GS3-09: Multimodal integration of real world clinical and genomic data for the prediction of CDK4/6 inhibitors outcomes in patients with HR+/HER2- metastatic breast cancer.

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Introduction: Addition of CDK4/6 inhibitors (CDK4/6i) to endocrine therapy (ET) have led to marked improvement of outcomes in patients (pts) with HR+/HER2− metastatic breast cancer (MBC). However, the responses vary significantly with a subset of patients experiencing early therapeutic resistance. In view of many potential alternative therapeutic approaches for these patients, we sought to develop machine learning (ML) models based on clinical and genomic characteristics at the time of metastatic recurrence, to predict outcomes on 1st line CDK4/6i+ET in pts with HR+/HER2- MBC.

Methods: We identified 535 pts with HR+/HER2- MBC who received 1st line CDK4/6i+ ET between 12/2013 and 10/2023 from MSK translational database for whom MSK-IMPACT targeted tumor sequencing was performed on samples collected pre-treatment or within 2 months of the start of CDK4/6i. The models were trained on pts with complete clinical and genomic data (n=370) with 10-fold cross validation and tested on the hold-out set (n=165). OncoCast-MPM ML framework and Gradient Boosting Machine (GBM) algorithm was used to generate 3 models to predict CDK4/6i progression-free survival (PFS) based on clinicopathological features (CF), genomic features (GF) and integrating CF and GF (CGF). The Kaplan-Meier estimator with log-rank test and Cox proportional hazard models were used to assess differences in PFS, and to calculate hazard ratios (HRs) between risk groups.

Results: The median PFS (mPFS) of the full cohort was 17.8 m (95% CI: 16.1-19.7), with 67% of pts having an event. The mPFS of the training and hold-out set cohorts were 17.3 m (95% CI: 15.2.1-19.6), and 18.3 (95% CI: 16.1-23.5) with 68% and with 65% of pts having an event, respectively. The model trained on CF identified 2 risk groups (RGs): good RG (n=221), with a mPFS of 23.2m (95% CI: 18.3-28.5), and poor RG (n=149), with a mPFS of 11.6m (95% CI: 8.78-13.71). The model trained on GF identified 2 RGs: good RG (n=209), with a mPFS of 28.1m (95% CI: 21.9-31.7), and poor RG (n=161), with a mPFS of 9.7m (95% CI: 8.4-11.9). The CGF integrated model identified 3 RGs: good RG (n=113), with a mPFS of 31.3m (95% CI: 24.9-44.4), intermediate RG (n=156), with a mPFS of 18.5m (95% CI: 15.2-21.9), and poor RG (n= 101), with a mPFS of 7.9 m (95% CI: 5.4-10). The HRs between the good and poor RGs were 1.95 (95% CI: 1.5-2.5; p= 2.6e-7), 2.4 (95% CI: 1.9-3.1; p= 2.0e-11) and 4.2 (95% CI: 3.0-5.9; p= 2.8e-16) for the CF, GF and CGF models, respectively, highlighting the superior stratification power achieved by integrated clinico-genomic features. Interestingly the top 10 key features used by the multimodal model represent the union of the top 5 clinical and molecular features of the unimodal models. These features, in order of importance were tumor mutational burden (TMB), fraction of genome altered (FGA), TP53 alteration, fraction of genome with loss of heterozygosity (LOH), presence of liver metastasis,

adjuvant treatment free interval < 1 year, primary tumor grade III, presence of visceral metastasis, primary tumor PR negativity and whole genome doubling. The results of the CGF model on the hold-out test set confirmed the presence of 3 RGs with similar HR to those identified in the training set, with no statistically significant difference in results between the training and tests sets.

Conclusions: The multimodal machine learning model integrating both clinical and genomic features, provided superior stratification and predictive power for outcomes on 1st line CDK4/6i combination compared to unimodal models. Precise risk stratification of HR+/HER2- MBC patients at the time of metastatic recurrence is key for devising therapeutic and monitoring strategies and trial design.