Background

- Genomic scars and HRD gene mutations are biomarkers for PARP inhibitor (PARPi) and platinum agent therapy response in breast cancer.
- Tests for these markers are usually performed by next generation sequencing (NGS) of tumor tissue or circulating tumor DNA (ctDNA) and have limitations such as sample accessibility, availability, and sub-sampling due to inter/intra-tumor heterogeneity.
- Previously, we predicted GI using CTC phenotypic features without the use of NGS in metastatic castration-resistant prostate cancer (mCRPC) pts with high accuracy (>76%) (ASCQ 2016). In addition, patients with phenotypically predicted GI (pGI) CTCs had significantly better PSA responses on Abiraterone + Veliparib (G3) vs. Abiraterone alone (G2) (ESMO 2018), and also responded better to platinum agents vs. taxanes (ESMO 2017).
- Here, we sought to develop and analytically validate an algorithm for predicting CTC pGI in TNBC.

Methods

- Training set: 521 CTCs from 28 mCRPC pts were detected with the Epic Sciences CTC platform and analyzed for 19 phenotypic digital pathology features, including protein expression and cell morphology. The same CTCs were single-cell sequenced for the number of large scale transitions (LSTs) as an indicator of GI. A linear regression algorithm to predict GI by CTC phenotype was developed, cross validated, and utilized to generate a CTC pGI score.
- Test set: 14 CTCs from 8 TNBC blood samples, median of 8 CTCs/pb, were sequenced for GI and phenotypically predicted.

Phenotype and Genotype Correlations (mCRPC)

(A) CTC Phenotypic Features

(B) Pearson Correlations of Phenotypic Features to GI Scores

Genotype Driving Phenotype (TNBC)

Driver Genes

Genetic Instability (GI) Phenotype

N/A

Low

Med

High

BRC1 A1/3

BRC2 A1/3

ATM

p53 etc

LST: 2

LST: 3

LST: 28

LST: 61

Representative TNBC High/Low GI CTC Images

Representative imagery from CTCs with high genenic instability (high LSTs/pGI) and low genenic instability (low LSTs/pGI) and key features associated with phenotypic classifier.

Conclusions

- Previous studies showed that pGI was an analytically validated biomarker with clinical utility to predict PARPi or platinum therapy response in mCRPC pts.
- Here we show the same test concept can be applied to TNBC.
- Further analytical validation in a larger cohort is ongoing.
- The ability to identify PARPi/platinum sensitivity using an IF CTC staining method for CTC phenotype without the use of NGS will help to stratify patients more rapidly, at reduced cost and aid in the acceleration of drug development.