The Oncologist®

Clinical Trial Results

Bicalutamide plus Aromatase Inhibitor in Patients with Estrogen Receptor-Positive/Androgen Receptor-Positive Advanced Breast Cancer

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT02910050
- **Sponsor:** 5010 Program of Sun Yat-sen University (No. 2016012)
- **Principal Investigator:** Fei Xu
- **IRB Approved:** Yes

Lessons Learned

- Studies targeting the androgen receptor (AR) signaling pathway in aromatase inhibitor (AI)-resistant breast cancer are limited.
- Bicalutamide, one of the commonly used AR inhibitors in prostate cancer, in combination with AI, did not show synergistic activity in patients with estrogen receptor-positive and AI-resistant disease in this phase II, single-arm study.
- The clinical benefit rate and objective response rate at 6 months were 16.7% and 0%, respectively, and the study was terminated after the first stage.

Abstract

Background. Endocrine resistance is a major problem in clinical practice. Studies have shown that androgen receptor (AR) signaling activation may be one of the mechanisms, and targeting AR showed some promising results in AR-positive triple-negative breast cancer. The aim of this study was to assess the efficacy and safety of bicalutamide plus another aromatase inhibitor in patients with nonsteroidal aromatase inhibitor (AI) or steroidal AI resistance and estrogen receptor (ER)-positive and AR-positive advanced breast cancer.

Methods. A Simon's two-stage, phase II, single-arm study was conducted. We assumed the clinical benefit rate (CBR) of 40% would be significant in clinical practice. In this case, if ≥4 patients of the 19 patients in the first stage benefited from treatment, the CBR would achieve the assumed endpoint. If fewer than four patients benefited from treatment in the first stage, the trial would be terminated. All patients received bicalutamide 50 mg per day orally plus another aromatase inhibitor. The primary outcome was CBR; secondary outcomes included objective response rate (ORR), progression-free survival (PFS), and tolerability.

Results. A total of 19 patients enrolled in the first stage, and 18 patients met all criteria for analysis. The trial terminated according to protocol after the first stage. After a median follow-up of 14 months, the CBR at 6 months was 16.7% (3/18); no patients with partial or complete response were observed. The median PFS was 2.7 months. Bicalutamide in combination with AI was well tolerated.

Conclusion. Bicalutamide in combination with another AI did not show synergistic activity in patients with ER-positive breast cancer and AI resistance. Results suggest that no more large-sample clinical trials should be conducted in this population for overcoming endocrine resistance. ***The Oncologist*** 2020;25:21–e15

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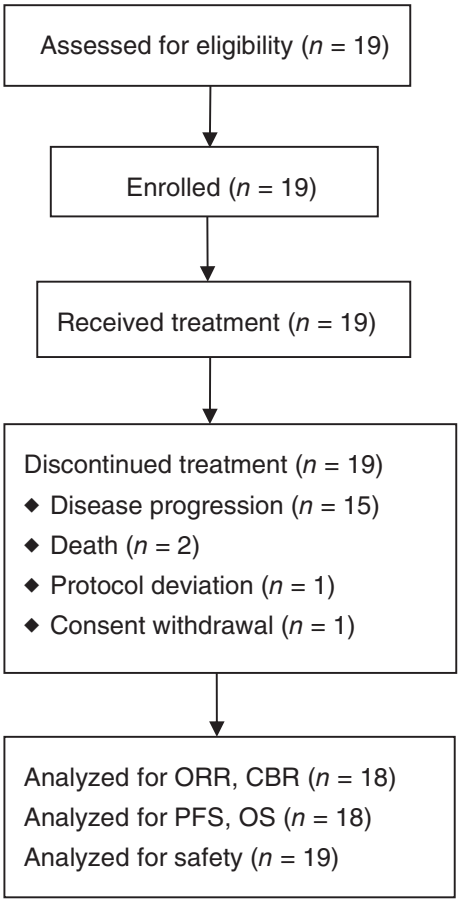

Figure 1. CONSORT flow diagram.
Abbreviations: CBR, clinical benefit rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Discussion

Bicalutamide, an AR inhibitor, has shown some promising efficacy and little toxicity in patients with triple-negative breast cancer; however, data for bicalutamide in patients with ER-positive, HER2-negative breast cancer resistant to AI are limited.

In this phase II, Simon's two-stage, single-arm study, we aimed to evaluate the efficacy and tolerability of bicalutamide plus another AI in patients with AI-resistant breast cancer. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is shown in Figure 1. To our knowledge, this is the first study to investigate the value of bicalutamide in overcoming AI resistance; however, the primary outcome did not meet the preplanned result, leading to termination of the study after the first stage.

Of the 18 patients who were analyzed, only 3 had stable disease at 6 months, and there were no partial or complete responses. The median PFS was 2.7 months (95% confidence interval, 2.2–3.8 months), which was similar to previously reported data. The treatment was well tolerated. The most commonly reported adverse event was pain at any site (3/19 patients). The results did not suggest that large-sample clinical trials of bicalutamide plus another AI should be conducted to overcome AI resistance in ER-positive, AR-positive breast cancer.

Trial Information	
Disease	Breast cancer
Disease	Advanced cancer/solid tumor only
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	No designated number of regimens
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Clinical benefit rate
Secondary Endpoint	Overall response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Tolerability
Additional Details of Endpoints or Study Design	
This study was planned to enroll a total of 58 patients and designed as a single-arm, two-stage trial. We assumed the clinical benefit rate would be 40% with type I error of 0.1 and type II error of 0.2. If fewer than four patients benefited from the treatment in the first stage, the trial would be terminated. On the contrary, if at least four patients benefited from the treatment in the first stage, the trial would continue recruiting patients. Patients meeting all eligibility requirements would receive bicalutamide 50 mg daily and aromatase inhibitor according to instructions in continuous 28-day cycles. Patients would receive another type of aromatase inhibitor if resistance to one type of aromatase inhibitor had been observed. Both premenopausal and postmenopausal women could participate in the trial, and premenopausal women should use luteinizing hormone releasing hormone analog continuously.	

The primary outcome was CBR; the secondary outcomes were PFS, ORR, and tolerability. CBR was defined as the ratio of patients who had response or stable disease according to RECIST version 1.1 definitions for over 24 weeks. ORR was defined as the ratio of patients with complete response or partial response according to RECIST 1.1. PFS was defined as time from treatment to disease progression or death.

Clinical assessment would be done every 2 months for the first half year, then every 3 months until disease progression, unacceptable adverse events due to treatment, or death. Patients would then be followed until 2 years after the last enrolled patient, death, consent withdrawal, or loss of follow-up. This study was approved by the ethics review board of our center, and written inform consent was obtained from all patients.

Investigator's Analysis	Level of activity did not meet planned endpoint.

Drug Information

Drug 1	
Generic/Working Name	Bicalutamide
Trade Name	Casodex
Company Name	AstraZeneca
Drug Type	Small molecule
Drug Class	Androgen receptor
Dose	50 milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of Administration	50 mg daily continuously
Drug 2	
Generic/Working Name	Letrozole or Anastrozole or Exemestane
Trade Name	Femera or Arimidex or Aromasin
Company Name	Novartis or AstraZeneca or Pfizer
Drug Type	Small molecule
Drug Class	Estrogen receptor
Dose	2.5 or 1 or 25 milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of Administration	Letrozole: 2.5 mg orally continuously Anastrozole: 1 mg orally continuously Exemestane: 25 mg orally continuously

Dose Escalation Table for Phase I Experimental

Dose level	Dose of drug: bicalutamide	Dose of drug: letrozole, anastrozole, or exemestane	Number enrolled	Number evaluable for toxicity
Initial dose	50 mg	2.5 mg, 1 mg, 25 mg	19	19

Patient Characteristics

Number of Patients, Male	0
Number of Patients, Female	18
Stage	Stage IV
Age	Median (range): 48 (32–70) years
Number of Prior Systemic Therapies	Median (range): 1 (0–4)
Performance Status: Eastern Cooperative Oncology Group	0 — 8 1 — 8 2 — 2 3 — 0 Unknown — 0

Detailed Patient Characteristics	
Characteristic	***n***
Visceral metastasis	
Yes	15
No	3
No. of metastatic organs	
1	4
2	7
≥3	7
Androgen receptor expression	
>50%	10
10%–50%	8
Progesterone receptor expression	
0%–10%	15
>10%	3
Estrogen receptor expression	
>50%	15
1%–50%	3
DFI	
De novo stage IV	2
DFI <24 m	3
60 m > DFI ≥ 24 m	7
DFI ≥60 m	6
Prior ET for primary disease	
SERM	11
Nonsteroidal aromatase inhibitor	3
Steroidal aromatase inhibitor	2
Prior estrogen therapy for metastatic disease	
Progression during adjuvant ET	4
Selective estrogen receptor modulator	1
Steroidal AI	3
Nonsteroidal AI	10
CT for metastatic disease	
Yes	10
No	8

Abbreviations: AI, aromatase inhibitor; CT, chemotherapy; DFI, disease-free interval; ET, endocrine therapy; SERM, selective estrogen receptor modulator.

Primary Assessment Method	
Title	New Assessment
Number of Patients Screened	19
Number of Patients Enrolled	19
Number of Patients Evaluable for Toxicity	19
Number of Patients Evaluated for Efficacy	18
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 0 (0%)
Response Assessment SD	*n* = 3 (16.7%)
Response Assessment PD	*n* = 15 (83.3%)
Response Assessment OTHER	*n* = 0 (0%)
(Median) Duration Assessments PFS	2.7 months; 95% confidence interval, 2.2–3.8 months

Kaplan-Meier Time Units					
Time of scheduled assessment and/or time of event, months	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/ No. at risk
0	0	0	100.00	100.00	18
1	2	0	100.00	88.89	16
2	2	0	88.89	77.78	14
3	5	0	77.78	50.00	9
4	4	0	50.00	27.78	5
5	0	0	27.78	27.78	5
6	2	0	27.78	16.67	3
7	1	0	16.67	11.11	2
8	0	0	11.11	11.11	2
9	2	0	11.11	0.00	0

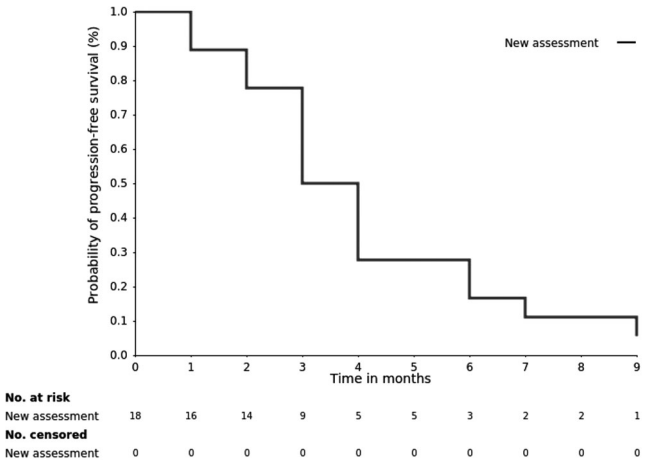

Figure 2. Progression-free survival of all patients.

Adverse Events							
All Cycles							
Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
Tumor pain	83	17	0	0	0	0	17
Alopecia	94	6	0	0	0	0	6
Hot flashes	94	6	0	0	0	0	6
Peripheral sensory neuropathy	94	6	0	0	0	0	6
Insomnia	94	6	0	0	0	0	6
Hypertension	94	0	6	0	0	0	6

Adverse events in all patients.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Dose-Limiting Toxicities				
Dose level	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity	Dose-limiting toxicity information
50 mg	19	19	0	0

Assessment, Analysis, and Discussion	
Completion	Study completed
Terminated Reason	Did not fully accrue
Investigator's Assessment	Level of activity did not meet planned endpoint.

Endocrine therapy is the mainstay of treatment and significantly improves overall survival in patients with estrogen receptor (ER)-positive advanced breast cancer. Aromatase inhibitors (AIs), including the nonsteroidal AIs (NSAI), letrozole and anastrozole, and the steroidal AI, exemestane, are widely used in first line treatment. However, resistance is the major obstacle in clinical practice [1]. Overcoming drug resistance is essential in endocrine therapy.

One of the potential mechanisms may be activation of androgen receptor (AR) signaling. AR is widely expressed in breast cancer cells. More than 70% of breast cancer is AR positive, and AR positivity is conserved during tumor progression [2, 3]. Studies showed that AR positivity was associated with good prognosis regardless of subtype [4, 5]. Studies have shown that cancer cells that are resistant to AI could convert to AR dependence rather than ER dependence, leading to activation of the EGFR pathway and then promotion of cell growth [6]. Furthermore, AR can promote proliferation of breast cancer cells, epithelial-mesenchymal transition, and metastasis through activation of the JAK/STAT3, MAPK, NOTCH, and PI3K/AKT/mTOR pathways [7, 8]. Preclinical studies showed that AR inhibitors could significantly inhibit cell proliferation and promote cell apoptosis in both triple-negative breast cancer and AI-resistant cell lines [9–11] AR may be not only a prognostic factor but also a new treatment target in breast cancer.

AR-targeted therapy has shown some promising preliminary results [12]. Bicalutamide, a nonsteroidal AR antagonist, interrupts the DNA-binding domain binding to androgen-related elements [13]. A phase II study showed that bicalutamide achieved 19% of clinical benefit rate (CBR) at 6 months and 12 weeks of median progression-free survival (PFS) in patients with ER-negative, AR-positive advanced breast cancer [14]. Other AR inhibitors and CYP17A inhibitors showed a CBR at 6 months of 7% to 29% in monotherapy or in combination with endocrine therapy in breast cancer and good safety in both monotherapy and combination [15–17]. The combination of AR antagonist with endocrine therapy may show more efficiency in ER-positive, AR-positive breast cancer that has progressed after one type of AI. However, studies of the combination of AI and bicalutamide have not been reported.

The aim of this study was to assess the efficacy and safety of bicalutamide plus another AI in patients with both ER- and AR-positive breast cancer after disease progression following one type of AI.

This study did not meet the primary outcome we planned. No improvement in CBR was observed when adding bicalutamide to a second line of AI in patients whose disease had progressed after a previous AI. As we know, the CBR at 6 months of steroidal AI is about 12%~20% in patients who experience disease progression after NSAI resistance [17, 18]. In our study, the CBR at 6 months was 16.7% and the median PFS was 2.7 months, which was consistent with the previously reported results and did not show synergistic effects in combination bicalutamide.

Adding AR inhibitors into AI did not improve the efficacy in patients whose tumors exhibited resistance to AI. There are conflicting evidences about AR as a prognostic or predictive factor in patients with breast cancer. A study showed that AR expression was related to tumor proliferation and nuclear grade. AR negativity and ER negativity were associated with high tumor aggressiveness [19]. Other studies showed that AR expression was associated with disease-free survival and overall survival, regardless of subtype [5, 20, 21]. However, the Breast International Group Trial 1-98 study showed that AR was associated with better clinicopathological factors but not with better disease-free survival and overall survival [22]. Most studies targeting AR in patients with breast cancer who had disease progression after NSAI failed to prove that AR signaling was the main mechanism of AI resistance [17, 23, 24]. AR inhibition may have value in patients with certain types of breast cancer, such as triple-negative breast cancer [14], AR gene amplification [23] or AR-positive, ER-positive, untreated advanced breast cancer [24].

It is likely that the mechanisms of AI resistance are heterogeneous in ER-positive breast cancer, so simply blocking AR signaling may be insufficient to overcome resistance. Mutations in the PI3KCA/AKT/mTOR pathway and cell cycle regulation are more frequently detected, which could lead to more successful outcomes in overcoming AI resistance [25].

In terms of safety, no new adverse events were reported in our study. The frequency and clinical pattern of adverse events were consistent with the previous study [14].

Bicalutamide in combination with AI did not show synergistic effect in patients with ER-positive, AR-positive, and AI-resistant disease. We suggest that no more large-sample clinical trials should be conducted in this population for overcoming AI resistance.

Disclosures
The authors indicated no financial relationships.

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