Response of Persistent Metastatic ER+/Her2- Breast Cancer to Fulvestrant plus Enzalutamide

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Abstract

Background: Breast cancers that are ER+/Her2- are most commonly treated with tamoxifen or aromatase inhibitors (AI) for various combinations. AI refractory tumor types are under investigational (II/III) trial. For patients with AI refractory metastatic breast cancer (MBC), Enzalutamide (Enza) has been found to improve progression-free survival in the phase II trial of Fulvestrant plus Enzalutamide (Fulv plus Enza). We conducted a brief phase I to demonstrate a lack of significant PK and every 4 weeks thereafter and Enza at 160 mg PO daily on a continual basis were administered.

Methods: Eligible patients were women with ECOG 0-2 who had progressed on prior AI therapy and had received Fulvestrant (Fulv) in the last 6 months, with or without prior Enzalutamide. Biopsies were required at study entry and at ~4 weeks on therapy. 32 patients were eligible, median age was 58 years, 6% were non-white, 12% were Hispanic, 2% were Asian, 5% were non-Hispanic Black. 94% were ER+ and 90% were Her2-. 59.4% had more than 1 metastatic site and 40.6% had 1 metastatic site. 39% had bone metastases (BM), 43% had lung metastases (LM), 32% had pleural effusion, and 4% had no metastases. PD-L1 was evaluated in 4% of baseline biopsies (p<0.02). Overall, PD-L1 increased significantly following Fulv plus Enza treatment (paired signal2-6).

Results: CBR24 was 22 (95% CI: 8.3 to 41.0) percent. The median time to progression was 57 (95% CI: 56 to 91) days when both were high, 14 days (95% CI: 13 to Inf) days when both were low. For patients with short PFS, CBR was 3% (95% CI: 0 to Inf) and 14 days (95% CI: 13 to Inf) days when both were low.

Conclusions: This clinical trial was successful in demonstrating the safety of Fulv plus Enza in AI refractory metastatic breast cancer. Further trials to identify the biologic characteristics of patients who benefit from Fulv plus Enza treatment are warranted.

Hypothesis

ER+ breast cancer resistant to traditional endocrine therapy may benefit from blocking both ER and AR by using an estrogen degrader combined with an AR antagonist.

Study Design

- Single arm, non-randomized, open-label treatment
  - Fulvestrant 500 mg IM days 1, 15, 29 and every 4 weeks thereafter and Enza at 160 mg PO daily on a continual basis were administered.
  - Prior Fulvestrant was allowed. Enzalutamide 160 mg po daily.
  - ER+/Her2- metastatic breast cancer
  - CBR at 24 weeks was primary endpoint. Assuming an undesirable rate of 10% and desirable rate of 90% and a two-sided alpha of 0.05, 33 patients were required to achieve 90% power. This was considered a Phase 1 dose-escalation clinical trial to determine the maximum tolerated dose (MTD).

Inclusion & Exclusion Criteria

- Single arm, non-randomized, open-label treatment
- Prior Fulvestrant was allowed. Enzalutamide 160 mg po daily.
- ER+/Her2- metastatic breast cancer
- CBR at 24 weeks was primary endpoint. Assuming an undesirable rate of 10% and desirable rate of 90% and a two-sided alpha of 0.05, 33 patients were required to achieve 90% power. This was considered a Phase 1 dose-escalation clinical trial to determine the maximum tolerated dose (MTD).

Clinical benefit rate and progression-free survival

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PD-L1 significantly increased with Fulvestrant plus Enzalutamide treatment. Baseline PD-L1 was measured by immunohistochemistry (IHC) and confirmed by flow cytometry. PD-L1 and CD68 were identified using Opal™ images and fluorescence-activated cell sorting (FACS) analysis.

RPPA indicated that the mTOR pathway was significantly active at baseline in tumor biopsies from patients with short versus long PFS.

Immune infiltrates differ in ESR1 mutant versus WT biopsies

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Figure 3. C-ABL pY245 significantly increased with Fulvestrant plus Enzalutamide treatment. Baseline PD-L1 was measured by immunohistochemistry (IHC) and confirmed by flow cytometry. PD-L1 and CD68 were identified using Opal™ images and fluorescence-activated cell sorting (FACS) analysis.

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