LBA3_PR Alpelisib (ALP) + fulvestrant (FUL) for advanced breast cancer (ABC): Results of the phase III SOLAR-1 trial

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Background: Hyperactivation of the phosphatidylinositol-3-kinase (PI3K) pathway can occur due to PIK3CA mutations, present in ~40% of patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) ABC. The Phase 3 randomized, double-blind SOLAR1 trial (NCT02437318) investigated the efficacy and safety of ALP (α-specific PI3K inhibitor) + FUL in pts with HR+, HER2– ABC.

Methods: Men/postmenopausal women with HR+, HER2– ABC and 1 prior line of endocrine therapy were randomized (1:1) to ALP (300 mg/day) + FUL (500 mg every 28 days + Cycle 1 Day 15) or placebo (PBO) + FUL. Primary endpoint was locally assessed progression-free survival (PFS) in the PIK3CA-mutant (mut) cohort; PFS was analyzed in the non-mut cohort as a proof of concept (PoC). Safety was assessed in the total population. Other analyses were tumor response and PFS by important prognostic subgroups, including PIK3CA mutation exon/domain and subtype.

Results: 572 pts enrolled; 341 had PIK3CA-mut ABC by tissue. Primary endpoint was met; PFS in the mut cohort was significantly longer with ALP+FUL vs PBO+FUL (HR 0.65; 95% CI 0.50–0.85; P = 0.00065; median 11.0 vs 5.7 months [mo]); median follow-up was 20.0 mo. Secondary endpoint of locally assessed PFS in the non-mut cohort did not meet predefined PoC criteria (HR 0.85; 95% CI 0.58–1.25; median 7.4 vs 5.6 mo). In pts with measurable, PIK3CA-mut ABC (n = 262), overall response rate was 36% for ALP+FUL vs 16% for PBO+FUL (p = 0.0002). Overall, most frequent all-grade (G) adverse events (AEs; single preferred term; ALP+FUL vs PBO+FUL) were hyperglycemia (64% vs 10%), diarrhea (58% vs 16%), nausea (45% vs 22%), decreased appetite (36% vs 10%) and rash (36% vs 6%). G 3/4 hyperglycemia (fasting plasma glucose >250 mg/dL) was observed in 37% of patients for ALP+FUL vs < 1% for PBO+FUL; G 3/4 rash in 10% vs < 1%. Discontinuations of ALP+FUL/PBO+FUL due to AEs were 5% vs 1%.

Conclusions: ALP+FUL met the primary endpoint by significantly extending PFS vs PBO+FUL and demonstrated a manageable tolerability profile. This is the first study to show statistically significant, clinically meaningful PFS treatment improvement with an α-specific PI3K inhibitor in PIK3CA-mut HR+, HER2– ABC.

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