4.2. Public data sources used in the current study:

- TCGA Cancer Genome Atlas:
  - NCT01364479
  - NCT01728248
  - NCT02169392
  - NCT02455336
- CTRP Cancer Therapeutics Response Portal V2:
  - NCT03414034
- CCLE Cancer Cell Line Encyclopedia:
  - NCT00602990
- RNA seq Biomarker Discovery pipeline: www.cancergenome.nih.gov
- ENrichment ontology and KEGG Genes found during feature selection were enriched for GeneName:
  - ASXL1 (n=118): 5.76E-01 (positive), 5.70E-01 (negative), 3.66E-01 (positive), 2.61E-01 (negative)
  - BCR (n=86): 4.93E-02 (positive), 4.33E-02 (negative), 3.47E-02 (positive), 2.98E-02 (negative)
  - TP53 (n=63): 0.00E+00 (negative), 1.38E-03 (positive), 4.17E-04 (positive), 0.00E+00 (negative)

Objective

- Discover potential RNA and DNA biomarkers that are associated with PC-075 sensitivity using in-vitro cell line sensitivity data and predictive regression models.

Methods

- **Biomarker Discovery pipeline**: 
  - Feature Selection Algorithm
  - Final Model construction
  - Model prediction
  - Biomarker Discovery

Results

The gene expression profile associated with sensitivity to PC-075 is positively enriched for pathways associated with highly proliferative/aggressive tumor growth

Results of the study:

- The top 2 genes with highest gene expression, TUBGCP4 and DVL1, are involved in mitotic activities associated with PLK1
- TUBGCP4 genes were the two highest ranked gene expression features found (ranked by VIF and p<0.01)
- Disheveled Segment Polarity Protein 1 (DVL1) is critical for cell division and microtubule stability. The DVL complex has been shown to be phosphorylated by PLK1
- Tubulin Gamma Complex Associated Protein 4 (TUBGCP4) is important for microtubule nucleation and is involved in the Regulation of PLK1 Activity at G2/M Transition pathway
- High TUBGCP4 expression is associated with an aggressive subtype (STEM-A) of ovarian cancer
- PC-075 has been shown to have significant anti-tumor activity in a xenograft A2780 STEM-A cell model (not shown)

**Mutation biomarkers associated with predicted sensitivity in CCLE cell line models**

- Sensitivity (AUC) was predicted for all 819 cell lines using tissue normalized gene expression profiles from CCLE
- 1-way ANOVA was then used to search for potential driver mutations (curated by the GDSC) associated with predicted sensitivity values
- 19 gene mutations show a significant association (p<0.05) with predicted sensitivity and are associated with aggressive tumor growth
- ASXL1 mutations are the highest ranked potential biomarker
- Tumors with ASXL1 mutations are highly aggressive and show poor prognosis in many indications