GS1-01: Imlunestrant, an Oral Selective Estrogen Receptor Degrader (SERD), as Monotherapy & Combined with Abemaciclib, for Patients with ER+, HER2- Advanced Breast Cancer (ABC), Pretreated with Endocrine Therapy (ET): Results of the Phase 3 EMBER-3 trial

Presenting Author(s): Komal Jhaveri

Abstract Number: SESS-3617

Background: Imlunestrant is a next-generation, brain-penetrant, oral SERD and pure estrogen receptor (ER) antagonist that delivers continuous ER inhibition, including in ESR1-mutant cancers.

Methods: This phase-3, randomized, open-label trial (NCT04975308) enrolled patients (pts) with ER+, HER2- ABC that recurred or progressed on/after an aromatase inhibitor, alone or with a CDK4/6 inhibitor (CDK/6i). No other prior therapy for ABC was allowed. Pts were randomized 1:1:1 to imlunestrant (400 mg once daily [QD]), physician's choice standard-of-care (SOC) ET (fulvestrant or exemestane per label), or imlunestrant (400 mg QD) + abemaciclib (150 mg twice daily). Primary endpoints were investigator-assessed PFS of imlunestrant vs SOC in pts with ESR1 mutations (ESR1m) and all pts and of imlunestrant + abemaciclib vs imlunestrant in all concurrently randomized pts. Secondary endpoints included OS (tested if the corresponding PFS was statistically significant), PFS by BICR, ORR, and safety.

Results: Overall, 874 pts were randomized (imlunestrant, n=331; SOC, n=330; imlunestrant + abemaciclib, n=213), 60% received prior CDK4/6i (imlunestrant, 59%; SOC, 57%; imlunestrant + abemaciclib, 65%). A total of 256 pts had ESR1m (imlunestrant, n=138; SOC, n=118). Imlunestrant significantly improved PFS vs SOC in pts with ESR1m (HR, 0.62; 95% CI, 0.46-0.82; P<0.001; median PFS [mPFS] 5.5 vs 3.8 months). Imlunestrant did not significantly improve PFS in the overall population (n=661; HR, 0.87; 95% CI, 0.72-1.04; P=0.12). Imlunestrant + abemaciclib significantly improved PFS vs imlunestrant in all pts (n=426; HR, 0.57; 95% CI, 0.44-0.73; P<0.001; mPFS 9.4 vs 5.5 months), with benefit observed regardless of ESR1m or PI3K pathway mutation status and in CDK4/6i pretreated pts. Investigator and BICR assessments were consistent across all endpoints. In all pts with measurable disease, ORR was 12% for imlunestrant; 8% for SOC; and 27% for imlunestrant + abemaciclib. All OS analyses were immature and ongoing; favorable trends were observed for imlunestrant vs SOC in pts with ESR1m (31% events; HR, 0.55; 95% CI, 0.35-0.86; P<0.01 [not statistically significant]) and in all pts (23% events; HR, 0.69; 95% CI, 0.50-0.96; [not inferentially tested]). OS analyses were less mature for imlunestrant + abemaciclib vs imlunestrant (15% events; HR, 1.34; 95% CI, 0.81-2.21; P=0.25). In post-hoc analyses, imlunestrant had lower 12-month cumulative incidence of central nervous system progression vs SOC in pts with ESR1m (2% vs 7%; HR, 0.18; 95% CI, 0.04-0.90) and all pts (2% vs 3%; HR, 0.47; 95% CI, 0.16-1.38), though absolute numbers were small.

Common all-grade TEAEs with imlunestrant were fatigue (23% vs 13% SOC), diarrhea (21% vs 12%), and nausea (17% vs 13%), mostly grade 1. Notably, all-grade bradycardia (2% vs 0% SOC), photopsia (0% each), and dyslipidemia (7% vs 9%) were infrequent or not observed with imlunestrant. Common grade ≥3 TEAEs with imlunestrant were anemia (2% vs 3% SOC), and neutropenia (2% each). Common all-grade/grade ≥3 TEAEs with imlunestrant + abemaciclib were diarrhea (86%/8%), nausea (49%/2%), and neutropenia (48%/20%). Grade ≥3 TEAEs rates were 17% for imlunestrant, 21% for SOC and 49% for imlunestrant + abemaciclib. Discontinuation of imlunestrant and imlunestrant + abemaciclib due to AEs was low (4% and 6%, respectively). Conclusion: Imlunestrant significantly improved PFS vs SOC in pts with ESR1m, and imlunestrant + abemaciclib significantly improved PFS vs imlunestrant in all pts regardless of ESR1m status. Imlunestrant had a favorable safety profile alone and combined with abemaciclib, thus providing an all-oral targeted therapy option for ET-pretreated pts with ER+, HER2- ABC.