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Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer
A Phase 1 Study

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IMPORTANCE Atezolizumab (anti–programmed cell death ligand 1 [PD-L1]) is well tolerated and clinically active in multiple cancer types. Its safety and clinical activity in metastatic triple-negative breast cancer (mTNBC) has not been reported.

OBJECTIVE To evaluate the safety, clinical activity, and biomarkers associated with the use of single-agent atezolizumab in patients with mTNBC.

DESIGN, SETTING, AND PARTICIPANTS Women with mTNBC (defined by investigator assessment) were enrolled between January 2013 and February 2016 in a multicohort open-label, phase 1 study at US and European academic medical centers. Median follow-up was 25.3 months (range, 0.4-45.6 months). Eligible patients regardless of line of therapy had measurable disease by Response Evaluation Criteria in Solid Tumors, version 1.1; Eastern Cooperative Oncology Group performance status of 0 to 1; and a representative tumor sample for assessment of immune cell (IC) PD-L1 expression.

INTERVENTIONS Atezolizumab was given intravenously every 3 weeks until unacceptable toxic effects or loss of clinical benefit.

MAIN OUTCOMES AND MEASURES Primary outcome was safety and tolerability. Activity and exploratory outcomes included objective response rate (ORR), duration of response, progression-free survival (PFS), and overall survival (OS). Outcomes were assessed in all patients and in key patient subgroups.

RESULTS Among 116 evaluable patients (median age, 53 years [range, 29-82 years]), treatment-related adverse events occurred in 73 (63%); 58 (79%) were grade 1 to 2. Most adverse events occurred within the first treatment year. The ORRs were numerically higher in first-line (5 of 21 [24%]) than in second-line or greater patients (6 of 94 [6%]). Median duration of response was 21 months (range, 3 to ≥38 months). Median PFS was 1.4 (95% CI, 1.3-1.6) months by RECIST and 1.9 (95% CI, 1.4-2.5) months by irRC. In first-line patients, median OS was 17.6 months (95% CI, 10.2 months to not estimable). Patients with PD-L1 expression of at least 1% tumor-infiltrating ICs had higher ORRs and longer OS (12% [11 of 91]; 10.1 [95% CI, 7.0-13.8] months, respectively) than those with less than 1% ICs (0 of 21; 6.0 [95% CI, 2.6-12.6] months, respectively). High levels of ICs (>10%) were independently associated with higher ORRs and longer OS.

CONCLUSIONS AND RELEVANCE Single-agent atezolizumab was well tolerated and provided durable clinical benefit in patients with mTNBC with stable or responding disease and in earlier lines of treatment.

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Supplemental content

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Patients with triple-negative breast cancer (TNBC) have a worse prognosis than those with other breast cancer subtypes.[1-4] The median overall survival (OS) of patients with metastatic TNBC (mTNBC) is 8 to 13 months.[4,5] Chemotherapy remains the main treatment for TNBC,[1] with no targeted therapies available for the majority of patients with this disease. Novel therapies are urgently needed for these patients.

Cancer immunotherapy is an attractive treatment strategy because tumor-infiltrating lymphocytes and programmed cell death ligand 1 (PD-L1) are associated with improved clinical outcomes in early TNBC.[6-9]

Agents targeting the PD-L1 and programmed cell death 1 (PD-1) pathway may trigger antitumor responses in TNBC.[10-12] Atezolizumab is an engineered, humanized monoclonal antibody that selectively inhibits the interaction of PD-L1 with its receptors PD-1 and B7.1, thereby reinvigorating tumor immunity.[13,14] Atezolizumab has demonstrated safety and durable long-term clinical benefit in a broad range of cancer types, including urothelial carcinoma and non–small cell lung cancer.[13,15-20]

The first-in-human phase 1 study PCD4989g investigated single-agent atezolizumab.[13] Herein, we report safety and clinical outcomes in the mTNBC cohort and describe early data exploring biomarkers of clinical activity.

Key Points

Question Is single-agent atezolizumab therapy safe and does it provide clinical benefit in patients with metastatic triple-negative breast cancer (mTNBC)?

Findings In this phase 1 study of 116 patients with mTNBC, the safety profile was consistent with that of atezolizumab in other tumor types. With a median follow-up of longer than 2 years, patients with an objective response to atezolizumab had a durable clinical response, and patients with higher tumor immune cell infiltration had better clinical outcomes.

Meaning Single-agent atezolizumab was well tolerated and showed durable clinical activity in patients with mTNBC.

Methods

Study Design and Patients

The PCD4989g open-label, multicenter phase 1 trial investigates atezolizumab monotherapy in advanced solid and hematologic malignant neoplasms. The study design, which includes a dose escalation phase and several tumor-specific dose expansion cohorts, has been previously reported.[13] This study was conducted in accordance with Good Clinical Practice and the Helsinki Declaration and approved by local/commercial institutional review boards (United States) or central ethics committees (UK, France, and Spain). All patients provided written informed consent. The study protocol can be found in Supplement 1.

Key eligibility criteria included measurable disease per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST); Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and a representative tumor sample (archival and/or fresh tissue). Triple-negative breast cancer was defined as lack of estrogen and progesterone receptors, and human epidermal growth factor receptor 2 expression by investigator assessment according to local practices. The first 25 patients in this cohort were selected for PD-L1 expression on at least 5% of tumor-infiltrating immune cells (ICs); enrollment was subsequently extended to all patients.

Procedures

Patients with mTNBC received atezolizumab intravenously at 15 or 20 mg/kg, or at a 1200-mg flat dose, every 3 weeks. Initially, patients received up to 16 cycles or 1 year of treatment (whichever occurred first). A subsequent protocol amendment allowed for treatment beyond 16 cycles/1 year and for retreatment of patients who had discontinued therapy, regardless of disease status. Treatment beyond RECIST disease progression until loss of clinical benefit was allowed per investigator discretion.

Outcomes

The primary study end point was safety and tolerability of atezolizumab. Key secondary end points included objective response rate (ORR), duration of response (DOR), progression-free survival (PFS) by standard RECIST[21] and immune-related response criteria (irRC) (to capture nonconventional tumor responses)[22]; OS was an exploratory end point. Disease control rate was measured as ORR plus stable disease (SD) for at least 24 weeks. Clinical activity was assessed by key baseline clinical characteristics. The association of pretreatment immune biomarkers (PD-L1 ICs, ICs, CD8-positive T cells, and CD163-positive macrophages) with ORR, PFS, and OS was evaluated. Pharmacodynamic measurements of immune modulation were conducted.

Assessments

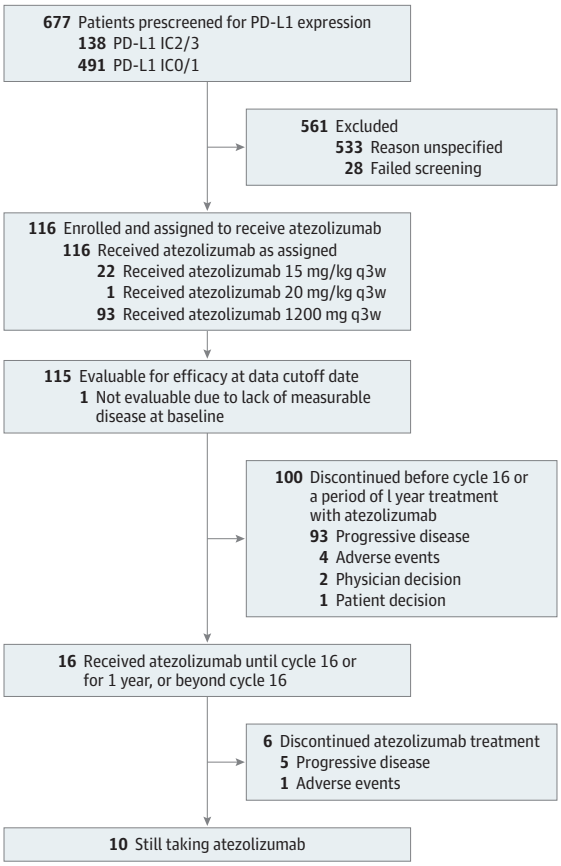
Adverse events (AEs) were graded per the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Patients who received any atezolizumab were evaluable for safety. Safety was assessed every 3 weeks and approximately 90 days following the final dose. Only serious AEs deemed related to prior study treatment were reported 90 days after the final dose. The criteria used to define AEs of special interest are presented in eMethods 2 in Supplement 2.

Following treatment discontinuation, survival data were collected approximately every 3 months, until death or loss to follow-up.

Immune Biomarkers

All patients provided pretreatment tumor tissue at study enrollment for biomarker analyses. Some patients provided tissue collected 10 to 21 days after atezolizumab exposure for tumor pharmacodynamic analyses. Using the Ventana SP142 immunohistochemistry assay (Ventana Medical Systems), baseline PD-L1 expression on ICs was evaluated with 4 scoring bins: IC3 (≥10%), IC2 (≥5% and <10%), IC1 (≥1% and <5%), and IC0 (<1%). The PD-L1 expression on tumor cells (TCs) was assessed as less than 1% (TC0) or at least 1% (TC1/2/3).

Figure 1. Study Flowchart



Flowchart shows enrolled and treated patients from the triple-negative breast cancer cohort of the PCD4989g study. Patients in this cohort were enrolled in the United States, United Kingdom, France, and Spain. Population definitions are depicted, including reasons for discontinuation, and noninclusion into efficacy analysis. Baseline programmed cell death ligand 1 (PD-L1) expression on tumor-infiltrating immune cells was evaluated with 4 scoring bins: IC3 (≥10%), IC2 (≥5% and <10%), IC1 (≥1% and <5%), and IC0 (<1%). q3w indicates every 3 weeks.

Tumor-infiltrating ICs (lymphocytes, macrophages, dendritic cells, and granulocytes) were identified by hematoxylin-eosin staining and scored as a percentage of the tumor area (TCs and desmoplastic stroma). CD8 and CD163 immunohistochemical analyses were centrally performed (HistoGeneX) using C8/144B and MRQ-26 antibody clones (Dako), respectively.

Statistical Analysis

Objective response rates with corresponding 95% CIs were calculated using the Clopper-Pearson method. Duration of response, PFS, and OS were assessed by the Kaplan-Meier method, with 95% CI for median PFS and OS estimated using the Brookmeyer-Crowley method. Patients who survived at least 6 weeks were analyzed for OS to avoid immortal bias; 6 weeks was assumed to be sufficient for patients to respond to atezolizumab therapy.

The log-rank (Mantel-Cox) test was used to evaluate associations between biomarker subgroups and clinical activity (OS and PFS). Multivariate analysis was used to assess the effect of ICs and CD8-positive T cells on clinical outcome against prognostic factors as covariates. Pharmacodynamic changes of immune biomarkers were evaluated using linear mixed-effects models. *P* values were adjusted using Bonferroni correction to account for multiple time points. Due to the exploratory nature of the analysis, only nominal *P* values were reported.

Results

Patients and Treatments

Patients in the mTNBC cohort were enrolled between January 2013 and February 2016 (**Figure 1**); 116 patients were evaluable for safety, and 115 were evaluable for ORR. At the data cutoff (December 31, 2016), the median follow-up duration was 25.3 months (range, 0.4-45.6 months).

Median patient age was 53 years (range, 29-82 years). A total of 114 of 116 (98%) had ECOG performance status 0 or 1 (eTable 1 in Supplement 2). Seventy-five (65%) had visceral disease, and 67 (58%) had received at least 2 lines of prior therapy for mTNBC. Ninety-one (78%) had PD-L1 IC1/2/3 tumors, of which 19 and 72 were treated in the first-line and second-line and beyond setting, respectively. Twenty-one (18%) had PD-L1 IC0 tumors, of whom 2 and 19 were treated in the first-line and second-line and beyond setting, respectively. Four patients with second-line and beyond disease had unknown PD-L1 status. The median treatment duration was 2.1 months (range, 0-45.6 months), with a median of 4 cycles (range, 1-58 cycles).

Safety

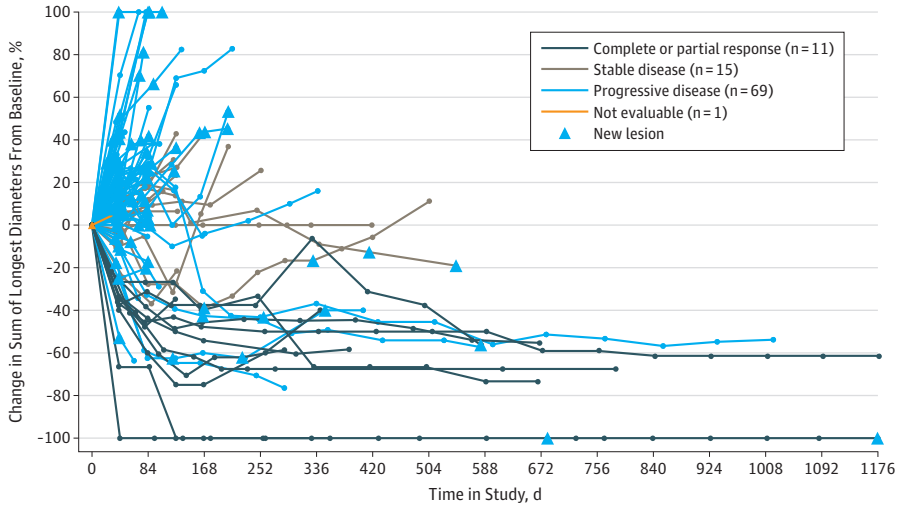
Adverse events were observed in 114 of 116 patients (98%), with grade 3 to 4 events observed in 46 (40%) and 13 patients (11%), respectively. Treatment-related AEs (TRAEs) occurred in 73 (63%) patients, with the majority (58 [79%]) being grade 1 to 2 (eTable 2 in Supplement 2). The most frequent TRAEs were pyrexia (19 [16%]), fatigue (15 [13%]), and nausea (13 [11%]), followed by diarrhea (12 [10%]), asthenia (11 [10%]), and pruritus (11 [10%]) (eTable 2 in Supplement 2). Thirteen (11%) patients experienced a grade 3 to 4 TRAE, with 2 grade 4 TRAEs (hyperglycemia and pneumonitis) observed in 1 patient. Reported grade 3 to 4 TRAEs of special interest included grade 3 pruritic rash, lichen planus, and adrenal insufficiency, and grade 4 pneumonitis. Two patients had grade 5 TRAEs (1 pulmonary hypertension and 1 death not otherwise specified in a hospitalized patient). Three patients (3%) discontinued atezolizumab therapy due to a TRAE, and 11 patients (10%) had TRAEs that led to dose interruption.

Most TRAEs occurred within 1 year after initiating atezolizumab (eTable 3 in Supplement 2). Fourteen patients were treated beyond 1 year, at which point the most common grade 1 to 2 TRAE was rash (n = 2); 1 incident of lichen planus was the only late grade 3 TRAE reported (eTable 4 in Supplement 2).

Clinical Activity

Disease burden was evaluated over time (**Figure 2**) and ORR determined by RECIST and irRC (**Table**). The ORR by RECIST was

Figure 2. Disease Burden Over Time and Overall Survival by Response



Change in tumor burden over time in all response-evaluable patients with triple-negative breast cancer receiving atezolizumab. Tumor burden was measured as the sum of the longest diameters. Confirmed investigator-assessed Response Evaluation Criteria in Solid Tumors responses are included for patients with postbaseline tumor measurements.

Table. Responses and Duration of Response by Subgroups

	No. (%)			
	Line of Treatment		PD-L1 IC Status	
Response	1L (n = 21)	2L+ (n = 94)[a]	IC0 (n = 21)[b]	IC1/2/3 (n = 91)[b]
By RECIST				
ORR, No. (%) [95% CI]	5 (24) [8-47]	6 (6) [2-13]	0 [0-17]	11 (12) [6-21]
Complete response	2 (10)	1 (1)	0	3 (3)
Partial response	3 (14)	5 (5)	0	8 (9)
Stable disease	3 (14)	12 (13)	3 (15)	11 (12)
Progressive disease	13 (62)	60 (64)	16 (80)	55 (60)
DCR, No. (%)	6 (29)	9 (10)	1 (5)	14 (15)
DOR, median (range), mo	21 (10-≥38)	19 (3-28)	NE (NE)	21 (3-≥38)
By irRC				
ORR, No. (%) [95% CI]	5 (24) [8-47]	10 (11) [5-19]	0 [0-17]	15 (16) [10-26]
Complete response	2 (10)	2 (2)	0	4 (4)
Partial response	3 (14)	8 (9)	0	11 (12)
Stable disease	7 (33)	13 (14)	4 (20)	15 (16)
Progressive disease	8 (38)	49 (52)	12 (60)	43 (47)
DCR, No. (%)	7 (33)	12 (13)	1 (5)	18 (20)
DOR, median (range), mo	NR (7-≥38)	25 (3-≥42)	NE (NE)	25 (3-≥42)

Abbreviations: 1L, first line; 2L+, second line and beyond; DCR, disease control rate; DOR, duration of response; IC, tumor-infiltrating immune cells; irRC, immune-related response criteria; NE, not evaluable; NR, not reached; ORR, objective response rate; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors, version 1.1.

[a] Patients with missing or unevaluable responses in the 1L (1 [5%] per irRC) and 2L+ (16 [17%] per RECIST and 22 [23%] per irRC) settings were not included.

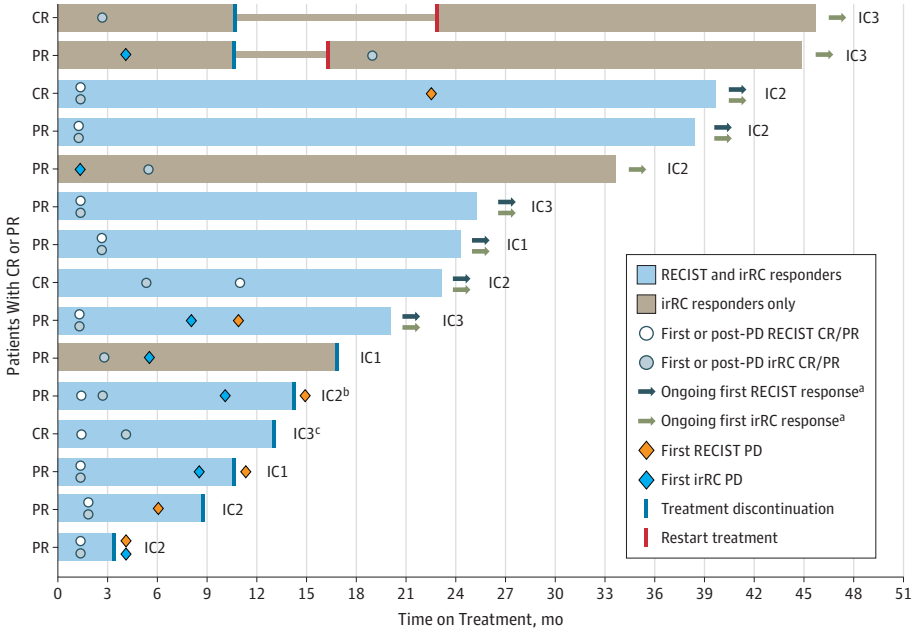
[b] Patients with missing or unevaluable responses in the IC0 (1 [5%] per RECIST and 4 [20%] per irRC) and IC1/2/3 (14 [15%] per RECIST and 18 [20%] per irRC) subgroups were not included (baseline PD-L1 expression on ICs was assessed as <1% [IC0] or ≥1% [IC1/2/3]). The DCR is percentage of patients with best response as CR, PR, or SD of at least 24 weeks.

10% (11 of 115; 95% CI, 4.9%-16.5%). Patients who received atezolizumab as first-line therapy had an ORR of 24% (5 of 21; 95% CI, 8.2%-47.2%), and those receiving it as second-line and beyond therapy had ORR of 6% (6 of 94; 95% CI, 2.4%-13.4%). The ORR by irRC was 13% (15 of 115; 95% CI, 7.5%-20.6%) in all patients, and 24% (5 of 21; 95% CI, 8.2%-47.2%) in first-line and 11% (10 of 94; 95% CI, 5.2%-18.7%) in second-line and beyond patients. Fifteen patients (13%) had a best response of SD by RECIST, and 20 (17%) had SD by irRC. Three patients with progressive disease and 1 patient with SD by RECIST were responders by irRC (**Figure 3**); all 4 patients showed durable clinical benefit (Figure 3). The all-patient disease control rate was 13% (15 of 115) by RECIST and 17% (19 of 115) by irRC.

Median DOR by RECIST and irRC was 21 (range, 3 to ≥38) months and 25 (3 to ≥42) months, respectively. In first-line patients, median DOR was 21 (range, 10 to ≥38) months by RECIST but had not been reached by the data cutoff when assessed by irRC (Table). Ongoing responses were observed in 6 of 11 patients (55%) by RECIST and 9 of 15 patients (53%) by irRC (Figure 3).

In all patients, median PFS was 1.4 (95% CI, 1.3-1.6) months by RECIST and 1.9 (95% CI, 1.4-2.6) months by irRC (eTable 5 and eFigure 1 in Supplement 2). Median OS was 8.9 (95% CI, 7.0-12.6) months with 1-, 2-, and 3-year landmark OS rates of 41% (95% CI, 32%-50%), 19% (95% CI, 11%-26%), and 16% (95% CI, 8%-24%) respectively. In efficacy-evaluable patients who survived for at least 6 weeks (n = 99), 9 of 11 patients (82%) and 13 of 15 patients (87%) with complete or partial responses by RECIST and irRC, respectively, were still alive (eFigure 2 in Supplement 2). Patients with SD by RECIST (15 of 99) had a

Figure 3. Duration of Treatment and Response in Patients With Triple-Negative Breast Cancer Treated With Atezolizumab



Time on treatment is plotted for patients with confirmed investigator-assessed Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST), and immune-related response criteria (irRC) responses. Baseline programmed cell death ligand 1 expression on tumor-infiltrating immune cells was evaluated with 4 scoring bins: IC3 (≥10%), IC2 (≥5% and <10%), IC1 (≥1% and <5%), and IC0 (<1%). Bar color indicates responders with complete response (CR) or partial response (PR) per RECIST and irRC (blue) or responders with CR or PR per irRC alone (taupe), and symbols describe response assessments. Circles indicate the type of CR or PR by RECIST (white) or irRC (blue). Diamonds indicate progressive disease (PD) by RECIST (orange) or irRC (turquoise). Arrows indicate ongoing first response by RECIST or irRC. Thin bars indicate off-treatment periods.

[a] No death or PD status.

[b] Patient is deceased.

[c] Atezolizumab had been withdrawn from this patient owing to grade 3 dementia unrelated to the study treatment; the patient had died by follow-up.

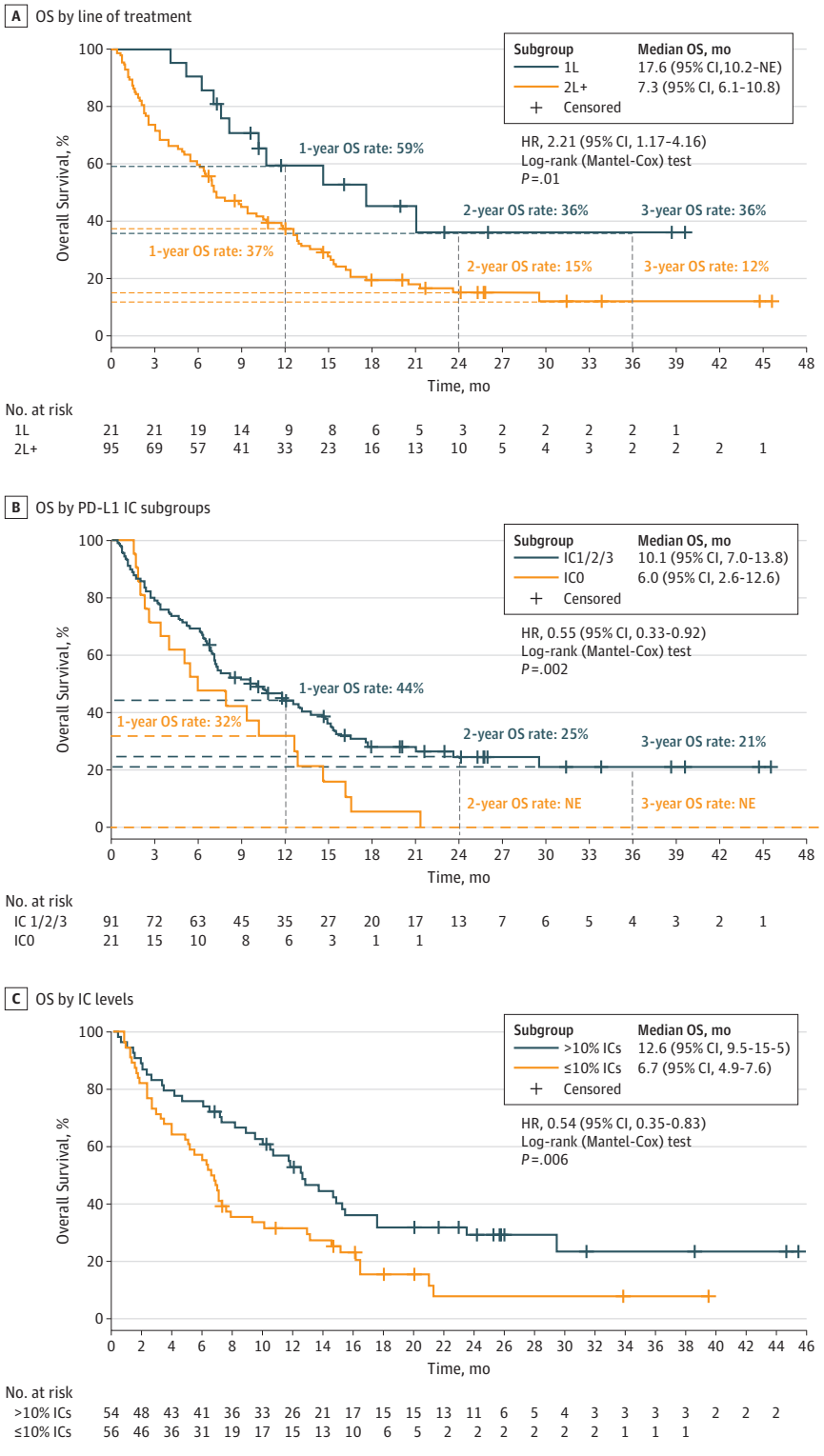
median OS of 15.9 (95% CI, 10.5-23.6) months, while those with progressive disease by RECIST (73 of 99) had a median OS of 7.3 (95% CI, 6.6-10.8) months (eFigure 2A in Supplement 2). The median OS for patients with SD (20 of 99) or progressive disease (57 of 99) by irRC was similar (eFigure 2B in Supplement 2). In patients receiving first-line atezolizumab, median OS was 17.6 months (95% CI, 10.2 months to not estimable), whereas it was 7.3 (95% CI, 6.1-10.8) months in those receiving second-line and beyond atezolizumab (**Figure 4**A).

We also evaluated prognostic clinical factors that influence the efficacy of checkpoint blockade in patients with melanoma[23,24] using univariate analysis (eFigure 3 in Supplement 2). Regardless of line of treatment, the presence of liver metastases was associated with worse clinical outcomes, including OS, PFS, and ORR. Tumor burden of at least 6.5 cm and lactate dehydrogenase (LDH) level at least 1.5 times the upper limit of normal were associated with shorter OS and lower ORR but not shorter PFS. Later lines of therapy and ECOG PS greater than 0 also had a nonsignificant finding of worse outcome, but to a lesser extent than other factors. Lactate dehydrogenase level was correlated with liver metastases and tumor size but not with line of therapy or ECOG PS (eTable 6 in Supplement 2). These correlations were nonoverlapping, and the effect on OS in patients with mTNBC was additive (eFigure 3F and G in Supplement 2).

Biomarker Analyses

Atezolizumab activity has been linked to increased IC and TC expression of PD-L1.[18,19] Analysis for PD-L1 IC was performed comparing IC0 vs IC1/2/3 (eTable 7 in Supplement 2). No PD-L1 IC0 patients (0 of 21) responded to atezolizumab by either RECIST or irRC, while ORR was 12% (11 of 91) and 16% (15 of 91) in PD-L1 IC1/2/3 patients by RECIST and irRC, respectively (Table). The disease control rate by RECIST was 15% (14 of 91) in the IC1/2/3 subgroup and 5% (1 of 21) in the IC0 subgroup. The DOR in PD-L1 IC1/2/3 patients was similar when assessed by RECIST or irRC (Table). The patients with PD-L1 IC1/2/3 had longer median OS than those with PD-L1 IC0 (IC1/2/3, 10.1 [95% CI, 7.0-13.8] months vs IC0, 6.0 [95% CI, 2.6-12.6] months) (Figure 4B). A similar ORR and OS nonsignificant result was seen using the higher PD-L1 expression cutoff of IC2/3 vs IC0/1 (eTable 8 and eFigure 4 in Supplement 2). Twenty-five patients expressed PD-L1 on TCs (TC1/2/3) and 87 had none (TC0). Twenty-three of 25 (92%) PD-L1 TC1/2/3 tumors were also PD-L1 IC1/2/3. There were no major differences in ORR between patients with TC0 vs TC1/2/3 regardless of criteria used (RECIST, TC0: 9.2%; 95% CI, 4.1%-17.3%; vs TC1/2/3: 12%; 95% CI, 2.5%-31.2%; irRC, TC0: 12.6%; 95% CI, 6.5%-21.5%; vs TC1/2/3: 16%; 95% CI, 4.5%-36.1%). The 2 patients whose tumors were PD-L1 TC1/2/3 and IC0 were nonresponders.

Figure 4. Measures of Clinical Efficacy



A, Kaplan-Meier curves depict the overall survival (OS) by line of treatment. B, Kaplan-Meier curves depict the OS by programmed cell death ligand 1 (PD-L1) expression on tumor-infiltrating immune cells (ICs). C, Kaplan-Meier curves depict the OS by level of ICs greater than 10%. Log-rank (Mantel-Cox) *P* value is exploratory. Baseline PD-L1 expression on ICs was assessed as less than 1% (IC0) or at least 1% (IC1/2/3). Two- and 3-year landmark OS rates for patients in the IC0 subgroup were not evaluable (NE). 1L indicates first line; 2L+, second line and beyond; HR, hazard ratio.

In this study, cutoffs associated with the population median were 10% for ICs (n = 110), 1.35% for CD8-positive T cells (n = 104), and 5.96% for CD163-positive macrophages (n = 97). All immune biomarkers were correlated with each other ($0.42 < r < 0.72$) (eFigure 5 in Supplement 2), suggesting that infiltration includes all immune partners within the tumor.

A nonsignificant finding of higher ORRs (eTable 9 in Supplement 2) and longer PFS and OS was observed with higher

baseline IC infiltration (Figure 4C and eFigure 6 in Supplement 2). Similarly, higher ORRs and longer PFS and OS were observed with higher baseline CD8-positive T-cell (eTable 9 and eFigure 7 in Supplement 2) but not CD163-positive macrophage infiltration (data not shown). In a multivariate analysis, considering line of therapy, LDH, ECOG PS, size of target lesion, and presence of liver metastasis, ICs greater than 10% (but not CD8 ≥ 1.35%) were independently associated with enhanced ORR, irRC-based PFS, and OS (eFigure 6 and eFigure 7 in Supplement 2).

Atezolizumab-induced changes in tumor immune biomarkers (PD-L1 TCs, PD-L1 IC, CD8-positive T cells, ICs, and CD163-positive macrophages) were evaluated in baseline vs posttreatment (10-20 d) tumor biopsies. There was a significant increase in PD-L1 IC expression after atezolizumab exposure in patients with mTNBC (n = 9; P = .04, effect size = 0.5 based on Wilcoxon sign-ranked pairwise test) (eFigure 8 in Supplement 2), irrespective of clinical outcomes (SD or progressive disease).

Discussion

This is the first report of the long-term safety, clinical activity, and candidate predictive biomarkers of response associated with atezolizumab monotherapy in patients with mTNBC. It includes several key findings that may affect the future development of atezolizumab for this disease. First, single-agent atezolizumab was generally well tolerated in patients with mTNBC, with TRAEs consistent with the known safety profile of atezolizumab in other tumor types and other PD-L1/PD-1 antagonists in patients with mTNBC.[25] Most serious TRAEs occurred within the first year of administration, with only 1 grade 3 TRAE (lichen planus) occurring beyond 1 year of dosing. Second, atezolizumab demonstrated measurable ORRs and durable clinical activity. Numerically higher ORRs occurred in patients with mTNBC treated in the first-line setting. Third, patients who had an objective response or SD for at least 24 weeks were more likely to be alive at data cutoff. Fourth, we observed atypical patterns of response to atezolizumab in some patients. Notably, irRC captured a higher proportion of patients with mTNBC with durable clinical benefit than standard RECIST. Finally, improved clinical activity was associated with higher levels of PD-L1–positive ICs, CD8-positive T cells, and ICs, the latter by both univariate and multivariate analysis.

Although cross-trial comparisons may be confounded by differences in patient selection and study design, our data compare favorably with data on other anti-PD-L1/PD-1 agents in mTNBC. In a phase 1b study testing single-agent pembrolizumab, the ORR was approximately 19% in PD-L1-selected patients (≥1% PD-L1 expression on TCs).[26] In a phase 2 study of pembrolizumab, the ORR was approximately 23% in PD-L1-selected first-line patients, and approximately 5% in the second-line and beyond setting, regardless of PD-L1 expression.[27] The ORR for heavily pretreated patients with mTNBC dosed with avelumab was approximately 5% in a phase 1 trial, with a nonsignificant finding of higher ORRs in patients with PD-L1–positive IC (≥10% expression).[28] Taken together, the data for PD-L1/PD-1 blockade appear encouraging for mTNBC.

Patients with mTNBC have a poor prognosis.[1-3] Bevacizumab and olaparib are the only approved targeted therapies for selected patients, where available.[29,30] This is the first study to report long-term and landmark OS rates at 2 years or longer in patients with mTNBC who received a PD-L1/PD-1 inhibitor. The median OS in atezolizumab-treated patients with mTNBC is comparable to that with standard chemotherapy,[4,5] without the AEs typical of chemotherapy. We found that patients with mTNBC responding to atezolizumab had longer median OS than nonresponders, while patients who had clinical benefit (SD) also had longer OS than those with PD. Notably, OS for patients with clinical benefit (complete response, partial response, or SD) was longer than for historical responders to standard chemotherapy,[4] suggesting that for patients with mTNBC who have an objective response, atezolizumab may provide greater clinical benefit with a more favorable safety profile than standard chemotherapy.

We also identified candidate predictive biomarkers of atezolizumab clinical activity in patients with mTNBC. Similar to the clinical features associated with response to PD-L1/PD-1 therapy in other tumor types,[23,24] patients with mTNBC with elevated LDH and/or liver metastases typically had reduced clinical benefit from atezolizumab therapy. In addition, a high tumor burden (a reported prognostic factor for TNBC[5]), later lines of therapy, and ECOG PS greater than 0 are potential predictive clinical factors of reduced atezolizumab clinical activity in mTNBC. Although there was a correlation between LDH and tumor burden or presence of liver metastases, their effects on survival were additive, and they could thus be used for further multivariate analysis of other variables. We also found that high levels of PD-L1–positive ICs, ICs, and CD8-positive T cells were associated with more favorable clinical outcomes to single-agent atezolizumab. Only ICs were associated with OS, PFS (by irRC), and ORR on multivariate analysis. These findings are consistent with multiple reports that ICs are predictive of response to standard chemotherapy in early TNBC.[6-8] Although only 9 paired biopsies were available for analysis, our observations that PD-L1 IC expression increases from baseline to on treatment suggests that atezolizumab may promote the activation of tumor-specific T-cell immunity. Randomized clinical studies are warranted to confirm these observations.

Combination immunotherapy regimens may increase the response rate to atezolizumab therapy, thus increasing the number of patients with mTNBC who could derive long-term clinical benefit from PD-1 pathway blockade. The combination of eribulin and pembrolizumab has shown promising activity (ORR, 26.4%) in mTNBC.[31] Combinations of anti-PD-L1/PD-1 agents with PARP inhibitors (niraparib or olaparib) or sequenced with chemotherapy or radiotherapy in mTNBC, or combined with chemotherapy in the neoadjuvant setting, have also shown early efficacy.[32-36] For atezolizumab, promising activity (ORR, 39%) was demonstrated in a phase 1b study of atezolizumab combined with nab-paclitaxel in patients with

heavily pretreated mTNBC.[37] Based on these data, the randomized, placebo-controlled phase 3 IMpassion130 trial is evaluating atezolizumab combined with nab-paclitaxel in untreated mTNBC.

Limitations

This report is limited by its single-arm study design, preventing direct comparisons with standard chemotherapy. Furthermore, trial enrollment was initially limited to PD-L1–selected patients with mTNBC and then broadened to all comers, which limits extrapolation to the overall mTNBC patient population. Regardless, these analyses provide useful insights into the long-term safety and efficacy of atezolizumab in mTNBC and can guide further clinical development.

Conclusions

In conclusion, with a median follow-up of longer than 2 years, atezolizumab was generally well tolerated in patients with mTNBC. Durable clinical activity and encouraging survival benefit, particularly in first-line patients or those with higher levels of ICs and PD-L1–positive ICs, suggest a potential therapeutic benefit with atezolizumab in mTNBC. Combination immunotherapy strategies, which may increase ORR and prolong the survival of more patients with mTNBC, could change the treatment paradigm for this disease. Early clinical data support this strategy, and phase 3 studies are already under way to evaluate the addition of chemotherapy to atezolizumab.

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