A phase I/II, single arm, non-randomized study of ribociclib, a CDK 4/6 inhibitor, in combination with bicalutamide, an androgen receptor inhibitor, in advanced AR-positive triple-negative breast cancer: A Big Ten Cancer Research Consortium Study (BTCRC-BRE15-024)

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

J. Knight-Shefner[1], R. M. O'Regan[2], E. Sampene[3], O. Danciu[4], K. Hoskins[4], M. E. Burkard[5], M. T. West[1], V. Carreno[1], I. Fernandez[1], K. B. Wisinski[1], M. N. Sharifi[1];
[1]Medicine, University of Wisconsin Carbone Cancer Center, Madison, WI, [2]Hematology and Oncology, University of Rochester, Rochester, NY, [3]Biostatistics, University of Wisconsin, Madison, WI, [4]Hematology and Oncology, University of Illinois Cancer Center, Chicago, IL, [5]Medicine, University of Iowa Holden Cancer Center, Iowa City, IA on behalf of the Big Ten Cancer Research Consortium.

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Background

Androgen Receptor+ Triple Negative Breast Cancer (AR+ TNBC)

- The androgen receptor (AR) is a nuclear hormone receptor like ER and PR.
- ~25-35% of TNBC expresses AR, determined by immunohistochemistry.
- AR+ TNBC is associated with lower proliferative activity, relative chemoresistance, and high rates of oncogenic PI3K pathway mutations.
- The luminal AR molecular subtype (LAR) relies on AR signaling and is susceptible to CDK 4/6 inhibition.

We hypothesized that the combination of ribociclib, a CDK 4/6 inhibitor, and bicalutamide, an androgen receptor inhibitor, will demonstrate clinical benefit for patients with advanced AR+ TNBC.

Approaches to targeting the AR in TNBC

- LAR has emerged in preclinical studies as a therapeutic target via androgen blockade.
- It is unclear whether AR / LAR subtype positivity by IHC is sufficient to predict benefit from AR targeted agents.
- AR splice variants previously found in prostate cancer are seen in AR+TNBC and drive AR inhibitor resistance.

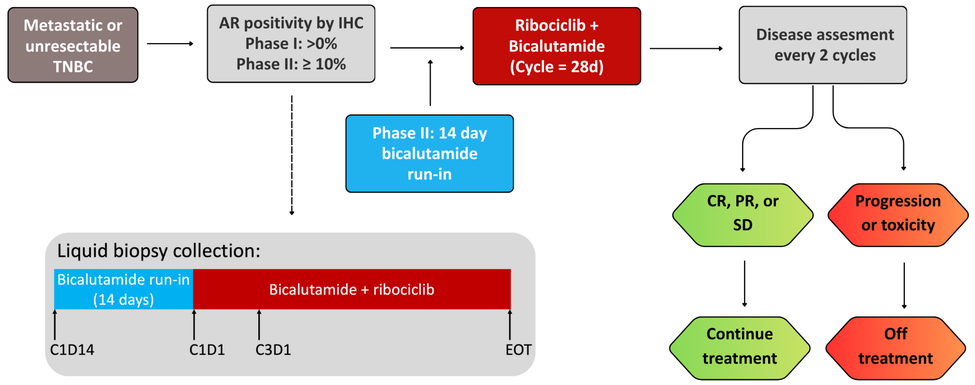
Study Design

Key Eligibility Criteria

- Patients ≥ 18 years of age with metastatic or unresectable AR+ TNBC, defined as ER/PR <10% and HER2 negative
- AR positivity defined as IHC staining of >0% (phase I) and ≥10% (phase II) tumor nuclei from tissue obtained at time of diagnosis
- Measurable disease per RECIST 1.1 criteria
- ECOG performance status 0-2
- Up to 3 prior lines of systemic therapy for metastatic disease
- No prior therapy with AR antagonists
- No prior CDK4/6 inhibitor
- No active CNS disease

Study Schema

- Dose escalation was by 3+3 design with fixed bicalutamide at 150 mg daily and ribociclib (1) 400 mg QD on days 1-21, (2) 400 mg on days 1-28, and (3) 600 mg on days 1-21.
- The RP2D was determined to be the standard doses of each agent: ribociclib 600 mg daily on days 1-21 of the 28-day cycle and bicalutamide 150 mg daily.



Primary Objective:
- Phase I: Maximum tolerated dose (MTD) & recommended Phase II dose (RP2D) for the combination of bicalutamide and ribociclib
- Phase II: Clinical Benefit Rate at 16 weeks

Secondary Objectives:
- Objective response rate (ORR), duration of response (DOR), overall survival (OS)
- Grade 3-4 adverse events or events leading to dose adjustment

Exploratory Objectives:
- Circulating tumor cells (CTCs) enumeration as biomarker of treatment response
- AR quantification and nuclear translocation in CTCs
- Identify AR splice variants in CTCs

Figure 1. Phase I/II Study Schema

Adverse Events

Table 4. Treatment-Related Adverse Events (grade ≥3 or occurring in ≥15% of patients)

	No. (%); n = 20		
Event	Any grade	Grade 3	Grade 4
Leukopenia	16 (80)	9 (45)	0 (0)
Neutropenia	15 (75)	9 (45)	3 (15)
Lymphopenia	9 (45)	2 (10)	0 (0)
Fatigue	9 (45)	0 (0)	0 (0)
Thrombocytopenia	8 (40)	2 (10)	0 (0)
Anemia	8 (40)	1 (5)	0 (0)
Nausea	7 (35)	0 (0)	0 (0)
AST elevation	5 (25)	1 (5)	0 (0)
Constipation	5 (25)	0 (0)	0 (0)
ALT elevation	4 (20)	0 (0)	0 (0)
Hot flashes	4 (20)	0 (0)	0 (0)
Creatinine elevation	4 (20)	0 (0)	0 (0)
Urinary tract infection	2 (10)	1 (5)	0 (0)
Skin infection	1 (5)	1 (5)	0 (0)

Toxicities

- There were no cases of febrile neutropenia.
- There were two grade 3 infections: one urinary tract infection and one skin infection.
- The grade 3 UTI was associated with grade 4 neutropenia, but not febrile neutropenia.

Demographics

Patient cohort

- 21 total patients enrolled, 19 initiated treatment.

Table 1. Baseline Clinical Characteristics

Characteristic	No. (%); n=21
Age, years	
Median	56
Range	37 to 75
Sex	
Female	21 (100)
Race/Ethnicity	
Non-Hispanic White	16 (76)
Black	4 (19)
Unknown	1 (5)
Prior therapies for metastatic disease	
0	11 (52)
1	9 (43)
2	1 (5)
Time from initial diagnosis to metastatic disease	**Months; n = 14**
Median	38.4
Range	2.2 to 136.1
AR+ Range by IHC (%)	**No. (%); n=18**
0-10	2 (11)
11-69	9 (50)
>70	7 (39)

Clinical Outcomes & Correlative Data

Efficacy

- Primary efficacy endpoint: 16-week clinical benefit (CBR16) for subjects in the phase II cohort (6) plus those in the phase I cohort treated at RP2D (6)
- 18/21 patients were evaluable for CBR16, defined as having started study therapy and with at least one set of disease evaluation scans
- 3/21 patients were not evaluable for CBR16
  - 1 never received treatment
  - 1 withdrew- increased symptoms prior to first scans
  - 1 with clinical progression prior to first scans
- Median time on study before disease progression was 2.6 months (n = 18, range 0.8 to 27.2)

Circulating tumor cell (CTC) gene expression profiling

- CTC gene expression of AR signaling genes and pathogenic splice variants was quantified by qPCR
- Not all samples with high AR IHC % have high CTC AR signaling/LAR gene expression
- AR pathogenic splice variants were detected in a subset of samples at the time of both intrinsic and acquired treatment resistance

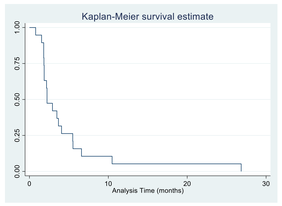


Figure 2a. PFS, Intention to treat (ITT) population

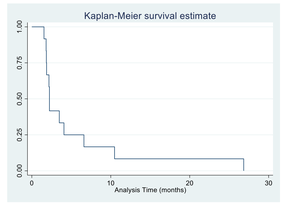


Figure 2b. PFS, RP2D population

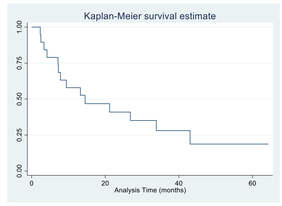


Figure 2c. OS, ITT population

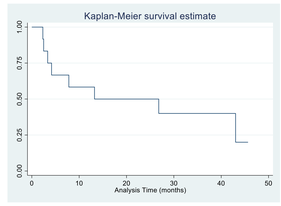


Figure 2d. OS, RP2D population

Table 2a. Best response at 16 weeks

	ITT population	RP2D
Best Response	**N = 21 (%)**	**N = 12 (%)**
Complete response	0 (0)	0 (0)
Partial response	2 (9.5)	2 (17)
Stable disease	8 (38)	4 (33)
Progressive disease	8 (38)	5 (42)

Table 2b. Clinical benefit at 16 weeks

	ITT population	RP2D
	N = 21 (%)	**N = 12 (%)**
Clinical benefit rate (CR + PR + SD)	10 (47.6)	6 (50)
Overall response rate (CR + PR)	2 (9.5)	2 (17)

Table 3. Progression Free (PFS) and Overall Survival (OS)

	ITT population	RP2D
	Months (Median, Range)	
PFS	2.23 (1.8 to 5.5)	2.23 (1.8 to 4.1)
OS	14.5 (7.2 to 43.0)	13.2 (3.4 to 43.0)

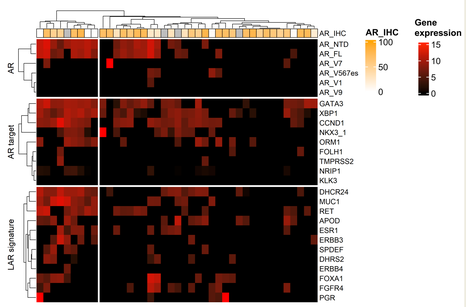


Figure 3. Androgen signaling in AR+ TNBC circulating tumor cells.

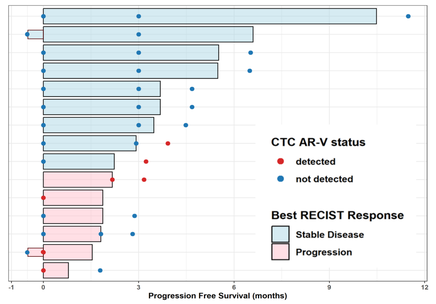


Figure 4. CTC AR splice variants are associated with both intrinsic and acquired treatment resistance.

Conclusions

- In AR+, triple-negative breast cancer, 6/12 (50%) patients treated with the RP2D of bicalutamide and ribociclib achieved disease control at 16 weeks with a median PFS of 2.23 months.
- The study ended early due to low enrollment (planned n = 37, final n = 21).
- A CTC AR signaling gene signature may be an emerging biomarker of treatment response to AR and CDK 4/6.
- AR splice variants are associated with both intrinsic and acquired treatment resistance.

Future Directions

- Combination androgen receptor inhibitor and CDK4/6 inhibitor therapy for AR+ TNBC remains a promising area of study to improve outcomes for patients with advanced disease.
- Future investigation of biomarkers beyond tissue AR IHC staining could be explored to improve patient selection.

Sites & Contacts

- University of Wisconsin - Madison
- University of Rochester
- University of Illinois – Chicago
- University of Iowa
- jknight-shefner@uwhealth.org
- msharifi@medicine.wisc.edu
- kbwisinski@medicine.wisc.edu

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