VOLUME 36 · NUMBER 9 · MARCH 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Enzalutamide for the Treatment of Androgen Receptor–Expressing Triple-Negative Breast Cancer

Tiffany A. Traina, Kathy Miller, Denise A. Yardley, Janice Eakle, Lee S. Schwartzberg, Joyce O'Shaughnessy, William Gradishar, Peter Schmid, Eric Winer, Catherine Kelly, Rita Nanda, Ayca Gucalp, Ahmad Awada, Laura Garcia-Estevez, Maureen E. Trudeau, Joyce Steinberg, Hirdesh Uppal, Iulia Cristina Tudor, Amy Peterson, and Javier Cortes

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on January 26, 2018.

Clinical trial information: NCT01889238.

Corresponding author: Tiffany A. Traina, MD, Memorial Sloan-Kettering Cancer Center and Weill Medical College of Cornell University, Evelyn H. Lauder Breast and Imaging Center, 300 East 66th St, New York, NY 10065; e-mail: trainat@mskcc.org.

0732-183X/18/3609w-884w/$20.00

ABSTRACT

Purpose
Studies suggest that a subset of patients with triple-negative breast cancer (TNBC) have tumors that express the androgen receptor (AR) and may benefit from an AR inhibitor. This phase II study evaluated the antitumor activity and safety of enzalutamide in patients with locally advanced or metastatic AR-positive TNBC.

Patients and Methods
Tumors were tested for AR with an immunohistochemistry assay optimized for breast cancer; nuclear AR staining > 0% was considered positive. Patients received enzalutamide 160 mg once per day until disease progression. The primary end point was clinical benefit rate (CBR) at 16 weeks. Secondary end points included CBR at 24 weeks, progression-free survival, and safety. End points were analyzed in all enrolled patients (the intent-to-treat [ITT] population) and in patients with one or more postbaseline assessment whose tumor expressed ≥ 10% nuclear AR (the evaluable subgroup).

Results
Of 118 patients enrolled, 78 were evaluable. CBR at 16 weeks was 25% (95% CI, 17% to 33%) in the ITT population and 33% (95% CI, 23% to 45%) in the evaluable subgroup. Median progression-free survival was 2.9 months (95% CI, 1.9 to 3.7 months) in the ITT population and 3.3 months (95% CI, 1.9 to 4.1 months) in the evaluable subgroup. Median overall survival was 12.7 months (95% CI, 8.5 months to not yet reached) in the ITT population and 17.6 months (95% CI, 11.6 months to not yet reached) in the evaluable subgroup. Fatigue was the only treatment-related grade 3 or higher adverse event with an incidence of > 2%.

Conclusion
Enzalutamide demonstrated clinical activity and was well tolerated in patients with advanced AR-positive TNBC. Adverse events related to enzalutamide were consistent with its known safety profile. This study supports additional development of enzalutamide in advanced TNBC.

J Clin Oncol 36:884-890. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Triple-negative breast cancer (TNBC) carries the worst prognosis among all breast cancer subtypes, with a median overall survival (OS) rarely extending beyond 12 to 18 months in advanced disease.[1-5] TNBC is a heterogeneous subgroup defined by a lack of expression of targetable receptors and can be subtyped further using genomic analyses. One subtype seems to be hormonally regulated, clustering closer to estrogen receptor (ER)–positive/progesterone receptor (PgR)–positive disease, despite lacking expression of these receptors.[6-8] Growth of this subtype is thought to be driven by signaling through the androgen receptor (AR).[8-12] AR-expressing TNBC cell lines and in vivo models have demonstrated growth activation by AR stimulation and decreased growth by AR antagonists.[6-8,13-16] Therefore, blocking the androgen signaling pathway with targeted agents may have therapeutic benefit in this subset of TNBC. Antitumor activity was observed in clinical trials of two AR inhibitors, bicalutamide and abiraterone acetate, supporting additional exploration of AR inhibition to treat advanced TNBC.[17,18]

Enzalutamide is a potent AR inhibitor that acts on multiple steps in the AR signaling pathway

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2016.71.3495

Data Supplement
DOI: https://doi.org/10.1200/JCO.2016.71.3495

DOI: https://doi.org/10.1200/JCO.2016.71.3495

and is currently approved for the treatment of patients with metastatic castration-resistant prostate cancer in > 50 countries in the chemotherapy-naïve setting and > 75 countries in the postchemotherapy setting[19] on the basis of significant survival advantages demonstrated in two large, randomized, placebo-controlled, phase III studies.[20,21] Here, we present the results of a phase II trial of enzalutamide in patients with TNBC whose tumors tested positive for AR expression by immunohistochemistry (IHC).

PATIENTS AND METHODS

Study Design

MDV3100-11 was a single-arm, open-label, phase II trial to evaluate the efficacy and safety of enzalutamide in patients with locally advanced or metastatic TNBC (ClinicalTrials.gov identifier: NCT01889238). The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent before any study-related procedures.

Patients

Eligible patients were 18 years of age or older with an Eastern Cooperative Oncology Group performance status of 0 to 1 and with locally advanced or metastatic AR-positive TNBC (defined as < 1% staining for ER and PgR and, for human epidermal growth factor receptor 2, 0 or 1+ by IHC staining or negative by in situ hybridization). Patients with ER-positive and/or PgR-positive primary tumors were eligible if they had advanced TNBC. Sufficient tissue from primary tumors or a recent core needle or incisional biopsy from a metastatic lesion to yield a definitive diagnosis of TNBC was required for central assessment of AR and exploratory biomarker development. IHC results were reported either as AR positive (> 0%) or AR negative (0%). Bone-only evaluable disease was allowed. Patients could have had any number of prior therapies for advanced disease. All patients had adequate end-organ function as defined in the protocol. Patients with CNS metastases, a history of seizure, significant cardiovascular disease, or laboratory abnormalities were not eligible.

Study Methods

Submission of tumor tissue for AR screening was allowed at any time in a patient's disease course and before treatment consent. IHC assays using two AR antibodies, AR441 (Dako, Carpinteria, CA) and SP107 (Ventana, Tucson, AZ), were optimized for testing breast cancer tissue.[22] IHC results using SP107 determined eligibility and were used to report study-related outcomes. Investigators were informed only that a patient was AR positive or negative. If available, RNA and DNA were extracted from remaining tumor tissue from all enrolled and treated patients and also from a subset of patients who submitted tissue through prescreening but did not receive enzalutamide (some of whom tested AR 0%) to perform next-generation sequencing.

Enrolled patients received enzalutamide 160 mg once per day until disease progression. Response was assessed every 8 weeks for the first 12 months, then every 12 weeks thereafter using standard radiologic methods. Safety was assessed through the collection of treatment-emergent adverse events (AEs; classified using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4), central laboratory tests, and physical examinations. Patients who discontinued enzalutamide for reasons other than disease progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were requested to continue with scheduled imaging assessments until objective progressive disease was documented. Patients were observed for safety and survival status upon study drug discontinuation.

Statistical Analysis and Study End Points

Two populations were prespecified. The intent-to-treat (ITT) population included all enrolled patients. The evaluable subgroup included patients with AR expression of ≥ 10% by IHC, based on the Translational Breast Cancer Research Consortium (TBCRC) 011 study,[17] and one or more postbaseline tumor assessment. The primary end point was clinical benefit rate at 16 weeks (CBR16), defined as confirmed complete response (CR) or partial response or stable disease at study week 16. The sample size was calculated using an optimal Simon two-stage design for the evaluable population. At least three of the first 26 evaluable patients had to achieve CBR16 to proceed to stage 2. If nine or more of 62 evaluable patients achieved CBR16 in the total study, the efficacy threshold would be met. The null hypothesis that the true CBR16 was 8% was tested against a one-sided alternative. This design yielded a one-sided type I error rate of 5% and

Table 1. Baseline Demographic and Clinical Characteristics of Evaluable and ITT Populations

Characteristic	Evaluable Subgroup (n = 78)	Nonevaluable Subgroup (n = 40)	ITT Population (N = 118)
Median age, years (range)	59 (32-85)	52 (36-84)	57 (32-85)
Race			
White	64 (82)	27 (68)	91 (77)
Black or African American	11 (14)	9 (23)	20 (17)
Asian	3 (4)	3 (8)	6 (5)
ECOG PS of 1	34 (44)	15 (38)	49 (42)
Prior neoadjuvant or adjuvant systemic therapy	64 (82)		99 (84)
Median DFI, months (range)	22 (0-253)	24 (0-271)	23 (0-271)
Primary tumor			
ER positive/PgR positive	19 (24)	3 (8)	22 (19)
Triple negative	51 (65)	32 (80)	83 (70)
Visceral disease	49 (63)	25 (63)	74 (63)
Measurable disease	59 (76)	38 (95)	97 (82)
Location of metastatic sites			
Bone	35 (45)	12 (30)	47 (40)
Liver	18 (23)	13 (33)	31 (26)
Lung	37 (47)	19 (48)	56 (47)
Lymph nodes	38 (49)	24 (60)	62 (53)
≥ 3 metastatic sites	49 (63)	30 (75)	79 (67)
Bone-only metastases	10 (13)	3 (8)	13 (11)
No. of prior lines of therapy for advanced BC			
Median (range)	1 (0-5)	2 (0-7)	1 (0-7)
0	17 (22)	5 (13)	22 (19)
1	30 (38)	13 (33)	43 (36)
2	9 (12)	10 (25)	19 (16)
≥ 3	22 (28)	12 (30)	34 (29)
Prior systemic therapies for advanced BC*	63	35	98
Capecitabine	26 (41)	17 (49)	43 (44)
Taxanes	29 (46)	20 (57)	49 (50)
Platinum	25 (40)	16 (46)	41 (42)
Eribulin	11 (17)	8 (23)	19 (19)

NOTE. Data are given as No. (%) except where otherwise noted.
Abbreviations: BC, breast cancer; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ITT, intent to treat; PgR, progesterone receptor.
*Percentages are calculated from the total number of patients who received at least one prior therapy for advanced BC (63 patients in the evaluable subgroup and 98 patients in the ITT population).

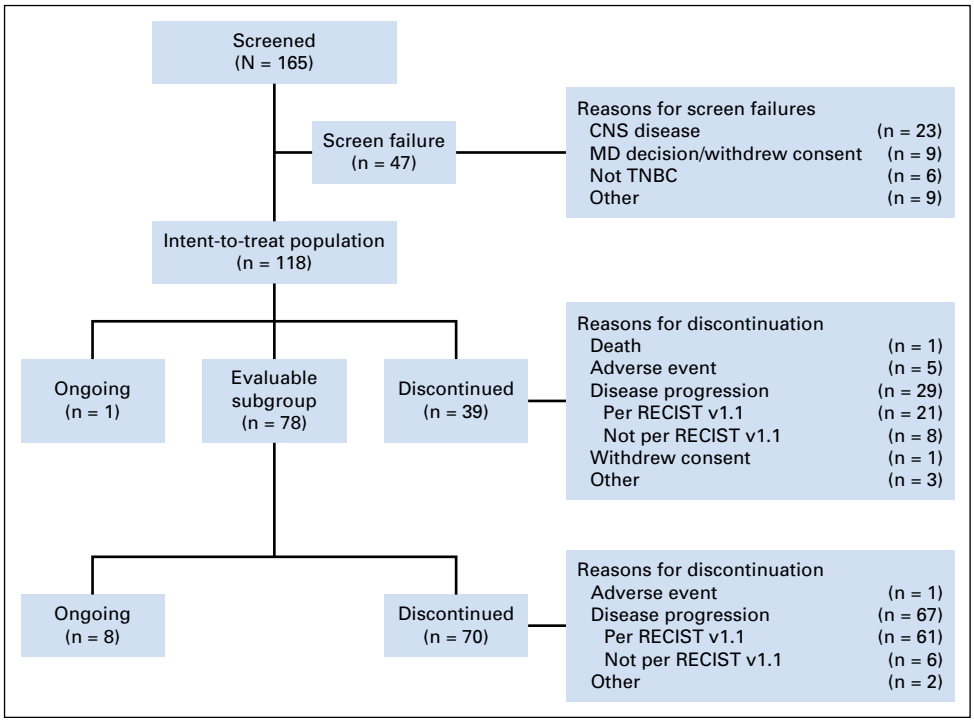

Fig 1. CONSORT diagram. MD, physician; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer.

power of 85% when the true response rate was 20%. Approximately 95 patients were expected to yield 62 evaluable patients.

Estimates of median progression-free survival (PFS) and OS, defined in the Appendix (online only), were determined using the Kaplan-Meier method. CIs were calculated using the Brookmeyer and Crowley method.[23]

RESULTS

Patient and Tumor Characteristics

From June 2013 to July 2014, 404 tumor tissue samples from prescreened patients were submitted. Of these, 368 were suitable for central diagnostic analysis. Nearly 80% of the evaluable samples expressed nuclear AR $>$ 0%, and $>$ 55% of samples had AR of $\geq$ 10%. Of 165 patients screened for study eligibility, 118 patients were enrolled at 45 clinical study sites across seven countries; 78 patients met the criteria for the evaluable subgroup. The data cutoff date for the primary analysis was September 15, 2015. An updated analysis of OS was performed with a data cutoff date of March 15, 2017. Patient demographics and clinical characteristics were consistent between the ITT population and evaluable subgroup (Table 1). Most patients (84%) received systemic adjuvant treatment of early-stage breast cancer. The median number of prior therapies received for locally advanced or metastatic TNBC was one (range, zero to seven prior therapies), and prior therapies included taxanes (50%), capecitabine (44%), platinum compounds (42%), and eribulin (19%). Fifty-five percent of patients (n = 65) received enzalutamide as their first regimen (n = 22, 19%) or second regimen (n = 43, 36%) for advanced TNBC. Most patients had visceral disease (63%), whereas 11% of patients had bone-only metastases.

Table 2. Clinical Benefit

Benefit	Evaluable Subgroup (n = 78)	ITT Population (N = 118)
CBR16		
No.	26	29
% (95% CI)	33 (23 to 45)	25 (17 to 33)
CBR24		
No.	22	24
% (95% CI)	28 (19 to 39)	20 (14 to 29)
CR or PR		
No.	6	7
%	8	6

Abbreviations: CBR16, clinical benefit rate at 16 weeks; CBR24, clinical benefit rate at 24 weeks; CR, complete response; ITT, intent-to-treat; PR, partial response.

Treatment

The median duration of enzalutamide treatment was 8.1 weeks (range, 0.9 to 87 weeks) in the ITT population. The most common reason for treatment discontinuation was disease progression. Nine patients were still receiving enzalutamide at the time of the data cutoff date (Fig 1).

Efficacy

Stage 1. In stage 1, 11 (42.3%) of 26 evaluable patients achieved CBR16; therefore, the study proceeded to stage 2.

Stage 2. This study met its primary end point, because among the first 62 evaluable patients enrolled, 24 (38.7%; 95% CI, 27% to 52%) achieved CBR16. Twenty nine (25%; 95% CI, 17% to 33%) of 118 ITT patients and 26 (33%; 95% CI, 23% to 45%) of 78 evaluable patients achieved CBR16; 24 ITT patients (20%; 95% CI, 14% to 29%) and 22 evaluable patients (28%; 95% CI, 19% to

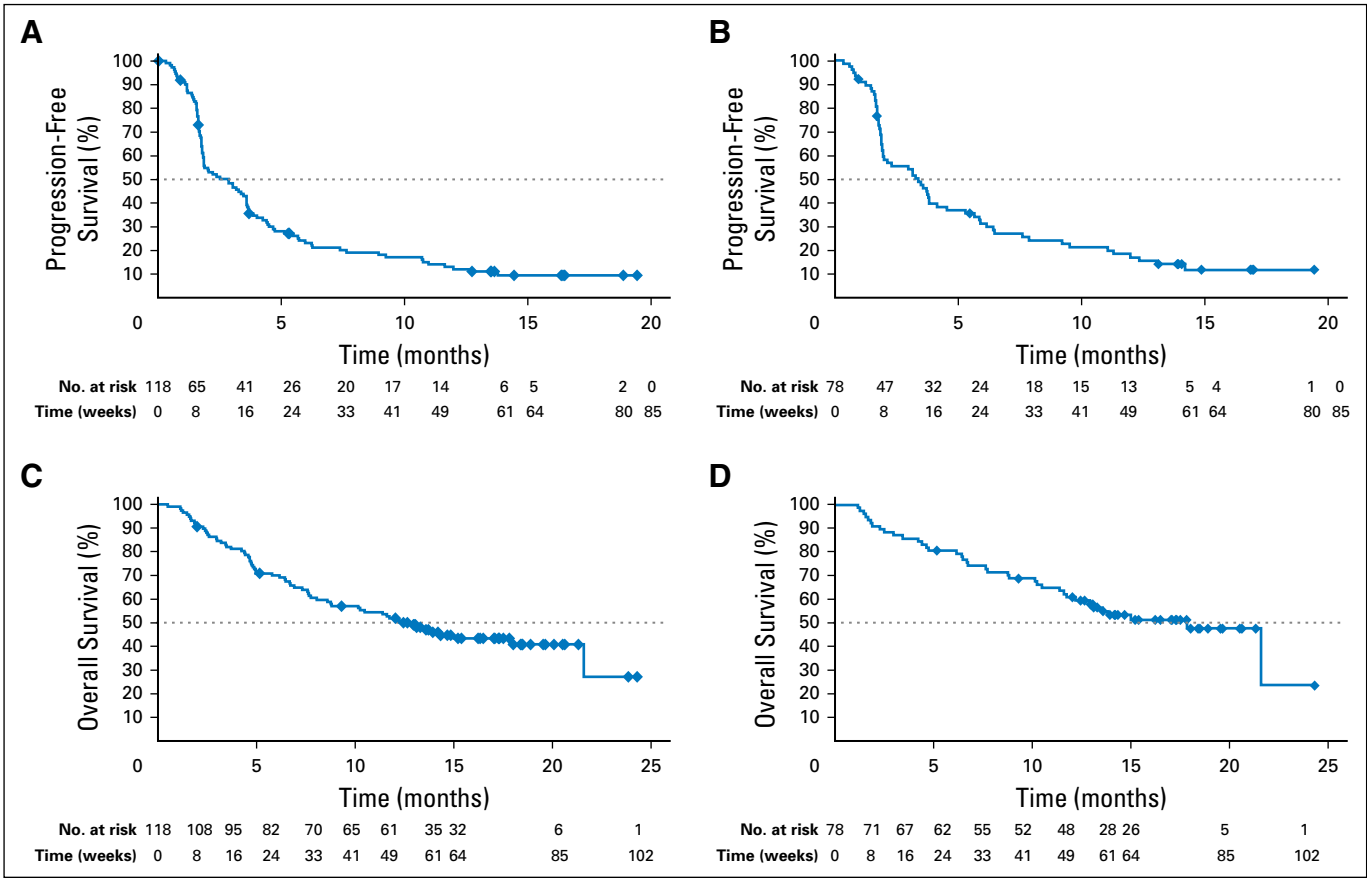

Fig 2. Kaplan-Meier plots of primary analysis of progression-free survival (PFS) in the (A) intent-to-treat (ITT) population and (B) evaluable subgroup and of overall survival (OS) in the (C) ITT population and (D) evaluable subgroup.

39%) achieved clinical benefit rate at 24 weeks (CBR24; Table 2). In the evaluable subgroup, one patient with a metastatic lung lesion achieved a confirmed CR, and five patients achieved a confirmed partial response. One additional confirmed CR was reported in the ITT population. Median PFS was 2.9 months (95% CI, 1.9 to 3.7 months) in the ITT population (Fig 2A) and 3.3 months (95% CI, 1.9 to 4.1 months) in the evaluable subgroup (Fig 2B). Median OS was 12.7 months (95% CI, 8.5 months to not yet reached) in the ITT population (Fig 2C) and 17.6 months (95% CI, 11.6 months to not yet reached) in the evaluable subgroup (Fig 2D).

An updated analysis of OS was performed after an additional 18 months of follow-up. Median OS was 12.7 months (95% CI, 8.5 to 16.5 months) in the ITT population (Fig 3A) and 16.5 months (95% CI, 12.7 to 20.0 months) in the evaluable subgroup (Fig 3B).

Safety

AEs of any grade or relationship occurring in ≥ 10% of patients are listed in Table 3. Eight patients discontinued treatment as a result of an AE. Events included headache, muscular weakness, anxiety, pleural effusion, back pain, metastatic pain, general physical deterioration, and CNS metastases. The only treatment-related grade 3 or greater AE occurring in ≥ 2% of patients was fatigue (3.4%). Serious AEs were reported in 25% of patients and were generally the consequence of progressive metastatic breast cancer; none were considered related to enzalutamide. Twelve patients had grade 5 AEs; 11 of these were deemed consequences of disease progression. One patient, a 62-year-old woman with a history of tobacco use and hypercholesterolemia, experienced a fatal cardiorespiratory arrest after stent implantation for a myocardial infarction.

DISCUSSION

This positive phase II study represents the largest prospective trial of an AR-targeted treatment of advanced TNBC. It met its primary objective, demonstrating enzalutamide's clinical activity in patients with AR-positive TNBC.

In this study, AR expression > 0% was observed in 80% of tumors and AR expression ≥ 10% was observed in 55% of tumors. Two other prospective clinical studies of AR inhibitors have been recently published.[17,18] The TBCRC 011 trial, evaluating bicalutamide, and the French Breast Cancer Intergroup (UCBG) 12-1 trial, evaluating abiraterone acetate, enrolled patients whose TNBC had AR expression of ≥ 10%; these studies reported AR expression > 10% (using AR441) in 12% and 38% of patients, respectively.[17,18] AR IHC assays have been largely developed for prostate cancer that expresses high amounts of AR with little to no dynamic range of AR expression.

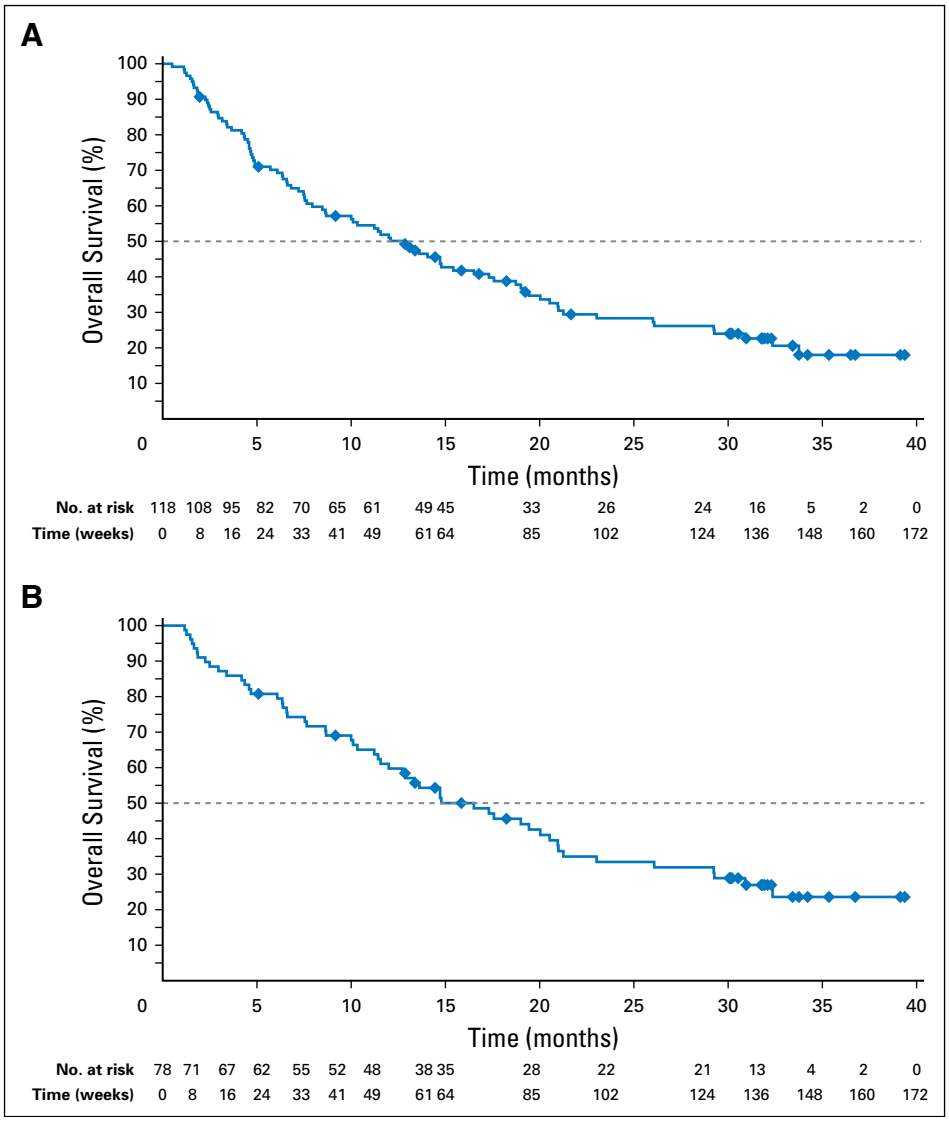

Fig 3. Kaplan-Meier plots of updated overall survival in the (A) intent-to-treat population and (B) evaluable subgroup.

Optimization of the IHC assays in this study was intended to lead to increased sensitivity and a potential for a higher prevalence of AR expression. The similar distribution pattern of AR IHC results between the tissue bank of screened samples and the ITT population support the consistency of these results (Appendix Fig A1, online only). However, the performance characteristics of IHC as a treatment-associated and potentially predictive assay were suboptimal. With a threshold of $\geq$ 10% nuclear expression, the positive predictive value of AR IHC was a modest 30%, which may restrict its clinical application.[22] This is a critical consideration in the development of a treatment-associated assay, because one would not want to exclude patients from receiving a potentially beneficial and well-tolerated treatment.

The CBR24 was 19% (95% CI, 7% to 39%) in TBCRC 011 and 20% (95% CI, 8% to 39%) in UCBG 12-1.[17,24] In our study of enzalutamide, CBR24 in a similarly defined population was slightly higher at 28% (95% CI, 19% to 39%). This could be explained by different mechanisms of action between agents. Unlike bicalutamide, enzalutamide has no known AR agonist activity and was superior to bicalutamide in two large randomized phase II studies in patients with prostate cancer.[25,26] Prednisone, a requisite concomitant medication for abiraterone acetate, stimulates the glucocorticoid receptor, which is expressed in approximately 25% of TNBCs. It is possible that glucocorticoid receptor stimulation from prednisone results in tumor growth, limiting the efficacy of abiraterone acetate. Furthermore, abiraterone acetate treatment results in appreciable increases in progesterone, potentially stimulating the PgR, albeit at low levels given in TNBC.

More than half of the enrolled patients received enzalutamide as their first or second treatment of metastatic disease, highlighting the interest and need for novel, well-tolerated therapies in earlier treatment settings.

TNBC has the poorest outcomes of the three major subtypes of breast cancer.[3,4,27-31] Attempts to treat TNBC with targeted agents have been met with little success. Modest or no improvements in PFS and OS highlight the high-risk nature of TNBC, as well as the difficulty in identifying relevant targets and effective therapies.[4,32-35] Data from this phase II study in a group of patients

Table 3. Summary of AEs Occurring in > 10% of Patients

AE	Any-Grade AEs in ≥ 10% of Patients		Grade ≥ 3 AEs	
	All AEs	Related AEs	All AEs	Related AEs
Any AE	92	72	31	10
Any serious AE	25	0	21	0
Fatigue	42	36	5	3
Nausea	33	25	1	0
Decreased appetite	19	13	0	0
Constipation	17	8	1	1
Diarrhea	15	10	0	0
Insomnia	14	6	0	0
Headache	14	8	0	0
Back pain	13	2	1	1
Arthralgia	13	8	0	0
Dyspnea	11	4	3	1
Hot flush	10	10	0	0

NOTE. Data are given as percentage of patients.
Abbreviation: AE, adverse event.

with AR-positive TNBC support and build upon the findings from others that there seems to exist a subset of patients with androgen-driven TNBC who may benefit from an AR-targeted agent.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Tiffany A. Traina, Joyce O'Shaughnessy, Eric Winer, Rita Nanda, Ayca Gucalp, Maureen E. Trudeau, Joyce Steinberg, Amy Peterson, Javier Cortes
Provision of study materials or patients: Tiffany A. Traina, Kathy Miller, Denise A. Yardley, Catherine Kelly, Rita Nanda, Maureen E. Trudeau, Javier Cortes
Collection and assembly of data: Tiffany A. Traina, Kathy Miller, Janice Eakle, Catherine Kelly, Rita Nanda, Ayca Gucalp, Ahmad Awada, Hirdesh Uppal, Iulia Cristina Tudor, Amy Peterson
Data analysis and interpretation: Tiffany A. Traina, Denise A. Yardley, Lee S. Schwartzberg, William Gradishar, Peter Schmid, Rita Nanda, Ahmad Awada, Laura Garcia-Estevez, Maureen E. Trudeau, Joyce Steinberg, Hirdesh Uppal, Iulia Cristina Tudor, Amy Peterson, Javier Cortes
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Kast K, Link T, Friedrich K, et al: Impact of breast cancer subtypes and patterns of metastasis on outcome. Breast Cancer Res Treat 150:621-629, 2015
2. Chacón RD, Costanzo MV: Triple-negative breast cancer. Breast Cancer Res 12:S3, 2010 (suppl 2)
3. Thomas ES, Gomez HL, Li RK, et al: Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol 25:5210-5217, 2007
4. von Minckwitz G, Puglisi F, Cortes J, et al: Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): An open-label, randomised phase 3 trial. Lancet Oncol 15: 1269-1278, 2014
5. Gerratana L, Fanotto V, Bonotto M, et al: Pattern of metastasis and outcome in patients with breast cancer. Clin Exp Metastasis 32:125-133, 2015
6. Farmer P, Bonnefoi H, Becette V, et al: Identification of molecular apocrine breast tumours by microarray analysis. Oncogene 24:4660-4671, 2005
7. Doane AS, Danso M, Lal P, et al: An estrogen receptor-negative breast cancer subset characterized by a hormonally regulated transcriptional program and response to androgen. Oncogene 25:3994-4008, 2006
8. Lehmann BD, Bauer JA, Chen X, et al: Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 121:2750-2767, 2011
9. Mayer IA, Abramson VG, Lehmann BD, et al: New strategies for triple-negative breast cancer: Deciphering the heterogeneity. Clin Cancer Res 20: 782-790, 2014
10. Rakha EA, Elsheikh SE, Aleskandarany MA, et al: Triple-negative breast cancer: Distinguishing between basal and nonbasal subtypes. Clin Cancer Res 15:2302-2310, 2009
11. Perou CM, Sørlie T, Eisen MB, et al: Molecular portraits of human breast tumours. Nature 406: 747-752, 2000
12. Sørlie T: Molecular portraits of breast cancer: Tumour subtypes as distinct disease entities. Eur J Cancer 40:2667-2675, 2004
13. Collins LC, Cole KS, Marotti JD, et al: Androgen receptor expression in breast cancer in relation to molecular phenotype: Results from the Nurses' Health Study. Mod Pathol 24:924-931, 2011
14. Loibl S, Müller BM, von Minckwitz G, et al: Androgen receptor expression in primary breast cancer and its predictive and prognostic value in patients treated with neoadjuvant chemotherapy. Breast Cancer Res Treat 130:477-487, 2011
15. Cochrane DR, Bernales S, Jacobsen BM, et al: Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. Breast Cancer Res 16:R7, 2014
16. Safarpour D, Pakneshan S, Tavassoli FA: Androgen receptor (AR) expression in 400 breast carcinomas: Is routine AR assessment justified? Am J Cancer Res 4:353-368, 2014
17. Gucalp A, Tolaney S, Isakoff SJ, et al: Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer. Clin Cancer Res 19:5505-5512, 2013
18. Bonnefoi H, Grellety T, Tredan O, et al: A phase II trial of abiraterone acetate plus prednisone in patients with triple-negative androgen receptor positive locally advanced or metastatic breast cancer (UCBG 12-1). Ann Oncol 27:812-818, 2016
19. Astellas Pharma: Xtandi prescribing information. https://www.astellas.us/docs/12A005-ENZ-WPI.PDF
20. Scher HI, Fizazi K, Saad F, et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367:1187-1197, 2012
21. Beer TM, Armstrong AJ, Rathkopf DE, et al: Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371:424-433, 2014
22. Kumar V, Yu J, Phan VT, et al: Androgen receptor immunohistochemistry as a companion diagnostic approach to predict clinical response to enzalutamide in triple-negative breast cancer. JCO Precis Oncol 1:1-19, 2017
23. Brookmeyer R, Browley JJ: A confidence interval for median survival time. Biometrics 38:29-41, 1982
24. O'Shaughnessy J, Campone M, Brain E, et al: Abiraterone acetate, exemestane or the combination in postmenopausal patients with estrogen receptor-positive metastatic breast cancer. Ann Oncol 27: 106-113, 2016
25. Shore ND, Chowdhury S, Villers A, et al: Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): A randomised, double-blind, phase 2 study. Lancet Oncol 17:153-163, 2016
26. Penson DF, Armstrong AJ, Concepcion R, et al: Enzalutamide versus bicalutamide in castration-resistant prostate cancer: The STRIVE trial. J Clin Oncol 34:2098-2106, 2016
27. Twelves C, Cortes J, Vahdat L, et al: Efficacy of eribulin in women with metastatic breast cancer: A pooled analysis of two phase 3 studies. Breast Cancer Res Treat 148:553-561, 2014
28. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357:2666-2676, 2007
29. Brufsky AM, Hurvitz S, Perez E, et al: RIBBON-2: A randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 29:4286-4293, 2011

30. Brufsky A, Valero V, Tiangco B, et al: Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: Subgroup analysis of the RIBBON-2 trial. Breast Cancer Res Treat 133: 1067-1075, 2012

31. Baselga J, Gómez P, Greil R, et al: Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer. J Clin Oncol 31:2586-2592, 2013

32. Carey L, Rugo H, Marcom S: TBCRC 001: EGFR inhibition with cetuximab added to carboplatinum in metastatic TNBC (basal like). J Clin Oncol 26, 2008 (suppl 15; abstr 1009)

33. O'Shaughnessy J, Osborne C, Pippen JE, et al: Iniparib plus chemotherapy in metastatic triple-negative breast cancer. N Engl J Med 364:205-214, 2011

34. O'Shaughnessy JA: Effective management of quality of life in metastatic breast cancer. Clin Adv Hematol Oncol 12:10-12, 2014 (suppl 4)

35. Rodriguez AA, Salazar N, Patel TA, et al: A randomized, parallel-arm, phase II trial to assess the efficacy of preoperative ixabepilone with or without cetuximab in patients with triple-negative breast cancer (TNBC). J Clin Oncol 32, 2014 (suppl; abstr 11333)

Affiliations

Tiffany A. Traina and **Ayca Gucalp**, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY; **Kathy Miller**, Indiana University Simon Cancer Center, Indianapolis, IN; **Denise A. Yardley**, Tennessee Oncology, Nashville; **Lee S. Schwartzberg**, The West Clinic, Memphis, TN; **Janice Eakle**, Florida Cancer Specialists, Fort Myers, FL; **Joyce O'Shaughnessy**, Texas Oncology-Baylor Charles A. Sammons Cancer Center, US Oncology, Dallas, TX; **William Gradishar**, Northwestern University Feinberg School of Medicine; **Rita Nanda**, University of Chicago, Chicago; **Joyce Steinberg**, Astellas Pharma, Northbrook, IL; **Peter Schmid**, Barts Cancer Institute, Queen Mary University London, London, United Kingdom; **Eric Winer**, Dana-Farber Cancer Institute, Boston, MA; **Catherine Kelly**, All Ireland Collaborative Oncology Research Group, Dublin, Ireland; **Ahmad Awada**, Jules Bordet Institute, Université Libre de Bruxelles, Brussels, Belgium; **Laura Garcia-Estevez**, Centro Integral Oncologico Clara Campal, Hospital Madrid Norte-Sanchinarro; **Javier Cortes**, Ramon y Cajal University Hospital, Madrid, and, Vall d'Hebron Institute of Oncology and Baselga Oncological Institute, Barcelona, Spain; **Maureen E. Trudeau**, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; and **Hirdesh Uppal**, **Amy Peterson**, and **Iulia Cristina Tudor**, Medivation, San Francisco, CA.

Support

Supported in part through National Institutes of Health/National Cancer Institute Cancer Center Support Grant No. P30 CA008748 and by Medivation, a Pfizer company, and Astellas Pharma, the codevelopers of enzalutamide.

Prior Presentation

Presented in part at the European Cancer Congress 2015, Vienna Austria, September 25-29, 2015, and at the American Society of Clinical Oncology annual meeting, May 29-June 2, 2015.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Enzalutamide for the Treatment of Androgen Receptor–Expressing Triple-Negative Breast Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Tiffany A. Traina
Consulting or Advisory Role: Genentech, Eisai, Mundipharma, Pfizer, AstraZeneca, Bayer, Immunomedics, Merck, Astellas Medivation, Celgene, Innocrin Pharma, Genomic Health
Research Funding: Astellas Pharma, Eisai, Pfizer, Novartis, Innocrin Pharma, AstraZeneca

Kathy Miller
No relationship to disclose

Denise A. Yardley
Speakers' Bureau: Genentech, Novartis, Eisai

Janice Eakle
No relationship to disclose

Lee S. Schwartzberg
Consulting or Advisory Role: Eisai, Amgen, Bristol-Myers Squibb, Helsinn Therapeutics, Tesaro, Spectrum Pharmaceuticals, Merck
Research Funding: Helsinn Therapeutics

Joyce O'Shaughnessy
Honoraria: AstraZeneca, Eli Lilly, Celgene, Novartis, Pfizer, Genentech, Merck, Seattle Genetics
Consulting or Advisory Role: Novartis, Pfizer, Eli Lilly, AstraZeneca, Celgene, Genentech, Merck
Travel, Accommodations, Expenses: Celgene, Eli Lilly, AstraZeneca, Merck, Seattle Genetics

William Gradishar
No relationship to disclose

Peter Schmid
Honoraria: AstraZeneca, Novartis, Pfizer, Boehringer Ingelheim, Genentech, Eisai
Consulting or Advisory Role: Genentech (I), Novartis, Merck, Celgene, Pfizer, AstraZeneca/MedImmune, Puma Biotechnology
Research Funding: AstraZeneca (Inst), Astellas Pharma (Inst), Medivation (Inst), Oncogenex (Inst), Genentech (Inst)

Eric Winer
Consulting or Advisory Role: Leap Therapeutics, Genentech, Tesaro, Eli Lilly

Catherine Kelly
No relationship to disclose

Rita Nanda
Honoraria: Genentech
Consulting or Advisory Role: Genentech, Merck, Novartis, Puma Biotechnology
Research Funding: Corcept Therapeutics, Celgene, Merck

Ayca Gucalp
Consulting or Advisory Role: Pfizer
Research Funding: Pfizer, Innocrin Pharma, Novartis, Merck

Ahmad Awada
Consulting or Advisory Role: Genentech, Bayer, Novartis

Laura Garcia-Estevez
No relationship to disclose

Maureen E. Trudeau
Stock or Other Ownership: RNA Diagnostics
Consulting or Advisory Role: RNA Diagnostics
Research Funding: Roche Canada (Inst), Novartis (Inst), Pfizer (Inst), Eisai (Inst), AstraZeneca (Inst), Astellas Pharma (Inst)

Joyce Steinberg
Employment: Astellas Pharma

Hirdesh Uppal
Employment: Medivation
Stock or Other Ownership: Medivation

Iulia Cristina Tudor
Employment: Medivation, Pfizer
Stock or Other Ownership: Medivation, Pfizer
Travel, Accommodations, Expenses: Medivation, Pfizer

Amy Peterson
Employment: BeiGene
Leadership: BeiGene
Stock or Other Ownership: BeiGene, Medivation, Agios, Aduro Biotech, Clovis Oncology, Gilead Sciences, Jazz Pharmaceuticals, Johnson & Johnson, Medtronic, Pfizer, Ultragenyx Pharmaceuticals
Patents, Royalties, Other Intellectual Property: Novel biomarker for the treatment of triple-negative breast cancer
Travel, Accommodations, Expenses: BeiGene

Javier Cortes
Honoraria: Roche, Celgene, Eisai, Novartis, Pfizer
Consulting or Advisory Role: Roche, Celgene, AstraZeneca, Cellestia Biotech, Biothera, Merus

Acknowledgment

We thank the investigators, the patients, and their families for their contribution to this clinical study. The authors acknowledge Clifford Hudis for his scientific and clinical support of the trial, as well as all of the investigators and staff who conducted the trial, and Virginia E. Paton from Medivation for her critical review of the article. Medical writing and editorial support funded by study sponsors were provided by Stephanie Vadasz and Paula Stuckart of Infusion Communications.

Appendix

Methods

Progression-free survival, a secondary end point, was defined as the time from the date of the first dose of study drug to the date of disease progression as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or the date of on-study death as a result of any cause, whichever occurred first. Patients who died after receiving the first dose of enzalutamide without postbaseline tumor assessments evaluable using RECIST 1.1 were considered to have a progression-free survival event on the date of death.

Overall survival was an exploratory end point and was defined as the time between the date of the first dose of study drug and the date of death as a result of any cause. For patients alive after the data cutoff date, overall survival was right censored at the last date known alive before the data cutoff. Patients with no postbaseline information were censored at the time of first day of treatment with enzalutamide plus 1 day.

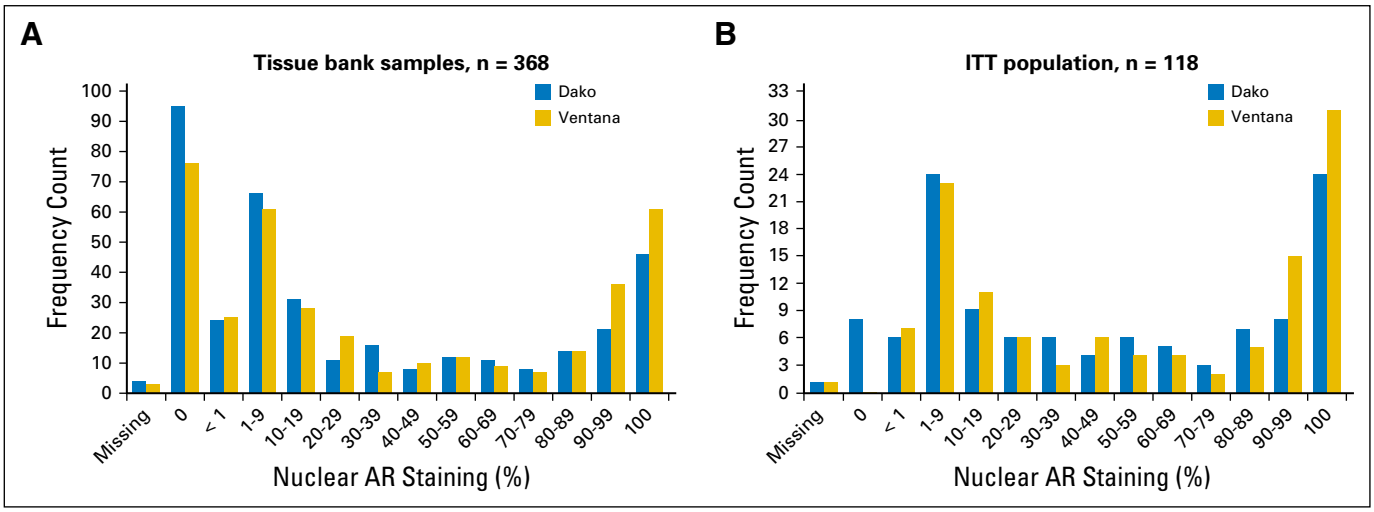

Fig A1. Nuclear androgen receptor (AR) staining by immunohistochemistry on breast tissue samples using AR441 (Dako, Carpinteria, CA) and SP107 (Ventana, Tucson, AZ). ITT, intent to treat.