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Adjuvant Atezolizumab for Early Triple-Negative Breast Cancer
The ALEXANDRA/IMpassion030 Randomized Clinical Trial

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IMPORTANCE Triple-negative breast cancer is an aggressive subtype with a high incidence in young patients, a high incidence in non-Hispanic Black women, and a high risk of progression to metastatic cancer, a devastating sequela with a 12- to 18-month life expectancy. Until recently, one strategy for treating early-stage triple-negative breast cancer was chemotherapy after surgery. However, it was not known whether the addition of immune therapy to postsurgery chemotherapy would be beneficial.

OBJECTIVE To evaluate the addition of immune therapy in the form of atezolizumab to postoperative chemotherapy in patients with the high-risk triple-negative breast cancer subtype.

DESIGN, SETTING, AND PARTICIPANTS In this open-label international randomized phase 3 trial conducted in more than 330 centers in 31 countries, patients undergoing surgery as initial treatment for stage II or III triple-negative breast cancer were enrolled between August 2, 2018, and November 11, 2022. The last patient follow-up was on August 18, 2023.

INTERVENTIONS Patients were randomized (1:1) to receive standard chemotherapy for 20 weeks with (n = 1101) or without (n = 1098) the immune therapy drug atezolizumab for up to 1 year.

MAIN OUTCOMES AND MEASURES The primary end point was invasive disease-free survival (time between randomization and invasive breast cancer in the same or opposite breast, recurrence elsewhere in the body, or death from any cause).

RESULTS The median age of enrolled patients was 53 years and most self-reported as being of Asian or White race and neither Latino nor Hispanic ethnicity. The study independent data monitoring committee halted enrollment at 2199 of 2300 planned patients. All patients stopped atezolizumab following a planned early interim and futility analysis. The trial continued to a premature final analysis. With invasive disease-free survival events in 141 patients (12.8%) treated with atezolizumab-chemotherapy and 125 (11.4%) with chemotherapy alone (median follow-up, 32 months), the final stratified invasive disease-free survival hazard ratio was 1.11 (95% CI, 0.87-1.42; *P* = .38). Compared with chemotherapy alone, the regimen of atezolizumab plus chemotherapy was associated with more treatment-related grade 3 or 4 adverse events (54% vs 44%) but similar incidences of fatal adverse events (0.8% vs 0.6%) and adverse events leading to chemotherapy discontinuation. Chemotherapy exposure was similar in the 2 treatment groups.

CONCLUSIONS AND RELEVANCE The addition of the immune therapy drug atezolizumab to chemotherapy after surgery did not provide benefit among patients with triple-negative breast cancer who are at high risk of recurrent disease.

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Visual Abstract
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Supplemental content

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Triple-negative breast cancer (TNBC) is a breast cancer subtype defined by the absence of *ERBB2*/HER2 DNA amplification or protein overexpression and low or no expression of estrogen and progesterone receptors. TNBC is associated with a high risk of progression to metastatic disease,[1] higher incidence in younger women compared with other subtypes,[2-4] and higher incidence in non-Hispanic Black women.[5,6] Historically, approximately one-third of individuals with stage II or III TNBC experience a metastatic recurrence, despite receiving the best-available chemotherapy, within 2 to 3 years after an early-stage diagnosis, which, in turn, has a life expectancy of only 12 to 18 months.[1] Consequently, innovation beyond conventional chemotherapy has been an unmet need. This trial investigated whether the efficacy of curative-intent adjuvant chemotherapy for TNBC is improved by adding immune therapy, which has become a standard in many other solid tumors and for selected patients with advanced TNBC. The introduction of modern immune therapy (blocking either the immunomodulatory receptor cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] or the immunoinhibitory receptor programmed cell death 1 [PD-1] protein and its ligand programmed death-ligand 1 [PD-L1]) has revolutionized clinical oncology.[7] Pivotal trials evaluating the addition of immune checkpoint inhibition to conventional chemotherapy demonstrated improved outcomes in several solid tumor types characterized by high tumor mutational burden,[8] including melanoma,[9-12] non–small cell lung,[13,14] and urothelial[15] cancers. Breast cancer, which has intermediate tumor mutational burden, was thus a logical target and early clinical data of immunotherapy with chemotherapy in metastatic TNBC were encouraging.[16-19] Evaluation of atezolizumab for early-stage diagnosis was subsequently supported by phase 3 trial results demonstrating significantly improved outcomes with the addition of immunotherapy to first-line chemotherapy for biomarker-selected (tumors with high expression of the target, PD-L1) advanced TNBC.[20-23]

The ALEXANDRA/IMpassion030 trial investigated combining atezolizumab with standard adjuvant chemotherapy for patients who had undergone surgery as their first treatment for stage II or III TNBC. We report results from the final analysis.

Key Points

Question Does the addition of 1 year of immune therapy to standard-of-care postoperative chemotherapy reduce the risk of recurrence in patients with high-risk early-stage triple-negative breast cancer after surgery?

Findings This international, open-label, phase 3 trial randomized 2199 patients with stage II or III triple-negative breast cancer who had completed definitive surgery to receive standard-of-care curative-intent chemotherapy with or without atezolizumab-mediated immune therapy and did not demonstrate an improvement in recurrence rates and/or death with the addition of immune therapy (primary end point: invasive disease–free survival).

Meaning The addition of the immunotherapy drug atezolizumab to postoperative chemotherapy is not effective in patients with triple-negative breast cancer who are at high risk of developing metastases.

Methods

This was an international, open-label, randomized phase 3 trial evaluating atezolizumab combined with standard adjuvant chemotherapy and continued as maintenance for early-stage TNBC. The trial protocol, amendments, informed consent forms, and patient information were approved by each site's ethics committee before study initiation. All patients provided written informed consent before enrollment. None received a stipend for participation. All authors attest that the trial was conducted in accordance with the protocol, its amendments, and Good Clinical Practice standards. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized trials.

Patients

Eligible patients were aged 18 years or older with nonmetastatic operable stage II or III TNBC (no *ERBB2* amplification or HER2 overexpression, <1% expression of estrogen and progesterone receptors, determined at a central laboratory according to the American Society of Clinical Oncology/College of American Pathologists criteria[24-26]; **Table 1**) that had been adequately excised (breast-conserving surgery or mastectomy). Sentinel lymph node biopsy and/or axillary lymph node dissection was mandatory to evaluate pathological nodal status. It was planned to enroll a population enriched (≥50%) for node-positive disease; patients with node-negative disease had to have a pathological tumor size of 2 cm or larger. A representative formalin-fixed paraffin-embedded tumor specimen was required from all patients before enrollment for central evaluation of PD-L1 status using the VENTANA SP142 immunohistochemistry assay (Roche Diagnostics). Patients with a history of invasive breast cancer; any T4 tumor; prior systemic anticancer treatment for the currently diagnosed breast cancer; or prior anthracycline, taxane, or immune checkpoint inhibitor therapy were ineligible. The protocol in Supplement 1 details complete eligibility criteria.

Treatment

All patients received standard combination chemotherapy comprising 80 mg/m^2 of paclitaxel weekly for 12 weeks followed by 60 mg/m^2 of dose-dense doxorubicin or 90 mg/m^2 of dose-dense epirubicin (investigator's choice) given with 600 mg/m^2 of cyclophosphamide every 2 weeks for 4 cycles, supported with granulocyte or granulocyte-macrophage colony-stimulating factor. Patients were randomized in a 1:1 ratio to receive chemotherapy with or without 840 mg of atezolizumab every 2 weeks for up to 10 doses, followed in the experimental group by 1200 mg of maintenance atezolizumab every 3 weeks for up to 1 year in total (**Figure 1**). Randomization used permuted blocks, with a fixed block size and the following stratification factors: axillary nodal status

Table 1. Baseline Patient Characteristics

Characteristics	No. (%) of patients	
	Atezolizumab + chemotherapy (n = 1101)	Chemotherapy alone (n = 1098)
Sex		
Female	1101 (100)	1094 (<100)
Male	0	4 (<0.05)
Age, y		
Median (IQR)	53 (44-61)	53 (44-62)
<65	916 (83)	905 (82)
≥65	185 (17)	193 (18)
Self-reported race, No./total (%)		
American Indian or Alaska Native	29/1015 (3)	28/999 (3)
Asian	423/1015 (42)	401/999 (40)
Black or African American	8/1015 (1)	2/999 (<0.5)
White	554/1015 (55)	567/999 (57)
Other[a]	1/1015 (<0.5)	1/999 (<0.5)
Self-reported ethnicity, No./total (%)		
Hispanic or Latino	75/1025 (7)	100/1006 (10)
Not Hispanic or Latino	950/1025 (93)	906/1006 (90)
Geographic region		
Asia[b]	423 (38)	395 (36)
Europe[c]	410 (37)	387 (35)
Russian Federation	179 (16)	188 (17)
South America[d]	66 (6)	93 (8)
US	14 (1)	17 (2)
Australia	9 (1)	18 (2)
ECOG performance status[e]		
0	887 (81)	895 (82)
1	214 (19)	203 (18)
Histology		
Ductal not otherwise specified	841 (76)	813 (74)
Lobular	39 (4)	54 (5)
Ductal with medullary features	27 (2)	52 (5)
Metaplastic	50 (5)	47 (4)
Tubular	9 (1)	14 (1)
Mucinous	3 (<0.5)	3 (<0.5)
Other	154 (14)	150 (14)
Histological grade at screening, No./total (%)		
Poorly differentiated	686/954 (72)	653/965 (68)
Moderately differentiated	205/954 (21)	234/965 (24)
Well differentiated	59/954 (6)	75/965 (8)
Anaplastic	4/954 (<0.5)	3/965 (<0.5)
Primary tumor stage		
T1	157 (14)	162 (15)
T2	868 (79)	882 (80)
T3	71 (6)	52 (5)
Other[f]	5 (<0.5)	2 (<0.5)
Axillary nodal status[g]		
0	577 (52)	573 (52)
1-3	390 (35)	390 (36)
≥4	134 (12)	135 (12)
AJCC stage at surgery, No./total (%)		
I[h]	4/1100 (<0.5)	1 (<0.5)
II	933/1100 (85)	940 (86)
III	163/1100 (15)	157 (14)
PD-L1 status[g]		
IC0	316 (29)	316 (29)
IC1-IC3	785 (71)	782 (71)
Surgery[g]		
Breast conserving	524 (48)	523 (48)
Mastectomy	577 (52)	575 (52)

Abbreviations: AJCC, American Joint Commission on Cancer; ECOG, Eastern Cooperative Oncology Group; IC, immune cell; PD-L1, programmed death - ligand 1.

[a] Native Hawaiian or other Pacific Islander (n = 1), multiple (n = 1).

[b] China, Hong Kong, Japan, Republic of Korea, Singapore, Taiwan, and Thailand.

[c] Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Poland, Romania, Spain, Switzerland, Turkey, Ukraine, and United Kingdom.

[d] Argentina, Brazil, Mexico, and Peru.

[e] A score of 0 represents fully active, able to carry on all predisease performance without restrictions, and a score of 1 represents restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.

[f] Includes primary tumor sizes T0, T in situ, T4, T4b, and missing.

[g] As recorded in the interactive voice- or web-based response system (iXRS).

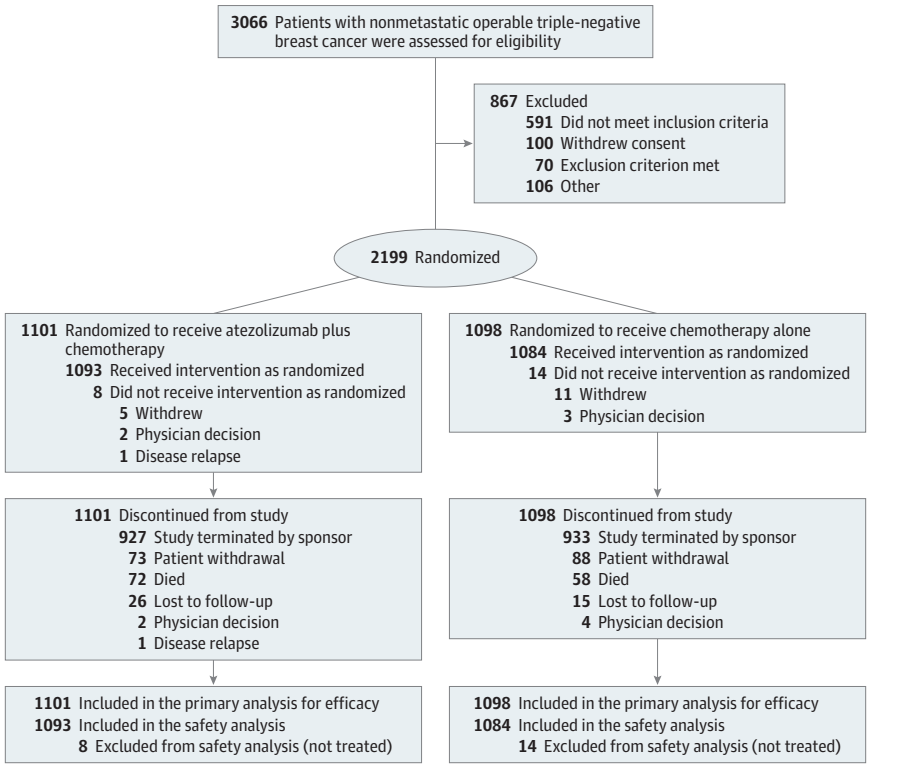
[h] Not eligible for the trial.

(0 vs 1-3 vs ≥4 lymph nodes positive for cancer); surgical approach (breast conserving vs mastectomy); and tumor PD-L1 status (PD-L1 expression on <1% of immune cells [ICs]: <1% [IC0] vs ≥1% [IC1-IC3]). The random allocations were generated by an external interactive voice- or web-based response system (iXRS) company, with participants enrolled at each site using the iXRS. In this open-label trial, the study team was blinded to PD-L1 status and had restricted access to the randomization lists.

End Points

The primary end point was invasive disease-free survival (invasive DFS), defined as the interval between randomization and the first ipsilateral invasive breast tumor recurrence, ipsilateral local-regional invasive breast cancer recurrence, ipsilateral second primary invasive breast cancer, contralateral invasive breast cancer, distant recurrence, or death from any cause in the intent-to-treat (ITT) population. Secondary end points included invasive DFS in the populations with PD-L1-positive (ICs ≥1%) and node-positive TNBC; overall survival; invasive DFS including second primary non-breast invasive cancer; recurrence-free interval; distant recurrence-free interval; DFS; and safety (occurrence and severity of adverse events).

Figure 1. Recruitment, Randomization, and Follow-Up in the ALEXANDRA/IMpassion030 Trial



Statistical Analysis

The study plan was to enroll 2300 patients from 31 countries. Early versions of the statistical analysis plan included 1 planned interim analysis at 80% information (310 of 388 invasive DFS events). The sample size for the analysis of invasive DFS was determined using Cytel East 6, reproduced (and updated for changes to the number of interim analyses) in R package rpact,[27-29] assuming approximately 80% power to detect an assumed hazard ratio (HR) of 0.75 using a 2-sided stratified log-rank test at the .05 significance level (type I error rate), piecewise annual hazard rates (0.047, 0.108, 0.035, 0.038, 0.029, 0.029, 0.014) for the control arm based on previous adjuvant triple-negative breast cancer trials,[30-32] 2.5% annual loss to follow-up, 1 interim analysis, and accrual over 51 months.

In November 2022, after enrolling 2199 (96%) of the planned patients, the independent data monitoring committee recommended temporarily halting recruitment, resulting in a health authority request to advance the planned interim analysis to mid-March 2023 and add a futility assessment. The study protocol (Supplement 1) and statistical analysis plan (Supplement 2) were updated to include an additional interim analysis at approximately 62% information (242 invasive DFS events) with a nonbinding futility analysis (futility boundary: HR >1). The second interim analysis at 80% information and the final analysis were updated to occur after 312 and 390 invasive DFS events, respectively. Other assumptions were unchanged. The final analysis of the key secondary end points including overall survival was planned according to the fixed-sequence hierarchical testing procedure.[33,34]

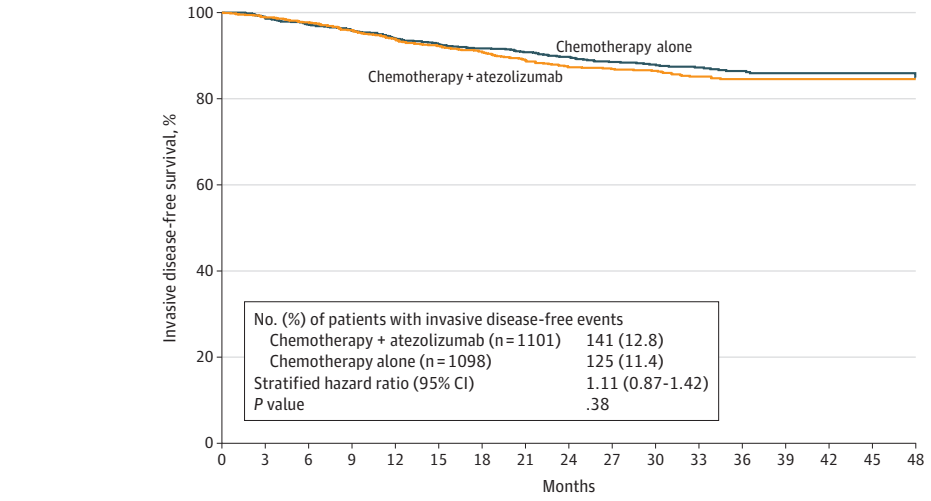
On March 15, 2023, following the interim and futility analyses and based on the independent data monitoring committee's recommendations, atezolizumab treatment was stopped and enrollment was permanently discontinued. By the final database lock (November 20, 2023), 266 of the planned 390 invasive DFS events had occurred. The final significance boundary for invasive DFS was calculated as .04988 (2-sided), considering the interim and final analyses at 239 and 266 invasive DFS events, respectively, and the overall protocol-specified significance level of .05 (type I error rate). Boundaries for statistical significance were determined based on the Lan-DeMets α-spending function with an O'Brien-Fleming boundary[35] with fixed-sequence hierarchical group-sequential testing, strongly protecting the family-wise error rate. Key secondary end points were to be tested only if the primary end point and preceding secondary end points crossed the significance boundaries.

Efficacy was analyzed in the ITT population, comprising all patients as randomized. Safety was analyzed in the safety population, comprising all patients who received at least 1 dose of study medication, as treated.

Assessments

Race (and ethnicity in patients enrolled in the US) was self-reported by patients from a fixed list according to each country's regulations to provide a more comprehensive description of the study population. Disease status was evaluated at clinic visits every 3 months during study treatment and for up to 3 years after randomization; every 6 months from 3 to 5 years

Figure 2. Final Analysis of Invasive Disease–Free Survival in the Intention-to-Treat Population



Chemotherapy + atezolizumab																	
No. at risk	1101	1053	1027	983	935	892	847	775	691	634	553	467	371	285	214	155	85
No. censored	0	36	50	75	101	129	162	215	286	340	418	496	589	675	746	805	878
Chemotherapy alone																	
No. at risk	1098	1041	1009	974	926	884	856	798	699	640	551	460	359	281	217	144	80
No. censored	0	45	60	81	110	139	158	208	298	348	433	520	617	693	757	830	893

The hazard ratio was estimated by stratified Cox regression analysis with the following strata: axillary nodal status, surgery (breast conserving vs mastectomy), and tumor programmed death ligand 1 status. The *P* value was estimated by a stratified log-rank test.

The median follow-up was 32.3 (IQR, 22.3-41.3) months for atezolizumab plus chemotherapy and 31.9 (IQR, 22.5-41.2) months for chemotherapy alone. The Kaplan-Meier plot is truncated at 48 months, when 165 patients (<8%) remained in follow-up.

after randomization; and annually thereafter until the study end. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 and patients were followed up for 30 days after the last study dose. Importantly, this resulted in longer follow-up in the atezolizumab group (30 days after the last dose of maintenance atezolizumab at 1 year) than in the control group (30 days after the last anthracycline and/or cyclophosphamide dose at 19 weeks). Additionally, during the maintenance phase, clinic visits were every 3 weeks in the atezolizumab group vs every 6 weeks in the chemotherapy-alone group.

Trial Oversight

The trial was sponsored by F. Hoffmann-La Roche Ltd and conducted in collaboration with the Breast International Group (BIG), Brussels, Belgium, with the participation of BIG member groups, Alliance Foundation Trials, and independent sites in Asia, Europe, North and South America, and Australia. Samples were tested centrally at the European Institute of Oncology and Q Squared Solutions (China). Data management was conducted by Institut Jules Bordet Clinical Trials Support Unit, Brussels, Belgium, and statistical analyses by Frontier Science Foundation, Kincraig, Scotland. The sponsor had no access to the full database before the steering committee released the results.

Results

Patients and Treatment

Between August 2, 2018, and November 11, 2022, 2199 patients were enrolled from more than 330 centers in 31 countries. Of these, 1101 were randomized to receive atezolizumab with their chemotherapy and 1098 to chemotherapy alone; 2177 were treated (Figure 1). Overall, 49% of patients had node-positive disease, 71% had PD-L1-positive tumors, and 61% had poorly differentiated histology; the highest recruiting countries were the Russian Federation (17%), Ukraine (13%), and China (12%; Table 1; eTable 1 in Supplement 3). The COVID-19 pandemic and Russia-Ukraine conflict had only a minor impact on the study conduct and no impact on the results and conclusions.

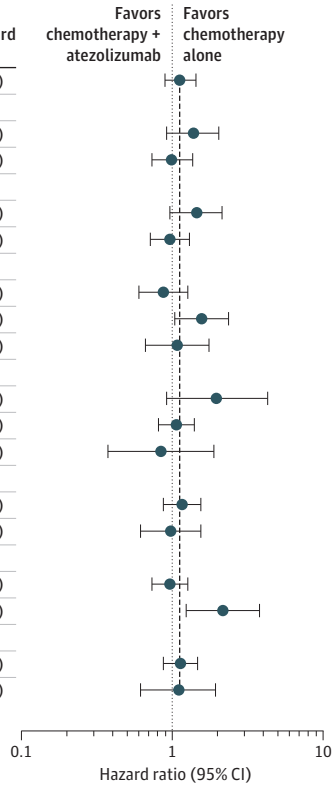
The median duration of atezolizumab treatment was 11.5 months (IQR, 9.4-11.8; range, 0-12.7 months), corresponding to 15 cycles (range, 1-16). Among 328 patients (30%) discontinuing atezolizumab prematurely, the most common reasons were adverse events (13%), patient withdrawal (5%), study termination (4%), and disease recurrence (4%). In both treatment groups, patients received a median of 4 doses (range, 1-4) of cyclophosphamide and epirubicin or doxorubicin, and 12 doses (range, 1-13) of paclitaxel.

Efficacy

The median follow-up at the final analysis was 32 months (range, 0-59 months). In the ITT population, invasive DFS events had been recorded among 266 patients: 141 (12.8%) in the atezolizumab plus chemotherapy group and 125 (11.4%) in the chemotherapy-alone group (**Figure 2**). The final stratified HR for invasive DFS was 1.11 (95% CI, 0.87-1.42; *P* = .38). eTable 2 in Supplement 3 shows the sensitivity analyses. Descriptive subgroup analyses of invasive DFS, including PD-L1-positive TNBC, showed no benefit from the addition of atezolizumab to chemotherapy (**Figure 3** and eFigure 1 in Supplement 3). Descriptive analysis of secondary efficacy end points suggested consistency with the invasive DFS results (**Table 2**; eFigure 2 in Supplement 3).

Figure 3. Final Unstratified Analysis of Invasive Disease–Free Survival in Key Subgroups, With Hazard Ratios Estimated by Unstratified Cox Regression

Subgroup	Chemotherapy + atezolizumab (n = 1101)	Chemotherapy alone (n = 1098)	Unstratified hazard ratio (95% CI)
All patients	1101	1098	1.12 (0.88-1.43)
PD-L1 status (iXRS)			
IC0	316	316	1.37 (0.93-2.03)
IC1-IC3	785	782	1.00 (0.74-1.36)
Surgery (iXRS)			
Breast conserving	524	523	1.45 (0.97-2.15)
Mastectomy	577	575	0.97 (0.71-1.31)
Axillary nodal status (iXRS)			
0	577	573	0.88 (0.60-1.28)
1-3	390	390	1.57 (1.03-2.39)
≥4	134	135	1.08 (0.67-1.75)
Primary tumor stage at first diagnosis			
T1	157	162	1.97 (0.91-4.26)
T2	868	882	1.06 (0.81-1.39)
T3	71	52	0.84 (0.37-1.90)
AJCC stage at surgery			
II	933	940	1.16 (0.88-1.55)
III	163	157	0.98 (0.62-1.54)
Age, y			
<65	916	905	0.96 (0.73-1.25)
≥65	185	193	2.17 (1.24-3.78)
Baseline ECOG performance status			
0	887	895	1.13 (0.87-1.48)
1	214	203	1.10 (0.62-1.95)



The dashed line represents the hazard ratio for all patients.

AJCC indicates American Joint Commission on Cancer; ECOG, Eastern Cooperative Oncology Group; IC, immune cell; iXRS, interactive voice- or web-based response system; PD-L1, programmed death ligand 1.

Table 2. Summary of Primary and Secondary Efficacy End Points in the Intention-to-Treat Population

End point	No. (%) of events		Stratified hazard ratio (95% CI)[a]	3-Year event free, % (SE)		Difference (95% CI)
	Atezolizumab + chemotherapy (n = 1101)	Chemotherapy alone (n = 1098)		Atezolizumab + chemotherapy (n = 1101)	Chemotherapy alone (n = 1098)	
Invasive disease-free survival	141 (12.8)	125 (11.4)	1.11 (0.87 to 1.42)	84.6 (1.23)	86.4 (1.18)	−1.8 (−5.2 to 1.5)
PD-L1 positive, No./total (%)	83/785 (10.6)	81/782 (10.4)	1.00 (0.73 to 1.35)	87.6 (1.31)	88.0 (1.32)	−0.4 (−4.0 to 3.2)
Node positive, No./total (%)	92/534 (17.2)	70/533 (13.1)	1.32 (0.97 to 1.80)	78.1 (2.10)	83.1 (1.93)	−5.0 (−10.6 to 0.6)
Overall survival	72 (6.5)	58 (5.3)	1.23 (0.87 to 1.73)	92.3 (0.93)	93.7 (0.85)	−1.3 (−3.8 to 1.2)
Invasive disease-free survival including second primary non-breast invasive cancer	144 (13.1)	135 (12.3)	1.05 (0.83 to 1.33)	84.4 (1.24)	85.3 (1.24)	−1.0 (−4.4 to 2.5)
Recurrence-free interval	119 (10.8)	113 (10.3)	1.04 (0.80 to 1.34)	86.7 (1.17)	87.7 (1.13)	−1.0 (−4.2 to 2.2)
Distant recurrence-free interval	86 (7.8)	88 (8.0)	0.97 (0.72 to 1.31)	90.0 (1.05)	90.3 (1.03)	−0.3 (−3.1 to 2.6)
Disease-free survival	145 (13.2)	135 (12.3)	1.06 (0.84 to 1.34)	84.3 (1.24)	85.3 (1.24)	−1.1 (−4.5 to 2.4)

Abbreviation: PD-L1, programmed death ligand 1.

[a] Hazard ratios were estimated by stratified Cox regression with the following strata: axillary nodal status, surgery (breast conserving vs mastectomy), and tumor PD-L1 status. Event-free percentages were based on Kaplan-Meier estimates.

Safety

Compared with chemotherapy alone, atezolizumab plus chemotherapy was associated with more treatment-related grade 3 or 4 adverse events (54% vs 44%) and treatment-related serious adverse events (19% vs 10%; eTable 3 in Supplement 3). Fifteen patients had fatal adverse events: 9 (0.8%) treated with atezolizumab plus chemotherapy and 6 (0.6%) with chemotherapy alone (eTable 4 in Supplement 3). Only 1 of these deaths was considered by the investigator to be treatment related (paclitaxel-attributed pneumonia in a 79-year-old patient receiving chemotherapy alone). Adverse events led to atezolizumab discontinuation in 13% of patients treated with atezolizumab plus chemotherapy (during the induction phase in 8%). However, chemotherapy discontinuation for adverse events was infrequent in both groups and the addition of atezolizumab did not affect chemotherapy dose intensity (eTable 3 in Supplement 3).

Table 3. Most Common Adverse Events (>15% of Patients) and Immune-Mediated Adverse Events (>10% of Patients) in the Safety Population[a]

	No. (%) of patients			
	Atezolizumab + chemotherapy (n = 1093)		Chemotherapy alone (n = 1084)	
Adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Most common				
Alopecia	735 (67)	NA	715 (66)	NA
Nausea	553 (51)	8 (1)	531 (49)	12 (1)
Anemia	423 (39)	71 (6)	424 (39)	70 (6)
Fatigue	326 (30)	23 (2)	269 (25)	19 (2)
ALT increased	297 (27)	49 (4)	242 (22)	25 (2)
Diarrhea	287 (26)	15 (1)	188 (17)	1 (<0.5)
Neutrophil count decreased	279 (26)	172 (16)	260 (24)	163 (15)
Neutropenia	247 (23)	178 (16)	255 (24)	173 (16)
AST increased	247 (23)	27 (2)	161 (15)	7 (1)
WBC decreased	240 (22)	110 (10)	200 (18)	95 (9)
Asthenia	235 (22)	17 (2)	231 (21)	11 (1)
Constipation	231 (21)	2 (<0.5)	210 (19)	0
Arthralgia	218 (20)	1 (<0.5)	150 (14)	1 (<0.5)
Decreased appetite	214 (20)	11 (1)	145 (13)	4 (<0.5)
Myalgia	202 (18)	2 (<0.5)	175 (16)	3 (<0.5)
Peripheral sensory neuropathy	196 (18)	3 (<0.5)	185 (17)	1 (<0.5)
Vomiting	177 (16)	7 (1)	147 (14)	6 (1)
Headache	177 (16)	1 (<0.5)	135 (12)	0
Pyrexia	170 (16)	0	113 (10)	1 (<0.5)
Rash	170 (16)	8 (1)	89 (8)	1 (<0.5)
Hypothyroidism	163 (15)	2 (<0.5)	6 (1)	0
Immune mediated				
Rash	471 (43)	22 (2)	327 (30)	5 (<0.5)
Hepatitis (diagnosis and laboratory abnormalities)	370 (34)	66 (6)	286 (26)	30 (3)
Hepatitis (laboratory abnormalities)	354 (32)	59 (5)	281 (26)	28 (3)
Hepatitis (diagnosis)	23 (2)	7 (1)	8 (1)	2 (<0.5)
Hypothyroidism	205 (19)	3 (<0.5)	10 (1)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; WBC, white blood cell count.

[a] Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Most adverse events occurred at similar incidences in the 2 treatment groups (**Table 3**). The most common with both regimens were alopecia, nausea, anemia, and fatigue. Compared with chemotherapy alone, atezolizumab plus chemotherapy was associated with higher incidences of diarrhea (26% vs 17%), increased aspartate aminotransferase (23% vs 15%), rash (16% vs 8%), and hypothyroidism (15% vs 1%). The most common immune-mediated adverse events were rash, hepatitis (predominantly laboratory abnormalities emerging during the induction period), and hypothyroidism (Table 3; eTable 5 in Supplement 3). Atezolizumab was interrupted for immune-mediated adverse events in 252 patients (23%).

Discussion

To our knowledge, this is the only phase 3 randomized trial involving patients with high-risk early-stage TNBC to evaluate adding a PD-L1 or PD-1 inhibitor to adjuvant chemotherapy in patients who undergo surgery as their initial treatment. Postoperative atezolizumab-mediated immune therapy did not add benefit to standard chemotherapy after surgery. The HR for invasive DFS of 1.11 (95% CI, 0.87-1.42; P = .38), and consistent descriptive results for secondary efficacy end points do not support adding atezolizumab to adjuvant chemotherapy for patients who have undergone primary surgery for early-stage TNBC. Safety results were consistent with the known safety profile of atezolizumab in early-stage TNBC[36] and across indications. Atezolizumab was associated with increased incidences of treatment-related grade 3 or 4 and serious adverse events, although more frequent visits during maintenance atezolizumab may bias comparison with chemotherapy alone. Atezolizumab did not compromise delivery of the standard chemotherapy backbone.

The negative results from the current trial contrast with those from randomized trials evaluating PD-L1 and PD-1 inhibitors in the neoadjuvant setting demonstrating significantly improved outcomes vs chemotherapy alone.[36-40] In the KEYNOTE-522 trial, pathological complete response rate, event-free survival (coprimary end points) and overall survival (secondary end point) were significantly improved with

pembrolizumab added to neoadjuvant chemotherapy followed by adjuvant pembrolizumab after surgery[37,38,41]; consequently, preoperative and postoperative pembrolizumab therapy has become the standard of care for otherwise unselected stage II and III TNBC.[42] The smaller IMpassion031 trial also demonstrated significantly improved pathological complete response rate (primary end point) with atezolizumab added to neoadjuvant chemotherapy and a suggestion of improved event-free, disease-free, and overall survival,[43] although the trial was neither powered nor designed to detect differences in these end points.[36] In contrast, the NeoTRIP trial did not demonstrate benefit from atezolizumab in the neoadjuvant setting, with no improvement in the primary end point of event-free survival[44] nor pathological complete response rate,[45] although differences in its trial design (eg, lack of anthracycline chemotherapy) may have contributed to the different outcome.

A reasonable interpretation of the accumulating evidence might be that neoadjuvant initiation of immunotherapy is more effective than adjuvant administration alone.[46] Because treatment stimulates immune cells close to the tumor, postoperative immune checkpoint inhibitor application, after removing the primary tumor and lymph nodes, may not represent the optimal biological context for immunotherapy. Preclinical research in TNBC mouse models indicated greater efficacy of neoadjuvant vs adjuvant immunotherapy.[46] Interestingly, among patients with resectable stage III or IV melanoma, event-free survival was significantly longer with perioperative pembrolizumab than with adjuvant-only pembrolizumab.[47] This finding appears consistent with cumulative findings in early-stage TNBC, emphasizing the importance of preoperative immune checkpoint blockade regimens and moving away from offering adjuvant-only treatment to patients eligible for chemoimmunotherapy for stage II or III TNBC. We cannot exclude the possibility that the efficacy and safety results of the current trial could have been different had another immune checkpoint inhibitor been investigated. The phase 3 trial of first-line pembrolizumab in advanced TNBC demonstrated significant improvement across end points,[22,23] whereas more heterogenous results have been seen for atezolizumab across 3 phase 3 trials involving patients with advanced disease (positive IMpassion130 trial,[20,21] negative IMpassion131,[48] and IMpassion132[49] trials), albeit there are important differences in trial designs, chemotherapy backbones, patient populations, and treatment settings. The ongoing placebo-controlled GeparDouze/NSABP B-59 trial[50] with a design similar to the KEYNOTE-522 trial will inform whether preoperative initiation of atezolizumab with chemotherapy followed by postoperative atezolizumab improves long-term outcomes.

The current trial provides the only results on cancer immunotherapy plus chemotherapy as adjuvant-only treatment, and no other immunotherapy trials are investigating this specific therapeutic approach. Based on these results, patients who receive surgery before any chemotherapy should not receive atezolizumab with their postoperative chemotherapy. The lack of benefit from adjuvant atezolizumab, together with the overall survival benefit observed with perioperative pembrolizumab in the KEYNOTE-522 trial, suggest that the preferred strategy for patients with high-risk TNBC is initial chemoimmunotherapy followed by surgery.[42] Globally, many patients with stage II or III TNBC still have surgery as their initial treatment.[51,52] Therefore, it is critical that findings from this trial are considered in multidisciplinary team discussions at the time of diagnosis.

Two trials aim to answer whether adjuvant immunotherapy offers benefit to patients with TNBC who have residual disease after neoadjuvant chemotherapy and surgery. In this postneoadjuvant TNBC setting, recent results from the A-BRAVE trial, although negative for the primary end point of DFS,[53] suggest improved overall survival (secondary end point) among patients receiving single-agent avelumab for residual disease following neoadjuvant chemotherapy. The ongoing randomized phase 3 SWOG S1418/BR-006 trial (NCT02954874) in a similar postneoadjuvant setting is comparing 1 year of pembrolizumab therapy vs observation among patients with residual disease after neoadjuvant chemotherapy who had received standard adjuvant therapy after surgery. It remains to be seen whether immune checkpoint blockade plays a role in this very specific high-risk setting, but, in both trials, systemic chemotherapy is being given before surgery.

Important study strengths include its global footprint, the large sample size, its unique nature as the only phase 3 trial evaluating immune checkpoint blockade as pure adjuvant therapy for TNBC, and central pathology review.

Limitations

There are several limitations to this trial. First, the trial was discontinued after 266 of the required 390 invasive DFS events for final analysis. Having crossed the prespecified (nonbinding) futility boundary for invasive DFS, the likelihood of demonstrating a significant improvement was deemed too low to justify continuing the trial. The hierarchical design means that analysis of all secondary end points is only descriptive and exploratory. Second, the premature trial termination shortened follow-up; thus, long-term safety information is limited and late-onset adverse events may not be captured. Third, the open-label design and more frequent monitoring throughout maintenance therapy in the atezolizumab plus chemotherapy group may have introduced bias. Fourth, the paclitaxel chemotherapy backbone may raise questions, given the differing outcomes in the metastatic setting with atezolizumab combined with nab-paclitaxel in the IMpassion130 trial (clinically relevant overall survival improvement)[20,21] and paclitaxel in the IMpassion131 trial (no benefit).[48] The fifth limitation is that *BRCA* status was available for only around 20% of patients enrolled in the trial. Sixth, despite enrolling globally, less than 1% of patients were Black.

Conclusions

Adding the immune checkpoint inhibitor atezolizumab to postoperative chemotherapy did not reduce risk of recurrence or death for patients with high-risk early-stage TNBC.

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Dr Dieterich reported being an employee of and owning stock in F. Hoffmann-La Roche Ltd.
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