BluePrint Luminal subtype predicts non-response to HER2-targeted therapies in HR+/HER2+ I-SPY2 breast cancer patients

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Introduction

- BluePrint molecular profile determines the mRNA levels of 80 genes that discriminate between 3 breast cancer subtypes based on functional molecular pathways: Luminal, HER2 and Basal.
- Previous studies suggest that within the HR+/HER2+ breast cancer subtype, patients classified as BluePrint (BP) Luminal subtype are more responsive to pertuzumab and trastuzumab (P/H) as opposed to trastuzumab (H) alone.
- In the I-SPY2 TRIAL (NCT01042379), HER2-targeted treatment arms include H, P/H, neratinib (N), T-DM1/pertuzumab (P), MK2206/H and AMG386/H; and patients were classified by BP molecular subtyping in addition to conventional receptors.

Can BluePrint subtype predict response to HER2-targeted agents in I-SPY2 HR+/HER2+ breast cancer patients? What are the pathway differences between the BP subtypes?

Methods

- We used Fisher’s exact test to assess association between BP subtypes and pCR
- To identify genes associated with BP Luminal vs. BP HER2 subtype, we applied a Wilcoxon rank sum test and fitted a logistic model, with the Benjamin-Hochberg (BH) multiple testing correction (BH p<0.05). We then performed pathway enrichment analysis using DAVID (ver. 6.8).
- Our study is exploratory and does not adjust for multiplicities of other biomarkers in the trial outside this study

Results

IHC/FISH HR+/HER2+ BluePrint Luminal subtype is associated with lower responses to HER2-targeted agents, with the exception of MK2206/H.

Semi-supervised heat map showing the expression of BluePrint genes in 152 IHC/FISH HR+/HER2+ patients

Immune-related biological processes were significantly enriched based on DAVID functional enrichment analysis

- HR+/HER2+ BP HER2-type patients demonstrated higher expression levels of immune-related genes e.g. CTLA4, ITGB2

Conclusion

- Our analysis suggests that IHC/FISH HR+/HER2+ BP Luminal subtype is associated with lower response rates to HER2-targeted agents, including Pertuzumab/Trastuzumab, and may need an alternative strategy.
- IHC/FISH HR+/HER2+ BP HER2 subtype appears associated with higher expression of immune-related genes, relative to BP Luminal; and suggests that immune signaling may contribute to HER2-targeted therapy sensitivity.

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