PS7-01: Efficacy of RLY-2608, a mutant-selective PI3Kα inhibitor in patients with PIK3CA-mutant HR+HER2- advanced breast cancer: ReDiscover trial

Presenting Author(s): Cristina Saura

Abstract Number: SESS-2211

Background
Oncogenic PIK3CA mutations constitutively activate PI3Kα and drive approximately 40% of HR+HER2- breast cancer (BC); however, the toxicity (hyperglycemia, rash, diarrhea, stomatitis) of non-selective inhibitors (i) limits their tolerability and efficacy. RLY-2608 is the first oral, mutant-selective, allosteric PI3Kαi designed to overcome these limitations. We report efficacy and safety of RLY-2608 + standard-dose fulvestrant (F) in pts with PIK3CA-mutant, HR+HER2- BC treated in the FIH study, ReDiscover (NCT05216432).

Methods
Previously treated adult pts with advanced HR+HER2- BC and PIK3CA mutation per local assessment were eligible. Key objectives were investigator-assessed efficacy per RECIST 1.1 and adverse events (AEs) per CTCAE v5.0. Safety was assessed in all pts, and efficacy in pts without detectable PTEN/AKT co-alterations treated at the RP2D.

Results
As of 24JUN24, 116 pts received RLY-2608 (100-1000 mg BID) + F. All pts received prior endocrine therapy and CDK4/6i with 51% having 2 prior systemic therapies for advanced disease including 57% with prior F/SERD and 22% with prior chemotherapy or antibody-drug conjugate.
Treatment-related AEs (TRAEs) were generally low-grade, manageable and reversible, most commonly hyperglycemia (42% any grade; 2% Gr 3), nausea (40%; 1% Gr 3), creatinine increased (34%; 0 Gr 3), fatigue (32%; 7% Gr 3), and diarrhea (28%; 1% Gr 3). There were no grade 4/5 TRAEs.
Sixty-two pts (30 kinase, 24 helical, 8 other) were treated at the 600 mg BID RP2D which provided exposure in the target therapeutic range and rapid decline in mutant PIK3CA ctDNA. Treatment was ongoing in 34/62 (55%) and discontinued in 28 (22 due to PD and 2 due to TRAE). Of 52 pts without PTEN/AKT alterations, mPFS was 9.2 months (95% CI 5.5-12.4), 18/26 (69.2%) evaluable for response had radiographic tumor reduction and 8 achieved an objective response (30.8%, 95% CI 14.3-51.8) with median time-to-response 8 weeks.

Conclusion
RLY-2608 demonstrates durable initial efficacy and favorable safety/tolerability across PIK3CA genotypes in heavily pretreated pts previously exposed to CDK4/6i with advanced PIK3CA-mutant HR+HER2- BC without concurrent PTEN/AKT alterations. These data validate RLY-2608 as the first allosteric pan-mutant selective PI3Kαi and warrant pivotal clinical development.