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ORIGINAL ARTICLE

IMpassion132 double-blind randomised phase III trial of chemotherapy with or without atezolizumab for early relapsing unresectable locally advanced or metastatic triple-negative breast cancer

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Background: Immune checkpoint inhibitors improve the efficacy of first-line chemotherapy for patients with programmed death-ligand 1 (PD-L1)-positive unresectable locally advanced/metastatic triple-negative breast cancer (aTNBC), but randomised data in rapidly relapsing aTNBC are scarce.

Patients and methods: IMpassion132 (NCT03371017) enrolled patients with aTNBC relapsing <12 months after last chemotherapy dose (anthracycline and taxane required) or surgery for early TNBC. PD-L1 status was centrally assessed using SP142 before randomisation. Initially patients were enrolled irrespective of PD-L1 status. From August 2019, enrolment was restricted to PD-L1-positive (tumour immune cell ≥1%) aTNBC. Patients were randomised 1:1 to placebo or atezolizumab 1200 mg every 21 days with investigator-selected chemotherapy until disease progression or unacceptable toxicity. Stratification factors were chemotherapy regimen (carboplatin plus gemcitabine or capecitabine monotherapy), visceral (lung and/or liver) metastases and (initially) PD-L1 status. The primary endpoint was overall survival (OS), tested hierarchically in patients with PD-L1-positive tumours and then, if positive, in the modified intent-to-treat (mITT) population (all-comer patients randomised pre-August 2019). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR) and safety.

Results: Among 354 patients with rapidly relapsing PD-L1-positive aTNBC, 68% had a disease-free interval of <6 months and 73% received carboplatin/gemcitabine. The OS hazard ratio was 0.93 (95% confidence interval 0.73-1.20, $P = 0.59$; median 11.2 months with placebo versus 12.1 months with atezolizumab). mITT and subgroup results were consistent. Median PFS was 4 months across treatment arms and populations. ORRs were 28% with placebo versus 40% with atezolizumab. Adverse events (predominantly haematological) were similar between arms and as expected with atezolizumab plus carboplatin/gemcitabine or capecitabine following recent chemotherapy exposure.

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Conclusions: OS, which is dismal in patients with TNBC relapsing within <12 months, was not improved by adding atezolizumab to chemotherapy. A biology-based definition of intrinsic resistance to immunotherapy in aTNBC is urgently needed to develop novel therapies for these patients in next-generation clinical trials.
Key words: disease-free interval, immune checkpoint, PD-L1, prognosis, rapid relapse, triple-negative breast cancer

INTRODUCTION

Until recently, standard systemic therapy for early triple-negative breast cancer (eTNBC) included anthracycline- and/or taxane-based therapy, administered in the adjuvant or neoadjuvant setting (potentially followed by capecitabine in the absence of a complete pathological response to neoadjuvant therapy).[1] Latterly, treatment options have improved with greater uptake of carboplatin and the introduction of agents targeting poly (ADP-ribose) polymerase 1 and the programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) pathway.

Among patients who develop metastatic TNBC following (neo)adjuvant anthracycline and/or taxane chemotherapy, approximately half of them experience relapse within 12 months of completing chemotherapy.[2,3] Early relapsing TNBC is a biologically and clinically distinct entity[4,5] characterised by aggressive disease that is intrinsically resistant to standard therapies, occurs in younger patients and has a lower prevalence of *BRCA* alterations, a higher prevalence of Ki-67 ≥50% and greater primary tumour burden, leading to dismal outcomes despite intensive therapy.[2,3,6]

At first relapse, PD-(L)1 inhibitors (atezolizumab, pembrolizumab and toripalimab) significantly improve the efficacy of first-line chemotherapy for patients with PD-L1-positive TNBC.[7-11] However, most recent trials of drugs targeting the PD-1/PD-L1 and AKT pathways (IMpassion130 and IMpassion131 evaluating atezolizumab,[9,12] TORCHLIGHT evaluating toripalimab[11] and IPATunity130 and PAKT evaluating ipatasertib and capivasertib[13,14]), excluded patients whose disease relapsed within 12 months of treatment for eTNBC. Moreover, up to one-third of patients in these trials had *de novo* metastatic disease,[7,11,12] which generally has a better prognosis than relapsed TNBC.[15] Consequently, data on prognosis and the effect of newer treatments in patients with rapidly relapsing disease are lacking. Guidelines advise against rechallenge with the same agent within 12 months of primary therapy,[16] and the exclusion of patients with early relapse from clinical trials poses a real challenge in clinical practice.

The IMpassion132 trial was designed to evaluate the anti-PD-L1 agent atezolizumab combined with chemotherapy specifically in patients with TNBC relapsing within 12 months of standard-of-care chemotherapy or surgery for eTNBC. Here, we report the overall survival (OS) results (primary endpoint).

PATIENTS AND METHODS

The international, double-blind, placebo-controlled, multicentre, phase III IMpassion132 trial (NCT03371017) assessed the efficacy and safety of atezolizumab combined with chemotherapy for patients with early relapsing unresectable locally advanced or metastatic TNBC (aTNBC). The protocol, informed consent forms, patient information and supporting study-related materials were approved by each site's institutional review board/ethics committee before study initiation. All patients provided written informed consent. The study was conducted in full conformance with the International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or laws and regulations of each participating site's country, whichever provided greater protection to the individual. The trial complied with the requirements of the ICH E2A guideline and applicable laws and regulations.

Eligible females or males had an unresectable local or metastatic recurrence of TNBC <12 months after the last treatment for eTNBC with curative intent (chemotherapy or primary surgery, whichever was later). Patients had to have received anthracycline- and taxane-containing neoadjuvant or adjuvant chemotherapy for eTNBC. Prior chemotherapy or systemic targeted therapy for aTNBC was not permitted.

Before randomisation, investigators selected one of two chemotherapy options: intravenous gemcitabine 1000 mg/m^2 plus carboplatin area under the curve 2 mg/ml/min both on days 1 and 8 every 21 days, or oral capecitabine 1000 mg/m^2 twice daily on days 1-14 every 21 days. Capecitabine was mandatory if patients had received platinum-containing therapy for eTNBC; the proportion of patients receiving capecitabine was capped at ∼30% of the overall population. TNBC status was defined according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines using the version applicable at the time of enrolment,[17-19] tested locally or centrally to confirm eligibility; TNBC status assessed locally before study entry was retrospectively centrally confirmed. PD-L1 status was assessed centrally using the VENTANA PD-L1 (SP142) immunohistochemistry assay (Roche Diagnostics, Rotkreuz, Switzerland). This was preferably done on a formalin-fixed paraffin-embedded (FFPE) tumour block from relapsed metastatic or locally advanced disease (or, if not feasible, on the diagnosis sample, primary surgical resection sample or the most recent FFPE tumour biopsy). PD-L1-negative status was defined as PD-L1-expressing tumour-infiltrating immune cells (ICs) on <1% of the tumour area and PD-L1-positive status was defined as ICs ≥1%. Initially patients were enrolled irrespective of PD-L1 status. However, in August 2019, after enrolment of 380 'all-comer' patients, the protocol was amended to restrict enrolment to PD-L1-positive aTNBC, based on results from the IMpassion130 trial indicating that benefit from atezolizumab was driven by the group with PD-L1-positive tumours[9] and subsequent regulatory approvals for atezolizumab in this indication. It was

planned to randomise ∼190 additional patients with PD-L1-positive tumours to provide ∼330 patients with PD-L1-positive aTNBC. Additional inclusion criteria included age ≥18 years, Eastern Cooperative Oncology Group performance status 0 or 1 and adequate haematological and end-organ function. Patients with untreated symptomatic or actively progressing central nervous system metastases were excluded. The protocol (available online) details additional eligibility criteria.

Stratification factors were investigator-selected chemotherapy (carboplatin plus gemcitabine versus capecitabine monotherapy), presence of visceral (lung and/or liver) metastases (yes versus no) and (until August 2019) tumour PD-L1 status (ICs <1% versus ≥1%). Patients were randomised in a 1 : 1 ratio to receive either placebo or atezolizumab 1200 mg on day 1 every 21 days with the chosen chemotherapy until disease progression according to RECIST version 1.1, unacceptable toxicity or patient/physician withdrawal. Crossover was not allowed. Unblinding at disease progression was permitted if knowledge of previous immune checkpoint inhibitor exposure was essential for enrolment into a different clinical trial or receipt of further regulatory authority-approved treatments.

Tumours were assessed every 8 weeks for the first year and every 12 weeks from the second year until disease progression as per according to RECIST version 1.1, withdrawal of consent or death. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs version 4.0. An independent data monitoring committee periodically reviewed safety data.

The primary endpoint was OS, defined as the interval between randomisation and death from any cause. OS was tested hierarchically first in patients with PD-L1-positive tumours and then, if positive, in the modified intent-to-treat (mITT) population [eligible all-comer patients randomised before August 2019, representing the 'natural' prevalence of PD-L1 positivity (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.04.001)].

Secondary endpoints included 12- and 18-month survival rates, investigator-assessed progression-free survival (PFS) according to RECIST version 1.1 (tested hierarchically in patients with PD-L1-positive tumours and then in the mITT

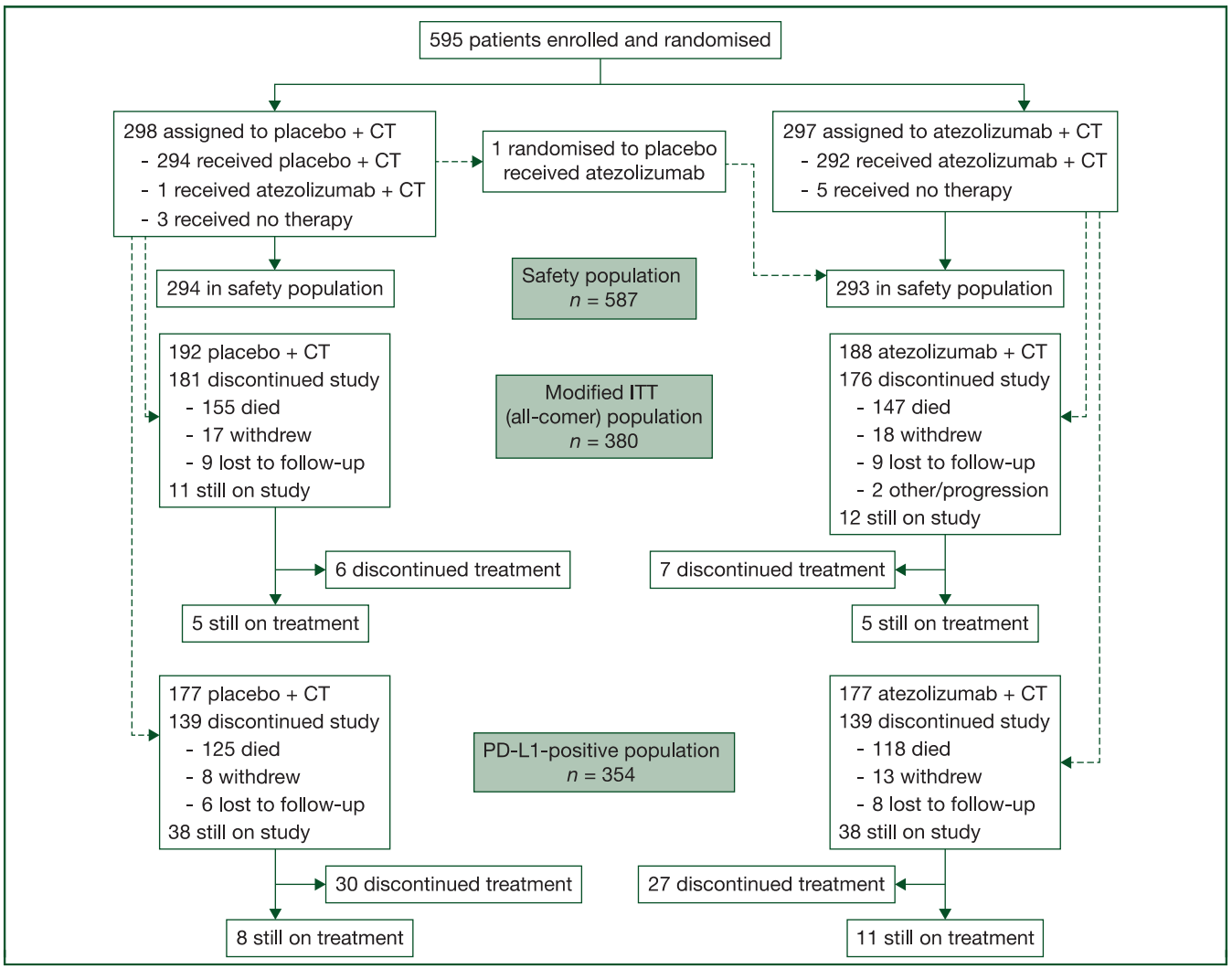


Figure 1. Patient disposition. At the clinical cut-off date, 76 patients with PD-L1-positive tumours remained on study (19 still on treatment, 57 off treatment but still in follow-up). In the modified ITT population, 23 were still on study (10 still on treatment, 13 off treatment but still in follow-up).
CT, chemotherapy; ITT, intent-to-treat; PD-L1, programmed death-ligand 1.

population), investigator-assessed objective response rate (ORR; tested with the same hierarchy), duration of objective response, clinical benefit rate (complete or partial response, or stable disease lasting ≥6 months) and safety.

The primary analysis was planned to occur when ∼247 deaths had occurred among patients with PD-L1-positive tumours. Assuming a median OS of 9 months in the control arm, this would allow detection of a target hazard ratio (HR) of 0.70, representing a 3.8-month improvement in median OS with atezolizumab, with 80% power and a two-sided log-rank test at $\alpha = 0.05$.

For efficacy analyses, patients were grouped according to the treatment assigned at randomisation. OS was compared between treatment arms based on a stratified log-rank test with randomisation stratification factors as documented in the interactive web response system [chosen chemotherapy, visceral metastases and (for the mITT analysis) PD-L1 status]. The HR was estimated using a stratified Cox regression model and the same stratification factors and reported with corresponding 95% confidence intervals (CIs). Medians were estimated using Kaplan–Meier methodology with 95% CIs using the Brookmeyer–Crowley method.

RESULTS

Between 11 January 2018 and 4 August 2023, 595 patients were enrolled from 126 sites in 28 countries in Europe, North and South America, Asia and Africa (Appendix 1). These included 354 patients with PD-L1-positive tumours and 380 in the mITT population (Figure 1). Eight patients received no study treatment.

Baseline characteristics were well balanced between the treatment arms in both analysis populations (Table 1) and the full-analysis set (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.04.001). Among patients with PD-L1-positive tumours, 68% had a disease-free interval (DFI) of <6 months and 73% received carboplatin/gemcitabine.

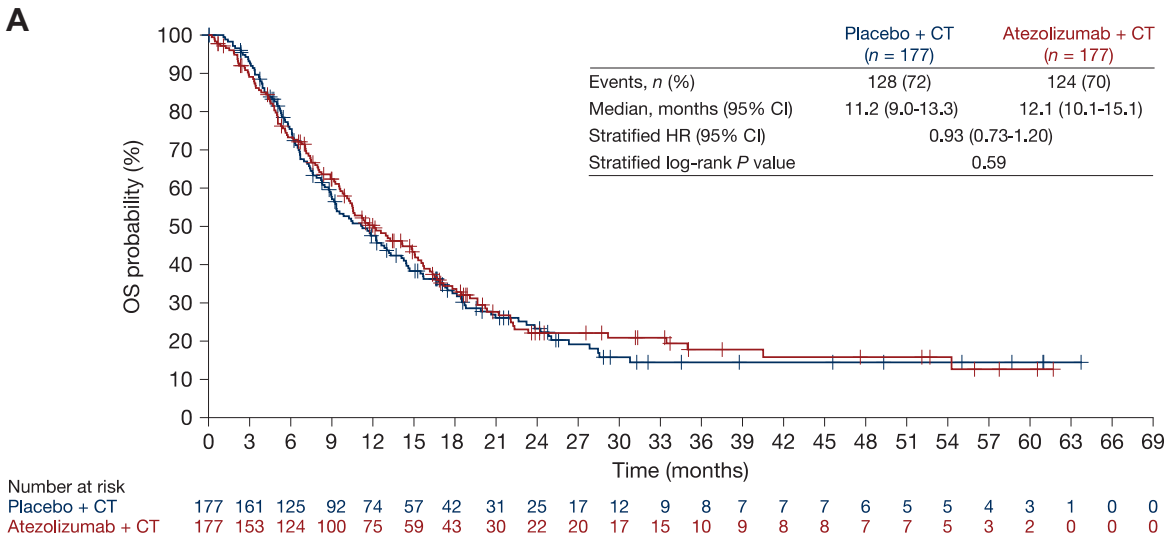
Table 1. Baseline characteristics

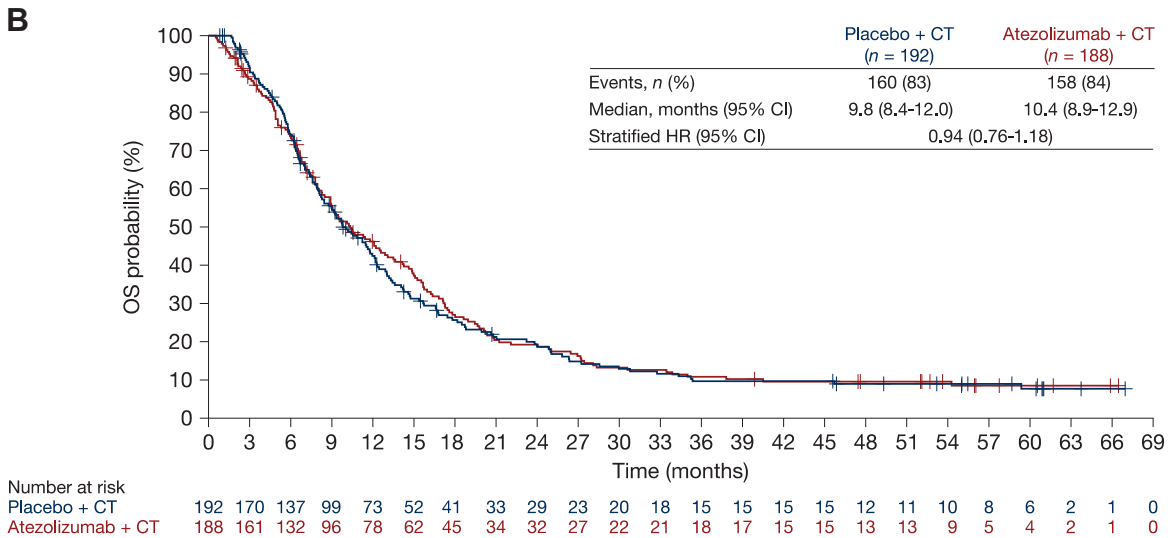
Characteristic, *n* (%)	PD-L1-positive TNBC (*n* = 354)		mITT population (*n* = 380)	
	Placebo + CT (*n* = 177)	Atezo + CT (*n* = 177)	Placebo + CT (*n* = 192)	Atezo + CT (*n* = 188)
Age, years				
Median (range)	48 (25-83)	48 (23-77)	49 (24-83)	49 (23-79)
18-40	46 (26)	46 (26)	49 (26)	44 (23)
41-64	110 (62)	117 (66)	121 (63)	130 (69)
≥65	21 (12)	14 (8)	22 (11)	14 (7)
Sex				
Female	177 (100)	177 (100)	192 (100)	188 (100)
Race				
White	108 (61)	105 (59)	146 (76)	135 (72)
Asian	48 (27)	48 (27)	22 (11)	27 (14)
Black/African American	8 (5)	5 (3)	6 (3)	5 (3)
American Indian/Alaska Native	2 (1)	3 (2)	2 (1)	4 (2)
Multiple	0	1 (1)	0	1 (1)
Unknown	11 (6)	15 (8)	16 (8)	16 (9)
ECOG performance status				
0	101 (57)	110 (62)	114 (59)	108 (57)
1	75 (42)	66 (37)	77 (40)	80 (43)
2	1 (1)	1 (1)	1 (1)	0
Prior chemotherapy				
Anthracycline	176 (99)	177 (100)	191 (99)	186 (99)
Taxane	176 (99)	176 (99)	191 (99)	186 (99)
Platinum	32 (18)	31 (18)	40 (21)	42 (22)
Capecitabine	47 (27)	52 (29)	33 (17)	44 (23)
DFI, months[a]				
<6	123 (69)	117 (66)	119 (62)	125 (66)
6-12	53 (30)	57 (32)	72 (38)	63 (34)
Metastatic disease	159 (90)	166 (94)	174 (91)	176 (94)
Lung and/or liver metastases	110 (62)	106 (60)	125 (65)	129 (69)
Lung	86 (49)	86 (49)	95 (49)	111 (59)
Liver	42 (24)	46 (26)	50 (26)	53 (28)
PD-L1 status[b]				
IC ≥1%	177 (100)	177 (100)	71 (37)	69 (37)
Chosen CT				
Carboplatin/gemcitabine	130 (73)	130 (73)	133 (69)	130 (69)
Capecitabine	47 (27)	47 (27)	59 (31)	58 (31)

Atezo, atezolizumab; CT, chemotherapy; DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; IC, immune cells; mITT, modified intent-to-treat; PD-L1, programmed death-ligand 1; TNBC, triple-negative breast cancer.

[a]DFI was calculated from the date of last chemotherapy administered or last curative surgery, whichever was later, to the date of diagnosis of metastatic or locally advanced unresectable disease. DFI was missing in one patient in the placebo arm; among patients with PD-L1-positive tumours in the atezolizumab arm (but not in the mITT population), DFI was <12 months with no further details in two patients and >12 months in one patient.

[b]As recorded in the interactive web response system.





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Subgroup	Total n	Placebo + CT (n = 177) n	Placebo + CT (n = 177) Median, months	Atezolizumab + CT (n = 177) n	Atezolizumab + CT (n = 177) Median, months	HR (95% Wald CI)
All patients	354	177	11.2	177	12.1	0.95 (0.74-1.22)
Age, years						
18-40	92	46	8.9	46	10.7	0.86 (0.53-1.40)
41-64	227	110	12.2	117	12.6	0.91 (0.67-1.24)
≥65	35	21	9.4	14	9.6	1.33 (0.56-3.16)
Race						
White	213	108	9.3	105	11.4	0.89 (0.66-1.21)
Asian	96	48	14.1	48	19.1	0.97 (0.56-1.69)
Black/African American	13	8	10.9	5	11.3	1.50 (0.35-6.38)
Other	32	13	15.5	19	10.6	1.14 (0.49-2.65)
ECOG performance status						
0	211	101	11.1	110	14.8	0.81 (0.58-1.12)
1	141	75	11.6	66	8.9	1.29 (0.87-1.90)
CT choice						
Carboplatin/gemcitabine	260	130	9.9	130	12.6	0.81 (0.61-1.09)
Capecitabine	94	47	12.6	47	10.5	1.41 (0.87-2.29)
Visceral (lung and/or liver) metastases						
Yes	216	110	9.0	106	11.3	0.90 (0.66-1.23)
No	138	67	14.5	71	13.1	1.03 (0.69-1.54)
Prior platinum						
Yes	63	32	11.2	31	11.2	1.36 (0.76-2.43)
No	291	145	11.1	146	12.6	0.86 (0.66-1.14)
Disease-free interval, months						
<6	240	123	9.4	117	11.3	0.95 (0.70-1.28)
≥6	111	53	12.8	58	13.1	0.95 (0.60-1.48)

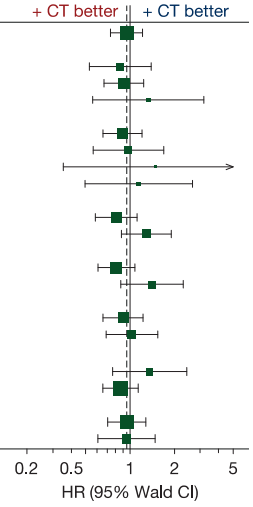

Figure 2. Overall survival. (A) Patients with PD-L1-positive tumours (median duration of follow-up: 9.8 months). (B) mITT population (median duration of follow-up: 9.2 months). (C) Subgroups of patients with PD-L1-positive tumours. The size of the symbol is proportional to the size of the population in the subgroup.
CI, confidence interval; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mITT, modified intent-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1.

At the data cut-off for the primary analysis (15 September 2023), the median duration of follow-up in patients with PD-L1-positive tumours was 9.8 (range 0.0-63.7) months, 19 patients (5%) were on study treatment and 57 (16%) were alive in follow-up (Figure 1). OS events had been reported in 252 patients with PD-L1-positive tumours: 128 (72%) in the placebo arm and 124 (70%) in the atezolizumab arm. There was no statistically significant improvement in OS with the addition of atezolizumab to chemotherapy (HR 0.93, 95% CI 0.73-1.20, $P = 0.59$) (Figure 2A). Median OS was 11.2 (95% CI 9.0-13.3) months in the placebo arm versus 12.1 (95% CI 10.1-15.1) months in the atezolizumab arm. One-year survival rates were 48% (95% CI 40% to 55%) in the placebo arm versus 50% (95% CI 43% to 58%) in the atezolizumab arm; corresponding 18-month rates were 32% (95% CI 25% to 40%) and 34% (95% CI 26% to 41%).

As the primary objective in PD-L1-positive aTNBC was not met, OS was not formally tested in the mITT population, according to the hierarchical design. The HR for OS was 0.94 (95% CI 0.76-1.18), with a median OS of 9.8 (95% CI 8.4-12.0) months in the placebo arm and 10.4 (95% CI 8.9-12.9) months with atezolizumab; 1-year survival rates were 42% (95% CI 35% to 50%) and 46% (95% CI 39% to 54%), respectively (Figure 2B). OS results in prespecified subgroups of patients with PD-L1-positive aTNBC (Figure 2C) and exploratory subgroups defined by geographical region (data not shown) were consistent with the primary analysis and 95% CIs for the HR point estimates crossed 1 in all subgroups analysed.

As the primary endpoint did not reach statistical significance, prespecified secondary endpoints were not formally tested. PFS was similar (median ∼4 months) across treatment arms and analysis populations (Table 2, Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.04.001). Among 313 patients with PD-L1-positive measurable disease, the unconfirmed ORRs were 28% with placebo versus 40% with atezolizumab, and median duration of response was 4.1 versus 6.6 months, respectively. In the mITT population, no difference between the placebo and atezolizumab arms was observed for ORR (32% versus 31%, respectively) or duration of response (median 5.2 versus 5.7 months, respectively).

The safety-assessable population included 587 patients. By the data cut-off date, 574 patients (96%) had discontinued atezolizumab/placebo, most commonly because of disease progression (470 patients; 80%). A further 19 patients (3%) discontinued because of symptomatic deterioration and 18 (3%) because of death. The median treatment duration was ∼3 months, regardless of treatment arm or selected chemotherapy backbone (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.04.001). Incidences of AEs and serious AEs were similar in the placebo and atezolizumab arms (Table 3). AEs of special interest (AESIs) were more common with atezolizumab than placebo, driven by immune-mediated rash, hypothyroidism and hyperthyroidism (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.04.001). However, incidences of grade 3/4 AESIs were similar in the two treatment arms, and similar proportions of patients in the placebo and atezolizumab treatment arms experienced AESIs requiring systemic corticosteroids (11% versus 13%, respectively; grade ≥3 in 6% versus 6%). There was no excess of AEs leading to treatment discontinuation or dose modification/interruption with atezolizumab.

Grade 3/4 AEs occurred in 71% of patients in the placebo arm and 67% in the atezolizumab arm (grade 4 in 21% in both arms). There were four fatal AEs in the atezolizumab arm: one (from sepsis) was considered by the investigator to be treatment related and three were not [one case each of seizure, coronavirus disease (COVID-19) and pneumothorax]. Two patients in the placebo arm had fatal AEs (one case each of pneumonitis and dyspnoea); both were considered by the investigator to be treatment related.

In the safety-assessable population, the most common AEs were haematological and gastrointestinal effects, occurring in similar proportions of patients in the two treatment groups (anaemia: 48% in the placebo arm versus 46% in the atezolizumab arm; nausea: 41% in both groups; neutropenia: 41% versus 37%; alanine transaminase increased: 34% versus 32%; aspartate aminotransferase increased: 31% versus 30%) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.04.001). The only any-grade AEs with a >5% absolute difference in

Table 2. Summary of secondary endpoints

Endpoint	PD-L1-positive TNBC		mITT population	
	Placebo + CT ($n = 177$)	Atezo + CT ($n = 177$)	Placebo + CT ($n = 192$)	Atezo + CT ($n = 188$)
PFS				
PFS events, *n* (%)	163 (92)	159 (90)	181 (94)	178 (95)
Median PFS, months (95% CI)	3.6 (3.4-4.2)	4.2 (3.7-5.6)	3.6 (3.1-3.8)	3.7 (2.8-4.0)
Stratified PFS HR (95% CI)	0.84 (0.67-1.06)		0.96 (0.78-1.19)	
1-year PFS rate, % (95% CI)	12 (7-17)	17 (11-22)	9 (5-13)	16 (10-21)
Response in patients with measurable disease	($n = 159$)	($n = 154$)	($n = 168$)	($n = 171$)
Unconfirmed objective response rate, *n* (%) [95% CI]	45 (28) [21-36]	61 (40) [32-48]	54 (32) [25-40]	53 (31) [24-39]
Difference, % (95% CI)	11 (>0 to 22)		−1 (−12 to 9)	
Median duration of response, months (95% CI)	4.1 (3.5-5.8)	6.6 (4.6-8.0)	5.2 (3.8-6.6)	5.7 (4.2-7.9)
Duration of response HR (95% CI)	0.73 (0.48-1.11)		0.95 (0.63-1.43)	
Clinical benefit rate, *n* (%) [95% CI]	55 (35) [27-43]	66 (43) [35-51]	61 (36) [29-44]	60 (35) [28-43]

Atezo, atezolizumab; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; mITT, modified intent-to-treat; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TNBC, triple-negative breast cancer.

Table 3. Summary of safety (treated patients)

Patients with AE, *n* (%)	Safety-assessable population (all treated patients)		Treated patients with PD-L1-positive TNBC	
	Placebo + CT ($n = 294$)	Atezo + CT ($n = 293$)	Placebo + CT ($n = 174$)	Atezo + CT ($n = 176$)
Any AE	283 (96)	281 (96)	167 (96)	165 (94)
Treatment-related AE	269 (91)	265 (90)	158 (91)	158 (90)
Grade 3/4 AE	210 (71)	195 (67)	125 (72)	118 (67)
Treatment-related grade 3/4 AE	190 (65)	181 (62)	114 (66)	112 (64)
Grade 5 AE	2 (1)	4 (1)	2 (1)	2 (1)
Treatment-related grade 5 AE	2 (1)	1 (<1)	2 (1)	0
Serious AE	57 (19)	67 (23)	34 (20)	39 (22)
Treatment-related serious AE	37 (13)	40 (14)	22 (13)	27 (15)
AE leading to any treatment withdrawal	32 (11)	44 (15)	20 (11)	32 (18)
AE leading to atezolizumab/placebo withdrawal	5 (2)	15 (5)	2 (1)	10 (6)
AE leading to chemotherapy withdrawal	31 (11)	41 (14)	20 (11)	30 (17)
AE leading to any treatment dose modification/ interruption	227 (77)	225 (77)	138 (79)	142 (81)
AE leading to atezolizumab/placebo dose modification/ interruption	144 (49)	151 (52)	83 (48)	99 (56)
AE leading to chemotherapy dose modification/ interruption	225 (77)	223 (76)	137 (79)	140 (80)
AE of special interest	160 (54)	180 (61)	103 (59)	111 (63)
Grade 3/4 AE of special interest	42 (14)	43 (15)	25 (14)	27 (15)

AE, adverse event; atezo, atezolizumab; CT, chemotherapy; PD-L1, programmed death-ligand 1.

incidence between treatment arms were decreased appetite (11% with placebo versus 17% with atezolizumab) and hyperthyroidism (0% versus 5%, respectively). The most common grade ≥3 AEs were neutropenia (30% versus 29% of patients in the placebo versus atezolizumab arms, respectively), neutrophil count decreased (19% versus 19%), anaemia (18% versus 16%), white blood cell count decreased (12% versus 11%) and leukopenia (10% versus 10%).

Safety results in patients with PD-L1-positive tumours were generally consistent with findings in the safety-assessable population (Table 3, Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.04.001). AEs leading to treatment discontinuation and atezolizumab dose modification or interruption were more common with atezolizumab than placebo.

In patients with PD-L1-positive tumours, post-progression therapy was recorded in 56% of patients in the placebo arm and 50% in the atezolizumab arm. The non-recording of post-progression therapy in the remaining patients comprised a mix of withdrawal from the study at the time of study treatment discontinuation (∼15% in each group) and the poor candidacy of this patient population for multiple lines of therapy. The most commonly administered agents in patients with PD-L1-positive aTNBC were eribulin (21% of the placebo group versus 18% of the atezolizumab group), capecitabine (12% versus 14%) and cyclophosphamide (6% versus 10%); 22 patients received anti-PD-(L)1 therapy (8% of patients initially randomised to placebo and 5% initially randomised to atezolizumab). In the mITT population, post-progression therapy was recorded in 57% of patients in the placebo arm and 58% in the atezolizumab arm, most commonly eribulin (26% versus 27%, respectively), capecitabine (20% versus 19%), vinorelbine (11% versus 11%), paclitaxel (9% versus 12%), gemcitabine (8% versus 12%) and carboplatin (9% versus 10%); 18 patients received anti-PD-(L)1 therapy (6% versus 3%).

DISCUSSION

To our knowledge, IMpassion132 is the only reported randomised phase III trial focusing solely on patients with early relapsing aTNBC, a population with a dismal prognosis and high unmet need.[2,20,21] Combining atezolizumab with standard chemotherapy in patients with PD-L1-positive early relapsing TNBC (<12 months after the last chemotherapy or surgery for eTNBC) did not significantly improve the poor outcomes observed in the control arm. TNBC has long been recognised as a heterogeneous group of histologically subtyped diseases with a spectrum of drivers.[22-24] Exposure to therapeutic agents may trigger a variety of resistance mechanisms.[23] This inherent biological complexity makes it challenging to select optimal patients for novel therapeutics in adequately powered trials,[24] and IMpassion132 was particularly ambitious, focusing on one of the most treatment-resistant populations within breast cancer.

The only other available data from a prospective randomised trial in a similar setting are from the subgroup of 65 patients with PD-L1-positive aTNBC [combined positive score (CPS) ≥10 using the 22C3 assay] and a DFI of 6-12 months treated with chemotherapy with/without pembrolizumab in the KEYNOTE-355 trial.[8] In this small subgroup, the OS HR was 1.44 (95% CI 0.73-2.82). However, cross-trial comparison between a fully powered trial (IMpassion132) and an exploratory subgroup analysis (KEYNOTE-355) has limited value.

To date, IMpassion132 represents the largest reported prospective dataset describing clinical outcomes in patients with TNBC relapsing <12 months after completing therapy for eTNBC. Median OS with chemotherapy (predominantly a

carboplatin/gemcitabine doublet) was 9.8 months (11.2 months in patients with PD-L1-positive tumours). Estimates of median OS in subset analyses of patients with early relapsing aTNBC in the KEYNOTE-355 trial[8] and the LOTUS randomised phase II trial evaluating paclitaxel with or without ipatasertib[21] are limited by small sample sizes, heterogeneous chemotherapy and dramatic variation in the performance of the chemotherapy-alone control arms (KEYNOTE-355: 19.7 months in 17 patients with CPS $\geq$10 and 13.3 months in 37 patients with CPS $\geq$1; LOTUS: 11.3 months in 14 patients).

In the real-world setting, a recent analysis from the Epidemio-Strategy-Medico-Economical-Metastatic Breast Cancer (ESME-MBC) database reported outcomes in 881 patients with TNBC relapse within <12 months after (neo) adjuvant anthracycline- and/or taxane-containing therapy.[2] Patients received diverse first-line regimens, including capecitabine in 15%, gemcitabine/platinum in 11%, taxane and bevacizumab in 17% and other combinations in 14%; 17% participated in a clinical trial. Median OS was 10.1 months (95% CI 9.3-10.9 months) and median PFS was 3.1 months (95% CI 2.9-3.4 months).[2] Of note, within this subgroup, approximately half had relapse within <6 months of chemotherapy and in these patients, OS was significantly worse than in those with relapse 6-12 months after completing primary treatment. In another analysis from the same database examining outcomes in patients with relapse 3-12 months after (neo)adjuvant taxane-containing chemotherapy, median OS was 10.1 months with carboplatin plus gemcitabine and 11.8 months with taxane plus bevacizumab.[25] Similarly, an analysis from Korean registry data of patients with distant metastasis within 1 year of completing adjuvant chemotherapy (n = 207) or during neoadjuvant chemotherapy (n = 44) showed a median OS of 14.3 months and a median PFS of 4.2 months.[3] Median PFS and OS in rapid-relapsing aTNBC are consistent in these datasets and IMpassion132, and illustrate the unmet need in this population.

It is important to recognise clinical trial design differences in definitions and populations between these datasets. IMpassion132 included patients with unresectable locally advanced TNBC, required neoadjuvant/adjuvant anthracycline and taxane, and DFI was calculated from the last day of chemotherapy or surgery. KEYNOTE-355 excluded patients with a DFI of <6 months. The ESME-MBC analyses were restricted to patients with distant metastatic TNBC; prior therapy had to include anthracycline and/or taxane, and surgery within 12 months was not included when defining early relapse. However, the consistently poor prognosis of patients with rapid relapse is incontrovertible.

In IMpassion132, two-thirds of patients had a DFI of <6 months. In the control arm, median OS with chemotherapy alone was 9.4 months in these patients compared with 12.8 months in those whose disease relapsed 6-12 months after completing chemotherapy or surgery for eTNBC, suggesting a particularly poor outcome in the subgroup of patients with a DFI of <6 months. This finding is consistent with observations from the ESME-MBC real-world dataset,[2] and reinforces the even greater unmet medical need in these patients with extremely rapid relapse. Plausibly, this subgroup may include a high percentage of patients receiving capecitabine in the post-neoadjuvant residual disease setting, as the longer chemotherapy duration in these patients shortens DFI according to the definitions used in this trial. Interestingly, there was no difference in atezolizumab treatment effect between these patients and the subgroup with a DFI of 6-12 months (HR of 0.95 in both subgroups). Of note, in patients with a DFI of $\geq$12 months, combining atezolizumab with nab-paclitaxel demonstrated a clinically meaningful effect on OS in the IMpassion130 trial, driven by the effect in patients with PD-L1-positive TNBC (HR 0.67, 95% CI 0.53-0.86; median 25.4 months with atezolizumab plus nab-paclitaxel versus 17.9 months with placebo plus nab-paclitaxel).[10] Indeed, it was results from this trial, and the subsequent regulatory approval of atezolizumab in this indication, that led to the protocol amendment enriching the IMpassion132 population with PD-L1-positive aTNBC. In contrast, in IMpassion131 evaluating the addition of atezolizumab to paclitaxel, there was no sign of an OS improvement (albeit OS results were very immature with events in only 39% of patients) and as yet there is no clear explanation for these differing outcomes or indeed the exceptionally long median OS in the paclitaxel control arm of IMpassion131 (28 months).[12]

There was an apparent difference in the direction of treatment effect between the subgroup of 94 patients receiving capecitabine and the subgroup of 260 receiving carboplatin/gemcitabine. Investigator bias towards platinum-containing therapy in more aggressive disease (e.g. in patients with rapid relapse following capecitabine for post-neoadjuvant residual disease) cannot be excluded; the longer median OS with capecitabine compared with carboplatin/gemcitabine in the control arm is supportive of selection bias. Numerical differences in ORR and duration of response in patients with PD-L1-positive aTNBC are intriguing and merit further exploration in the context of molecular analyses.

IMpassion132 provides the first randomised data on the safety and tolerability of combining atezolizumab with non-taxane regimens in aTNBC. Incidences of AEs were similar between arms and the safety profile of atezolizumab in combination with carboplatin/gemcitabine or capecitabine was consistent with the known risks of the individual study drugs, driven primarily by chemotherapy-related haematological toxicities. Importantly, although more patients treated with atezolizumab than placebo had AEs leading to treatment withdrawal, chemotherapy delivery was not impaired, as evidenced by similar dose intensity in the two treatment arms, and no new or unexpected safety signals were identified. The higher incidence of grade 3/4 AEs in both treatment arms compared with historical rates in patients treated with single-agent atezolizumab[26] is consistent with underlying symptoms in a population of patients with poor-prognosis advanced disease and recent exposure to anticancer therapy. Fatal AEs were rare in both arms.

One of the challenges when designing this trial was the paucity of data in early relapsing aTNBC. Retrospective analyses of the ESME-MBC dataset reported after IMpassion132 was initiated provide some insight into treatment outcomes in this setting within the French health care system between 2008 and 2020. IMpassion132 builds on this knowledge base, providing global prospective data in a rapidly evolving treatment landscape. A limitation of both datasets is the absence of patients treated with immune checkpoint inhibitors as primary therapy, which will be an increasingly common clinical situation.

Patients with TNBC and early relapse continue to represent a treatment conundrum and unfortunately results from the IMpassion132 trial do not show improved outcomes with the addition of a PD-L1 inhibitor. Patients in IMpassion132 had experienced rapid relapse despite receiving multi-agent systemic therapy for eTNBC, which is likely to contribute to clonal evolution. This highlights the importance of ongoing translational research to decipher the heterogeneity of the multi-level 'omic' characteristics of these aggressive tumours and identify therapeutic strategies. Future patients who meet the clinical criteria of IMpassion132 may be candidates for innovative new agents and/or combination regimens in this poor-prognosis setting. Recent data from small, non-randomised proof-of-concept studies suggest that modulation of the tumour microenvironment or combination with a more effective chemotherapy-delivering backbone regimen may be required to maximise the impact of immune checkpoint blockade. For example, combining atezolizumab and paclitaxel with bevacizumab in the single-arm phase II ATRACTIB study yielded encouraging activity in predominantly PD-L1-negative aTNBC (with relapse after $>$12 months).[27] Results from Arm 7 of the BEGONIA trial suggested activity of immune checkpoint blockade combined with the antibody—drug conjugate datopotamab deruxtecan in predominantly PD-L1-negative late-relapsing or *de novo* aTNBC.[28] In this desperate landscape, the promising potential of antibody—drug conjugates to improve outcomes when partnered with immunotherapy merits further investigation.

Importantly, although currently approved indications for immunotherapy combined with chemotherapy do not exclude patients with early relapsing aTNBC, available data cast some doubt on its utility in this population. In the future, we can expect that more patients with early relapse will already have been exposed to immune checkpoint inhibitors as part of their primary therapy, and alternative strategies are likely to play a more prominent role. Clinical trials for these patients with a very poor prognosis bordering on 1 year of life after diagnosis should be a high priority for academic institutions and industry alike, and IMpassion132 provides a unique randomised prospective dataset that can be applied to future trial designs. A biology-based definition of intrinsic resistance to immune checkpoint blockade in aTNBC is urgently needed to optimally treat these patients and design next-generation (combination) clinical trials. Careful consideration of how best to include these patients in future trials in the first-line aTNBC setting is critical. Ensuring that these patients with treatment-resistant aTNBC are adequately represented in clinical trials and can ultimately, as a group, derive real benefit from novel approved therapies is a high priority.

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RDen reports personal fees for advisory boards from AstraZeneca, Roche, Pfizer, Merck, Lilly and Eisai, personal fees for invited speaker engagements from AstraZeneca, Roche, Pfizer, Merck, Lilly, Roche and AstraZeneca, fees (to institution) for speaker engagements from Roche and research grants (personal and institutional) for investigator-initiated research from Roche. FA has received research grants (to institution) from AstraZeneca, Daiichi Sankyo, Roche, Lilly, Pfizer, Owkin, Novartis and Guardant Health, honoraria (paid to institution) for advisory board participation/speaker engagements from AstraZeneca, Daiichi Sankyo, Roche, Lilly, Pfizer, Owkin, Novartis, Guardant Health, N-Power Medicine, Servier, Gilead and Boston Pharmaceuticals and personal honoraria for advisory boards from Lilly. AG reports consulting/advisory roles for Novartis, MSD, AstraZeneca and Gilead Sciences, research funding (to institution) from MSD, Roche/Genentech, AstraZeneca, Roche, Sanofi/Aventis, Daiichi Sankyo/AstraZeneca and Novartis and travel/accommodation/expenses from Mylan and Menarini. MM has received research grants from Roche, PUMA and Novartis, consulting/advisory fees from AstraZeneca, Amgen, Taiho Oncology, Roche/Genentech, Novartis, PharmaMar, Eli Lilly, PUMA, Taiho Oncology, Daiichi Sankyo, Menarini/Stemline and Pfizer and speakers' honoraria from AstraZeneca, Lilly, Amgen, Roche/Genentech, Novartis, and Pfizer. PS reports personal fees for advisory boards from AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Pfizer, Puma, Roche, Gilead, Eisai, MSD, Seagen, Amgen, Celgene and Lilly and research funding (to institution) from Astellas, AstraZeneca, Genentech, Novartis, Oncogenex, Roche and Medication. FS reports speaker honoraria from Amgen, AstraZeneca, Daiichi Sankyo, Exact Sciences, Gilead, Lilly, MSD, Pfizer, Novartis, OnkoZert, Roche and ClinSol and participates in advisory boards for Atheneum, Lilly, MSD, Gilead,

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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.

REFERENCES

1. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30(8):1194-1220.
2. Grinda T, Antoine A, Jacot W, et al. Real-world clinical and survival outcomes of patients with early relapsed triple-negative breast cancer from the ESME national cohort. *Eur J Cancer*. 2023;189:112935.
3. Kim H, Kim HJ, Kim H, et al. Real-world data from a refractory triple-negative breast cancer cohort selected using a clinical data warehouse approach. *Cancers (Basel)*. 2021;13(22):5835.
4. Zhang Y, Asad S, Weber Z, et al. Genomic features of rapid versus late relapse in triple negative breast cancer. *BMC Cancer*. 2021;21(1):568.
5. Cai SL, Liu JJ, Liu YX, et al. Characteristics of recurrence, predictors for relapse and prognosis of rapid relapse triple-negative breast cancer. *Front Oncol*. 2023;13:1119611.
6. Karaayvaz M, Cristea S, Gillespie SM, et al. Unravelling subclonal heterogeneity and aggressive disease states in TNBC through single-cell RNA-seq. *Nat Commun*. 2018;9(1):3588.
7. 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(10265):1817-1828.
8. Cortes J, Rugo HS, Cescon DW, et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. *N Engl J Med*. 2022;387(3):217-226.
9. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108-2121.
10. 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;32(8):983-993.
11. Jiang Z, Ouyang Q, Sun T, et al. Toripalimab plus nab-paclitaxel in metastatic or recurrent triple-negative breast cancer: a randomized phase 3 trial. *Nat Med*. 2024;30(1):249-256.
12. Miles D, Gligorov J, Andre F, et al. 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. *Ann Oncol*. 2021;32(8):994-1004.
13. Dent R, Kim S-B, Oliveira M, et al. Abstract GS3-04: Double-blind placebo (PBO)-controlled randomized phase III trial evaluating first-line ipatasertib (IPAT) combined with paclitaxel (PAC) for *PIK3CA/AKT1/PTEN*-altered locally advanced unresectable or metastatic triple-negative breast cancer (aTNBC): primary results from IPATunity130 Cohort A. *Cancer Res*. 2021;81:GS3-04.
14. Schmid P, Abraham J, Chan S, et al. Capivasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer: the PAKT trial. *J Clin Oncol*. 2020;38(5):423-433.
15. den Brok WD, Speers CH, Gondara L, et al. Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. *Breast Cancer Res Treat*. 2017;161(3):549-556.
16. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*. 2021;32(12):1475-1495.
17. 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. *Arch Pathol Lab Med*. 2018;142(11):1364-1382.
18. Hammond ME, Hayes DF, Wolff AC, 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 Oncol Pract*. 2010;6(4):195-197.
19. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol*. 2020;38(12):1346-1366.
20. Schmid P, Turner NC, Barrios CH, et al. First-line ipatasertib, atezolizumab, and taxane triplet for metastatic triple-negative breast cancer: clinical and biomarker results. *Clin Cancer Res*. 2024;30(4):767-778.
21. Dent R, Oliveira M, Isakoff SJ, et al. Final results of the double-blind placebo-controlled randomized phase 2 LOTUS trial of first-line ipatasertib plus paclitaxel for inoperable locally advanced/metastatic triple-negative breast cancer. *Breast Cancer Res Treat*. 2021;189(2):377-386.
22. Abdou Y, Goudarzi A, Yu JX, et al. Immunotherapy in triple negative breast cancer: beyond checkpoint inhibitors. *NPJ Breast Cancer*. 2022;8(1):121.
23. Zheng Y, Li S, Tang H, et al. Molecular mechanisms of immunotherapy resistance in triple-negative breast cancer. *Front Immunol*. 2023;14:1153990.
24. Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest*. 2011;121(7):2750-2767.
25. Vasseur A, Carton M, Guiu S, et al. Efficacy of taxanes rechallenge in first-line treatment of early metastatic relapse of patients with HER2-negative breast cancer previously treated with a (neo)adjuvant taxanes regimen: a multicentre retrospective observational study. *Breast*. 2022;65:136-144.
26. F. Hoffmann-La Roche. Summary of clinical safety—BP40657 (IMscin001).
27. Gion M, Cortez Castedo P, Blancas I, et al. Efficacy and safety of first-line atezolizumab + bevacizumab + paclitaxel in patients with advanced triple-negative breast cancer: the ATRACTIB phase 2 trial. San Antonio Breast Cancer Symposium 2023, abstract PS16-02. 2023. Available at https://atgproductions.net/atgclients/sabcs/2023_SABCS_Abstract_Report-12-1-23_Compressed.pdf. Accessed April 19, 2024.
28. Schmid P, Wysocki PJ, Ma CX, et al. Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): updated results from BEGONIA, a phase Ib/II study. *Ann Oncol*. 2023;34:S334-S390 (Abstract 379MO).

Appendix 1. PARTICIPATING INVESTIGATORS

Investigator	Centre		Patients randomised
Michelino De Laurentiis	Istituto Nazionale per lo Studio e la Cura dei Tumori Fondazione G. Pascale, Napoli	Italy	14
Marco Colleoni	IRCCS Istituto Europeo Di Oncologia (IEO), Milan	Italy	13
Giampaolo Bianchini	Ospedale San Raffaele S.r.l., Milan	Italy	12
Valentina Guarneri	IRCCS Istituto Oncologico Veneto (IOV), Padova	Italy	11
Lorenzo Livi	Azienda Ospedaliero-Universitaria Careggi, Firenze	Italy	8
Lucia Del Mastro	Azienda Ospedaliero Universitaria San Martino, Genova	Italy	4
Saverio Cinieri	Ospedale Antonio Perrino, Brindisi	Italy	4
Vanesa Gregorc	Fondazione Del Piemonte Per L'Oncologia IRCC Di Candiolo, Candiolo	Italy	3
Marina Cazzaniga	Ospedale San Gerardo, Monza	Italy	1
Zhongsheng Tong	Tianjin Cancer Hospital, Tianjin	China	12
Huiping Li	Beijing Cancer Hospital, Beijing	China	11
Xichun Hu	Fudan University Shanghai Cancer Center, Shanghai	China	7
Shui Wang	Jiangsu Province Hospital, Nanjing	China	6
Xiaojia Wang	Zhejiang Cancer Hospital, Hangzhou	China	5
Ying Cheng	Jilin Cancer Hospital, Changchun	China	4
Herui Yao	Sun Yat-Sen Memorial Hospital, Guangzhou	China	4
Haibo Wang	The Affiliated Hospital of Medical College Qingdao University, Qingdao City	China	3
Jun Qian	The First Affiliated Hospital of Bengbu Medical College, Bengbu City	China	3
Ting Wang	The First Affiliated Hospital of The Fourth Military Medical University (Xijing Hospital), Xi'an	China	3
Fei Ma	Cancer Hospital, Chinese Academy of Medical, Beijing City	China	3
Xinzheng Li	Shanxi Province Cancer Hospital, Taiyuan City	China	2
Wenhui Guo	Fujian Medical University Union Hospital, Fujian	China	2
Shu Wang	Peking University People's Hospital, Beijing	China	1
Wenhe Zhao	Sir Run Run Shaw Hospital Zhejiang University, Hangzhou	China	1
Guosheng Ren	The First Affiliated Hospital, Chongqing Medical University, Chongqing	China	1
Qingyuan Zhang	Harbin Medical University Cancer Hospital, Harbin	China	1
Delphine Loirat	Institut Curie Site Paris—Service D'oncologie Médicale, Paris	France	22
Olivier Tredan	Centre Leon Berard, Lyon	France	12
Anthony Goncalves	Institut Paoli-Calmettes, Marseille	France	7
Veronique D'Hondt	Centre Régional de Lutte Contre Le Cancer Val D'aurelle Paul Lamarque, Montpellier	France	6
Suzette Delaloge	Gustave Roussy, Villejuif	France	5
Isabelle Desmoulins	Centre Georges-François Lecler, Dijon	France	3
Lionel Uwer	Centre Alexis Vautrin, Vandoeuvre-Les-Nancy	France	1
Véronique Dieras	Centre Eugene Marquis, Rennes	France	1
Ahmet Bilici	Medipol University Medical Faculty, Istanbul	Turkey	26
Öztürk Ates	Ankara Oncology Hospital, Ankara	Turkey	9
Sercan Aksoy	Hacettepe University Medical Faculty, Ankara	Turkey	7
Erhan Gokmen	Ege University Medical Faculty, Izmir	Turkey	5
Ozlem Ercelep	Marmara University Pendik Training and Research Hospital, Istanbul	Turkey	4
Sernaz Topaloglu	Trakya Universitesi Tip Fakultesi, Medikal Onkoloji Bilim Dali, Edirne	Turkey	2
Mehmet Artac	Necmettin Erbakan University Meram Medical Faculty, Konya	Turkey	2
Yeon Hee Park	Samsung Medical Center, Seoul	Republic of Korea	27
Seock Ah Im	Seoul National University Hospital, Seoul	Republic of Korea	15
Jee Hyun Kim	Seoul National University Bundang Hospital, Bundang-gu	Republic of Korea	5
Kyung Hae Jung	Asan Medical Center, Seoul	Republic of Korea	5
Joo Hyuk Sohn	Severance Hospital, Yonsei University Health System, Seoul	Republic of Korea	2
Begona Bermejo De Las Heras	Hospital Clínico Universitario de Valencia, Valencia	Spain	15
Miguel Martin	Hospital General Universitario Gregorio Marañon, Madrid	Spain	8
Ana Godoy Ortiz	Hospital Clinico Universitario Virgen de la Victoria, Malaga	Spain	8
Cristina Saura	Hospital Universitari Vall d'Hebron, Barcelona	Spain	6
Ines Marrodan Ciordia	Hospital de Cruces, Barakaldo	Spain	4
Maria Gion	Hospital Ramon y Cajal, Madrid	Spain	3
Roberto Hegg	Hospital Perola Byington, Sao Paulo	Brazil	8
Jose Pedrini	Hospital Nossa Senhora da Conceicao, Porto Alegre	Brazil	7
Ruffo de Freitas Junior	Hospital Araujo Jorge, Goiania	Brazil	7
Marcelo Salgado	Hospital do Cancer de Pernambuco—HCP, Recife	Brazil	6
Nicolas Silva Lazaretti	Hospital Sao Vicente de Paulo, Passo Fundo	Brazil	3
Lilian Arruda	Núcleo de Pesquisa São Camilo, Sao Paulo	Brazil	2
Renata Meneguetti	Instituto de Pesquisa Grupo NotreDame Intermedica, Sao Paulo	Brazil	1
Cristiano Vendrame	Centro de Oncologia de Santa Catarina, Chapeco	Brazil	1
Fabio Santos	Oncocentro Serviços Medicos E Hospitalares, Fortaleza	Brazil	1
Mark Harries	Guys and St Thomas NHS Foundation Trust, London	UK	8
Anne Armstrong	Christie Hospital NHS Trust, Manchester	UK	7
Olga Oikonomidou	Western General Hospital, Edinburgh Cancer Center, Edinburgh	UK	7

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Appendix 1. Continued

Investigator	Centre		Patients randomised
Peter Schmid	Barts, London	UK	6
Simon Waters	Velindre Cancer Centre, Newport	UK	2
Lucy McAvan	University Hospital Coventry, Coventry	UK	1
Apurna Jegannathen	Royal Stoke University Hospital, Stoke on Trent	UK	1
David Eaton	Royal Lancaster Infirmary, Lancaster	UK	1
David Miles	Mount Vernon Cancer Centre, Northwood	UK	1
Ricardo Villalobos Valencia	Centro Medico Dalinde, Mexico City	Mexico	21
Claudia Arce Salinas	Instituto Nacional De Cancerologia, Mexico City	Mexico	8
Alberto Suarez Zaizar	CENEIT Oncologicos, Mexico City	Mexico	5
Mona Frolova	FSBI "National Medical Research Center of Oncology N.N. Blokhin", Moscow	Russia	10
Alexey Manikhas	City Clinical Oncology Dispensary, St Petersburg	Russia	5
Vladimir Semiglazov	FBI "Scientific Research Institute of Oncology n. a. N. N. Petrov", St Petersburg	Russia	5
Lyudmila Zhukova	Moscow Clinical Scientific Center, Moscow	Russia	4
Alexandr Vasiliev	Private Healthcare Institution Clinical Hospital RZhD Medicine, St Petersburg	Russia	2
Daniil Stroyakovskii	Moscow City Oncology Hospital #62, Oblast	Russia	1
Ivana Bozovic Spasojevic	Institute of Oncology and Radiology of Serbia, Belgrade	Serbia	10
Jasna Pesic	Oncology Institute of Vojvodina, Sremska Kamenica	Serbia	5
Ana Cvetanovic	Clinical Centre Nis, Nis	Serbia	3
Zafir Murtezani	University Hospital Medical Center Bezanijska Kosa, Belgrade	Serbia	1
Tjoung-Won Park-Simon	Medizinische Hochschule Hannover, Hannover	Germany	5
Andreas Schneeweiss	Nationales Centrum für Tumorerkrankungen (NCT), Heidelberg	Germany	2
Christoph Salat	Gemeinschaftspraxis Prof. Dr.med. Christoph Salat und Dr.med. Oliver J. Stötzer, München	Germany	2
Sherko Kümmel	Klinikum Essen-Mitte Ev. Huyssens-Stiftung/Knappschafts GmbH, Essen	Germany	1
Joachim Rom	Klinikum Frankfurt Höchst GmbH, Frankfurt	Germany	1
Pauline Wimberger	Universitätsklinikum "Carl Gustav Carus", Dresden	Germany	1
Christoph Thomssen	Universitätsklinikum Halle (Saale), Halle	Germany	1
Laszlo Landherr	Budapesti Uzsoki Utcai Kórház, Budapest	Hungary	2
Laszlo Budi	Borsod-Abauj-Zemplen Megyei Korhaz es Egyetemi Oktato Korhaz, Miskolc	Hungary	2
Katalin Boer	Szent Margit Hospital, Budapest	Hungary	1
Gabor Rubovszky	Orszagos Onkologiai Intezet, Budapest	Hungary	2
László Csaba Mangel	Pécsi Tudományegyetem, Pecs	Hungary	2
Meri Utriainen,	Helsinki University Central Hospital, Helsinki	Finland	5
Minna Tanner	Tampere University Hospital, Tampere	Finland	4
Rhizlane Belbaraka	Centre Hospitalier Universitaire Mohamed VI, Marrakech	Morocco	5
Ali Tahri	Clinique Specialise Menara, Marrakech	Morocco	2
Hassan Errihani	Institut National D'Oncologie Sidi Med Benabdellah, Rabat	Morocco	1
Newfal Mellas	Centre Hospitalier Universitaire Hassan II, Fes	Morocco	1
Erika Hamilton	Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN	USA	4
Adam Brufsky	Magee-Woman's Hospital, Pittsburgh, PA	USA	1
Kathleen Harnden	Inova Schar Cancer Institute, Fairfax, VA	USA	1
Gail Lynn Wright	Florida Cancer Specialists & Research Institute, St. Petersburg, FL	USA	1
Fadi Kayali	Florida Cancer Specialists—Fort Myers (Broadway), Sarasota, FL	USA	1
Bernardo Rapoport	Medical Oncology Centre of Rosebank, Johannesburg	South Africa	5
Maria Coccia-Portugal	Private Oncology Centre, Pretoria	South Africa	2
Georgia Savva Demetriou	Wits Clinical Research, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg	South Africa	1
Zbigniew Nowecki	Narodowy Inst. Onkologii im. Sklodowskiej-Curie Panstw. Inst. Bad, Warsaw	Poland	7
Jolanta Smok-Kalwat	Świętokrzyskie Centrum Onkologii, Kielce	Poland	1
Oxana Shatkovskaya	Kazakh Scientific Research Institution of Oncology and Radiology, Almaty	Kazakhstan	7
Rebecca Dent	National Cancer Centre, Singapore	Singapore	4
Berisa Hasanbegovic	Clinical Center University of Sarajevo, Sarajevo	Bosnia and Herzegovina	4
Mauricio Burotto	Bradford Hill Centro de Investigaciones Clinicas, Santiago	Chile	3
Paola Celedon	Clinica Vespucio, La Florida	Chile	1
Noyde Batista Albuerne	Hospital Hermanos Ameijeiras, La Habana	Cuba	2
Elias Gracia Medina	Instituto Nacional de Oncología y Radiología (INOR), La Habana	Cuba	1
Fernando Gonçalves	Centro Hospitalar do Porto—Hospital de Santo António, Porto	Portugal	2
Catarina Abreu	Hospital de Santa Maria, Lisboa	Portugal	1
Juan Carlos Alcedo	The Panama Clinic, Panama City	Panama	2
Sandra Ostoich	Hospital Provincial del Centenario, Rosario	Argentina	1
Cristian Micheri	Instituto de Oncología de Rosario, Rosario	Argentina	1
Guillermo Valencia	Instituto Nacional de Enfermedades Neoplasicas, Lima	Peru	2
Vladimir Todorovic	Clinical Center of Montenegro, Podgorica	Montenegro	1