 (18.3)	0	40 (8.7)	4.1 (0.5-50.7)	14.5 (0.1-41.6+)	0	19 (4.4)	0	9 (2.1)	2.0 (0.0-12.0)	15.8 (0.3-55.1+)	0
Hyperthyroidism	22 (4.8)	1 (0.2)	18 (3.9)	3.9 (1.1-33.3)	1.7 (0.2-34.0+)	0	5 (1.2)	0	5 (1.2)	2.8 (0.5-3.6)	0.5 (0.3-2.0)	0
Pneumonitis	18 (3.9)	2 (0.4)	15 (3.3)	5.3 (0.9-41.3)	2.4 (0.5-12.2+)	1 (0.2)	1 (0.2)	0	0	1.0 (1.0-1.0)	NE (6.2+-6.2+)	0
Hepatitis (diagnosis)[b]	11 (2.4)	7 (1.5)	8 (1.7)	4.6 (0.9-28.8)	2.0 (0.3-32.7)	2 (0.4)	7 (1.6)	1 (0.2)	6 (1.4)	5.4 (1.4-10.7)	0.8 (0.2-1.4)	1 (0.2)
Colitis	7 (1.5)	2 (0.4)	7 (1.5)	8.1 (3.0-26.3)	0.8 (0.5-10.2)	1 (0.2)	3 (0.7)	1 (0.2)	3 (0.7)	2.1 (1.4-6.4)	0.5 (0.2-1.4)	0
Adrenal insufficiency	5 (1.1)	1 (0.2)	4 (0.9)	4.8 (2.1-12.9)	4.2 (0.3-32.9+)	1 (0.2)	0	0	0	—	—	0
Severe cutaneous reactions	4 (0.9)	1 (0.2)	3 (0.7)	14.1 (0.6-33.7)	3.3 (0.9-5.6+)	2 (0.4)	3 (0.7)	0	2 (0.5)	3.7 (0.5-10.3)	0.5 (0.2-38.2+)	0
Myositis[c]	3 (0.7)	1 (0.2)	1 (0.2)	15.2 (1.3-23.9)	NE (0.5-13.8+)	0	1 (0.2)	1 (0.2)	0	1.2 (1.2-1.2)	NE (12.1+-12.1+)	0
Hypophysitis	1 (0.2)	1 (0.2)	1 (0.2)	4.3 (4.3-4.3)	5.8 (5.8-5.8)	0	0	0	0	—	—	0

Data are presented as n (%) or median (range). + denotes censored values. Includes AEs occurring in >10 patients in the A + nP group, excluding hepatitis (laboratory abnormalities), and additionally including colitis, adrenal insufficiency, myositis/rhabdomyolysis, hypophysitis, and severe cutaneous reactions.

A + nP, atezolizumab plus nab-paclitaxel; AE, adverse event; AESI, adverse event of special interest; NE, not estimable; P + nP, placebo plus nab-paclitaxel.

[a] Grouped MedDRA preferred terms.

[b] Sponsor-defined group of terms representing events suggestive of hepatitis.

[c] Includes myositis and rhabdomyolysis.

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DATA SHARING

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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