ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer

D. Miles[1*], J. Gligorov[2], F. André[3], D. Cameron[4], A. Schneeweiss[5], C. Barrios[6], B. Xu[7], A. Wardley[8,9†], D. Kaen[10], L. Andrade[11], V. Semiglazov[12], M. Reinisch[13], S. Patel[14], M. Patre[15], L. Morales[15], S. L. Patel[16], M. Kaul[14], T. Barata[17] & J. O'Shaughnessy[18], on behalf of the IMpassion131 investigators[‡]

[1]Mount Vernon Cancer Centre, Northwood, UK; [2]Medical Oncology Department, Institut Universitaire de Cancérologie Assistance Publique—Hôpitaux de Paris-Sorbonne Université, Paris; [3]Department of Medical Oncology, Gustave Roussy, Université Paris Sud, Villejuif, France; [4]University of Edinburgh, Edinburgh, UK; [5]Division of Gynecologic Oncology, National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany; [6]Latin American Cooperative Oncology Group, Porto Alegre RS, Brazil; [7]National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; [8]National Institute for Health Research Manchester Clinical Research Facility at The Christie NHS Foundation Trust, Manchester; [9]Outreach Research & Innovation Group, Manchester, UK; [10]Centro Oncológico Riojano Integral and Universidad Nacional de La Rioja, La Rioja, Argentina; [11]Clinical Oncology, Santa Casa de Misericórdia da Bahia, Salvador, Brazil; [12]NN Petrov Research Institute of Oncology, St. Petersburg, Russia; [13]Kliniken Essen-Mitte, Essen, Germany; [14]Product Development Oncology, Genentech, Inc., South San Francisco, USA; [15]Global Product Development Medical Affairs Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [16]Patient-Centered Outcomes Research, Genentech, Inc., South San Francisco, USA; [17]Pharma Development Biostatistics Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [18]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, USA

Available online XXX

Background: In the phase III IMpassion130 trial, combining atezolizumab with first-line nanoparticle albumin-bound-paclitaxel for advanced triple-negative breast cancer (aTNBC) showed a statistically significant progression-free survival (PFS) benefit in the intention-to-treat (ITT) and programmed death-ligand 1 (PD-L1)-positive populations, and a clinically meaningful overall survival (OS) effect in PD-L1-positive aTNBC. The phase III KEYNOTE-355 trial adding pembrolizumab to chemotherapy for aTNBC showed similar PFS effects. IMpassion131 evaluated first-line atezolizumab—paclitaxel in aTNBC.

Patients and methods: Eligible patients [no prior systemic therapy or ≥12 months since (neo)adjuvant chemotherapy] were randomised 2:1 to atezolizumab 840 mg or placebo (days 1, 15), both with paclitaxel 90 mg/m^2 (days 1, 8, 15), every 28 days until disease progression or unacceptable toxicity. Stratification factors were tumour PD-L1 status, prior taxane, liver metastases and geographical region. The primary endpoint was investigator-assessed PFS, tested hierarchically first in the PD-L1-positive [immune cell expression ≥1%, VENTANA PD-L1 (SP142) assay] population, and then in the ITT population. OS was a secondary endpoint.

Results: Of 651 randomised patients, 45% had PD-L1-positive aTNBC. At the primary PFS analysis, adding atezolizumab to paclitaxel did not improve investigator-assessed PFS in the PD-L1-positive population [hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.60-1.12; $P = 0.20$; median PFS 6.0 months with atezolizumab—paclitaxel versus 5.7 months with placebo—paclitaxel]. In the PD-L1-positive population, atezolizumab—paclitaxel was associated with more favourable unconfirmed best overall response rate (63% versus 55% with placebo—paclitaxel) and median duration of response (7.2 versus 5.5 months, respectively). Final OS results showed no difference between arms (HR 1.11, 95% CI 0.76-1.64; median 22.1 months with atezolizumab—paclitaxel versus 28.3 months with placebo—paclitaxel in the PD-L1-positive population). Results in the ITT population were consistent with the PD-L1-positive population. The safety profile was consistent with known effects of each study drug.

Conclusion: Combining atezolizumab with paclitaxel did not improve PFS or OS versus paclitaxel alone.

ClinicalTrials.gov: NCT03125902.

Key words: advanced breast cancer, atezolizumab, immune checkpoint inhibitor, PD-L1, paclitaxel, triple-negative breast cancer

DOI of original article: https://doi.org/10.1016/j.annonc.2021.05.355

*Correspondence to: Dr David Miles, Mount Vernon Cancer Centre, Rickmansworth Road, Northwood, HA6 2RN, UK. Tel: +44-7810-481281

E-mail: David.miles@doctors.org.uk (D. Miles).

† Current affiliation: AstraZeneca Limited, Cambridge, UK.

‡ See Appendix for individual names.

INTRODUCTION

Triple-negative breast cancer (TNBC) is a heterogeneous disease entity with high unmet medical need. The relative genomic instability of TNBC, increased immune infiltration and high programmed death-ligand 1 (PD-L1) expression in some TNBC tumours compared with other breast cancer subtypes[1,2] provide the rationale for immunotherapy in TNBC.

Early clinical studies demonstrated durable responses with the anti-PD-L1 monoclonal antibody atezolizumab as monotherapy or in combination with nanoparticle albumin-bound (nab)-paclitaxel for advanced TNBC (aTNBC), particularly in patients with PD-L1-positive tumours.[3,4] The subsequent phase III IMpassion130 trial established atezolizumab as a new standard of care for PD-L1-positive aTNBC.[5-7] Combining atezolizumab with nab-paclitaxel as first-line therapy for unresectable locally advanced or metastatic TNBC showed significantly improved progression-free survival (PFS) and a clinically meaningful overall survival (OS) effect (7.5-month difference in median OS) in patients with PD-L1-positive tumours.[5-7] These results led to United States Food and Drug Administration (FDA) accelerated approval of the combination of atezolizumab and nab-paclitaxel for patients with unresectable locally advanced or metastatic PD-L1-positive TNBC[8] and European Medicines Agency approval of atezolizumab plus nab-paclitaxel as first-line treatment for unresectable locally advanced or metastatic PD-L1-positive TNBC.[9]

Subsequent trials in aTNBC have assessed different immunotherapy agents, alternative chemotherapy backbones and additional patient populations. These include the KEYNOTE-355 trial, which evaluated the addition of pembrolizumab to first-line chemotherapy for aTNBC, demonstrating significantly improved PFS with immunotherapy.[10] The IMpassion131 trial evaluated atezolizumab in combination with paclitaxel as first-line treatment for aTNBC. Here we report the primary PFS and patient-reported outcome (PRO) results and final OS and safety results from IMpassion131.

PATIENTS AND METHODS

IMpassion131 (NCT03125902) was a global, randomised, double-blind, placebo-controlled phase III trial. The protocol (Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2021.05.801), informed consent forms and all amendments were approved by the Institutional Review Board/Ethics Committee at each participating site. The trial was conducted in full conformance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki, and applicable United States FDA regulations, the European Union Clinical Trial Directive or local, regional and national laws.

Eligible male or female patients had metastatic or unresectable locally advanced measurable TNBC (per the American Society of Clinical Oncology—College of American Pathologists guidelines[11,12]), had received no prior chemotherapy or targeted therapy for aTNBC and had completed any prior (neo)adjuvant chemotherapy for early breast cancer $\geq$12 months before being randomised to the trial. Patients had to be eligible for taxane therapy and have an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with leptomeningeal disease were excluded, as were patients with known central nervous system (CNS) disease (except for treated asymptomatic CNS metastases), unless all of the following criteria were met: measurable disease outside the CNS; no metastases to mid brain, pons, medulla or spinal cord; no ongoing need for corticosteroids as therapy for CNS disease (stable dose of anticonvulsants allowed); no stereotactic radiation within 7 days before randomisation or whole-brain radiation within 14 days before randomisation; and no evidence of progression or haemorrhage after completion of CNS-directed therapy. All patients provided written informed consent before undertaking any study-specific procedures.

Patients were randomised in a 2:1 ratio to receive intravenous paclitaxel 90 mg/m^2 on days 1, 8 and 15 every 28 days in combination with either intravenous atezolizumab 840 mg or placebo, administered on days 1 and 15 every 28 days. Patients were to receive dexamethasone 8-10 mg or equivalent before at least the first two infusions of paclitaxel. Thereafter, it was recommended, but not mandated, to minimise the dose of dexamethasone (or equivalent) premedication as far as clinically feasible. This recommendation was based on reports in the literature that this approach is feasible[13] and because of potential dampening of the activity of immunotherapy when administered concomitantly with steroids.[14] Treatment was continued until disease progression according to RECIST version 1.1, unacceptable toxicity or consent withdrawal.

There were four stratification factors: prior taxane (yes versus no), tumour PD-L1 status [immune cell (IC) PD-L1 expression on $<$1% versus $\geq$1% of the tumour area, as assessed by VENTANA PD-L1 (SP142) immunohistochemistry assay (Ventana Medical Systems, Oro Valley, AZ)], liver metastases (yes versus no) and geographical region (North America versus Western Europe/Australia versus Eastern Europe/Asia Pacific versus South America).

The hierarchical statistical design was informed by results from the IMpassion130 trial.[5] The primary endpoint was investigator-assessed PFS. PFS was tested first in the PD-L1-positive population (defined as IC $\geq$1%). The target hazard ratio (HR) in the PD-L1-positive population was 0.62 (identical to that observed in IMpassion130), representing an increase in median PFS from 5.0 months with paclitaxel alone to 8.0 months with the combination of atezolizumab—paclitaxel. Assuming 80% power with a 5% two-sided α, 155 PFS events in the PD-L1-positive population would be required to detect the target HR. PFS was compared between treatment arms using a stratified log-rank test with the stratification factors PD-L1 status, prior taxane and presence of liver metastases. The HR was estimated using a stratified Cox regression model with the same stratification variables. Kaplan—Meier methodology was used to estimate median PFS for each treatment arm, with 95%

confidence intervals (CIs) calculated according to Brookmeyer—Crowley methodology. If atezolizumab demonstrated a significant PFS benefit in the PD-L1-positive population, PFS was to be tested in the intention-to-treat (ITT) population.

Secondary efficacy endpoints included OS and objective response rate. These secondary endpoints were to be tested (hierarchically in the PD-L1-positive population and then in the ITT population) only if all previous tests (PFS in the PD-L1-positive and ITT populations) were statistically significant. Additional secondary efficacy endpoints included time to deterioration (defined as a $\geq$10-point decrease) in global health status/health-related quality of life (GHS/HRQoL) using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2021.05.801). Safety evaluation was a secondary objective, as well as extensive translational research. PFS, as assessed by an independent review committee (IRC), was carried out as a sensitivity analysis. Additional PROs, including treatment side-effect bother, were exploratory endpoints. The final analysis of OS was planned to occur after deaths in 122 (51%) of the anticipated 240 patients with PD-L1-positive TNBC.

Before randomisation, one of four pathologists [HistoGeneX, Antwerp, Belgium, trained by Ventana for PD-L1 (SP142) specifically for TNBC] determined PD-L1 status centrally in formalin-fixed paraffin-embedded tumour samples using the PD-L1 (SP142) immunohistochemical assay. TNBC status was confirmed centrally, although for some patients, eligibility was based on local assessment following a protocol amendment. Tumours were assessed at baseline and every 8 weeks for the first year after randomisation, and every 12 weeks thereafter until disease progression, withdrawal of consent, death or study closure, whichever occurred first. The tumour assessment technique (contrast protocol for computed tomography scans and/or magnetic resonance imaging) used at screening was used throughout the trial. Tumour response was assessed according to RECIST version 1.1. All imaging data were collected for central review by the IRC. Adverse events (AEs) were recorded at each cycle, graded according to the National Cancer Institute Common Terminology Criteria version 4.0.

RESULTS

Patient population

Between 25 August 2017 and 5 September 2019, 651 patients were enrolled from 150 sites in Europe, North and South America, Asia and Africa; 431 were randomised to receive atezolizumab—paclitaxel and 220 to placebo—paclitaxel. Of 651 randomised patients, 292 (45%) had PD-L1-positive (IC $\geq$1%) tumours. Samples from primary (336/651) versus recurrent/metastatic breast cancer (315/651) showed numerically higher PD-L1 prevalence (48% versus 42%, respectively; not significant). Two patients did not receive any study treatment (one patient withdrawal and one physician decision) and two patients in the placebo—paclitaxel arm received atezolizumab in error, thus the safety population included 649 patients (432 in the atezolizumab—paclitaxel arm and 217 in the placebo—paclitaxel arm) (Figure 1).

Baseline characteristics were well balanced between the treatment arms in both the PD-L1-positive population and the ITT population (Table 1). Approximately half of the patients had received prior taxane therapy, one-third had *de novo* metastatic TNBC and one-quarter had liver metastases.

Efficacy

The data cut-off for the primary PFS analysis was 15 November 2019. At this date, the median duration of follow-up in the PD-L1-positive (primary analysis) population was 9.0 months (range 0.5-25.4 months) in the atezolizumab—paclitaxel arm versus 8.6 months (range 0.0-26.1 months) in the placebo—paclitaxel arm. Corresponding values in the ITT population were 8.8 versus 8.5 months, respectively. Investigator-assessed PFS events had been recorded in 61% of patients in the PD-L1-positive population and 67% of patients in the ITT population.

Adding atezolizumab to paclitaxel did not significantly improve investigator-assessed PFS in the PD-L1-positive population (HR 0.82, 95% CI 0.60-1.12; log-rank $P = 0.20$). Median PFS was 6.0 months with atezolizumab—paclitaxel versus 5.7 months with placebo—paclitaxel (Figure 2A). The Kaplan—Meier curves remained overlapping for the first 7-8 months and then started to diverge. In the ITT population, median PFS was 5.7 versus 5.6 months, respectively (Figure 2B); the PFS HR was 0.86 (95% CI 0.70-1.05). In accordance with the hierarchical statistical design, PFS was not formally tested in the ITT population.

The sensitivity analysis of IRC-assessed PFS showed an HR of 0.73 (95% CI 0.54-1.00) in the PD-L1-positive population (Figure 2C). In subgroup analyses of PFS, the effect was generally consistent with the primary results (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.05.801).

Unconfirmed best overall response rates favoured the atezolizumab arm in both the PD-L1-positive population [63% (95% CI 56-70%) with atezolizumab—paclitaxel versus 55% (95% CI 45-65%) with placebo—paclitaxel] and the ITT population [54% (95% CI 49-58%) versus 47% (95% CI 41-54%), respectively]. Among responding patients, median duration of response was 7.2 months (95% CI 5.5-13.6 months) in atezolizumab-treated patients and 5.5 months (95% CI 4.0-6.3 months) in placebo-treated patients in the PD-L1-positive population. Corresponding durations in the ITT population were 6.4 (95% CI 5.6-7.4) versus 5.5 (95% CI 4.7-6.3) months, respectively. Confirmed response rates are provided in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.05.801.

At the final OS analysis with a data cut-off of 4 September 2020, the median duration of follow-up in the PD-L1-positive population was 15.2 (range 0.5-35.0) months

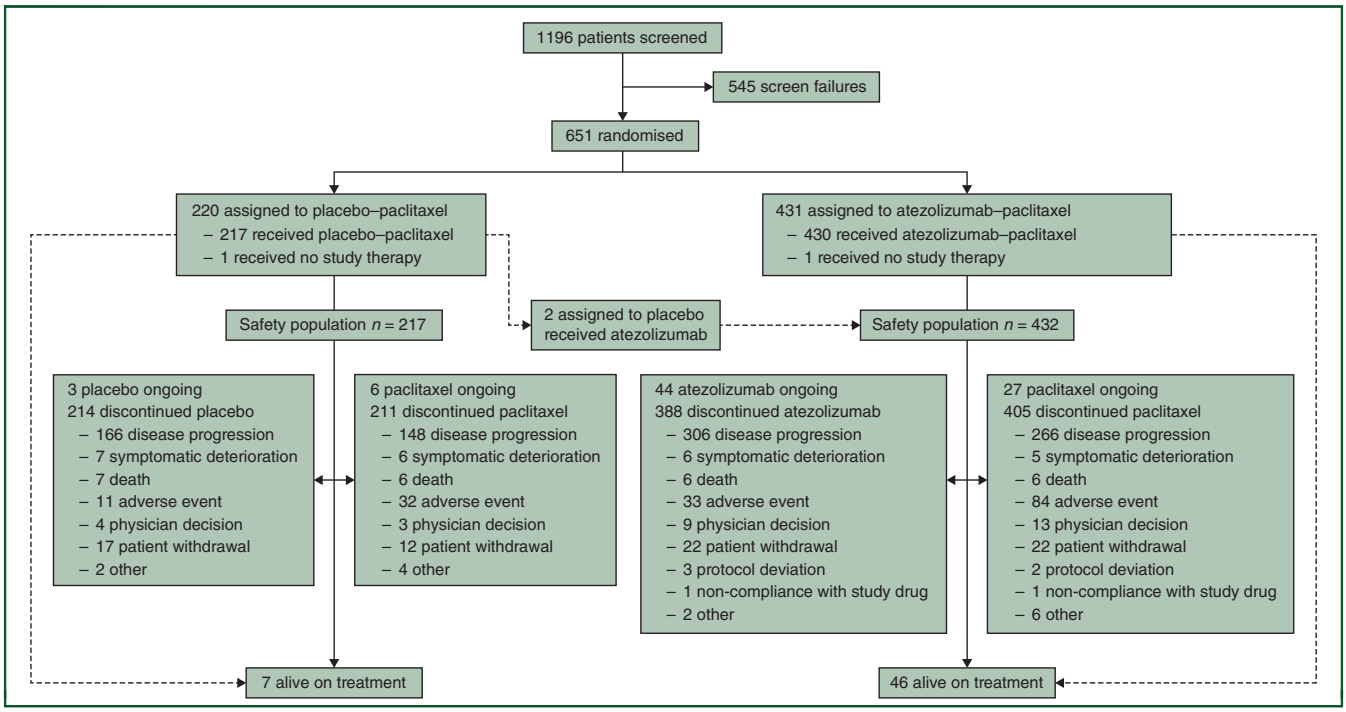

Figure 1. **Patient profile.**

versus 15.8 (range 0.0-35.3) months in the atezolizumab—paclitaxel versus placebo—paclitaxel arms, respectively. In the ITT population, the median duration of follow-up was 14.2 versus 14.5 months, respectively. At the final data cut-off, deaths had been recorded in 123 (42%) of 292 patients in the PD-L1-positive population (44% versus 39% in the atezolizumab—paclitaxel versus placebo—paclitaxel arms, respectively). The HR for OS was 1.11 (95% CI 0.76-1.64); median OS was 22.1 months (95% CI 19.2-30.5 months) with atezolizumab—paclitaxel versus 28.3 months (95% CI 19.1-not estimable) with placebo—paclitaxel (Figure 3A). The 1-year OS rates were 75% (95% CI 68-81%) versus 83% (95% CI 76-91%), respectively, and the 2-year OS rates were 48% (95% CI 39-57%) versus 51% (95% CI 37-64%),

Table 1. **Baseline characteristics**

Characteristic	PD-L1-positive population		ITT population	
	Placebo—paclitaxel (n = 101)	Atezolizumab—paclitaxel (n = 191)	Placebo—paclitaxel (n = 220)	Atezolizumab—paclitaxel (n = 431)
Median (range) age, years	53 (25-78)	55 (23-83)	53 (25-81)	54 (22-85)
Sex, *n* (%)				
Female	101 (100)	191 (100)	220 (100)	430 (100)
Male	0	0	0	1 (<1)
Race, *n* (%)				
White	59 (58)	111 (58)	128 (58)	246 (57)
Asian	30 (30)	57 (30)	66 (30)	123 (29)
Black or African American	4 (4)	8 (4)	10 (5)	21 (5)
Multiple/other	1 (1)	1 (1)	2 (1)	4 (1)
Unknown	7 (7)	14 (7)	14 (6)	37 (9)
ECOG performance status, *n* (%)				
0	59 (58)	118 (62)	130 (59)	262 (61)
1	42 (42)	73 (38)	90 (41)	169 (39)
Metastatic sites, *n* (%)				
Lung	41 (41)	94 (49)	100 (45)	230 (53)
Liver	24 (24)	37 (19)	61 (28)	118 (27)
Bone	18 (18)	44 (23)	60 (27)	140 (32)
>3 metastatic sites, *n* (%)	13 (13)	35 (18)	48 (22)	105 (24)
PD-L1 positive,[a] *n* (%)	101 (100)	191 (100)	101 (46)	191 (44)
Prior taxane, *n* (%)	54 (53)	97 (51)	107 (49)	208 (48)
Prior anthracycline, *n* (%)	50 (50)	98 (51)	110 (50)	212 (49)
Stage IV at initial diagnosis, *n* (%)	30 (30)	56 (29)	69 (31)	137 (32)

ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PD-L1, programmed death-ligand 1.
[a] As reported on interactive web-response system (for stratification).

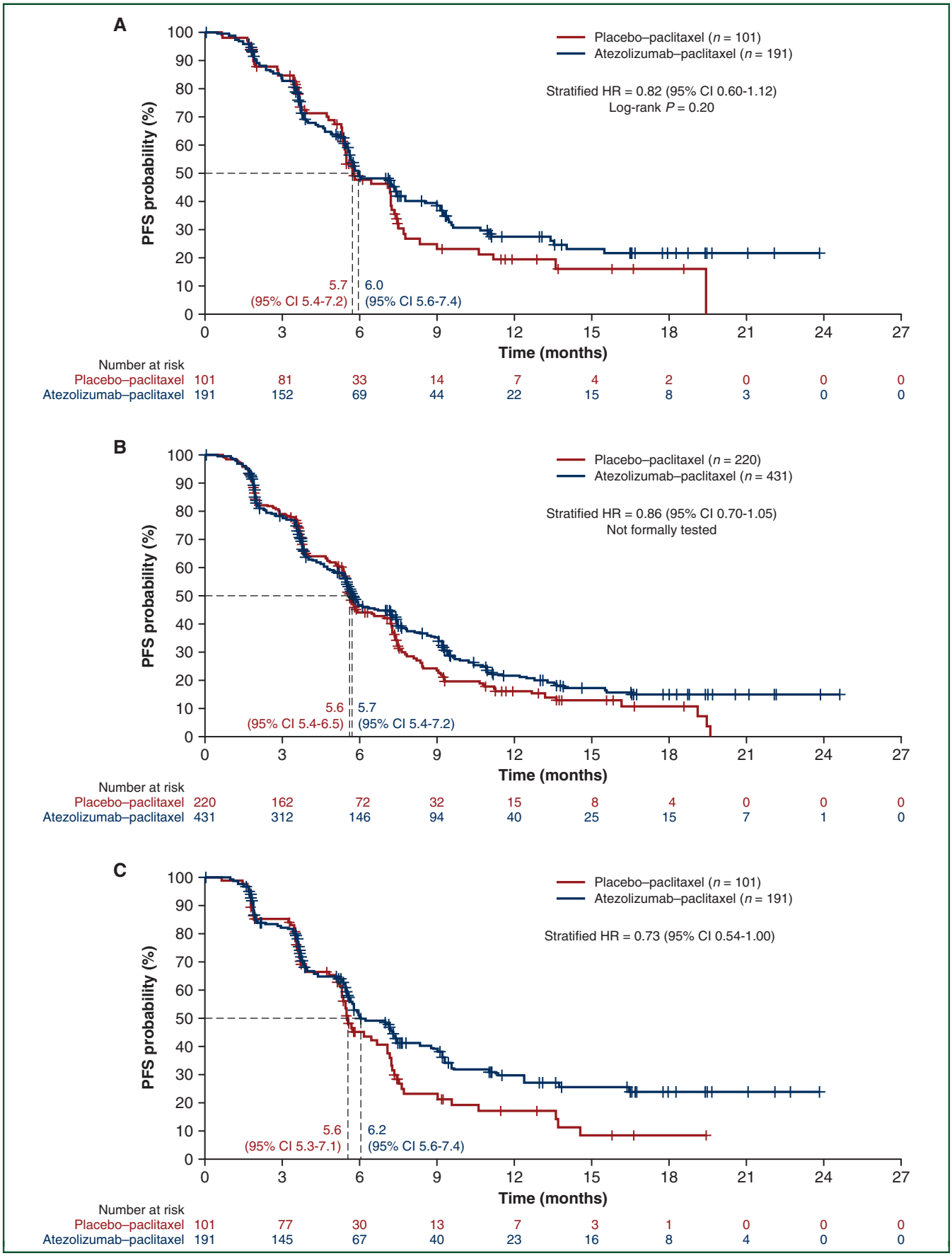

Figure 2. PFS (data cut-off 15 November 2019).

(A) investigator assessed in the PD-L1-positive population (primary analysis, events in 61% of patients); (B) investigator assessed in the ITT population (events in 67% of patients); (C) IRC assessed in the PD-L1-positive population.

CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

https://doi.org/10.1016/j.annonc.2021.05.801

respectively. Results were similar in the ITT population [deaths in 311 (48%) of 651 patients; 44% from disease progression]: the OS HR was 1.12 (95% CI 0.88-1.43) (Figure 3B). Median OS was 19.2 months (95% CI 16.6-22.1 months) with atezolizumab—paclitaxel versus 22.8 months (95% CI 17.1-28.3 months) with placebo—paclitaxel. The 1-year OS rates in the ITT population were 69% (95% CI 64-73%) in the atezolizumab—paclitaxel arm versus 73% (95% CI 67-79%) in the placebo—paclitaxel arm. The 2-year OS rates were 42% (95% CI 36-48%) versus 45% (95% CI 36-54%), respectively. A total of 223 patients (34%) were alive in follow-up at the time of final OS analysis (30% of the atezolizumab arm versus 42% of the placebo arm).

An exploratory analysis of updated investigator-assessed PFS at the time of the data cut-off for the final OS analysis showed a HR of 0.73 (95% CI 0.56-0.96) in the PD-L1-positive population [median 7.2 (95% CI 5.7-9.0) months with atezolizumab—paclitaxel versus 6.4 (95% CI 5.5-7.3) months with placebo—paclitaxel] (Supplementary Figure S2A, available at https://doi.org/10.1016/j.annonc.2021.05.801). In the ITT population, median PFS was 5.9 versus 5.6 months, respectively (Supplementary Figure S2B, available at https://doi.org/10.1016/j.annonc.2021.05.801); the PFS HR was 0.82 (95% CI 0.68-0.98).

No difference between treatment arms was observed for time to deterioration in GHS/HRQoL in either the PD-L1-positive population [HR 0.88 (95% CI 0.59-1.34); median 12.5 months with atezolizumab—paclitaxel versus 12.0 months with placebo—paclitaxel] or the ITT population [HR 0.97 (95% CI 0.73-1.30); median 12.5 versus 17.4 months, respectively], indicating that baseline HRQoL was maintained for a similar duration in both arms. Time to deterioration in function scales (physical, role, cognitive) showed consistent results (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.05.801).

Treatment exposure

The median duration of atezolizumab/placebo and paclitaxel was six cycles in both treatment arms; mean and median dose intensities of paclitaxel were similar in the two treatment arms (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.05.801). Although the protocol recommended minimising the steroid dose after the first two paclitaxel infusions, *post hoc* exploratory analyses after unblinding indicated that the majority of patients (∼98%) received steroids during the study as prophylactic or premedication treatment. Most patients continued corticosteroid premedication throughout paclitaxel therapy, at a similar median steroid dose per cycle (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2021.05.801).

At the data cut-off for the final OS analysis, 254 patients (59%) in the atezolizumab—paclitaxel arm and 147 (67%) in the placebo—paclitaxel arm had received further anticancer therapy after disease progression, most commonly with capecitabine (29% versus 34%, respectively). Post-progression immunotherapy-based treatment was infrequent (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.05.801).

Safety

Compared with placebo—paclitaxel, atezolizumab—paclitaxel was associated with a slightly higher incidence of serious AEs (25% versus 18% with placebo—paclitaxel) and grade 3/4 AEs (53% versus 46%, respectively), but no increase in grade 5 AEs (2% in both arms). Fatal AEs in the atezolizumab-containing arm comprised one case each of sepsis, pulmonary sepsis, multiple organ dysfunction syndrome, cardiac failure, polymyositis and respiratory distress and three cases of unexplained death. In the placebo arm, fatal AEs comprised two cases of pneumonia and one case each of sepsis, cardiac failure and suicide.

The most common AEs (≥25% in either arm) were alopecia, anaemia, peripheral neuropathy, diarrhoea, fatigue and nausea. Generally, the incidences of specific AEs were similar between the two treatment groups. The main exceptions (with a ≥5% absolute difference between treatment arms) were diarrhoea, vomiting, decreased appetite, hypothyroidism and hyperthyroidism, all of which were more common with atezolizumab-containing therapy than paclitaxel alone (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2021.05.801 and Table 2). The only grade 3/4 AE with a ≥2% difference between treatment arms was alanine aminotransferase increased (3% with atezolizumab—paclitaxel versus <1% with placebo—paclitaxel). All of these are known side-effects of atezolizumab. A higher proportion of patients in the atezolizumab—paclitaxel than the placebo—paclitaxel arm experienced AEs leading to any treatment discontinuation (21% versus 15%, respectively; 19% versus 15%, respectively, leading to discontinuation of paclitaxel; and 8% versus 5%, respectively, leading to discontinuation of atezolizumab/placebo).

The incidence of AEs of special interest (all grades and grade 3/4) was higher with atezolizumab—paclitaxel than placebo—paclitaxel (Table 2). There was a higher incidence of low-grade hypothyroidism and hyperthyroidism with atezolizumab—paclitaxel, but no difference in the proportion of patients with rash (any grade or grade ≥3). Apart from one patient with fatal polymyositis (occurring after seven cycles of treatment, mentioned above), most of the AEs of special interest were low grade and manageable. Ten patients (2%) in the atezolizumab—paclitaxel arm experienced AEs of special interest that required systemic corticosteroids and led to discontinuation of atezolizumab [versus one patient (<1%) in the placebo—paclitaxel arm leading to placebo discontinuation].

DISCUSSION

In the IMpassion131 trial, the primary objective was not met: combining atezolizumab with paclitaxel did not significantly improve investigator-assessed PFS in patients with PD-L1-positive aTNBC. Similarly, there was no evidence of a treatment effect on PFS in the ITT population, and the

addition of atezolizumab to paclitaxel did not improve OS (secondary endpoint) in either the PD-L1-positive or the ITT population. However, the final OS results provide no evidence of a detrimental effect and allay initial concerns raised following release of very early results.

Efficacy findings contrast with those of the IMpassion130 trial evaluating a different chemotherapy backbone (nab-paclitaxel rather than paclitaxel), which showed significantly improved PFS with the addition of atezolizumab to nab-paclitaxel [HR 0.80 (95% CI 0.69-0.92) in the ITT population and HR 0.62 (95% CI 0.49-0.78) in the PD-L1-positive population[5]] and a clinically meaningful effect on OS in the PD-L1-positive population [HR 0.67 (95% CI 0.53-0.86), not formally tested[7]]. The baseline characteristics of the patient populations in the two trials are similar with respect to median age and the proportion of patients with PD-L1-positive tumours, liver metastases and prior anthracycline and taxane exposure (albeit taxane-pretreated patients in IMpassion130 were less likely than those in IMpassion131 to be re-exposed to the same taxane, given the nab-paclitaxel backbone in IMpassion130). There was a slightly smaller proportion of patients with *de novo* metastatic disease in IMpassion131 than in IMpassion130 (31% versus 37%, respectively) and a higher proportion of Asian patients (29% versus 18% in IMpassion130). The higher prevalence of PD-L1 positivity in primary compared with metastatic samples is consistent with observations in IMpassion130, in which the prevalence was 44% in primary tissue versus 36% in metastatic tissue.[15] Median PFS in the control arm of the two trials was remarkably similar in the ITT populations (5.6 months with paclitaxel alone in IMpassion131 versus 5.5 months with nab-paclitaxel alone in IMpassion130) and the PFS HRs in the ITT populations were similar, with overlapping 95% CIs. In the PD-L1-positive populations,

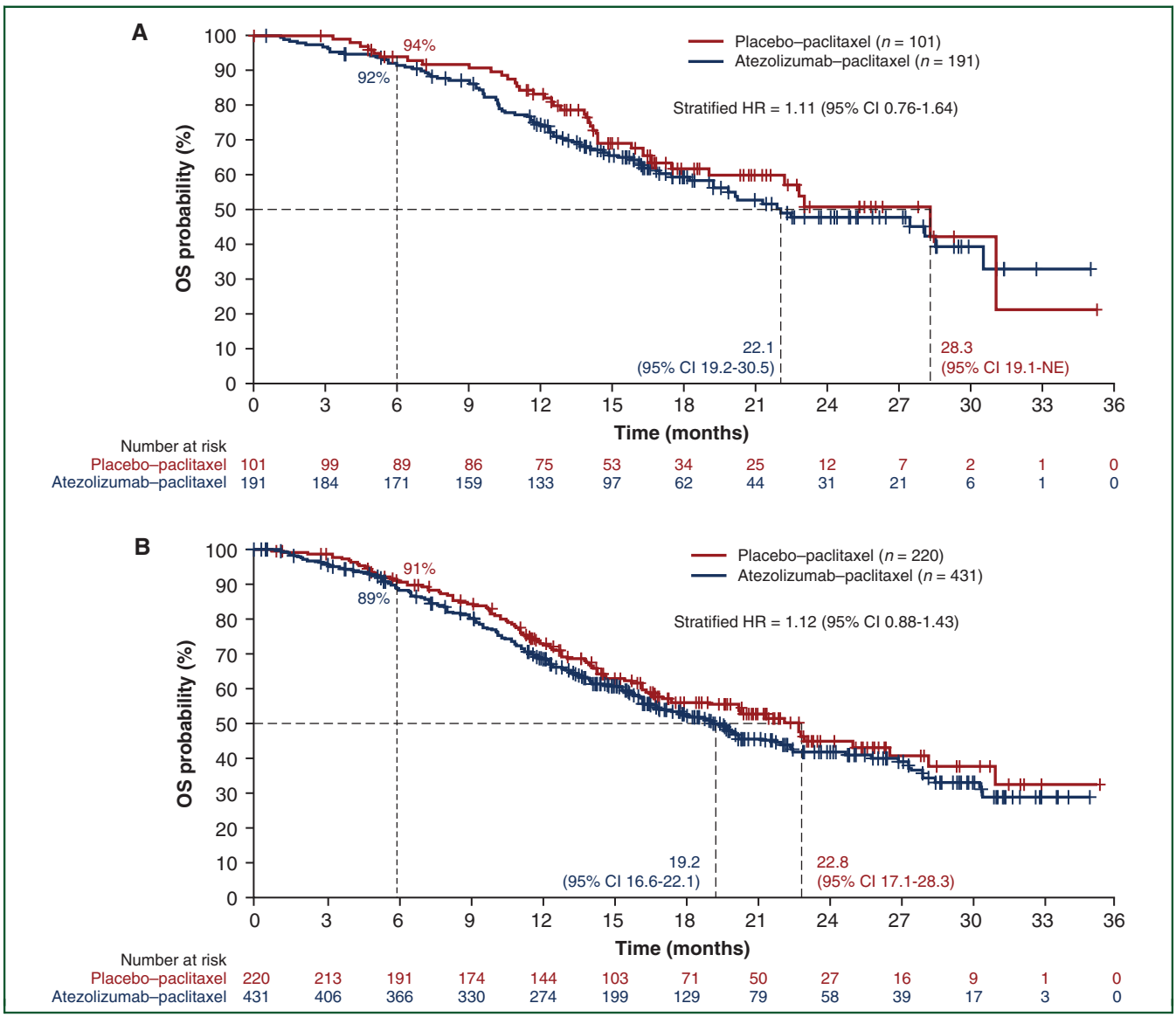

Figure 3. OS (data cut-off 4 September 2020).
(A) PD-L1-positive population; (B) ITT population.
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; OS, overall survival; PD-L1, programmed death-ligand 1.

https://doi.org/10.1016/j.annonc.2021.05.801

Table 2. AEs of special interest for atezolizumab (safety population; data cut-off 4 September 2020)

Immune-mediated AEs by medical concept, *n* (%)	Placebo—paclitaxel (*n* = 217)		Atezolizumab—paclitaxel (*n* = 432)	
	Any grade	Grade 3/4[a]	Any grade	Grade 3/4[a]
Any	116 (53)	11 (5)	268 (62)	49 (11)
Hepatitis (diagnosis)[b]	2 (0.9)	0	7 (2)	2 (0.5)
Pneumonitis	3 (1)	0	16 (4)	3 (0.7)
Hypothyroidism	12 (6)	0	60 (14)	0
Hyperthyroidism	0	0	25 (6)	0
Diabetes mellitus	2 (0.9)	2 (0.9)	5 (1)	4 (0.9)
Adrenal insufficiency	0	0	3 (0.7)	0
Infusion-related reactions	7 (3)	0	15 (3)	3 (0.7)
Pancreatitis	1 (0.5)	1 (0.5)	9 (2)	7 (2)[c]
Colitis	2 (0.9)	2 (0.9)	3 (0.7)	1 (0.2)
Rash	66 (30)	2 (0.9)	141 (33)	4 (0.9)
Ocular inflammatory toxicity	1 (0.5)	0	4 (0.9)	0
Severe cutaneous reactions	2 (0.9)	0	1 (0.2)[d]	0
Myositis + rhabdomyolysis	0	0	2 (0.5)[e]	0
Myositis	0	0	2 (0.5)[e]	1 (0.2)
Guillain—Barré syndrome	0	0	1 (0.2)[f]	1 (0.2)
Myasthenia gravis	0	0	1 (0.2)[g]	1 (0.2)
Meningoencephalitis	0	0	1 (0.2)[h]	0
Nephritis	1 (0.5)[i]	0	2 (0.5)	1 (0.2)
Meningitis	0	0	1 (0.2)[h]	0
Hypophysitis	1 (0.5)[f]	1 (0.5)	1 (0.2)[i]	0

AE, adverse event.

[a] Grade 3/4 AE refers to the highest grade observed; there was only one AE of special interest with fatal outcome (polymyositis in one patient in the atezolizumab arm, considered by the investigator to be related to atezolizumab).

[b] Sponsor-defined group of terms that represent events suggestive of a hepatitis diagnosis (as opposed to events associated with liver function test abnormalities only, which are not presented separately in the table but are included in the total number of AEs of special interest).

[c] No grade 4 pancreatitis events except grade 4 enzyme elevations.

[d] One grade 2 case of bullous dermatitis.

[e] Includes one fatal case of polymyositis.

[f] One grade 3 case.

[g] One grade 4 case.

[h] One grade 1 case of photophobia.

[i] One grade 1 case.

There were no cases of rhabdomyolysis, encephalitis, vasculitis, myocarditis, haemolytic anaemia or haemophagocytic lymphohistiocytosis.

median PFS was slightly longer with paclitaxel in IMpassion131 than with nab-paclitaxel in IMpassion130 (5.7 versus 5.0 months, respectively) and there was a more marked difference in HRs. Turning to OS, performance of the control arms differed substantially between the trials, especially in the PD-L1-positive population (median OS of 28.3 months with paclitaxel alone in IMpassion131 versus 17.9 months with nab-paclitaxel alone in IMpassion130[7]). However, the median OS in IMpassion131 should be interpreted with considerable caution, being based on events in only 39 (39%) of 101 patients and with extensive censoring before the median, translating into uncertainty with a wide 95% CI. Ongoing translational research may be of value in uncovering possible explanations for the IMpassion131 results; the lack of information on *BRCA* status is a limitation, as imbalances between treatment arms for this prognostic factor may not be detected. Furthermore, at the event-driven final OS analysis with the prespecified number of OS events in the PD-L1-positive population in IMpassion131, median follow-up was 14.2 months in atezolizumab-treated patients compared with 19.7 months in atezolizumab-treated patients in IMpassion130 (events in 74% of the ITT population).[7] We observed no major differences between treatment arms in the type and extent of treatment administered after progression in IMpassion131.

Findings from IMpassion131 also contrast with recently published results from the KEYNOTE-355 trial, which evaluated a broader range of chemotherapy backbones (including both nab-paclitaxel and paclitaxel, as well as gemcitabine/carboplatin) with a different immunotherapy agent, pembrolizumab.[10] The overall aim of KEYNOTE-355 was broadly similar to that of IMpassion131, but there were important differences with respect to eligibility, PD-L1 testing, chemotherapy backbone and statistical design. The PFS HR in the ITT population was 0.82, similar to IMpassion131. However, the PFS HR in the PD-L1-positive population, although identified using a different assay, was 0.65. Despite longer follow-up, OS results have not yet been reported from KEYNOTE-355. Interestingly, there was no evidence that paclitaxel was a worse chemotherapy partner than nab-paclitaxel,[10] although the taxane backbone was chosen by the investigator and therefore the populations treated with each formulation of paclitaxel may differ substantially.

An exploratory analysis of updated PFS results at the time of the final OS analysis suggests an effect of atezolizumab, with maintained and even enhanced separation of the curves when compared with the primary PFS results. Although there appears to be no difference between treatment arms during the first 7-8 months of treatment,

the subsequent diversion of the curves raises the question why the difference occurs much later in the IMpassion131 trial, in contrast to IMpassion130. One of the hypotheses is the impact of concomitant steroids during paclitaxel therapy, potentially dampening the effect of immunotherapy. This remains an unanswered question, and the hypothesis is undermined by observations in KEYNOTE-355, which showed benefit from immunotherapy combined with a paclitaxel backbone as well as with a nab-paclitaxel backbone, albeit this was an unstratified subgroup with very small sample size. Like IMpassion131, the Kaplan—Meier curves for PFS in the PD-L1-positive and ITT populations overlap for the first few months, without immediate separation.

The safety profile of the atezolizumab—paclitaxel combination was generally consistent with the known effects of the individual study drugs and experience from the IMpassion130 trial.[5] The proportion of atezolizumab-treated patients with hypothyroidism was identical in IMpassion130 and IMpassion131 (14% any grade; 0% grade 3/4). However, in contrast to IMpassion130, there was no increase in the incidence of rash with atezolizumab in IMpassion131. No new safety signals were seen and no cumulative effects emerged with longer follow-up. There was no evidence that atezolizumab compromised the ability to deliver paclitaxel, nor did toxicity explain the lack of benefit. There was no imbalance in toxicity-related mortality observed between arms. These findings are supported by results of PRO analyses, demonstrating that the addition of atezolizumab to paclitaxel did not compromise patients' HRQoL or day-to-day functioning, or impose additional side-effect bother.

In conclusion, results from IMpassion131 do not show a significant benefit from combining atezolizumab with paclitaxel, contrasting with findings from previously published trials of first-line immune checkpoint blockade for metastatic TNBC. The reasons for this difference remain undefined.

ACKNOWLEDGEMENTS

We thank the patients, their families, the investigators and study staff at participating sites, members of the independent data monitoring committee, Valerie Easton, Margarita Donica, Ken Russell and Youssef Ghazi (former and current employees of F. Hoffmann-La Roche Ltd), Vidya Maiya (Genentech, Inc.), Helene Cauwel and Stephanie Rondeau (Cytel). Support for third-party medical writing assistance for this manuscript was provided by Jennifer Kelly, MA (Medi-Kelsey Ltd, Ashbourne, UK), funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

FUNDING

This work was supported by F. Hoffmann-La Roche Ltd, Basel, Switzerland (no grant number).

DISCLOSURE

DM has received honoraria for advisory boards from Roche/Genentech, Genomic Health and Eisai and has been an invited speaker for Roche/Genentech and Genomic Health. JG has received consulting fees from Daichi, Eisai, Genomic Health, Ipsen, Macrogenics, MSD, Mylan, Novartis, Onxeo, Pfizer and Roche/Genentech; research grants (to institution) from Daichi, Eisai, Genomic Health, Novartis, Pfizer, Roche/Genentech and Immunomedics; and travel/accommodation/expenses from Eisai, Genomic Health, Novartis, Pfizer and Roche/Genentech. FA has received research grants (to institution) from AstraZeneca, Lilly, Novartis, Pfizer and Roche and travel/accommodation/expenses from AstraZeneca, GlaxoSmithKline, Novartis and Roche. DC's institution has received honoraria for his advisory/consultancy roles with Roche and AstraZeneca. AS has received honoraria for scientific talks from Roche, Celgene, AstraZeneca, Pfizer, MSD, Tesaro, Lilly and Novartis, and for advisory/consultancy roles from Roche and AstraZeneca; research funding (to institution) from Roche, Celgene, AbbVie and Molecular Partner; and travel support from Roche, Pfizer and Celgene. CB has received honoraria for advisory/consultancy roles from Boehringer Ingelheim, GSK, Novartis, Pfizer, Lilly, Roche/Genentech, Eisai, MSD, AstraZeneca and Bayer; research grants/funding (to institution) from AbbVie, Amgen, Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Celgene, Covance, Lilly, Medivation, Merck Serono, MSD, Novartis, Pfizer, PharmaMar and Roche/Genentech; and travel/accommodation/expenses from Boehringer Ingelheim, GSK, Novartis, Pfizer, Lilly, Roche/Genentech, Eisai, MSD, AstraZeneca and Bayer. BX has received honoraria for consulting/advisory roles from Novartis, Roche and AstraZeneca and research funding (to institution) from Pfizer, Roche, AstraZeneca, Novartis and Daiichi-Sankyo. AW reports personal fees from Roche, NAPP, Amgen, MSD, Novartis, Pfizer, AstraZeneca, Pierre Fabre, ACCORD, Athenex, Gerson Lehmann Group, Coleman Expert Network Group and Guidepoint Global, and also reports personal fees and other from Lilly and Daiichi-Sankyo (all outside the submitted work) and employment with AstraZeneca after completion of this work. DK reports consulting fees from Roche, Boehringer Ingelheim, Pfizer, MSD, BMS, Novartis, AstraZeneca, Raffo-Tecnofarma, Varifarma and Takeda and research funding (to institution) from Roche, Lilly Oncology, Clovis, MSD, AbbVie, Takeda, Novartis, Pfizer and Array BioPharma Inc. LA reports consulting/advisory roles for Zodiac Pharma, Janssen-Cilag and Roche/Genentech; speakers' bureau for Janssen-Cilag, Zodiac Pharma, Merck Sharp & Dohme, Roche/Genentech and Novartis; research funding (to institution) from Bayer, Roche/Genentech, Janssen-Cilag and Regeneron; and travel/accommodation/expenses from Zodiac Pharma. MR reports consulting fees/advisory roles for Roche Pharma AG, Novartis, MSD, AstraZeneca, Hexal, Lilly, Somatex and Pfizer and travel/accommodation/expenses from Pfizer, Celgene and Novartis. MP, LM and TB are employees of and hold shares in F. Hoffmann-La Roche Ltd. SP, SLP and MK are employees of Genentech, Inc., and hold shares in F. Hoffmann-La Roche Ltd. JO'S has received honoraria for advisory/consultancy from AbbVie Inc., Agendia, Amgen Biotechnology, AstraZeneca, Bristol-

Myers Squibb, Celgene Corporation, Eisai, Genentech, Genomic Health, GRAIL, Immunomedics, Heron Therapeutics, Ipsen Biopharmaceuticals, Jounce Therapeutics, Lilly, Merck, Myriad, Novartis, Odonate Therapeutics, Pfizer, Puma Biotechnology, Prime Oncology, Roche, Seattle Genetics, Syndax Pharmaceuticals and Takeda. VS has declared no conflicts of interest.

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).

REFERENCES

1. Loi S, Michiels S, Salgado R, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. *Ann Oncol*. 2014;25:1544-1550.
2. Mittendorf EA, Philips AV, Meric-Bernstam F, et al. PD-L1 expression in triple-negative breast cancer. *Cancer Immunol Res*. 2014;2:361-370.
3. Adams S, Diamond JR, Hamilton E, et al. Atezolizumab plus nab-paclitaxel in the treatment of metastatic triple-negative breast cancer with 2-year survival follow-up: a phase 1b clinical trial. *JAMA Oncol*. 2019;5(3):334-342.
4. Emens LA, Cruz C, Eder JP, et al. Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study. *JAMA Oncol*. 2019;5(1):74-82.
5. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379:2108-2121.
6. Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21:44-59.
7. Emens LA, Adams S, Barrios CH, et al. First-line atezolizumab plus *nab*-paclitaxel for unresectable, locally advanced or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis. *Ann Oncol*. 2021. In press.
8. Genentech. Tecentriq Prescribing Information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761034s018lbl.pdf. Accessed December 6, 2020.
9. Roche. Tecentriq Summary of Product Characteristics. Available at https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf. Accessed December 6, 2020.
10. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet*. 2020;396:1817-1828.
11. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline focused update. *J Clin Oncol*. 2018;36:2105-2122.
12. Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28:2784-2795.
13. Berger MJ, Vargo C, Vincent M, et al. Stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction. *Support Care Cancer*. 2015;23:2019-2024.
14. Aldea M, Orillard E, Mansi L, et al. How to manage patients with corticosteroids in oncology in the era of immunotherapy? *Eur J Cancer*. 2020;141:239-251.
15. Emens LA, Molinero L, Loi S, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer: biomarker evaluation of the IMpassion130 study. *J Natl Cancer Inst*. 2021. https://doi.org/10.1093/jnci/djab004.

APPENDIX

Collaborators

Q. Zhang, B. Xu, Z. Shao, X. Wang, C. Geng, X. Yan, Z. Tong, K. Shen, Y. Yin, T. Sun, J. Yang, J. Feng, M. Yan, Y. Wang, Q. Liu, S. Zhang (China); M. De Laurentiis, A. Santoro, V. Guarneri, M. Colleoni, C. Natoli, L. Cortesi, S. Placido, L. Gianni, F. Ferrau, L. Livi, A. Zambelli, L. Del Mastro, G. Tonini, F. Montemurro, G. Bianchi, R. Pedersini, S. Prete, G. Allegrini, G. Naso, P. Vici (Italy); D. Loirat, A. Mailliez, F. Priou, O. Tredan, F. Dalenc, C. Perrin, J. Gligorov, M. Timar David, N. Dohollou, L. Teixeira, F. Brocard, A. Arnaud, S. Delaloge, J.-P. Spano, L. Mansi (France); L. Andrade, F. Damian, J. Pedrini, S. Aleixo, R. Hegg, R. Junior (Brazil); M. Reinisch, M. Schmidt, C. Wenzel, E.-M. Grischke, A. Schneeweiss, M. Just, N. Harbeck, C. Schumacher, U. Peters, D. Fischer, H. Forstbauer, R. Liersch (Germany); E. Warner, N. Bouganim, C. Doyle, J. Price Hiller, T. Vandenberg, M. Pavic, A. Robinson, G. Roldan Urgoiti, N. Califaretti (Canada); A. Alacacioglu, M. Gumus, B. Yalcin, I. Cicin, F. Kose, K. Uygun, M. Kaplan, E. Cubukcu (Turkey); A. Wardley, M. Harries, D. Miles (UK); D. Doval, S. Gupta, P. Mohapatra, S. Chatterjee, N. Ghadyalpatil, M. Singhal, S. Nag, A. Agarwal (India); I. Wolf, E. Gal Yam, R. Yerushalmi, T. Peretz, G. Fried, N. Ben Baruch, D. Katz (Israel); E. Hamilton, F. Kayali, A. Brufsky, M. Telli, G. Wright, R. Oyola, T. Rakowski, S. Graff (USA); S. Tjulandin, V. Semiglazov (Russian Federation); A. Aparicio, M. Ruiz Borrego, L. Merino, J. Guerra Martinez, E. Lopez (Spain); T. Yamashita, S. Ohtani, K. Inoue, Y. Ito, N. Niikura, T. Nakayama, Y. Sagara, Y. Yanagita, Y. Kamada, K. Kaneko (Japan); D. Kaen, A. Nervo (Argentina); A. Eniu, M. Schenker (Romania); P. Priester, B. Melichar, M. Zimovjanova, P. Sormova (Czech Republic); J. Sufliarsky, M. Kakalejcik (Slovakia); R. Belbaraka, H. Errihani (Morocco); D. Le Than, D. Pham (Vietnam); G. Aravantinos, C. Papadimitriou, G. Koumakis, C. Papandreou (Greece); P. Podolski (Croatia); K. Tabane (South Africa).