Ribociclib improves survival in hormone receptor-positive (HR+) /HER2-negative (HER2-) advanced breast cancer (BC). Deeper understanding of the biology associated with ribociclib efficacy is needed, especially within the HER2-enriched (HER2E) subtype given recent analysis of MONALEESA program (Prat, JCO, 2021). Here, we performed gene expression (GE) analysis with/without ribociclib monotherapy in BC patient-derived xenografts (PDX).

**Background**

- Eighteen PDXs representative of HR+/HER2- (n=11, 61%), HER2+ (n=3, 63%) and triple-negative (n=6, 6%) BC (Table 1) were treated with ribociclib monotherapy (75 mg/kg/day). The % change in tumor volume from baseline was calculated at day 35.
- RNA was obtained from flash-frozen tumors at baseline and change in tumor volume from baseline was calculated at day 35.
- Paired GE analyses across PDXs identified 12 upregulated genes during treatment, including estrogen activation-related genes (ESR1, PGR, FOXA1, MAPT or BLVRA); and 12 downregulated genes, including proliferation-related genes (MKI67 or KIF2C) and HER2E-related genes (ERBB2 or TME45B) (Fig. 1).

**Results**

- Baseline PAM50 subtype distribution was Luminal B (44%), HER2E (33%) and Basal-like (B-L) (22%) (Fig. 1).
- HER2E and Luminal B PDXs showed a statistically significant higher response to ribociclib (mean change in volume >40% and >140%), than B-L (≤60%) (Fig. 2).
- Baseline GE analysis identified 6 genes highly expressed in responders (FOXA1, ERBB2, GRB7, MLPH, GPR160 and CXXC5), and 7 lower expressed genes (SFRP1, KRT17, MYC, CDH3, KRT5 and KRT14) (Fig. 3).
- Paired GE analyses across PDXs identified 12 upregulated genes during treatment, including estrogen activation-related genes (ESR1, PGR, FOXA1, MAPT or BLVRA); and 12 downregulated genes, including proliferation-related genes (MKI67 or KIF2C) and HER2E-related genes (ERBB2 or TME45B) (Fig. 4).

**Conclusion**

In BC PDXs, B-L biology associates with lower response to ribociclib monotherapy than Luminal or HER2E. Ribociclib induces a luminal phenotype with high GE of estrogen-regulated genes and low GE of proliferation genes, a biological switch that could explain the better efficacy of ribociclib in the ET-resistant HER2E subtype observed in clinical trials when combined with ET.