Enzalutamide has clinical activity in breast cancer as a single agent and in combination with exemestane. Activity is seen in both triple negative AR+ BC and also ER+AR+ BC. Clinical data in Her2+ AR+ BC is too immature to make conclusions. The proposed clinical trials for Years 3–5 appear to be justified based on clinical activity and the current preclinical data.
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</table>
Introduction

The central thesis of this grant is to understand the role of AR signaling in breast cancer subtypes, and understand how to best use an inhibitor of AR signaling, enzalutamide (enza), as a therapeutic agent in breast cancer. With the recognition that AR is expressed in all subtypes of breast cancer, that overexpression is frequently associated with relative resistance to therapy (both anti-estrogen and chemotherapy) (work of our group and others), and with the advent of increasingly potent AR signaling inhibitors in prostate cancer, the area of anti-AR therapeutics in breast cancer is one of the most active worldwide. The preclinical portion of this grant serves to understand mechanism of action of AR signaling inhibition alone or in combination with other targeted agents in ER+, Her2+, or TNBC in preclinical models, and then perform biomarker analysis in human tissues obtained before, during and after treatment with enzalutamide. The clinical portion of this grant serves to obtain these tissues in concert with the overall clinical development of enzalutamide in the subtypes of breast cancer.

Keywords

Breast cancer (BC) subtypes; androgen receptor (AR); preclinical modeling; enzalutamide; AR inhibition; resistance mechanisms; predictive biomarkers.

Overall Project Summary

This report will include both the tasks that were mandated in the SOW, but also will highlight the therapeutic clinical results from the companion therapeutic trials that were sponsored by our Pharma partners, Medivation and Astellas.

Clinical Aim 1: To identify pretreatment molecular characteristics associated with lack of response and/or prolonged PFS (Patient Tissues).

Task 1: Write & Activate the Serial Biopsy Trial (Elias, LoRusso, Traina, advocates, Richer)

- Written protocol completed Month 1
- Submitted to Scientific Review Committee Month 1
- Submitted to IRBs (all institutions) Month 1
- DoD Human Research Protection Office (HRPO) Month 2
- Activation and first patient enrolled Month 3
- IND already available

This task was completed on time. The DOD sponsored serial biopsy trial has been written and approved by HRPO and has been activated at University of Colorado site. Its title is “Exploratory Development of Predictive Biomarkers for Patients with Androgen-Receptor Positive (AR) Breast Cancer (BC) Treated with Enzalutamide (MDV3100); COMIRB 13-1473. The same trial is about to be IRB approved at MSKCC (Traina, local PI). MSKCC has been accruing well to the therapeutic trials and have all the new trials activated. Thus that site will continue to participate. Due to changes in personnel (Dr. LoRusso moved to Yale Cancer Center), Karmanos Cancer Center was deactivated, and with the approval of the Dept of Defense, the University of Tennessee is in the process of being activated (PI, Lee Schwartzberg, MD). They have also been top accouters to the enzalutamide breast cancer trials.
Task 2: Accrue 12 patients treated with enzalutamide onto serial biopsy trial (Elias, LoRusso, Traina, advocates)
Year 0-Year 2 Month 7
- First 12 patients accrued completed (12) Month 7
- First 12 patients – clinical database complete Month 15
- All initial biopsies collected from 1st 12 patients Month 12

The first patient was accrued in 10/2013. Thus far, five patients have been accrued to the serial biopsy trial (all at University of Colorado). There were two screen failures. We do expect that the accrual will accelerate once MSKCC and University of Tennessee have opened this trial. All five patients have adequate tissue obtained from pretreatment and 2-4 weeks into treatment. One patient has provided post-progression tissue and two have refused. Two patients remain on therapy.

Task 3: Tissue assays and bioinformatics analysis (Richer, Thor, Jones, Elias, LoRusso, Traina, Petricoin, Gao)
- First 12 patients completed Month 18
- Bioinformatic analysis completed Month 24

The timeline for this task has not yet been reached.

Clinical Aim 2: To determine if a decrease in Ki67 or increase in apoptosis as measured by TUNEL in biopsies taken before treatment as compared to after 2-4 weeks of treatment or other to be determined genes or proteins are associated with lack of response and/or prolonged PFS.

Task 1: Accrue 24 patients treated with single agent enzalutamide (Elias, LoRusso, Traina, advocates)
- First half of patient accrual completed (12) Month 15
- First 12 patients – clinical database complete Month 15
- All 2-week biopsies collected from 1st 12 patients Month 15

Task 2: Tissue assays and bioinformatics analysis (Richer, Thor, Jones, Elias, LoRusso, Traina, Petricoin, Gao)
- 12 single agent patients Month 18
- Bioinformatic analysis completed Month 24

The timeline for these tasks have not yet been reached.

Clinical Aim 3: To determine if changes in molecular determinants between pre-treatment biopsies and tissue at time of disease progression can help identify resistance mechanisms.

Task 1: Accrue 24 patients treated with single agent enzalutamide (Elias, LoRusso, Traina, advocates)
- All relapse biopsies collected from 1st 12 patients Month 24

The timeline for this task has not yet been reached.

Clinical Aim 4: To determine if enza can overcome de novo resistance to exemestane in postmenopausal women with T2 or larger ER+ BC treated preoperatively.

Task 1: Trial II: Randomized Preoperative trial in AR+/ER+ BC (Elias, LoRusso, Traina, advocates, Richer)
- Written protocol completed Month 21
- Submitted to Scientific Review Committee Month 21
- Submitted to IRBs (all institutions) Month 22
- DoD Human Research Protection Office (HRPO) Month 24
The clinical development of enzalutamide in breast cancer has been rapid. Both Medivation and Astellas have been fully committed to this endeavor. Findings are summarized:

- The phase I of single agent enzalutamide has been completed and confirmed that the FDA approved dose in prostate cancer in men (160 mg daily) is safe and tolerable in women. Additionally, the pharmacokinetic profile of enzalutamide in women is similar to that in men.
- Because enzalutamide is a very strong p450 CYP3A4 inducer, several phase Ib trials have been completed to examine the pharmacologic interaction of enza with other anti-estrogen agent (anastrozole, exemestane) in ER+ BC.
- Enzalutamide when added to anastrozole 1 mg daily reduced the AUC of anastrozole alone by 80%. This was associated with an increase in serum estradiol in some patients. For this reason, this combination is no longer in development.
- Enzalutamide when added to exemestane 25 mg daily reduced the AUC of exemestane by about 50%. This was not associated with an increase in estradiol. However, since the FDA approval for exemestane included approval for double dose exemestane (50 mg daily) when combined with strong CYP3A4 inducers, enza plus exemestane 50 mg daily was evaluated. Pharmacokinetic analysis of this combination demonstrated that exemestane 50 mg AUC (when combined with enza) was equivalent to exemestane 25 mg daily alone. As presented at ASCO 2014. Of 39 evaluated patients, 12 remain on therapy for more than 16 weeks (range 114-450 days). Thus this combination is moving forward in development.
- A current PK trial combining enza with fulvestrant is nearing completion.
- The initial immunohistochemistry assay for AR used a 10% staining cutoff to determine positivity. With the observation preclinically that cell lines that had lower levels of AR expression were sensitive to enzalutamide inhibition, the more recent clinical trials are now using a cutoff of 1% to select eligible patients.
- A randomized double-blinded phase II trial of exemestane with or without enzalutamide in women with metastatic ER+ AR+ breast cancer is underway and is open at each of the sites involved with this grant. Upon progression, an open label combination therapy is available for patients who had single agent exemestane initially. These latter patients are eligible for our ongoing DOD grant biopsy trial.
- A phase Ib of single agent enza in AR+ TNBC was completed. Currently a phase II trial is underway. These patients are eligible for our ongoing DOD grant biopsy trial.
- Based on our preclinical work, a trial of enzalutamide plus trastuzumab has opened in 3rd or greater line Her2+ AR+ BC. These patients are eligible for our ongoing DOD grant biopsy trial.

Clinical Aim 5: To determine the maximum tolerated dose and toxicity of enza when combined with the most promising combinations as defined in the preclinical modeling experiments during Years 1-2. As an example, a combination of enza with everolimus +/- a chemotherapy agent in previously treated metastatic TNBC.

Task 1: Trial III: Phase I/II trial in AR+/TN BC: Enzalutamide plus everolimus (Traina, Elias, LoRusso, advocates, Richer)
- Written protocol completed Month 21
- Submitted to Scientific Review Committee Month 21
- Submitted to IRBs (all institutions) Month 22
- DoD Human Research Protection Office (HRPO) Month 24

The timeline for this task has not yet been reached.

Milestone Meeting Month 21
**Key Research Accomplishments:**

Nothing to report. Tissue collection ongoing. Enzalutamide has clinical activity in breast cancer as a single agent and in combination with exemestane.

**Conclusion:**

Enzalutamide has clinical activity in breast cancer as a single agent and in combination with exemestane. Activity is seen in both triple negative AR+ BC and also ER+AR+ BC. Clinical data in Her2+ AR+ BC is too immature to make conclusions. The proposed clinical trials for Years 3-5 appear to be justified based on clinical activity and the current preclinical data.

**Publications, Abstracts, and Presentations:**

**Papers:**


Designated as Highly Cited by the journal Breast Cancer Research.

**Submitted:**


**Abstracts:**


Traina TA, Yardley DA, Patel MR, Schwartzberg LS, Elias A, Gucalp A, Blaney ME, Gibbons J, Hudis CA, LoRusso P. A phase 1 open-label study evaluating the safety, tolerability, and pharmacokinetics of enzalutamide alone or combined with an


Website(s) or other Internet site(s)
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Expert Opinion piece in Oncology PracticeUpdate http://www.practiceupdate.com/journalscan/9370 or http://prac.co/j/5960d32c-988b-423e-ba24-14ca5c8cc39a?elsca1=soc_share-this acknowledgement of federal support –no

Highlight of Cochrane DR et al Breast Cancer Research 2014 in Feb issue of 2014 NATURE REVIEWS CLINICAL ONCOLOGY. acknowledgement of federal support –yes

Inventions, Patents and Licenses: Nothing to report

Reportable Outcomes: Nothing to report

Other Achievements: Nothing to report

References:

Papers:

Designated as Highly Cited by the journal Breast Cancer Research.

Submitted:

Abstracts:


Website(s) or other Internet site(s)
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Expert Opinion piece in Oncology PracticeUpdate http://www.practiceupdate.com/journalscan/9370 or http://prac.co/j/5960d32c-988b-423e-ba24-14ca5c8cc39a?elsca1=soc_share-this acknowledgement of federal support –no

Highlight of Cochrane DR et al Breast Cancer Research 2014 in Feb issue of 2014 NATURE REVIEWS CLINICAL ONCOLOGY. acknowledgement of federal support –yes

Appendices

Please see following 4 pages.
Enzalutamide plus exemestane: a pilot study to assess safety, pharmacokinetics, and effects on circulating estrogens in women with advanced hormone-positive breast cancer

Lee S. Schwartzberg,1 Denise A. Yandell,2,3 Anthony Ellis4 Manish R. Patel,5 Acya Gucalp,6 Howard A. Burris,2,3 Amy C. Peterson,7 Alison L. Hannah,8 Martha E. Blaney,9 Jackie Gibbons,10 Iulia Cristina Tudor,10 Joyce L. Steinberg,1 Patricia Loffruttu,1 Jeffrey R. Infante,12 Clifford A. Hudis,12 and Tiffany A. Trainor1

1The West Clinic, Memphis, TN; 2Sanofi Cancer Research Institute, Nashville, TN; 3Tennessee Oncology, PLLC, Nashville, TN; 4Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO; 5Vanderbilt Cancer Center and Research Institute, Nashville, TN; 6Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; 7Medivation Inc., San Francisco, CA; 8Avidatech, Inc., Northbrook, IL; 9Department of Oncology, Barona Cancer Institute, Joinville, Brazil; 10Wayne State University, Detroit, MI

BACKGROUND
Androgen Receptor Signaling in ER/PR-Positive Breast Cancer
• Enzalutamide mimics androgen receptor (AR) agonist activity to promote 100% of intracellular AR signaling
• Androgen receptor (AR) is expressed in 75% of patients with ER/PR-positive breast cancer
• Selective blockade of the AR results in increased intracellular androgen receptor
• Activation of AR receptors has been associated with resistance to endocrine therapy

Enzalutamide has been shown to reduce mean exposure to both anastrozole (1 mg) and exemestane (25 mg/25 mg) daily
• Exposure, exemestane AUC (ng.h/mL)

STUDY DESIGN
Objectives
• Evaluate the safety of enzalutamide combined with exemestane 25 mg to 50 mg daily
• Evaluate exposure to exemestane with enzalutamide compared with exemestane alone

Prior exemestane use and non-naïve disease (range)

EXEMESTANE EXPOSURE WHEN COMBINED WITH ENZALUTAMIDE

Enzalutamide, aromatase inhibitors, and CYP3A4
• Enzalutamide is a steroidal glucocorticoid with activity against the AR and is metabolized by CYP3A4
• Enzalutamide was previously shown to reduce mean exposure to tamoxifen (10 mg) and exemestane (25 mg/25 mg) daily
• CYP3A4 plays a role in the metabolism of exemestane

Adverse Events Appear Similar Between the Two Dose Cohorts

RESULTS
Table 3. Baseline Demographics and Disease Characteristics for Exemestane Alone and Exemestane + Enzalutamide

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exemestane Alone</th>
<th>Exemestane + Enzalutamide</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 (46, 70)</td>
<td>56 (46, 70)</td>
<td>0.90</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>90 (83, 97)</td>
<td>91 (84, 97)</td>
<td>0.66</td>
</tr>
<tr>
<td>Black</td>
<td>1 (1, 1)</td>
<td>0 (0, 0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other</td>
<td>9 (8, 11)</td>
<td>8 (7, 10)</td>
<td>0.50</td>
</tr>
<tr>
<td>Menopause</td>
<td>99 (75, 100)</td>
<td>99 (75, 100)</td>
<td>0.98</td>
</tr>
<tr>
<td>ER status</td>
<td>100 (75, 100)</td>
<td>100 (75, 100)</td>
<td>1.00</td>
</tr>
<tr>
<td>PR status</td>
<td>99 (75, 100)</td>
<td>99 (75, 100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Grade</td>
<td>99 (75, 100)</td>
<td>99 (75, 100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stage</td>
<td>99 (75, 100)</td>
<td>99 (75, 100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Histology</td>
<td>100 (75, 100)</td>
<td>100 (75, 100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Prior hormone therapy</td>
<td>93 (86, 99)</td>
<td>92 (85, 98)</td>
<td>0.66</td>
</tr>
<tr>
<td>Prior exemestane use</td>
<td>9 (1, 1)</td>
<td>0 (0, 0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Enzalutamide treatment reduced plasma exposure to exemestane (AUC) by 50%-
• Reduction in exposure to exemestane by 50% was observed between exemestane 25 mg alone and exemestane 25 mg + enzalutamide
• Exemestane AUC values were similar for both exemestane 25 mg alone and exemestane 25 mg + enzalutamide

CONCLUSIONS
• This study defined a 50 mg dose of exemestane for use in combination with standard dose enzalutamide 160 mg/day

ACKNOWLEDGEMENTS
Enzalutamide assay was funded by Medivation, Inc. and Astellas. The study was funded by Medivation, Inc. and Astellas. It was monitored by Timothy Lohret, PhD from Infusion Communications.
INTRODUCTION AND BACKGROUND

Breast cancers are biologically diverse and distinct subtypes are classified by the presence or absence of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) overexpression.

- Distinct subtypes are classified by the presence or absence of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) overexpression.
- BREAST CANCERS ARE BIOLGICALLY DIVERSE.

- 75% of tumors harbor one or more alterations in the estrogen receptor (ER) signal transduction pathway.
- Most of these tumors lack estrogens and estrogen receptor-dependent ER signaling.
- The vast majority of breast cancers lack estrogen receptor (ER)-positive tumors.
- AR expression has been implicated as a mechanism of resistance to endocrine therapy.
- mRNA compared with other subtypes. AR signaling can promote cell survival and proliferation.

- In breast cancer, the safety, tolerability, and efficacy of enzalutamide have been evaluated in several phase I and II studies.

- The phase III AFFIRM trial included patients with metastatic hormone-refractory prostate cancer (HRPC). Enzalutamide showed significant clinical benefits in terms of overall survival (OS) and time to progression as compared with placebo. Enzalutamide was generally well tolerated (Table 1).

- This trial enrolled patients with metastatic hormone-refractory prostate cancer (HRPC). Enzalutamide showed significant clinical benefits in terms of overall survival (OS) and time to progression as compared with placebo. Enzalutamide was generally well tolerated.

- Enzalutamide is a novel oral androgen receptor (AR) antagonist.

- Enzalutamide is a novel oral androgen receptor (AR) antagonist.

- Patients received enzalutamide 200 mg daily (10 mg/kg/d) for 7 weeks and then every 12 weeks thereafter in both stage 1 and 2. Study Treatments

- *For inclusion in stage 1, patients were required to have a histologically confirmed breast cancer.

- *For inclusion in stage 1, patients were required to have a histologically confirmed breast cancer.

- Inclusion Criteria

- ≥2 lines of systemic therapy in the first 7 weeks and then every 12 weeks thereafter in both stage 1 and 2.

- Inclusion Criteria

- ≥2 lines of systemic therapy in the first 7 weeks and then every 12 weeks thereafter in both stage 1 and 2.

- Exclusion Criteria

- Known/suspected brain metastases or other malignancies.

- Known/suspected brain metastases or other malignancies.

- There was no significant difference in efﬁcacy.

- Overall response rate (ORR) was higher in patients treated with more extensive systemic therapy.

- There was no significant difference in efﬁcacy.

- Overall response rate (ORR) was higher in patients treated with more extensive systemic therapy.

CONCLUSIONS

- This will be the first study to examine the safety, tolerability, and efﬁcacy of enzalutamide in patients with incurable breast cancer.

- Measures of efﬁcacy are exploratory.

ACKNOWLEDGMENTS

Evaluating enzalutamide in ovarian cancer... bliot (2010-2011) at the Fred and Edythe Kavli Institute for Stem Cell Biology and Regenerative Medicine. Dr. Eric Schuler, MD, PhD, from Complete Healthcare Communications, Inc.

The information contained in this investigational use a drug that has not been approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA).
A Phase 1 open-label, dose-escalation study evaluating the safety, tolerability, and pharmacokinetics of enzalutamide (previously MDV3100) alone or in combination with an aromatase inhibitor in women with advanced breast cancer

Tiffany A. Traina,1 Lee Schwartzberg,2 Denise A. Yardley,3,4 Manish Patel,1 Anthony Elias,6 Ayca Gucalp,1 Amy C. Peterson,7 Alison Hannah,7 Jackie Gibbons,1 Iulia Christina Tudor,7 Martha Blaney,7 Clifford A. Hudis,1 Patricia LoRusso8

1Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; 2The West Clinic, Memphis, TN; 3Sarath Cannon Research Institute, Nashville, TN; 4Tennessee Oncology, PLLC, Nashville, TN; 5Florida Cancer Specialists and Research Institute, Sarasota, FL; 6Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO; 7Medivation Inc., San Francisco, CA; 8Department of Oncology, Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI

BACKGROUND
The androgen receptor (AR) in breast cancer:
- Enzalutamide is a potent AR antagonist indicated in castration-resistant prostate cancer.
- Enzalutamide is the first AR antagonist indicated in breast cancer; phase 2 studies have shown activity in AR+ tumors.

OBJECTIVES
- Primary: To determine the maximum tolerated dose (MTD) of enzalutamide
- Secondary: To determine the recommended dose (RD) for further testing.

STUDY DESIGN
- Dose escalation: Stage 1 (160 mg/day, with or without food) vs Stage 2.
- Combination cohorts: Enzalutamide 160 mg/day ± exemestane (exe) or anastrozole (ana).
- Patients: AR+/ER+/PgR+ BrCa, AR+ TNBC, HER2+ BrCa.

RESULTS

- Pharmacokinetics of exemestane and anastrozole:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Exemestane</th>
<th>Anastrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>1.2 ng/mL</td>
<td>0.05 ng/mL</td>
</tr>
<tr>
<td>50 mg</td>
<td>6.1 ng/mL</td>
<td>2.0 ng/mL</td>
</tr>
</tbody>
</table>

- Pharmacodynamics of enzalutamide in combination with exemestane:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Exemestane AUC (ng·h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>1.2 ng·h/mL</td>
</tr>
<tr>
<td>50 mg</td>
<td>6.1 ng·h/mL</td>
</tr>
</tbody>
</table>

- Safety and tolerability of enzalutamide alone or in combination with exemestane:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Grade 3/4 Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalone</td>
<td>16</td>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Exemalone</td>
<td>16</td>
<td>1 (6.3%)</td>
</tr>
</tbody>
</table>

- Conclusion:

- Enzalutamide at 160 mg/day, with or without food, is the recommended dose for both women and men.

ACKNOWLEDGMENTS

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BACKGROUND
The androgen receptor in breast cancer

- Enzalutamide (enza) is a potent androgen receptor (AR) inhibitor that has been approved for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) who have previously received docetaxel.

![Figure 1. Enzalutamide MDA](image1.jpg)

- The Phase II PRIMO trial evaluated enza in chemotherapy-naïve patients with advanced prostate cancer who had subsequently received docetaxel.

![Figure 2. Enzalutamide synthesis](image2.jpg)

- Enza is a potent AR inhibitor that blocks the conversion of androgens to estrogens by inhibiting aromatase, resulting in a concomitant increase in androgens.

- Enza may also add to the activity of AR by blocking potential growth stimulation of the AR due to increased circulating androgens.

- A potent androgen inhibitor (aPI) will be used.

![Figure 3. Figure 3. Study design (NCT01597193)](image3.jpg)

- Stage 2: To determine the effects of enza on the pharmacokinetics, pharmacodynamics, safety, and tolerability of either enza (mg) or enza (mg).

- Stage 1: Enzalutamide 160 mg/day, with or without food, is the recommended dose.

- Stage 2: Enzalutamide reduces mean exposure to both anastrozole and exemestane.

![Figure 4. Pharmacokinetics of enzalutamide in combination with anastrozole, docetaxel, and exemestane.](image4.jpg)

Table 1. Data supporting AR signaling in breast cancer subtypes

<table>
<thead>
<tr>
<th>Enza concentration</th>
<th>βAR</th>
<th>ER/PR</th>
<th>AR</th>
<th>HER2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 ng/mL</td>
<td>75 ng/mL</td>
<td>50 ng/mL</td>
<td>25 ng/mL</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 5. Adverse events with combination therapy](image5.jpg)

- Adverse events with single-agent enzalutamide

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Single-agent enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>44%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
</tr>
</tbody>
</table>

Objectives

1. To determine the pharmacokinetics, safety, and tolerability of enza in women with breast cancer to identify the recommended dose for further testing.

Table 2. Baseline patient demographics and characteristics

<table>
<thead>
<tr>
<th>Stage 1: Enzalutamide</th>
<th>Stage 2: Enzalutamide and AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>62 (24-87)</td>
</tr>
<tr>
<td>Number of prior regimens for breast cancer</td>
<td>2</td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3. Adverse events with single-agent enzalutamide

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Single-agent enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>44%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
</tr>
</tbody>
</table>

RESULTS

Stage 1: Enzalutamide 160 mg/day, with or without food, is the recommended dose for both women and men with prostate cancer.

Stage 2: Enzalutamide reduces mean exposure to both anastrozole and exemestane.

![Figure 6. Estradiol (A) and estrone (B) levels during exposure to enzalutamide](image6.jpg)

Table 4. Adverse events with enzalutamide in combination with anastrozole or exemestane

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Enzalutamide + anastrozole</th>
<th>Exemestane + enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>44%</td>
<td>22%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Table 5. Patients on study for ≥16 weeks

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Single-agent enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>44%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Enzalutamide, taken daily at a dose of 160 mg, is generally well tolerated as a single agent and in combination with either enza or enza. Adverse events have been observed, but have been tolerable.

- Enzalutamide can be combined with enza and effective aromatase inhibition is maintained.

- The study has been expanded to evaluate 50 mg enza plus enzalutamide: data expected in 2014.

- Enzalutamide reduced mean exposure to an enza and the effects on the hormonedrugs were variable.

- AR expression in this aBC population is representative of that reported in the literature. 3,7

- 12 of the 23 patients enrolled into the AI cohorts had been on study for 16 weeks or longer.

- Three global phase 2 clinical trials are ongoing.


- Protocol MDV3100-12: a randomized trial investigating enzalutamide plus exemestane versus enzalutamide plus placebo in hormone receptor-positive breast cancer (primary endpoint: progression-free survival).

- Protocol N87-CL-11: an open-label study investigating enzalutamide with trastuzumab in HER2+ AR+ metastatic or locally advanced breast cancer (primary endpoint: clinical benefit rate >24 weeks).

Acknowledgments

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REFERENCES