Invest New Drugs (2017) 35:87–94
DOI 10.1007/s10637-016-0403-2

PHASE I STUDIES

Phase 1b study of orteronel in postmenopausal women with hormone-receptor positive (HR+) metastatic breast cancer

Murtuza Rampurwala[1,2] · **Kari B. Wisinski**[1,2] · **Mark E. Burkard**[1,2] · **Sima Ehsani**[1,2] · **Ruth M. O'Regan**[1,2] · **Lakeesha Carmichael**[3] · **KyungMann Kim**[1,3] · **Jill Kolesar**[1,4] · **Amye J. Tevaarwerk**[1,2,5]

Received: 29 September 2016 / Accepted: 20 October 2016 / Published online: 8 November 2016

Summary *Introduction* Suppressing both androgens and estrogens may circumvent hormone receptor resistance in breast cancer by reducing androgen receptor stimulation. Selective inhibition of the 17, 20-lyase enzyme by orteronel leads to decreased androgen production in men and would be anticipated to reduce estrogen and androgen production in women. Thus, we conducted a phase 1b study of orteronel in postmenopausal women with hormone-receptor positive (HR+) metastatic breast cancer. *Methods* The primary objective was to identify the recommended phase 2 dose (R2PD) of orteronel in women; escalation was via standard 3 + 3 design. The initial dose was 300 mg BID and escalated to 400 mg BID. Cycle length was 28 days. Enrolled patients had HR+ metastatic breast cancer and were evaluated every 8 weeks for disease progression. *Results* Eight heavily pre-treated women enrolled [median age: 57 yo (range 47–73)]. Four received 300 mg BID at dose level 1; 4 received 400 mg BID at dose level 2. No dose limiting toxicities (DLTs) were observed. Adverse events (AE) at least possibly related to orteronel included grade 1–2 nausea ($n = 4$) and bone pain ($n = 3$), and grade 1 hypokalemia, hot flashes, myalgia and AST elevation ($n = 2$). The only grade 3 AE was hypertension ($n = 2$) with 8 patients receiving 34 cycles of treatment. No objective responses were seen; clinical benefit was seen in 2 patients with stable disease for more than 6 months. Serum estrogens and testosterone were suppressed from baseline on both doses of orteronel. *Conclusions* Orteronel 400 mg BID is well tolerated in postmenopausal women, and significantly suppresses serum estrogens and testosterone. Clinical benefit was seen among heavily pretreated postmenopausal women with HR+ metastatic breast cancer.

Keywords 17, 20 Lyase · Cytochrome P450 17A1 · Estrogen receptor · Progesterone receptor · Androgen receptor · Steroid metabolism

Introduction

Metastatic breast cancer remains an incurable disease. An estimated 40,000 and 520,000 women die respectively in the U.S. and globally each year from metastatic breast cancer.[1, 2] For women with metastatic breast cancer, systemic therapy palliates symptoms and prolongs survival. Patients with estrogen receptor (ER) or progesterone receptor (PR) expressing (hormone receptor-positive [HR+]) breast cancer benefit from endocrine therapies such as aromatase inhibitors, tamoxifen, and fulvestrant, all of which impact the effect of estrogens on ER.[3] These endocrine therapies are the treatment of choice for women with HR+ metastatic breast cancer because of their favorable side-effect profile and high likelihood of clinical benefit. However, metastatic breast cancer inevitably develops resistance to these therapies. Combining endocrine therapy with

Electronic supplementary material The online version of this article (doi:10.1007/s10637-016-0403-2) contains supplementary material, which is available to authorized users.

✉ Amye J. Tevaarwerk
at4@medicine.wisc.edu

[1] University of Wisconsin Carbone Cancer Center, Madison, WI, USA

[2] Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

[3] Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI, USA

[4] University of Wisconsin School of Pharmacy, Madison, WI, USA

[5] Department of Medicine, Hematology/Oncology, University of Wisconsin, 1111 Highland Ave, WIMR Rm 6037, Madison, WI 53705, USA

targeted agents like mammalian target of rapamycin (mTOR) inhibitor like everolimus or cyclin-dependent kinase (CDK) 4/6 inhibitors have demonstrated improved effectiveness over endocrine therapy alone. [4, 5] However, women develop inevitable progression on these treatments with limited subsequent therapy options other than cytotoxic chemotherapy. Novel methods and drugs to overcome resistance to endocrine therapy are needed.

One logical therapeutic target is the androgen receptor (AR). Depending on the population, subtype of breast cancer and method of detection, AR is expressed in 70–90 % of primary breast cancers, with a frequency comparable to or higher than that of either ER or PR.[6–8] Selecting for ER positivity enriches for AR expression.[9] Further, overexpression of AR correlates with tamoxifen resistance.[10] Plasma testosterone levels correlates with inferior prognosis in postmenopausal breast cancer, especially when levels rise in response to endocrine therapy.[11, 12] This suggests that androgenic activity may stimulate growth in at least a subset of HR+ breast cancer. AR stimulation by androgens represents a potential mechanism of resistance to endocrine therapy. This could be especially important in the setting of AI-based endocrine therapy, where the conversion of androgens to estrogens is blocked, and androgen levels rise compared to pretreatment levels.[13, 14] Therapies that simultaneously decrease serum androgens and estrogens might circumvent this mechanism.

Inhibition of the 17, 20-lyase (CY17) results in decreased synthesis of androgens and ultimately estrogens, but not necessarily in decreased synthesis of mineralo- or glucocorticoids (Figure 1). Lyase inhibitors or other drugs targeting AR are in clinical use for men with castrate-resistant prostate cancer (e.g. ketoconazole, abiraterone and enzalutamide). Inhibition of CY17 may be of clinical utility in postmenopausal women with HR+ metastatic breast cancer: at a minimum, CY17 inhibitors should lead to lowered serum estrogen levels and be expected to have activity similar to an AI. However, given that CY17 inhibitors lower both androgens and estrogens, they may be more effective than aromatase inhibitors based on dual effects at both the ER and AR. Thus, CY17 inhibitors represent a novel therapeutic endocrine therapy for metastatic breast cancer. Orteronel (TAK-700) is a selective, reversible, non-steroidal inhibitor of CY17. Orteronel has been studied in men with prostate cancer and was found to improve progression-free survival (PFS) both in the chemotherapy naïve and docetaxel treated patients.[15, 16] However, orteronel has not been tested in women for safety or efficacy.

To address this, we conducted a phase Ib trial of orteronel in postmenopausal women with metastatic HR+ breast cancer. The primary endpoints are toxicity and changes in steroid hormone levels which together define the recommended phase two dose (RP2D).

Methods

This single-institution phase 1, open-label, non-randomized study was approved by the institutional review board at the University of Wisconsin and was conducted in accordance with the Declaration of Helsinki. Participants provided written informed consent prior to enrolling in the trial. A 3 + 3 design was used for the dose escalation cohort, and the recommended Phase II dose (R2PD) was defined as the dose level at which less than one-third of participants experienced a dose-limiting toxicity (DLT). RP2D was defined based on toxicity and changes in steroid hormone levels.

Eligibility Postmenopausal women with an Eastern Cooperative Oncology Group (ECOG) performance status < 2 (Karnofsky > 60 %) with adequate hematologic, renal, hepatic and cardiac function were eligible. Postmenopausal status was defined as 1) age ≥ 55 years and amenorrheic for 12 or more months or 2) age less than 55 years and amenorrheic for 12 or more months in the absence of any treatment with an intervening agent expected to cause menstrual dysregulation or 3) bilateral salpingo-oopherectomy (BSO) regardless of age. A documented serum follicular stimulating hormone (FSH) level and serum estradiol level consistent with postmenopausal status was required in the absence of BSO. The study required histologically confirmed, measureable or evaluable, advanced or metastatic HR+ breast cancer for which no standard curative

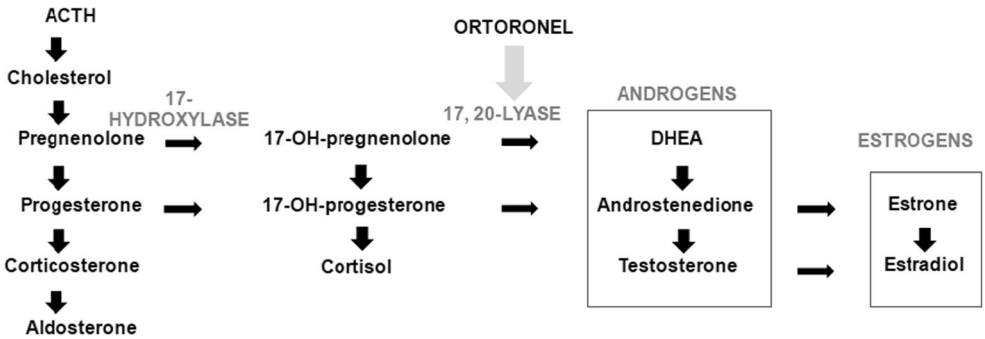

Fig. 1 Adrenal steroidogenesis pathway; targeted inhibition of 17, 20-lyase by orteronel. Abbreviations: *ACTH* Adrenocorticotropic Hormone, *DHEA* Dehydroepiandrosterone

treatment existed. Breast cancer was defined as HR+ if either the ER and/or PR were reported as (1) Allred > 4, (2) Immunohistochemistry (IHC) 1+, 2+, 3+ or (3) percentage of positive staining > 10 %. In the case of discrepancy in primary vs metastatic ER/PR testing, the metastatic results were used to determine eligibility. Women with definitively treated and stable brain metastases were eligible for the study.

For the dose escalation cohort, there was no restriction in terms of prior lines of hormonal therapy (prior therapy with abiraterone or aminoglutethimide excluded patients from this cohort). Medical therapy for breast cancer (except bisphosphonates or denosumab) was not allowed within 21 days of initiating study drug. Patients on continuous corticosteroid therapy within 21 days prior to study treatment initiation were ineligible. Patients had to have recovered to baseline or ≤ grade 1 from all-prior treatment related toxicities. Patients with uncontrolled hypertension despite appropriate medical therapy, endocrine disorders including, but not limited to, Cushing's or Addison's disease, active chronic hepatitis B or C, life-threatening illness unrelated to cancer, or any serious medical or psychiatric illness that could potentially interfere with participation in the study were excluded. Following the dose escalation cohort, a 9-patient dose-expansion cohort was proposed (measurable disease, no more than 1 prior line of endocrine therapy and no prior cytotoxic chemotherapy in the metastatic setting) to demonstrate clinically significant decrease in serum estradiol following treatment with orteronel at RP2D. However, this dose expansion cohort was suspended after 1 patient enrolled. Accrual was subsequently closed due to changes in the development strategy by the sponsor.

Treatment plan Orteronel was given orally, twice daily (BID) and continuously on a 28-day treatment cycle as outlined in Figure 2, starting at the RP2D in men (300 mg BID). Doses were determined by the dose level assignment (see Supplementary Table 1). Treatment was continuous until disease progression, unacceptable toxicity or withdrawal of consent. Dose modification was based on grade and attribution of any adverse events (AE). Specific management recommendations were defined in the protocol for adrenal insufficiency, mineralocorticoid excess, hypertension and hyperglycemia.[17] Patients were followed for 4 weeks after discontinuing study treatment or until death, whichever occurred first. Patients removed from study for unacceptable AE(s) were followed until resolution or stabilization of the AE.

Mineralocorticoid excess and adrenal insufficiency were side effects of orteronel seen in phase I clinical trials in men.[17] Some men were able to tolerate higher dose of orteronel with concomitant glucocorticoids; thus, alternate dose levels 1b and 2b of orteronel + daily glucocorticoids were included in the dose escalation schema (Supplementary Table 1). These alternate dose levels were to be used if significant number of patients had symptoms consistent with mineralocorticoid excess and/or adrenal insufficiency in dose level 1a or 2a.

Assessments Patients were monitored with history, physical exams, laboratory testing and electrocardiograms at baseline and every 4 weeks for the first 6 months of the study. Subsequently, these were performed at least every 12 weeks. Cardiac function was monitored at baseline, after 2 cycles, and after 6 cycles of treatment. Patients were assessed per standard criteria with baseline imaging followed by re-evaluation every 8 weeks for the first 6 months. Subsequently, disease evaluations were performed at least every 12 weeks. Response and progression were evaluated using revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1.[18] AEs were graded according to the National

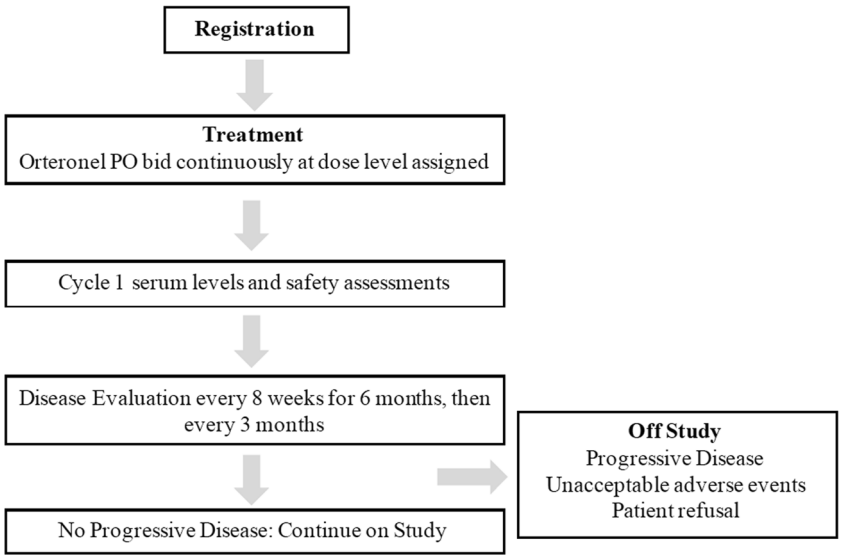

Fig. 2 Study consort diagram with treatment schema

Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[19]

DLTs were defined as those that occurred during Cycle 1 and at least possibly related to orteronel. Hematologic DLTs included grade 3 or higher neutropenia regardless of duration, grade 4 thrombocytopenia or any grade of thrombocytopenia if associated with a clinically significant or life-threatening bleed. Non-hematologic DLTs were defined as any grade 3–4 toxicities, except nausea, vomiting, diarrhea or rash not yet treated with maximal medical therapy. Symptoms thought to be at least possibly related to orteronel requiring initiation of systemic steroids or other systemic endocrine therapies during cycle 1 including (but not limited to) new onset diabetes or hypothyroidism were considered a DLT. Any toxicity preventing delivery of > 75 % of the protocol specified cycle 1 treatment or dose delay of > 14 days starting prior to Cycle 2 Day 1 when at least possibly related to orteronel was also defined as a DLT.

Pharmacodynamic assays Serum endocrine hormone levels including estradiol, estrone, progesterone, cortisol, cortisone, androstenedione and testosterone were measured using a validated liquid chromatography-mass spectrometry (LC-MS/MS) assay on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 1 Day 28 of treatment and then on Day 1 of subsequent cycles.

Statistical analysis The primary objective of the dose escalation cohort of this study was to determine the RP2D of orteronel in postmenopausal women with HR+ metastatic breast cancer. Secondary objectives were to determine overall response rate (ORR) and disease control rate (DCR) in all patients treated with orteronel, determine toxicity of orteronel at RP2D, and to determine pharmacodynamic activity of orteronel by assessing serum endocrine hormone levels before and after administration of orteronel. A minimum of 6 and a maximum of 18 patients were to be enrolled in the dose escalation cohort. The dose escalation phase employed a traditional 3 + 3 dose escalation schema involving cohorts of 3–6 patients at each dose level. All patients were evaluated for toxicity from the time of their first treatment with orteronel. DLTs were to be tabulated by dose level, and thus descriptive in nature. Patients with measurable disease at baseline, who received at least one cycle of therapy, and had their disease re-evaluated were considered evaluable for response. Serum endocrine hormone levels including estradiol, estrone, testosterone, progesterone, androstenedione, cortisol, and cortisone were summarized using means, standard deviations, medians, and interquartile ranges for each dose level and both dose levels combined. For both dose levels combined, changes in hormone levels from baseline were also summarized using descriptive statistics and plots of these hormone levels for each patient.

Results

Participant and disease characteristics Eight participants (median age 57 years, range 47–73 years) were enrolled on the study between November 2012 and November 2013; 7 participants in the dose escalation cohort and 1 participant in the dose expansion cohort. None of the tumors in the patients enrolled were known to be HER2 amplified although one had unknown HER2 status and had not received prior HER2-targeted therapy. Patients were heavily pre-treated: 7 had prior endocrine therapy for metastatic cancer (median 4 lines, range 0–5) and 5 had prior chemotherapy regimens for metastatic cancer (median 2, range 0–7). Sites of metastatic disease included bone ($n = 5$), liver ($n = 3$), lymph nodes ($n = 4$), soft tissue ($n = 2$), and lungs ($n = 2$). Table 1 summarizes the relevant demographics and other baseline characteristics.

Treatment 4 patients received orteronel 300 mg BID at dose level 1: participant 2 was diagnosed with brain metastases while on cycle 1 of treatment and taken off study; she was

Table 1 Patient baseline demographics, disease characteristics and treatment dose level

No	Age	Histology	ER	PR	Her2	Prior Therapy [a]		Sites of Metastatic Disease	Dose Level
						Hormonal (n)	Chemotherapy (n)		
1	58	Ductal carcinoma	+	–	–	4	2	Bone, Liver, Lymph nodes, Soft tissue	1a
2	56	Ductal carcinoma	+	+	–	5	2	Lymph nodes	1a
3	63	Lobular carcinoma	+	–	–	4	4	Bone, Liver	1a
4	47	Ductal carcinoma	+	+	–	0	7	Lymph nodes, Soft tissue	1a
5	47	Ductal carcinoma	+	+	–	4	1	Bone, Liver, Lung	2a
6	71	Lobular carcinoma	+	+	unknown	2	0	Bone	2a
7	55	Ductal carcinoma	+	+	–	1	0	Bone	2a
8	73	Ductal carcinoma	+	+	–	2	0	Lung, Lymph nodes	Expansion

[a] prior therapies for metastatic disease

deemed not evaluable for response and replaced by participant 4 at dose level 1. 3 patients received orteronel 400 mg BID at dose level 2. Participant 8 received orteronel at the dose of 400 mg BID in the dose expansion cohort for cycle 1; this was reduced to 300 mg BID for cycle 2 onwards due to grade 3 hypertension.

Orteronel was well tolerated – no DLTs were observed. No patients had symptoms concerning for mineralocorticoid excess or adrenal insufficiency requiring steroids and hence, the alternate dose levels with exogenous glucocorticoid supplementation were not utilized. The RP2D was identified as 400 mg BID.

Safety and tolerability Common adverse events at least possibly related to orteronel therapy and experienced by more than 1 patient included grade 1–2 nausea ($n = 4$), grade 1–2 bone pain ($n = 3$), grade 1 hypokalemia ($n = 2$), grade 1 hot flashes ($n = 2$), grade 1 myalgia ($n = 2$), and grade 1 AST elevation ($n = 2$). The only grade 3 adverse event was hypertension in two patients at the 400 mg BID dosing. The first patient developed hypertension in the 5th cycle of treatment that resolved following dose reduction and the patient continued therapy for a total of 9 cycles. The second patient needed dose reduction to 300 mg BID and tolerated therapy well for 3 more cycles. No grade 4 toxicities were observed with orteronel therapy. Adverse events observed in patients treated with orteronel in the study are enumerated in Table 2.

Table 2 Treatment-related adverse events at least possibly related to orteronel

Adverse Event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Fatigue	1 (12 %)		
Nausea	3 (37 %)	1 (12 %)	
Chills	1 (12 %)		
Hot Flashes	2 (25 %)		
Skin changes	1 (12 %)		
Headache		1 (12 %)	
Hirsuitism	1 (12 %)		
Bone Pain	2 (25 %)	1 (12 %)	
Myalgia	2 (25 %)		
Hypertension			2 (25 %)
Hypokalemia	2 (25 %)		
Hyperglycemia	1 (12 %)		
Hypoglycemia	1 (12 %)		
Hypocalcaemia	1 (12 %)		
Hypophosphatemia		1 (12 %)	
QT prolongation	1 (12 %)		
AST elevation	2 (25 %)		
Lymphopenia		1 (12 %)	
Creatinine elevation	1 (12 %)		

Efficacy The 7 patients in the dose escalation cohort received a total of 32 cycles of treatment (the single participant in the dose expansion cohort received 2 cycles). No objective responses were seen, however, 2 patients had prolonged stable disease and remained on therapy for more than 6 months. Duration of therapy, best response and reason treatment was stopped are shown in Table 3.

Pharmacodynamic analysis Serum endocrine hormone levels including estradiol, estrone, progesterone, cortisol, cortisone, androstenedione and testosterone were measured on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of subsequent cycles. Figure 3 provides plots of hormone levels by time point for each patient.

Declines in estrone, testosterone, cortisone and androstenedione levels from baseline were observed for dose levels 1a and 2a. In the combined dose group, estradiol levels decreased from 5.4 pg/mL (SD = 5.6) at baseline to 0.39 (SD = 0.87) at Cycle 3 Day 1, estrone levels decreased from 23.1 pg/mL (SD = 12.4) at baseline to 4.1 (SD = 6) at Cycle 3 Day 1, testosterone levels decreased from 134.9 pg/mL (SD = 95.7) at baseline to 17.1 (SD = 23.6) at Cycle 3 Day 1, androstenedione levels decreased from 1.08 pg/mL (SD = 0.53) at baseline to 0.08 (SD = 0.04) at Cycle 3 Day 1, and cortisone levels decreased from 24.6 ng/mL (SD = 8.6) at baseline to 4.8 (SD = 2.6) at Cycle 3 Day 1. Serum progesterone level responses were more varied and difficult to interpret given large fluctuations in levels.

Supplemental Table 2 summarizes hormone levels by time point and dose level, and supplemental Table 3 summarizes changes in hormone levels from baseline are summarized in the combined dose group.

Discussion

Aromatase inhibitors remain the cornerstone of treatment for HR+ metastatic breast cancer in postmenopausal women. However, 30–50 % of HR+ tumors display de novo resistance

Table 3 Treatment history with dose levels, number of cycles of treatment and reason for treatment discontinuation

No	Dose Level	Cycles (n)	Best Response	Off Treatment Reason
1	1a	1	PD	Disease progression
2	1a	1	PD	Disease progression
3	1a	2	PD	Disease progression
4	1a	3	SD	Disease progression
5	2a	2	PD	Disease progression
6	2a	9	SD	Disease progression
7	2a	12	SD	Disease progression
8	Expansion	4	SD	Disease progression

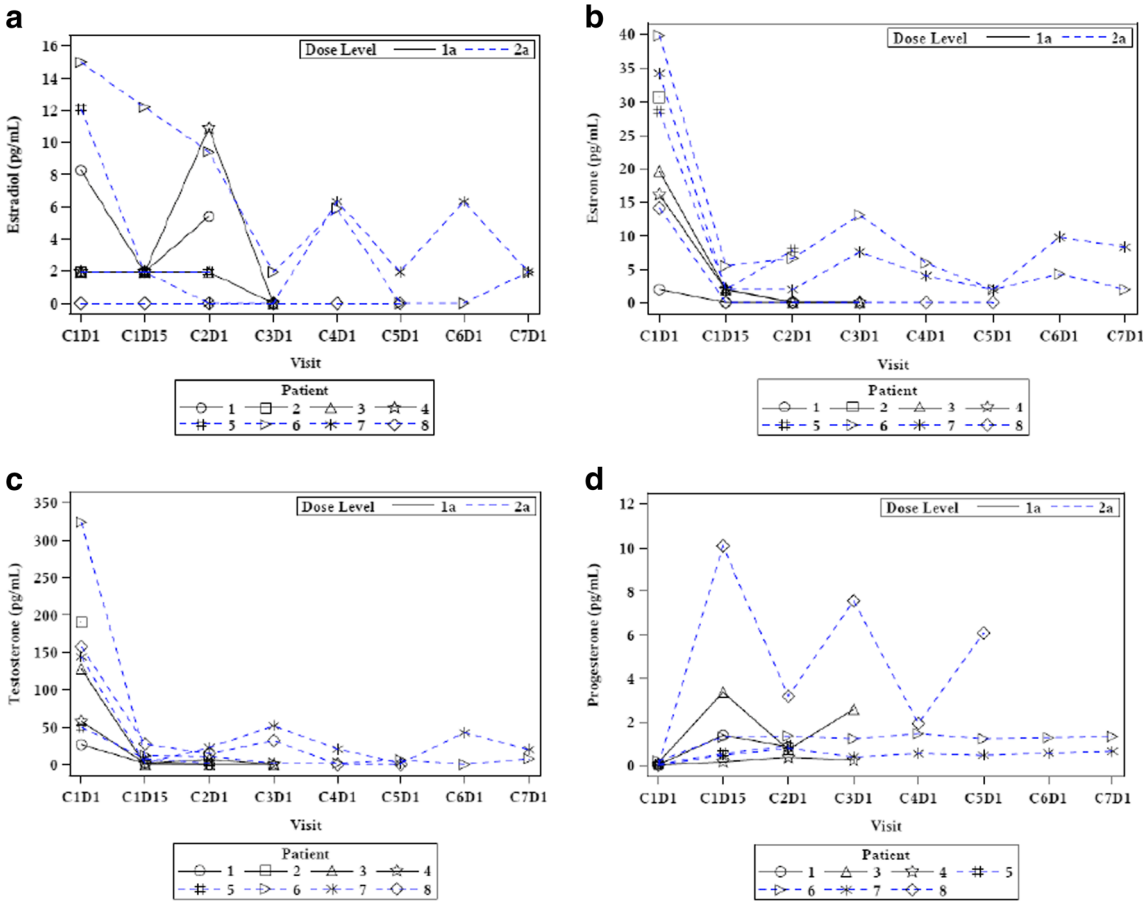

Fig. 3 Spaghetti plot depicting hormone level changes by time point for each patient. **a** estradiol **b** estrone **c** testosterone **d** progesterone

to endocrine therapies and metastatic HR+ tumors generally develop acquired resistance at some point during treatment.[20, 21] AR is expressed at detectable levels in 70–90 % of primary breast cancers and is associated with a well-differentiated state and a favorable prognosis.[22, 23] However, a high ratio of AR:ER (≥2.0) is associated with inferior disease-free survival (DFS) and overall survival (OS) as well as an inferior response to endocrine therapy.[20] Activation of the AR by androgens in the setting of AI therapy represents a potential resistance mechanism in HR+ breast cancer.

Therapies that simultaneously decrease both serum androgens and estrogens might circumvent resistance to aromatase inhibitors and enhance therapeutic efficacy. This is an attractive strategy given the availability of 17,20 lyase inhibitors approved or being studied for the treatment of prostate cancer. Orteronel (TAK-700) is a selective, reversible, non-steroidal inhibitor of CYP17, known to decrease serum androgens levels in men.[17] We conducted a phase Ib study of orteronel as a single agent in postmenopausal women with HR+ metastatic breast cancer. Orteronel 400 mg BID was identified as the R2PD and given that it exhibited significant and sustained decreases in serum estrogen and androgens levels, represents the R2PD for this agent in women. No significant toxicity was noted and no concomitant glucocorticoids were required. With multiple prior lines of therapy, no objective responses were seen; however, two patients experienced clinical benefit for over 6 months consisting of stable disease for 12 and 9 months. Importantly, serum estrogen levels remained suppressed over multiple cycles despite the lack of concomitant AI. Thus, orteronel 400 mg BID is a safe treatment for HR+ breast cancer and warrants testing at an earlier line of therapy.

Other trials of lyase inhibitors have been completed in HR+ metastatic breast cancer. A randomized phase II trial of abiraterone + prednisone (AP) vs AP + exemestane vs exemestane alone was conducted in 297 patients with ER+ metastatic breast cancer progressing on a non-steroidal AI. This trial did not show any improvement in PFS or OS in the abiraterone-containing arms compared with exemestane alone. Increased progesterone levels were noted in both of the arms receiving abiraterone, and were proposed as an explanation for the lack of benefit.[24]

Analysis of progesterone levels in our study were complicated by substantial fluctuations over time: other studies have suggested that rise in progesterone could potentially represent a mechanism of resistance to therapy with lyase inhibitors. Enzalutamide, a more potent AR antagonist, is being evaluated in a phase II randomized trial in combination with exemestane in ER+ metastatic breast cancer (ongoing at this time).[25]

Our study has several strengths with the key being that orteronel alone can lead to adequate and sustained estrogen suppression without the need of concomitant aromatase inhibitors in postmenopausal women. Despite multiple prior lines of therapy, 4 patients had clinical benefit with stable disease through several cycles of treatment. Orteronel was well tolerated and there was no need for supplemental glucocorticoids. We acknowledge limitations of our study in terms of a small sample size and a heavily pretreated population and hence a low probability of disease response.

Several key questions remain regarding the patient population that might benefit the most from lyase inhibition. Although a reasonable hypothesis could be that HR+ metastatic breast cancer expressing AR would benefit the most from agents suppressing androgens and estrogens, biomarker analysis from the abiraterone study failed to show any predictive value from AR expression in tissue and circulating tumor cells predicting benefit.[26] Preclinical studies have shown a high AR/ER ratio (≥2) is predictive of resistance to endocrine therapies alone and this may be a population, which could benefit from combined androgen and estrogen suppression with lyase inhibitors.[20] Another key therapeutic question is whether lyase inhibitors need to be combined with aromatase inhibitors in the treatment of HR+ breast cancer. This was the rationale behind both the abiraterone and enzalutamide studies. However, our study shows a similar suppression in estradiol levels (93 %) with orteronel alone as compared to anastrozole (84.9 %), letrozole (87.8 %) and exemestane (92.2 %) and thus potentially avoiding the need of combination therapy with aromatase inhibitors.[27, 28] In the place of aromatase inhibitors, an interesting combination could potentially be lyase inhibitors with progesterone inhibitors based on the rise in progesterone that which may act as a growth stimulus in HR+ breast cancer.[24, 29] These questions should be addressed in developing subsequent trials of lyase inhibitors for HR+ metastatic breast cancer patients.

In conclusion, orteronel represents a novel promising therapeutic strategy of lyase inhibition in postmenopausal HR+ metastatic breast cancer and having identified the RP2D in our study lays the foundation for larger confirmatory studies in this population.

Acknowledgments The authors would like to thank all of the participants enrolled in this trial, the UW research staff, and the physicians who participated.

Compliance with ethical standards

Conflict of interest Murtuza Rampurwala declares that he has no conflict of interest.
Kari B Wisinski declares that she has no conflict of interest.
Mark E Burkard declares that he has no conflict of interest.
Sima Ehsani declares that she has no conflict of interest.
Ruth M O'Regan declares that she has no conflict of interest.
Lakeesha Carmichael declares that she has no conflict of interest.
KyungMann Kim declares that he has no conflict of interest.
Jill Kolesar declares that she has no conflict of interest.
Amye J Tevaarwerk declares that she has no conflict of interest.

Funding This study was funded by Millennium Pharmaceuticals. This work was supported by the NCI Cancer Center Support Grant P30 CA014520 and NCI U01CA062491 Early Clinical Trials of Anti-Cancer Agents with Phase I Emphasis. AJT and MEB have received support from the Clinical and Translational Science Award (CTSA) program, through the NIH National Center for Advancing Translational Sciences (NCATS), grants UL1TR000427and KL2TR000428, while MR has received support from T32 CA009614.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Stewart B, Wild C (2014) World Cancer Report
2. American Cancer Society (2015) Cancer Facts & Figures. In.
3. Ravdin PM, Green S, Dorr TM et al (1992) Prognostic significance of progesterone receptor levels in estrogen receptor-positive patients with metastatic breast cancer treated with tamoxifen: results of a prospective southwest oncology group study. J Clin Oncol Off J Am Soc Clin Oncol 10:1284–1291
4. Baselga J, Campone M, Piccart M et al (2012) Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 366:520–529
5. Finn RS, Crown JP, Lang I et al (2015) The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 16:25–35
6. Kuenen-Boumeester V, Van der Kwast TH, Claassen CC et al (1996) The clinical significance of androgen receptors in breast cancer and their relation to histological and cell biological parameters. Eur J Cancer 32A:1560–1565
7. Moinfar F, Okcu M, Tsybrovskyy O et al (2003) Androgen receptors frequently are expressed in breast carcinomas: potential relevance to new therapeutic strategies. Cancer 98:703–711

8. Vera-Badillo FE, Templeton AJ, de Gouveia P et al (2014) Androgen receptor expression and outcomes in early breast cancer: a systematic review and meta-analysis. J Natl Cancer Inst 106:djt319
9. Allegra JC, Lippman ME, Thompson EB et al (1979) Distribution, frequency, and quantitative analysis of estrogen, progesterone, androgen, and glucocorticoid receptors in human breast cancer. Cancer Res 39:1447–1454
10. De Amicis F, Thirugnansampanthan J, Cui Y et al (2010) Androgen receptor overexpression induces tamoxifen resistance in human breast cancer cells. Breast Cancer Res Treat 121:1–11
11. Harvell DM, Richer JK, Singh M et al (2008) Estrogen regulated gene expression in response to neoadjuvant endocrine therapy of breast cancers: tamoxifen agonist effects dominate in the presence of an aromatase inhibitor. Breast Cancer Res Treat 112:489–501
12. Micheli A, Meneghini E, Secreto G et al (2007) Plasma testosterone and prognosis of postmenopausal breast cancer patients. J Clin Oncol 25:2685–2690
13. Gallicchio L, Macdonald R, Wood B et al (2011) Androgens and musculoskeletal symptoms among breast cancer patients on aromatase inhibitor therapy. Breast Cancer Res Treat 130:569–577
14. Morris KT, Toth-Fejel S, Schmidt J et al (2001) High dehydroepiandrosterone-sulfate predicts breast cancer progression during new aromatase inhibitor therapy and stimulates breast cancer cell growth in tissue culture: a renewed role for adrenalectomy. Surgery 130:947–953
15. Fizazi K, Jones R, Oudard S et al (2015) Phase III, randomized, double-blind, multicenter trial comparing orteronel (TAK-700) plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer that has progressed during or after docetaxel-based therapy: ELM-PC 5. J Clin Oncol 33:723–731
16. Saad F, Fizazi K, Jinga V et al (2015) Orteronel plus prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial. Lancet Oncol 16:338–348
17. Dreicer R, MacLean D, Suri A et al (2014) Phase I/II trial of orteronel (TAK-700)–an investigational 17,20-lyase inhibitor–in patients with metastatic castration-resistant prostate cancer. Clin Cancer Res 20:1335–1344
18. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
19. Institute NC (2009) Common terminology criteria for adverse events v4.0. In
20. Cochrane DR, Bernales S, Jacobsen BM et al (2014) Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. Breast Cancer Res 16:R7
21. Anderson H, Bulun S, Smith I, Dowsett M (2007) Predictors of response to aromatase inhibitors. J Steroid Biochem Mol Biol 106:49–54
22. Park S, Koo J, Park HS et al (2010) Expression of androgen receptors in primary breast cancer. Ann Oncol 21:488–492
23. Hu R, Dawood S, Holmes MD et al (2011) Androgen receptor expression and breast cancer survival in postmenopausal women. Clin Cancer Res 17:1867–1874
24. O'Shaughnessy J, Campone M, Brain E et al (2016) Abiraterone acetate, exemestane or the combination in postmenopausal patients with estrogen receptor-positive metastatic breast cancer. Ann Oncol 27:106–113
25. Yardley D, Awada A, Cortes J (2014) A phase II randomized, double-blind, placebo-controlled multicenter trial evaluating the efficacy and safety of enzalutamide in combination with exemestane in estrogen or progesterone receptor-positive and HER2-normal advanced breast cancer. J Clin Oncol 32:5s, **(suppl; abstr TPS653). NCT02007512**
26. Li W, O'Shaughnessy J, Ricci D (2014) Evaluation of biomarker association with efficacy for abiraterone acetate (AA) plus prednisone (P) with or without exemestane (E) in postmenopausal patients (pts) with estrogen receptor-positive (ER+) metastatic breast cancer (mBCa) progressing after a nonsteroidal aromatase inhibitor (NSAI). J Clin Oncol 32:5s, **suppl; abstr 520**
27. Geisler J, King N, Anker G et al (1998) In vivo inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients. Clin Cancer Res 4:2089–2093
28. Geisler J, Haynes B, Anker G et al (2002) Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. J Clin Oncol 20:751–757
29. Lange CA, Sartorius CA, Abdel-Hafiz H et al (2008) Progesterone receptor action: translating studies in breast cancer models to clinical insights. Adv Exp Med Biol 630:94–111