Identification of Biomarkers Involved in CDK4/6 Inhibitor Therapy Resistance and the Molecular Response to Treatment for Metastatic ER+/HER2- Breast Cancer

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Background

- While breast cancer in general has good 5-year survival rates, metastatic breast cancer specifically has a poor 5-year survival rate of ~25%.  
- Probability of metastatic recurrence rises every year after initial treatment ends; 20-30% of all early breast cancers will eventually experience a metastatic recurrence.  
- Primary treatment of ER+/HER2- metastatic breast cancer uses hormone therapy, but developing resistance is common and can be quick.

Molecular Profile

- Palbociclib, a CDK4/6 inhibitor (CDK4/6i) that halts cell cycle progression, significantly improves PFS in conjunction with standard hormone therapies used to treat ER+/HER2- metastases, but resistance is still inevitable.

Methods

- **Analysis of Clinical Outcomes and Treatment Response**
  - 65 ER+/HER2- patients from MD Anderson’s CDK4/6i cohort – a collection of metastatic breast cancer patients that received CDK4/6i therapy and then progressed – were selected for analysis.
  - All 65 patients chosen received palbociclib as their CDK4/6i.
  - All have had biopsies performed on treatment-naive metastases; biopsies stored as FFPE slides.
  - The 65 patients were divided into 6 categories depending on PFS and the type of treatment received.

  - Early progressors could also be referred to as ‘intrinsic resistance’ and late progressors as “acquired resistance”.

Methods (cont.)

- **RNA processing and DEG analysis pipeline**

  - **QC**
  - Filtered and trimmed reads on raw sequences
  - QC (multiQC)
  - DEG and GSEA analysis
  - Generation of preliminary gene signatures
  - Gather biological information for genes of interest

Results - Clinical

- **Results - Gene Analysis**
  - All steps up to normalization of reads using DESeq2 have been completed.
  - Overall data quality appears good:
    - fastQC data reveals a majority of samples have good quality sequences with minimal overall contamination.
  - Alignment rates match expectations based on previous literature using STAR alignment in sequencing data.
  - B.) OS for early progressors vs. late progressors shows results which match expectations given that early and late progressors are defined by PFS.
  - C.) PFS for early first line treatment vs early second line treatment was the only significant KM plot among all first vs second line comparisons.

Discussion

- There is a significant difference in OS based on acquired vs. intrinsic resistance.
- Suggests the existence of unique biomarkers that are characteristic of an intrinsic resistance phenotype.

Next Steps

- Complete normalization of quantified RNA-seq data using DESeq2.
- Perform DEG and GSEA analysis on normalized sequencing data.
- Look for patterns found in palbociclib cohort KM plots in the larger CDK4/6i cohort.

References

4. Finn et al. (2015). \( \frac{16}{1} \), 25-35.
5. McCarty et al. (2019), Front Oncol, 9, 666.