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Atezolizumab y Nab-Paclitaxel en el cáncer de mama avanzado triple negativo

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Abstracto

FONDO

El cáncer de mama irresecable localmente avanzado o metastásico triple negativo (receptor hormonal negativo y receptor 2 del factor de crecimiento epidérmico humano [HER2] negativo) es una enfermedad agresiva con malos resultados. Las nanopartículas de paclitaxel unidas a albúmina (nab) pueden mejorar la actividad anticancerígena de atezolizumab.

MÉTODOS

En este ensayo de fase 3, asignamos al azar (en una proporción de 1:1) a pacientes con cáncer de mama triple negativo metastásico no tratado para recibir atezolizumab más nab-paclitaxel o placebo más nab-paclitaxel; los pacientes continuaron la intervención hasta que se produjo la progresión de la enfermedad o un nivel inaceptable de efectos tóxicos. Los factores de estratificación fueron la recepción o no de terapia neoadyuvante o adyuvante con taxanos, la presencia o ausencia de metástasis hepáticas al inicio del estudio y la expresión del ligando de muerte programada 1 (PD-L1) al inicio del estudio (positivo versus negativo). Los dos criterios de valoración principales fueron la supervivencia libre de progresión (en la población por intención de tratar y el subgrupo positivo para PD-L1) y la supervivencia general (probada en la población por intención de tratar; si el hallazgo fuera significativo, entonces ser evaluado en el subgrupo PD-L1 positivo).

RESULTADOS

Cada grupo incluyó 451 pacientes (mediana de seguimiento, 12,9 meses). En el análisis por intención de tratar, la mediana de supervivencia libre de progresión fue de 7,2 meses con atezolizumab más nab-paclitaxel, en comparación con 5,5 meses con placebo más nab-paclitaxel (cociente de riesgo de progresión o muerte, 0,80; intervalo de confianza del 95%). [IC], 0,69 a 0,92; p = 0,002); entre los pacientes con tumores PD-L1 positivos, la mediana de supervivencia libre de progresión fue de 7,5 meses y 5,0 meses, respectivamente (índice de riesgo, 0,62; IC del 95 %, 0,49 a 0,78; P <0,001). En el análisis por intención de tratar, la mediana de supervivencia general fue de 21,3 meses con atezolizumab más nab-paclitaxel y 17,6 meses con placebo más nab-paclitaxel (cociente de riesgo de muerte, 0,84; IC del 95 %, 0,69 a 1,02; P = 0,08); entre los pacientes con tumores PD-L1 positivos, la mediana de supervivencia general fue de 25,0 meses y 15,5 meses, respectivamente (cociente de riesgos instantáneos, 0,62; IC del 95 %, 0,45 a 0,86). No se identificaron nuevos efectos adversos. Los eventos adversos que llevaron a la interrupción de cualquier agente ocurrieron en el 15,9% de los pacientes que recibieron atezolizumab más nab-paclitaxel y en el 8,2% de los que recibieron placebo más nab-paclitaxel.

CONCLUSIONES

Atezolizumab más nab-paclitaxel prolongó la supervivencia libre de progresión entre pacientes con cáncer de mama metastásico triple negativo tanto en la población por intención de tratar como en el subgrupo PD-L1 positivo. Los eventos adversos fueron consistentes con los perfiles de seguridad conocidos de cada agente. (Financiado por F. Hoffmann–La Roche/Genentech; número IMpassion130 ClinicalTrials.gov, [NCT02425891](#)).

El cáncer de mama triple negativo es el término utilizado para describir los cánceres de mama que carecen de expresión de receptores de estrógeno y progesterona y no sobreexpresan el receptor 2 del factor de crecimiento epidérmico humano (HER2). Las pacientes con cáncer de mama triple negativo tienen malos resultados clínicos.^{1,2} La quimioterapia sigue siendo el tratamiento sistémico primario, y las pautas internacionales respaldan el uso de taxanos o antraciclinas como agente único como terapia de primera línea.³⁻⁵ Las estimaciones de la mediana de supervivencia general varían, pero siguen siendo aproximadamente 18 meses o menos.⁶⁻⁸ En pacientes con cáncer de mama triple negativo, la expresión del ligando 1 de muerte programada (PD-L1) se produce principalmente en las células inmunitarias infiltrantes de tumores en lugar de en las células tumorales^{9,10} y puede inhibir las respuestas inmunitarias anticancerígenas.^{11,12} Por lo tanto, la inhibición de la muerte programada 1 (PD-1) y PD-L1 puede ser una estrategia de tratamiento útil.

Atezolizumab selectively targets PD-L1 to prevent interaction with the receptors PD-1 and B7-1 (a costimulatory cell-surface protein), reversing T-cell suppression. Single-agent atezolizumab is approved for the treatment of metastatic urothelial carcinoma and non–small-cell lung cancer (NSCLC).^{13,14} Atezolizumab has also been shown to have a good safety profile and clinical activity in patients with other solid tumors,¹² including triple-negative breast cancer.¹⁵ Chemotherapy may enhance tumor-antigen release and antitumor responses to immune checkpoint inhibition. Taxanes in particular may additionally activate toll-like receptor activity and promote dendritic-cell activity.¹⁶ Nanoparticle albumin-bound (nab)–paclitaxel was selected as a partner because, at the time that the trial was designed, the glucocorticoid premedication that is required with solvent-based paclitaxel (per the label) had been hypothesized to affect immunotherapy activity.¹⁷

The safety profile and activity of atezolizumab with nab-paclitaxel have been shown in patients with advanced NSCLC (in phase 1b and 3 studies) and those with triple-negative breast cancer (in a phase 1b study).¹⁸⁻²⁰ The phase 1b study involving patients with breast cancer showed that atezolizumab-mediated immunodynamic effects were not abrogated with concurrent administration of nab-paclitaxel.²⁰ Here we report the results of the IMpassion130 trial, an international, randomized, double-blind, placebo-controlled trial of first-line atezolizumab plus nab-paclitaxel, as compared with placebo plus nab-paclitaxel, in patients with locally advanced or metastatic triple-negative breast cancer.

Methods

OVERSIGHT

The trial sponsor, F. Hoffmann–La Roche/Genentech, provided atezolizumab and placebo and collaborated with an academic steering committee regarding the trial design and data collection, analysis, and interpretation. Celgene provided nab-paclitaxel; the company had no role in the trial design or data collection or analysis but did review the manuscript. The trial was conducted according to the guidelines of Good Clinical Practice and the principles of the Declaration of Helsinki. All the patients provided written informed consent. Protocol approval was obtained from independent review boards or ethics committees at each site. An independent data and safety monitoring committee reviewed unblinded safety and trial-conduct data every 6 months. All the authors verify that the trial was conducted according to the protocol and vouch for the accuracy and completeness of the data. All the drafts of the manuscript were prepared by the authors, with editorial assistance from professional medical writers funded by the sponsor.

PATIENTS

Eligible patients were 18 years of age or older and had metastatic or unresectable locally advanced, histologically documented triple-negative breast cancer (lack of estrogen- and progesterone-receptor expression and no overexpression of HER2, according to American Society of Clinical Oncology–College of American Pathologists guideline criteria, as evaluated by local institutions).^{21,22} Patients had a representative tumor specimen (formalin-fixed, paraffin-embedded archival or fresh pretreatment relapsed-disease tumor tissue) that could be evaluated for prospective central testing of PD-L1 expression (SP142 PD-L1 immunohistochemical assay, Ventana Medical Systems). Patients were eligible to receive taxane monotherapy and had received no previous chemotherapy or targeted therapy for metastatic triple-negative breast cancer. Radiation therapy and previous chemotherapy (including taxanes) in the context of curative therapy (if treatment was completed ≥ 12 months before randomization) were allowed. Measurable disease

according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability), and adequate hematologic and organ function were also required.

Key exclusion criteria were untreated central nervous system (CNS) disease (patients with asymptomatic treated CNS metastases were permitted), a history of autoimmune disease, previous immune checkpoint–targeting therapies, recent treatment with a systemic immunostimulatory agent (received within the previous 4 weeks or 5 half-lives of the drug, whichever was shorter), and the use of systemic glucocorticoid or immunosuppressive medications. The full eligibility criteria (including exceptions to exclusions regarding glucocorticoid therapy) are provided in the [protocol](#), available with the full text of this article at NEJM.org.

TRIAL DESIGN AND PROCEDURES

Patients were randomly assigned in a 1:1 ratio, with the use of a permuted block method and an interactive voice–Web response system, to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. Stratification factors were the presence or absence of liver metastases, use or nonuse of neoadjuvant or adjuvant taxane treatment, and PD-L1 expression on tumor-infiltrating immune cells as a percentage of tumor area (<1% [PD-L1 negative] vs. ≥1% [PD-L1 positive]) according to immunohistochemical testing. Scoring regarding PD-L1 expression has been described previously^{15,23} (see the Supplementary Methods section in the [Supplementary Appendix](#), available at NEJM.org). The trial sponsor, site personnel, and patients were unaware of patients' PD-L1 status.

Patients received atezolizumab at a dose of 840 mg or placebo, administered intravenously, on days 1 and 15 and received nab-paclitaxel at a dose of 100 mg per square meter of body-surface area, administered intravenously, on days 1, 8, and 15 of every 28-day cycle. Patients received the trial intervention until progression, according to RECIST, version 1.1, or an unacceptable level of toxic effects occurred. In the absence of toxic effects, nab-paclitaxel was to be administered for six cycles or more. In the absence of disease progression, the discontinuation of atezolizumab or placebo or of nab-paclitaxel (owing to toxic effects) could occur independently. Dose reductions of atezolizumab or placebo were not permitted; prespecified modifications of the nab-paclitaxel dose were permitted in order to manage the toxic effects of chemotherapy. Tumor imaging occurred at baseline and every 8 weeks for 12 months and then every 12 weeks. Follow-up for survival occurred every 3 months after the discontinuation of the intervention.

The two primary efficacy end points, investigator-assessed progression-free and overall survival, were evaluated in both the intention-to-treat population, which included all the patients who had undergone randomization, and the subgroup of patients with PD-L1–positive tumors (expression on tumor-infiltrating immune cells ≥1% [PD-L1–positive subgroup]). Key secondary efficacy end points were the rate and duration of objective response, as assessed by the investigators according to RECIST, version 1.1. Safety was evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0, of the National Cancer Institute. Additional details regarding the trial design, including key protocol amendments, are available with the protocol.

STATISTICAL ANALYSIS

The trial was initially designed to randomly assign approximately 350 patients for the evaluation of a primary end point of progression-free survival. During the course of the trial, enrollment was expanded to 900 patients to accommodate the addition of overall survival as a second primary end point. Definitive analyses of progression-free survival in the intention-to-treat population and in the PD-L1–positive subgroup were planned, at which time the first interim analysis of overall survival was also planned. The type I error (0.05) was controlled and split between the analyses of progression-free survival (0.01) and overall survival (0.04), with hierarchical testing for overall survival first in the intention-to-treat population and then in the PD-L1–positive subgroup (see the Supplementary Methods section in the [Supplementary Appendix](#)). The trial had 95% power for the primary analysis of progression-free survival among patients in the intention-to-treat population and 88% power for the analysis of overall survival.

Progression-free survival and overall survival were compared between the trial groups with the use of a stratified log-rank test, and hazard ratios for disease progression and death were estimated with the use of a stratified Cox proportional-hazards model. Kaplan–Meier analysis was applied to progression-free survival and overall survival, and the Brookmeyer–Crowley method was used to construct the 95% confidence interval for each median duration. Similar methods were applied to the duration of response for descriptive purposes, and the analysis was not stratified. The comparisons of the response rate between groups were made with the use of the stratified Cochran–Mantel–Haenszel test.

Results

PATIENTS AND TRIAL INTERVENTIONS

From June 2015 through May 2017, a total of 902 patients (intention-to-treat population) were enrolled at 246 sites in 41 countries; a total of 348 patients (38.6%) were enrolled in Europe, 230 (25.5%) in the United States and Canada, 145 (16.1%) in Asia, 137 (15.2%) in Latin America, and 42 (4.7%) in Australia (see the [Supplementary Appendix](#)). A total of 451 patients were randomly assigned to each group ([Figure 1](#)). The PD-L1–positive subgroup included 369 patients (40.9%; 185 patients in the atezolizumab–nab-paclitaxel group and 184 in the placebo–nab-paclitaxel group).

Overall, the characteristics of the patients at baseline were well balanced between the two trial groups, and the baseline characteristics of the patients in the PD-L1–positive subgroup appeared to be generally representative of the intention-to-treat population ([Table 1](#)). Approximately half the patients had been treated with neoadjuvant or adjuvant taxane or anthracycline chemotherapy ([Table 1](#)).

The numbers of patients who were still receiving the trial intervention at the time of analysis (data cutoff, April 17, 2018) are shown in [Figure 1](#). For patients in the atezolizumab–nab-paclitaxel group, the median duration of atezolizumab treatment was 24.1 weeks and the median duration of nab-paclitaxel treatment was 22.1 weeks. For patients in the placebo–nab-paclitaxel group, the median duration that placebo was received was 22.1 weeks and the median duration of nab-paclitaxel treatment was 21.8 weeks. The mean (\pm SD) cumulative dose of nab-paclitaxel was 1980.0 \pm 1303.1 mg per square meter in the atezolizumab–nab-paclitaxel group and 1764.4 \pm 1238.3 mg per square meter in the placebo–nab-paclitaxel group. (Additional exposure and dose-intensity data are provided in Table S1 in the [Supplementary Appendix](#).) Palliative radiation therapy was administered in 32 patients (7.1%) in the atezolizumab–nab-paclitaxel group and in 24 (5.3%) in the placebo–nab-paclitaxel group.

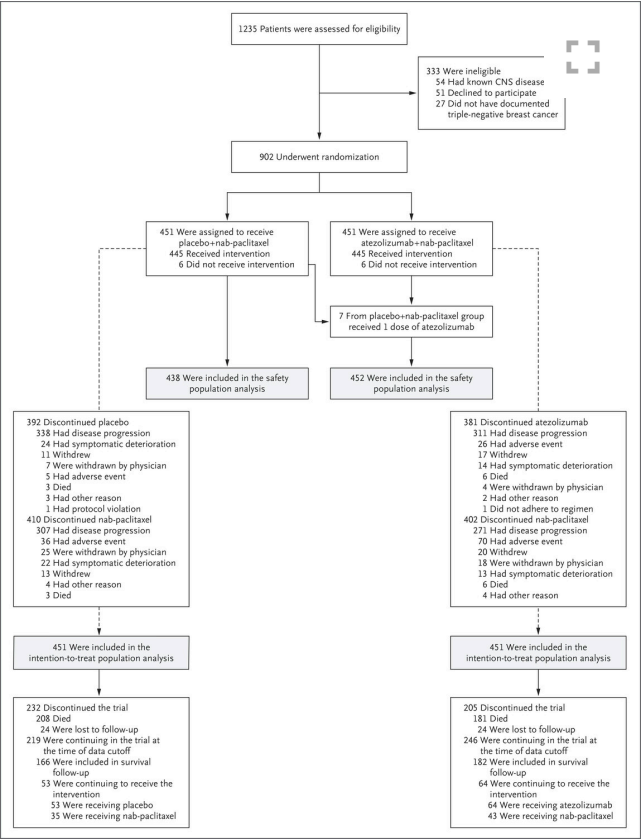
FINAL PROGRESSION-FREE SURVIVAL ANALYSIS

At the time of data cutoff, the median follow-up was 12.9 months in the intention-to-treat population (13.0 months in the atezolizumab–nab-paclitaxel group and 12.5 months in the placebo–nab-paclitaxel group). A total of 358 patients (79.4%) in the atezolizumab–nab-paclitaxel group and 378 (83.8%) in the placebo–nab-paclitaxel group had disease progression or died. Progression-free survival was significantly longer in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group (median, 7.2 months vs. 5.5 months; stratified hazard ratio for progression or death, 0.80; 95% confidence interval [CI], 0.69 to 0.92; P=0.002) ([Figure 2A](#)).

In the PD-L1–positive subgroup, 138 of 185 patients (74.6%) in the atezolizumab–nab-paclitaxel group and 157 of 184 patients (85.3%) in the placebo–nab-paclitaxel group had disease progression or died. A significantly lower risk of progression or death was observed with atezolizumab–nab-paclitaxel than with placebo–nab-paclitaxel (median progression-free survival, 7.5 months vs. 5.0 months; stratified hazard ratio for progression or death, 0.62; 95% CI, 0.49 to 0.78; P<0.001) ([Figure 2B](#)). At 1 year, the rate of progression-free survival was higher in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group (29.1% vs. 16.4%).

In sensitivity analyses, the assessments of progression-free survival were confirmed by means of central review (stratified hazard ratio for progression or death, 0.78 [95% CI, 0.67 to 0.91] in the intention-to-treat

FIGURE 1



Randomization, Trial Populations, and Follow-up.

TABLE 1

Table 1. Characteristics of the Patients at Baseline.*				
Characteristic	Intention-To-Treat Population Atezolizumab + Nab-Paclitaxel (N = 451)	Placebo + Nab-Paclitaxel (N = 451)	PD-L1–Positive Atezolizumab + Nab-Paclitaxel (N = 185)	PD-L1–Negative Placebo + Nab-Paclitaxel (N = 184)
Age				
Median (range) — yr	55 (20–82)	56 (26–86)	53 (26–82)	53 (28–85)
Distribution — no. (%)				
18–40 yr	63 (14.0)	51 (11.3)	31 (16.8)	24 (13.0)
41–64 yr	284 (63.0)	285 (63.2)	111 (60.0)	117 (63.6)
≥65 yr	104 (23.1)	115 (25.5)	43 (23.2)	43 (23.4)
Female sex — no. (%)	448 (99.3)	450 (99.8)	184 (99.5)	184 (100)
Race or ethnic group — no. (%)†				
White	308 (68.3)	301 (66.7)	125 (67.6)	129 (70.1)
Asian	85 (18.8)	76 (16.9)	38 (20.5)	28 (15.2)
Black	26 (5.8)	33 (7.3)	9 (4.9)	14 (7.6)
Native American	17 (3.8)	23 (5.1)	8 (4.3)	9 (4.9)
Hawaiian or other Pacific Islander	1 (0.2)	0	0	0
Multiple	2 (0.4)	3 (0.7)	0	0
Unknown	12 (2.7)	15 (3.3)	5 (2.7)	4 (2.2)
ECOG performance-status score — no./total no. (%)‡				
0	256/450 (56.9)	270/450 (60.0)	107/185 (57.8)	112/184 (60.9)
1	193/450 (42.9)	179/450 (39.8)	77/185 (41.6)	72/184 (39.1)
2	1/450 (0.2)	1/450 (0.2)	1/185 (0.5)	0
Metastatic disease — no./total no. (%)	404/450 (89.8)	408/450 (90.7)	162/185 (87.6)	159/183 (86.9)
No. of sites of metastatic disease — no./total no. (%)				
0–3	332/450 (73.8)	341/449 (75.9)	149/185 (80.5)	140/183 (76.5)
≥4	118/450 (26.2)	108/449 (24.1)	36/185 (19.5)	43/183 (23.5)
Site of metastatic disease				
Liver — no. (%)§	126 (27.9)	118 (26.2)	44 (23.8)	39 (21.2)
Bone — no. (%)	145 (32.2)	141 (31.3)	54 (29.2)	49 (26.6)
Brain — no. (%)	30 (6.7)	31 (6.9)	15 (8.1)	11 (6.0)
Lung — no. (%)	226 (50.1)	242 (53.7)	86 (46.5)	98 (53.3)
Lymph node only — no./total no. (%)	33/450 (7.3)	23/449 (5.1)	18/185 (9.7)	13/183 (7.1)
Previous therapy — no. (%)				
Neoadjuvant or adjuvant therapy	284 (63.0)	286 (63.4)	125 (67.6)	117 (63.6)
Taxane§	231 (51.2)	230 (51.0)	96 (51.9)	94 (51.1)
Anthracycline	243 (53.9)	242 (53.7)	109 (58.9)	101 (54.9)

* The summary statistics are based on the full population indicated in the column heading. If data regarding the baseline characteristic were not available for all patients, the total number of patients who could be evaluated for this characteristic is presented. The characteristics of the patients at baseline were well balanced between the two trial groups, and the baseline characteristics of the patients in the PD-L1–positive subgroup appeared to be generally representative of the intention-to-treat population. Percentages may not total 100 because of rounding. Nab-paclitaxel denotes nanoparticle albumin-bound paclitaxel.

† Race and ethnic group were reported by the patients.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher numbers indicating greater disability. A score of 0 indicates no disability, a score of 1 that the patient is ambulatory and capable of light work but restricted in physically strenuous activity, and a score of 2 that the patient is ambulatory, awake and active more than 50% of waking hours, and capable of all self-care but unable to work. Two patients were enrolled with an ECOG performance-status score of 1 but had a score of 2 at the start of the trial intervention.

§ Data were from the case-report form.

Characteristics of the Patients at Baseline.

FIGURE 2

population and 0.63 [95% CI, 0.49 to 0.81] in the PD-L1–positive subgroup). The effects of treatment on progression-free survival in key subgroups are shown in [Figure 3](#). The median progression-free survival was longer with atezolizumab–nab-paclitaxel than with placebo–nab-paclitaxel in the majority of subgroups, including subgroups that were defined on the basis of trial stratification factors and other baseline characteristics, in both the intention-to-treat population and the PD-L1–positive subgroup (Fig. S1 in the [Supplementary Appendix](#)).

INTERIM OVERALL SURVIVAL ANALYSIS

At the time of the data cutoff and first interim analysis of overall survival in the intention-to-treat population, 181 of 451 patients (40.1%) in the atezolizumab–nab-paclitaxel group and 208 of 451 (46.1%) in the placebo–nab-paclitaxel group had died. The median overall survival was 21.3 months in the atezolizumab–nab-paclitaxel group and 17.6 months in the placebo–nab-paclitaxel group (stratified hazard ratio for death, 0.84; 95% CI, 0.69 to 1.02; P=0.08 [not significant]) ([Figure 2C](#)).

In the PD-L1–positive subgroup, 64 of 185 patients (34.6%) in the atezolizumab–nab-paclitaxel group and 88 of 184 (47.8%) in the placebo–nab-paclitaxel group died. Because of the hierarchical statistical analysis procedure, formal testing of overall survival in the PD-L1–positive subgroup was not conducted at this interim analysis. However, Kaplan–Meier analyses showed a median overall survival of 25.0 months in the atezolizumab–nab-paclitaxel group and 15.5 months in the placebo–nab-paclitaxel group (stratified hazard ratio for death, 0.62; 95% CI, 0.45 to 0.86) ([Figure 2D](#)).

Subsequent anticancer therapy was administered to 242 patients (53.7%) in the atezolizumab–nab-paclitaxel group and to 272 (60.3%) in the placebo–nab-paclitaxel group and was generally balanced between the two groups. Most patients received chemotherapy during follow-up, and only a minority (<4%) received immunotherapy (Table S2 in the [Supplementary Appendix](#)).

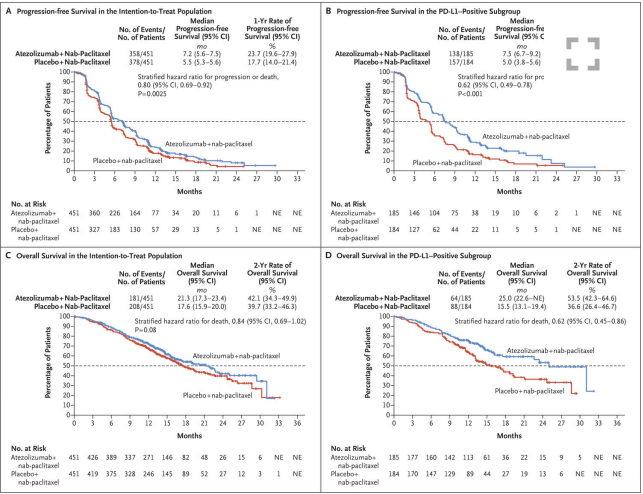
RESPONSE RATE AND DURATION OUTCOMES

In the intention-to-treat population, the rate of objective response, as assessed by the investigator, was 56.0% in the atezolizumab–nab-paclitaxel group, as compared with 45.9% in the placebo–nab-paclitaxel group ([Table 2](#)). A total of 7.1% of the patients in the atezolizumab–nab-paclitaxel group had a complete response, as compared with 1.6% of those in the placebo–nab-paclitaxel group. In the PD-L1–positive subgroup, the response rate was 58.9% with atezolizumab–nab-paclitaxel and 42.6% with placebo–nab-paclitaxel; a total of 10.3% of the patients in the atezolizumab–nab-paclitaxel group had a complete response, as compared with 1.1% of those in the placebo–nab-paclitaxel group ([Table 2](#)).

In the intention-to-treat population, the median duration of response was 7.4 months in the atezolizumab–nab-paclitaxel group and 5.6 months in the placebo–nab-paclitaxel group. In the PD-L1–positive subgroup, the median duration of response was 8.5 months with atezolizumab–nab-paclitaxel and 5.5 months with placebo–nab-paclitaxel ([Table 2](#), and Fig. S2 in the [Supplementary Appendix](#)).

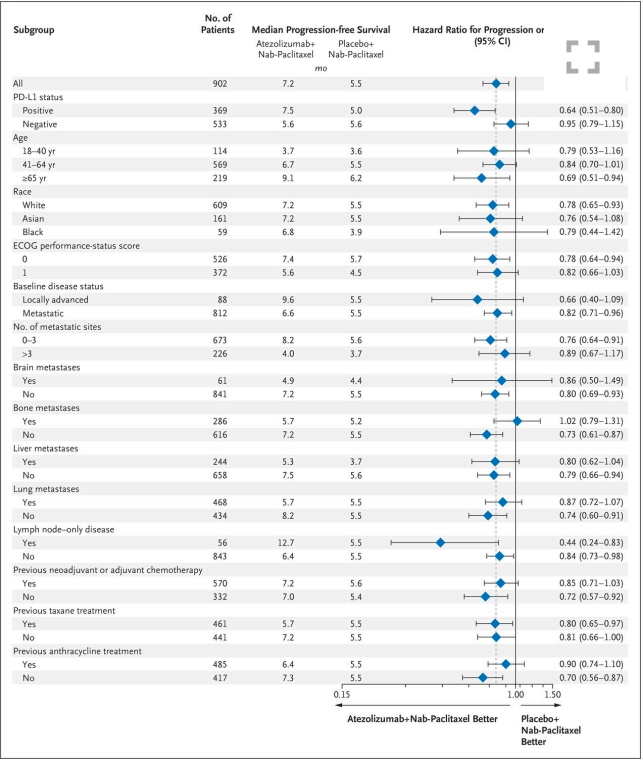
SAFETY

Among patients in the safety population, adverse events, regardless of attribution, occurred in 99.3% of 452 patients in the atezolizumab–nab-paclitaxel group and in 97.9% of 438 patients in the placebo–nab-paclitaxel group ([Table 3](#), and Tables S3 and S4 in the [Supplementary Appendix](#)). The most common adverse events were similar in the two groups ([Table 3](#), and Table S4 in the [Supplementary Appendix](#)), with no



Kaplan–Meier Analysis of Progression-free Survival and Overall Survival.

FIGURE 3



Forest-Plot Analyses of Progression-free Survival in Key Subgroups.

TABLE 2

new adverse events identified. Alopecia was the most common event in each group. The frequencies of nausea, cough, neutropenia, pyrexia, and hypothyroidism were at least 5 percentage points greater in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group. The rate of adverse events of grade 3 or 4 was 48.7% in the atezolizumab–nab-paclitaxel group and 42.2% in the placebo–nab-paclitaxel group, and the most common events in these groups (as assessed by the investigator) were neutropenia, decreased neutrophil count, peripheral neuropathy, fatigue, and anemia ([Table 3](#)). The frequency of peripheral neuropathy of grade 3 or 4 was higher in the atezolizumab–nab-paclitaxel group (25 patients [5.5%]) than in the placebo–nab-paclitaxel group (12 patients [2.7%]). Serious adverse events occurred in 103 patients (22.8%) in the atezolizumab–nab-paclitaxel group and in 80 (18.3%) in the placebo–nab-paclitaxel group ([Table S3](#) in the [Supplementary Appendix](#)).

A total of 259 patients (57.3%) in the atezolizumab–nab-paclitaxel group and 183 (41.8%) in the placebo–nab-paclitaxel group had an adverse event of special interest, which was suggestive of a potential immune-related cause ([Tables S3 and S5](#) in the [Supplementary Appendix](#)). Grade 3 or 4 adverse events of special interest occurred in 34 patients (7.5%) in the atezolizumab–nab-paclitaxel group and in 19 (4.3%) in the placebo–nab-paclitaxel group. Two grade 5 adverse events of special interest occurred (autoimmune hepatitis in 1 patient in the atezolizumab–nab-paclitaxel group and hepatic failure in 1 patient in the placebo–nab-paclitaxel group). Immune-related hypothyroidism occurred at a higher frequency in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group (17.3% vs. 4.3%); all the events were of grade [1 or 2](#), and none led to the discontinuation of the trial regimen. Pneumonitis was infrequent, occurring in 3.1% of the patients in the atezolizumab–nab-paclitaxel group and in 0.2% of those in the placebo–nab-paclitaxel group; only 1 patient (in the atezolizumab–nab-paclitaxel group) had an event of grade 3 or 4.

Adverse events that were attributed to the trial regimen by the investigators are reported in [Table S6](#) in the [Supplementary Appendix](#). Fatal adverse events occurred in 6 patients (1.3%) in the atezolizumab–nab-paclitaxel group and in 3 (0.7%) in the placebo–nab-paclitaxel group ([Table S3](#) in the [Supplementary Appendix](#)); three deaths in the atezolizumab–nab-paclitaxel group (from autoimmune hepatitis, mucosal inflammation, and septic shock, in 1 patient each) and one death in the placebo–nab-paclitaxel group (from hepatic failure) were considered by the investigators to be related to the trial regimen ([Table S6](#) in the [Supplementary Appendix](#)). Adverse events that led to withdrawal of any agent occurred in 15.9% of the patients who received atezolizumab–nab-paclitaxel group and in 8.2% of those who received placebo–nab-paclitaxel group. A total of 29 patients (6.4%) had adverse events that led to the discontinuation of atezolizumab, and 6 (1.4%) had adverse events that led to the discontinuation of placebo ([Table S3](#) in the [Supplementary Appendix](#)).

Discussion

We report here the primary results from IMpassion130, a phase 3 trial of an anti–PD-L1 or anti–PD-1 antibody in patients with metastatic triple-negative breast cancer. Administered as first-line treatment, the combination of atezolizumab with nab-paclitaxel led to significantly longer progression-free survival than was seen with placebo plus nab-paclitaxel in both the intention-to-treat population and the subgroup of patients with PD-L1–positive tumors. Although the boundary for declaring a statistical advantage for atezolizumab–nab-paclitaxel in the intention-to-treat population at this first interim analysis of overall survival was not crossed, and formal testing was not performed in the PD-L1–positive subgroup, numerical increases in median overall survival were observed in both the intention-to-treat population and the PD-L1–positive subgroup.

A clinical benefit with atezolizumab–nab-paclitaxel was particularly notable in the PD-L1–positive subgroup, as shown by a median progression-free survival that was significantly longer by 2.5 months (7.5 months with atezolizumab–nab-

Table 2. Secondary Efficacy Outcomes.*					
Variable	Atezolizumab + Nab-Paclitaxel	Placebo + Nab-Paclitaxel	Difference (95% CI)	P Value	Odds or Hazard Ratio (95% CI)
percentage points					
Response					
Intention-to-treat population — no. of patients†	450	449			
Objective response					
No. of patients	252	206			
% of patients (95% CI)	56.0 (51.3–60.6)	45.9 (41.2–50.6)	10.1 (3.4–16.8)	0.002	1.52 (1.16–1.97)‡
Complete response					
No. of patients	32	7			
% of patients (95% CI)	7.1 (4.9–9.9)	1.6 (0.6–3.2)			
Partial response					
No. of patients	220	199			
% of patients (95% CI)	48.9 (44.2–53.6)	44.3 (39.7–49.1)			
Stable disease					
No. of patients	113	119			
% of patients (95% CI)	25.1 (21.2–29.4)	26.5 (22.5–30.8)			
Progressive disease					
No. of patients	69	104			
% of patients (95% CI)	15.3 (12.1–19.0)	23.2 (19.3–27.4)			
Patients who had missing data or could not be evaluated — no. (%)	16 (3.6)	20 (4.5)			
PD-L1–positive subgroup — no. of patients†	185	183			
Objective response					
No. of patients	109	78			
% of patients (95% CI)	58.9 (51.5–66.1)	42.6 (35.4–50.1)	16.3 (5.7–26.9)	0.002	1.96 (1.29–2.98)‡
Complete response					
No. of patients	19	2			
% of patients (95% CI)	10.3 (6.3–15.6)	1.1 (0.1–3.9)			
Partial response					
No. of patients	90	76			
% of patients (95% CI)	48.6 (41.3–56.1)	41.5 (34.3–49.0)			
Stable disease					
No. of patients	38	49			
% of patients (95% CI)	20.5 (15.0–27.1)	26.8 (20.5–33.8)			
Progressive disease					
No. of patients	31	46			
% of patients (95% CI)	16.8 (11.7–22.9)	25.1 (19.0–32.1)			
Patients who had missing data or could not be evaluated — no. (%)	7 (3.8)	10 (5.5)			
Duration of response‡					
Intention-to-treat population — no. of patients	252	206			
Median duration of response (95% CI) — mo	7.4 (6.9–9.0)	5.6 (5.5–6.9)			0.78 (0.63–0.98)
Patients with ongoing response at data-cutoff date — no. (%)¶	78 (31.0)	52 (25.2)			
PD-L1–positive subgroup — no. of patients	109	78			
Median duration of response (95% CI) — mo	8.5 (7.3–9.7)	5.5 (3.7–7.1)			0.60 (0.43–0.86)
Patients with ongoing response at data-cutoff date — no. (%)¶	39 (35.8)	19 (24.4)			
* The objective response rate and duration of response were evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1, as determined by the investigators. P values are for the difference analyses. Odds ratios are presented for analyses of response, and unstratified hazard ratios for progression or death, without P values, are shown for between-group analyses of duration of response.					
† Data include only patients who had measurable disease at baseline.					
‡ The result was not significant on the basis of an alpha level of 0.1%.					
§ The duration of response was assessed among patients with an objective response.					
¶ Patients who had an ongoing response at the data-cutoff date (April 17, 2018) were those who were alive and did not have progressive disease.					

Secondary Efficacy Outcomes.

TABLE 3

Table 3. Key Adverse Events.*				
Event	Atezolizumab + Nab-Paclitaxel (N = 452)		Placebo + Nab (N = 449)	
	Any Grade	Grade 3 or 4	Any Grade	
	number of patients with event (percent)			
Alopecia	255 (56.4)	3 (0.7)	252 (57.5)	1 (0.2)
Nausea	208 (46.0)	5 (1.1)	167 (38.1)	8 (1.8)
Cough	112 (24.8)	0	83 (18.9)	0
Peripheral neuropathy	98 (21.7)	25 (5.5)	97 (22.1)	12 (2.7)
Neutropenia	94 (20.8)	37 (8.2)	67 (15.3)	36 (8.2)
Pyrexia	85 (18.8)	3 (0.7)	47 (10.7)	0
Hypothyroidism	62 (13.7)	0	15 (3.4)	0

* Shown are the single most frequent adverse event of any grade, adverse events of any grade for which the rates differed by at least 5 percentage points between groups, and adverse events of grade 3 or 4 for which the rates differed by at least 2 percentage points between groups.

Key Adverse Events.

paclitaxel vs. 5.0 months with placebo–nab-paclitaxel; hazard ratio for progression or death, 0.62), by a median overall survival that was 10 months longer at this interim analysis (25.0 months vs. 15.5 months; hazard ratio for death, 0.62 [not statistically tested]), and a numerically higher objective response rate (58.9% vs. 42.6%). These data confirm phase 1 observations of improved outcomes in patients with high PD-L1 expression who were receiving treatment with atezolizumab,¹⁵ pembrolizumab,²⁴ or avelumab.²⁵ As has been found regarding existing chemoimmunotherapy data from patients with other solid tumors who received atezolizumab plus chemotherapy²⁶ or pembrolizumab plus chemotherapy,²⁷ this trial establishes the benefit of adding a checkpoint inhibitor to standard chemotherapy for the first-line treatment of metastatic triple-negative breast cancer, with most of the benefit realized in the PD-L1–positive subgroup.

Combination therapy with atezolizumab plus nab-paclitaxel had a safety profile that was consistent with the known toxic effects of each agent. Consistent with observations from other atezolizumab–chemotherapy combination trials,^{19,26} no new adverse-event signals were observed. The incidence of grade 3 or 4 adverse events of special interest was higher in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group (7.5% vs. 4.3%). Discontinuations of either agent were higher in the atezolizumab–nab-paclitaxel group than in the placebo–nab-paclitaxel group; however, atezolizumab did not compromise the dose intensity of nab-paclitaxel.

This trial has a number of strengths. The trial groups were well balanced with respect to clinical characteristics at baseline and subsequent post-protocol therapies, which suggests that the observed improvements with regard to efficacy were not confounded by these factors. The unique spectrum of adverse events that are associated with immune checkpoint blockade does necessitate supplementary monitoring and treatment practices beyond those that are required for chemotherapy.²⁸ The trial showed activity for the combination of atezolizumab and nab-paclitaxel in patients with metastatic triple-negative breast cancer; it remains to be determined whether these findings extend to other chemoimmunotherapy combinations. Previous data have shown that tumor-infiltrating lymphocytes were associated with clinical benefit in patients with triple-negative breast cancer.^{15,29–31} Similarly, improved clinical benefit was observed in patients with immune-enriched molecular subtypes of metastatic triple-negative breast cancer.³²

A benefit with atezolizumab–nab-paclitaxel in patients with PD-L1–positive tumors that was shown in our trial provides evidence of the efficacy of immunotherapy in at least a subset of patients. It is important for patients’ PD-L1 expression status on tumor-infiltrating immune cells to be taken into consideration to inform treatment choices for patients with metastatic triple-negative breast cancer.

NOTES

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SUPPLEMENTARY MATERIAL

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REFERENCES

1.

den Brok WD, Speers CH, Gondara L, Baxter E, Tyldesley SK, Lohrisch CA. Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. *Breast Cancer Res Treat* 2017;161:549-556.

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2.

Bonotto M, Gerratana L, Poletto E, et al. Measures of outcome in metastatic breast cancer: insights from a real-world scenario. *Oncologist* 2014;19:608-615.

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3.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology — breast cancer. V1. 2018 (https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf).

[↶ Go to Citation](#) [Google Scholar](#)

4.

Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for advanced breast cancer (ABC 4). *Ann Oncol* 2018;29:1634-1657.

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5.

Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26:Suppl 5:v8-v30.

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La FDA aprueba atezolizumab para el cáncer de mama triple negativo metastásico o localmente avanzado irresecable positivo para PD-L1

El 8 de marzo de 2019, la Administración de Alimentos y Medicamentos otorgó la aprobación acelerada a atezolizumab (TECENTRIQ, Genentech Inc.) en combinación con paclitaxel unido a proteínas para pacientes adultos con cáncer de mama triple negativo (TNBC) localmente avanzado o metastásico irresecable cuyos tumores expresan PD-L1 (células inmunitarias infiltrantes de tumores [IC] teñidas con PD-L1 de cualquier intensidad que cubra $\geq 1\%$ del área del tumor), según lo determinado mediante una prueba aprobada por la FDA.

La FDA también aprobó el ensayo VENTANA PD-L1 (SP142) como dispositivo de diagnóstico complementario para seleccionar pacientes con TNBC para atezolizumab.

La aprobación se basó en IMpassion130 (NCT02425891), un ensayo aleatorizado, multicéntrico, internacional, doble ciego, controlado con placebo que incluyó a 902 pacientes con TNBC localmente avanzado o metastásico irresecable que no habían recibido quimioterapia previa para la enfermedad metastásica. Los pacientes fueron aleatorizados (1:1) para recibir infusiones intravenosas de atezolizumab (840 mg) o placebo los días 1 y 15 de cada ciclo de 28 días, más paclitaxel unido a proteínas (100 mg/m²) administrado mediante infusión intravenosa los días 1, 8 y 15 de cada ciclo de 28 días.

Las muestras de tumores (de archivo o frescas) se evaluaron prospectivamente utilizando el ensayo VENTANA PD-L1 (SP142) en un laboratorio central y los resultados se utilizaron como factor de estratificación para la aleatorización y para definir la población positiva para PD-L1 para análisis preespecificados.

En pacientes cuyos tumores expresan PD-L1, la mediana de supervivencia libre de progresión (SSP) fue de 7,4 meses (6,6, 9,2) para los pacientes que recibieron atezolizumab con paclitaxel unido a proteína y de 4,8 meses (3,8, 5,5) para aquellos que recibieron placebo con paclitaxel unido a proteína. El índice de riesgo estratificado para la SSP fue de 0,60 (IC del 95 %: 0,48; 0,77; $p < 0,0001$) a favor del brazo de atezolizumab más paclitaxel unido a proteína. La tasa de respuesta objetiva (TRO) en

pacientes con respuestas confirmadas fue del 53 % en comparación con el 33 % para los brazos de atezolizumab y placebo, respectivamente. Los datos de supervivencia general eran inmaduros, con un 43% de muertes en la población por intención de tratar (ITT).

Las reacciones adversas más comunes (informadas en ≥ 20 % de los pacientes) con atezolizumab con paclitaxel unido a proteínas fueron alopecia, neuropatías periféricas, fatiga, náuseas, diarrea, anemia, estreñimiento, tos, dolor de cabeza, neutropenia, vómitos y disminución del apetito.

Esta indicación está aprobada bajo aprobación acelerada basada en la supervivencia libre de progresión. La aprobación continua de esta indicación puede depender de la verificación y descripción del beneficio clínico en uno o más ensayos confirmatorios.

La dosis recomendada de atezolizumab para pacientes con TNBC cuyos tumores expresan PD-L1 es de 840 mg administrados como infusión intravenosa durante 60 minutos, seguidos de 100 mg/m² de paclitaxel unido a proteína. Para cada ciclo de 28 días, se administra atezolizumab los días 1 y 15, y paclitaxel unido a proteínas los días 1, 8 y 15 hasta la progresión de la enfermedad o una toxicidad inaceptable.

Vea la información de prescripción completa de TECENTRIQ

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761034s018lbl.pdf).

La FDA otorgó a esta solicitud una revisión prioritaria. Una descripción de los programas acelerados de la FDA se encuentra en la Guía para la industria: Programas acelerados para afecciones graves: medicamentos y productos biológicos. ([regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics)).

Los profesionales de la salud deben informar todos los eventos adversos graves que se sospeche que están asociados con el uso de cualquier medicamento y dispositivo al Sistema de informes MedWatch

(<https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>) de la FDA o llamando al 1-800-FDA-1088.

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Consulte las aprobaciones recientes en el podcast de la OCE, Drug Information Soundcast in Clinical Oncology

(<http://www.fda.gov/DISCO>) (DISCO).

viernes, 8 de marzo de 2019

La FDA concede la aprobación acelerada de Tecentriq de Genentech en combinación con Abraxane para personas con cáncer de mama metastásico triple negativo y PD-L1 positivo

Esta combinación de Tecentriq es el primer régimen de inmunoterapia contra el cáncer aprobado para el cáncer de mama

El cáncer de mama triple negativo es una enfermedad agresiva, con una gran necesidad médica insatisfecha

Sur de San Francisco, CA – 8 de marzo de 2019 –

Genentech, miembro del Grupo Roche (SIX: RO, ROG; OTCQX: RHHBY), anunció hoy que la Administración de Alimentos y Medicamentos de EE. UU. (FDA) ha concedido la aprobación acelerada a Tecentriq[®] (atezolizumab) más quimioterapia (Abraxane[®] [proteína paclitaxel- partículas unidas para suspensión inyectable (unidas a albúmina); *nab*- paclitaxel]) para el tratamiento de adultos con cáncer de mama triple negativo (TNBC) localmente avanzado o metastásico irresecable en personas cuyos tumores expresan PD-L1, según lo determinado por un estudio de la FDA. prueba aprobada. Esta indicación está aprobada bajo aprobación acelerada basada en la supervivencia libre de progresión (SSP). La aprobación continua de esta indicación puede depender de la verificación y descripción del beneficio clínico en uno o más ensayos confirmatorios. El Programa de Aprobación Acelerada de la FDA permite la aprobación condicional de un medicamento que satisface una necesidad médica no cubierta para una enfermedad o afección grave o potencialmente mortal.

"La aprobación de la FDA de esta combinación de Tecentriq es un avance importante en el tratamiento de las personas con cáncer de mama triple negativo metastásico PD-L1 positivo, una enfermedad con una gran necesidad médica no cubierta", dijo Sandra Horning, MD, directora médica y jefa de Desarrollo de productos globales. "Esta combinación de Tecentriq es el primer régimen de inmunoterapia contra el cáncer aprobado para el cáncer de mama, lo que representa un importante paso adelante en la comprensión de esta enfermedad".

"El régimen Tecentriq es una nueva e interesante opción de tratamiento para determinadas personas que viven con cáncer de mama metastásico triple negativo, una forma de la enfermedad difícil de tratar", afirmó Hayley Dinerman, directora ejecutiva de la Triple Negative Breast Cancer Foundation. "La quimioterapia sola ha sido la base del tratamiento durante muchos años, por lo que es alentador tener ahora una combinación de inmunoterapia disponible para personas con enfermedad PD-L1 positiva".

Esta aprobación acelerada se basa en datos del estudio de fase III IMpassion130, que demostró que Tecentriq más *nabpaclitaxel* redujo significativamente el riesgo de empeoramiento de la enfermedad o muerte (SSP) en un 40 por ciento en comparación con *nabpaclitaxel* solo (mediana de SLP = 7,4 frente a 7,4). 4,8 meses; HR=0,60, IC 95%: 0,48-0,77, $p<0,0001$) en pacientes PD-L1 positivos con TNBC irresecable localmente avanzado o metastásico que no habían recibido quimioterapia previa para la enfermedad metastásica. Los resultados de supervivencia general (SG) fueron inmaduros con un 43 por ciento de eventos en todos los pacientes aleatorizados (intención de tratar; ITT), y se compartirán más datos con la FDA y se presentarán en una próxima reunión médica.

La seguridad en el grupo de Tecentriq más *nab*- paclitaxel pareció consistente con los perfiles de seguridad conocidos de los medicamentos individuales, y no se identificaron nuevas señales de seguridad con la combinación. Los efectos secundarios de grado 3-4 más comunes (≥ 2 por ciento) con Tecentriq más *nab*- paclitaxel fueron niveles bajos de glóbulos blancos, hormigueo o entumecimiento en manos y pies, disminución del recuento de neutrófilos, sensación de cansancio, niveles bajos de glóbulos rojos, niveles bajos de potasio en sangre. nivel, neumonía y aumento del nivel sanguíneo de una enzima hepática (AST). Los efectos secundarios más comunes (≥ 20 por ciento) fueron pérdida de cabello, sensación de cansancio, hormigueo o entumecimiento en las manos y los pies, náuseas, diarrea, niveles bajos de glóbulos rojos, estreñimiento, tos, dolor de cabeza, niveles bajos de glóbulos blancos, disminución del apetito y vómitos. .

Para aquellos que califican, Genentech ofrece programas de asistencia al paciente para personas a las que su médico les recetó Tecentriq a través de Genentech Access Solutions. Comuníquese con Genentech Access Solutions al (866) 422-2377 o visite <http://www.Genentech-Access.com/Tecentriq> para obtener más información.

e el estudio IMpassion130

El estudio IMpassion130 es un estudio de fase III, multicéntrico, aleatorizado y doble ciego que evalúa la eficacia, seguridad y farmacocinética de Tecentriq más *nab*- paclitaxel en comparación con placebo más *nab*- paclitaxel en personas con TNBC localmente avanzado o metastásico irresecable que no han recibido tratamiento previo. Terapia sistémica para el cáncer de mama metastásico. En el estudio participaron 902 personas que fueron asignadas al azar por igual (1:1). Los criterios de valoración coprimarios son la SSP según la evaluación del investigador (RECIST 1.1) en la población ITT y en la población PD-L1 positiva y la SG en la población ITT. Los resultados de OS fueron inmaduros en la población ITT. Los criterios de valoración secundarios incluyen la tasa de respuesta objetiva y la duración de la respuesta.

Sobre el cáncer de mama triple negativo

Breast cancer is the most common cancer among women worldwide. According to the American Cancer Society, approximately 271,000 people in the United States will be diagnosed with breast cancer, and more than 42,000 will die from the disease in 2019. Breast cancer is not one, but many diseases based on the biology of each tumor. In triple-negative breast cancer, tumor cells lack hormone receptors and do not have excess HER2 protein. Approximately 15 percent of breast cancers are triple-negative based on the results of diagnostic tests. It is an aggressive form of the disease with few treatment options.

About Tecentriq

Tecentriq is a monoclonal antibody designed to bind with a protein called PD-L1 expressed on tumor cells and tumor-infiltrating immune cells, blocking its interactions with both PD-1 and B7.1 receptors. By inhibiting PD-L1, Tecentriq may enable the re-activation of T cells. Tecentriq may also affect normal cells.

Abraxane is a registered trademark of Abraxis Bioscience, LLC, a wholly owned subsidiary of Celgene Corporation.

Tecentriq U.S. Indication (pronounced 'tē-SEN-trik')

Tecentriq is a prescription medicine used to treat adults with:

type of breast cancer called triple-negative breast cancer (TNBC).

Tecentriq may be used with the medicine paclitaxel protein-bound when your breast cancer:

- has spread or cannot be removed by surgery, **and**
- your cancer tests positive for “PD-L1.”

The approval of Tecentriq in these patients is based on a study that measured progression-free survival. There is an ongoing study to confirm clinical benefit.

It is not known if Tecentriq is safe and effective in children.

Important Safety Information

What is the most important information about Tecentriq?

Tecentriq can cause the immune system to attack normal organs and tissues and can affect the way they work. These problems can sometimes become serious or life threatening and can lead to death.

Patients should call or see their healthcare provider right away if they get any symptoms of the following problems or these symptoms get worse.

Tecentriq can cause serious side effects, including:



- **Lung problems (pneumonitis)** –signs and symptoms of pneumonitis may include new or worsening cough, shortness of breath, and chest pain
- **Liver problems (hepatitis)** –signs and symptoms of hepatitis may include yellowing of the skin or the whites of the eyes, severe nausea or vomiting, pain on the right side of the stomach area (abdomen), drowsiness, dark urine (tea colored), bleeding or bruising more easily than normal, and feeling less hungry than usual
- **Intestinal problems (colitis)** –signs and symptoms of colitis may include diarrhea (loose stools) or more bowel movements than usual, blood or mucus in stools or dark, tarry, sticky stools, and severe stomach area (abdomen) pain or tenderness
- **Hormone gland problems (especially the thyroid, adrenal glands, pancreas, and pituitary)** –signs and symptoms that the hormone glands are not working properly may include headaches that will not go away or unusual headaches, extreme tiredness, weight gain or weight loss, dizziness or fainting, feeling more hungry or thirsty than usual, hair loss, changes in mood or behavior (such as decreased sex drive, irritability, or forgetfulness), feeling cold, constipation, the voice gets deeper, urinating more often than usual, nausea or vomiting, and stomach area (abdomen) pain
- **Problems in other organs** –signs and symptoms may include severe muscle weakness, numbness or tingling in hands or feet, confusion, blurry vision, double vision, or other vision problems, changes in mood or behavior, extreme sensitivity to light, neck stiffness, eye pain or redness, skin blisters or peeling, chest pain, irregular heartbeat, shortness of breath, or swelling of the ankles
- **Severe infections** –signs and symptoms of infection may include fever, cough, flu-like symptoms, pain when urinating, and frequent urination or back pain
- **Severe infusion reactions** –signs and symptoms of infusion reactions may include chills or shaking, itching or rash, flushing, shortness of breath or wheezing, swelling of the face or lips, dizziness, fever, feeling like passing out, and back or neck pain

Getting medical treatment right away may help keep these problems from becoming more serious. A healthcare provider may treat patients with corticosteroid or hormone replacement medicines. A healthcare provider may delay or completely stop treatment with Tecentriq if patients have severe side effects.

Before receiving Tecentriq, patients should tell their healthcare provider about all of their medical conditions, including if they:

- have immune system problems (such as Crohn's disease, ulcerative colitis, or lupus); have had an organ transplant; have lung or breathing problems; have liver problems; have a condition that affects the nervous system (such as myasthenia gravis or Guillain-Barre syndrome); or are being treated for an infection
- are pregnant or plan to become pregnant. Tecentriq can harm an unborn baby. Patients should tell their healthcare provider right away if they become pregnant or think they may be pregnant during treatment with Tecentriq. **Females who are able to become pregnant:**
 - A healthcare provider should do a pregnancy test before they start treatment with Tecentriq.
 - They should use an effective method of birth control during their treatment and for at least 5 months after the last dose of Tecentriq.
- are breastfeeding or plan to breastfeed. It is not known if Tecentriq passes into the breast milk. Patients should not breastfeed during treatment and for at least 5 months after the last dose of Tecentriq.

Los pacientes deben informar a su proveedor de atención médica sobre todos los medicamentos que toman, incluidos los medicamentos recetados y de venta libre, vitaminas y suplementos a base de hierbas.

Los efectos secundarios más comunes de Tecentriq cuando se usa con paclitaxel unido a proteínas incluyen:



- pérdida de cabello
- sensación de cansancio
- hormigueo o entumecimiento en manos y pies
- náuseas
- diarrea
- niveles bajos de glóbulos rojos (anemia)
- constipación
- tos
- dolor de cabeza
- glóbulos blancos bajos
- disminución del apetito
- vómitos

Tecentriq puede causar problemas de fertilidad en las mujeres, lo que puede afectar la capacidad de tener hijos. Los pacientes deben hablar con su proveedor de atención médica si tienen dudas sobre la fertilidad.

Estos no son todos los posibles efectos secundarios de Tecentriq. Los pacientes deben pedir más información a su proveedor de atención médica o farmacéutico. Los pacientes deben llamar a su médico para recibir asesoramiento médico sobre los efectos secundarios.

Informe los efectos secundarios a la FDA al (800) FDA-1088 o <http://www.fda.gov/medwatch> . Informe los efectos secundarios a Genentech al (888) 835-2555.



Visite <http://www.Tecentriq.com> para obtener la información de prescripción completa de Tecentriq para obtener información de seguridad importante adicional.

Acerca de Genentech en cáncer de mama

Genentech ha estado avanzando en la investigación del cáncer de mama durante más de 30 años con el objetivo de ayudar a la mayor cantidad posible de personas con esta enfermedad. Nuestros medicamentos, junto con las pruebas de diagnóstico complementarias, han mejorado sustancialmente los resultados del cáncer de mama HER2 positivo. A medida que nuestra comprensión de la biología del cáncer de mama mejora rápidamente, estamos trabajando para identificar nuevos biomarcadores y enfoques de tratamiento para otros subtipos de la enfermedad, incluidos los triple negativos y los receptores hormonales positivos.

Acerca de Genentech en inmunoterapia personalizada contra el cáncer

Durante más de 30 años, Genentech ha estado desarrollando medicamentos con el objetivo de redefinir el tratamiento en oncología. Hoy, estamos invirtiendo más que nunca para llevar la inmunoterapia personalizada contra el cáncer (PCI) a las personas con cáncer. El objetivo de PCI es brindar a cada persona un tratamiento personalizado para aprovechar su propio sistema inmunológico para combatir el cáncer. Genentech está estudiando más de 20 medicamentos en investigación, 10 de los cuales se encuentran en ensayos clínicos. En cada estudio evaluamos biomarcadores para identificar qué personas pueden ser candidatas apropiadas para nuestros medicamentos. Para obtener más información, visite <http://www.gene.com/cancer-immunotherapy>.

Acerca de Genentech

Fundada hace más de 40 años, Genentech es una empresa líder en biotecnología que descubre, desarrolla, fabrica y comercializa medicamentos para tratar a pacientes con afecciones médicas graves y potencialmente mortales. La empresa, miembro del Grupo Roche, tiene su sede en el sur de San Francisco, California. Para obtener información adicional sobre la empresa, visite <http://www.gene.com>.

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