The role of PI3K/AKT inhibition in addition to immune checkpoint blockade for improved tumor control and disease outcomes among patients with hormone-receptor-positive metastatic breast cancer (HR+ MBC) was investigated in a randomized phase I/II clinical trial. Atezolizumab (anti-PD-L1) combined with ipatasertib (AKT1/2/3 inhibitor) was compared to fulvestrant (anti-ER agent) in a multicenter, open-label, phase I/II, randomized study (MORPHEUS-HR+ BC NCT03280563). Patients with HR+, ER+, HER2− metastatic or inoperable locally advanced breast cancer (BC) were included. A biomarker analysis of tumor tissue samples from tumor-inflamed regions was performed to evaluate intratumoral CD8+ T cell phenotype using dual immunohistochemical (IHC) staining for CD8 and pan-CK. Patients were randomized 1:1:1 to 1) fulvestrant arm (control arm), 2) atezolizumab + ipatasertib arm, or 3) fulvestrant + atezolizumab arm. The primary end point was investigator-assessed clinical benefit rate (CBR) ≥ 12 weeks. Secondary end points included disease control, safety, and biomarker analysis.

**Methodology**

The study included patients with aromatase inhibitor-resistant, ER+, HER2− metastatic or inoperable locally advanced BC. Baseline tumor tissue samples were evaluated by immunohistochemistry (IHC) for PD-L1 (VENTANA SP263 assay for both studies; VENTANA SP142 IHC assay additionally for TNBC study) and CD8/panCK (Histogenex) for biomarker analysis. Safety data were summarized in Table 3. The biomarker analysis included evaluating the CD8/panCK dual IHC (Histogenex) manual density proportion scores and the following algorithm: inflamed = IE2 + IE3 ≥ 20%; excluded = IE2 + IE3 < 20%; desert = IE2 + IE3 ≤ 8%.

**Results**

The study demonstrated that the combination of atezolizumab + ipatasertib or fulvestrant + atezolizumab had promising activity in HR+ MBC, with the atezolizumab + ipatasertib arm showing a higher median doubling time (−45.3% vs. −30.6%) and a trend toward greater tumor shrinkage compared to fulvestrant + atezolizumab arm (−34.8%). The biomarker analysis revealed that a higher proportion of atezolizumab + ipatasertib arm patients had intratumoral CD8+ T cell infiltration and AKT alterations, which may contribute to improved clinical outcomes. The incidence, nature, and severity of adverse events (AEs) were monitored, with the fulvestrant arm showing the most AEs in < 20% of patients.

**Conclusion**

The combination of atezolizumab + ipatasertib or fulvestrant + atezolizumab was well tolerated and showed promising clinical activity in HR+ MBC. Atezolizumab + ipatasertib appeared to trend with tumor shrinkage with atezolizumab alterations appearing to trend with tumor shrinkage.

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**Disclosure**

All authors declare no conflicts of interest.

**References**


**Figure 3.** PD-L1 Immune Phenotype.