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Gedatolisib (geda) + fulvestrant ± palbociclib (palbo) vs fulvestrant in patients (pts) with HR+/ HER2-/PIK3CA wild-type (WT) advanced breast cancer (ABC): First results from VIKTORIA-1

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Background

In HR+/HER2- ABC, resistance to 1L endocrine therapy (ET) and CDK4/6 inhibition (CDK4/6i) is common and likely involves the PI3K/AKT/mTOR (PAM) pathway. Adding PAM inhibition (PAMi) with gedatolisib may restore sensitivity and improve efficacy relative to PI3K α , AKT, and mTORC1 inhibitors (Rosetti 2024). In phase 1b, 2L/3L geda/palbo/fulvestrant demonstrated 56% ORR; 12.9 mos median PFS; and 33.9 mos median OS (Layman 2024 & 2025).

Methods

The randomized, open-label phase 3 VIKTORIA-1 trial enrolled pts with HR+/HER2- ABC that progressed during/after CDK4/6i plus AI and assessed *PIK3CA* status. A total of 392 pts with *PIK3CA* WT disease were randomized to 28-day cycles of: geda/palbo/fulvestrant (triplet); geda/fulvestrant (doublet); or fulvestrant. Doses were geda 180 mg IV QWx3; palbo 125 mg QDx21; fulvestrant 500 mg IM Q2W (cycle 1) then Q4W. Co-primary endpoints were PFS assessed by BICR comparing the triplet to fulvestrant, then, if positive, the doublet to fulvestrant. Statistical comparisons were performed by stratified log-rank test. Secondary endpoints include OS, safety, and response.

Results

At data cut-off (30/5/2025), median study follow-up was 10.1 mos. Topline results showed the trial met its primary endpoints, with mPFS for the triplet vs fulvestrant of 9.3 vs 2.0 mos (HR, 0.24; 95% CI, 0.17-0.35; $P<0.0001$) and doublet (7.4 vs 2.0 mos; HR, 0.33; 95% CI, 0.24-0.48; $P<0.0001$). This abstract includes previously unreported data: PFS benefit consistence across pre-specified subgroups; response (ORR: 32%, including 1 CR, [triplet]; 28.3% [doublet]; and 1% [fulvestrant]); and interim OS analysis (HR: 0.69, 95% CI, 0.43-1.12 [triplet] and 0.74, 95% CI, 0.46-1.19 [doublet]). Safety profiles were generally consistent with the individual agents, with low rates of discontinuation of assigned therapy due to treatment-related adverse events (2.3% for triplet; 3.1% for doublet). Hyperglycemia incidence was 9.2% and 11.5%, respectively, with grade 3 severity in 2.3% of pts in both geda groups.

Conclusions

These data support gedatolisib combination therapy as a potential new standard of care for the 2L treatment of pts with HR+/HER2-/PIK3CA WT ABC.

Clinical trial identification

NCT055001886.

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Disclosure

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