

# Integrated Analysis of Cancer Mutations and Drug-Gene Interactions for Targeted Therapy

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## Introduction

### Studying drug-gene interaction for personalized therapy

- ❖ Cancer is known to be caused by genetic perturbations.
- ❖ Challenges: these mutation patterns are highly heterogeneous meaning that these different combination of mutations would still result in the same disease phenotypes.
- ❖ “One size fits all” paradigm for treatment becomes flawed.
- ❖ Within the same category of cancer types, different patients responds differently to a variety of treatment therapies.

### Objectives

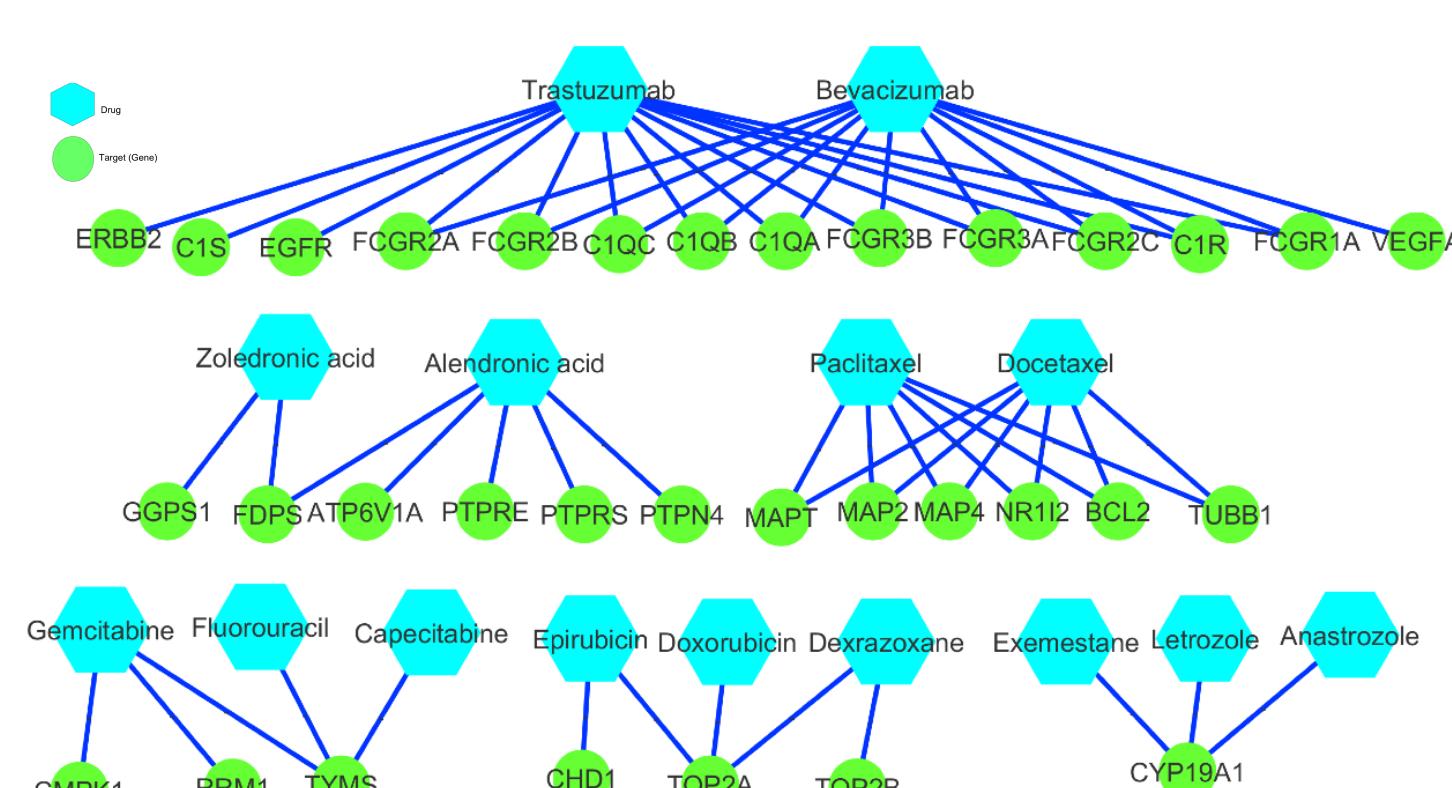
- ❖ To understand the role of mutation heterogeneity using network-centric analysis approach for cancer mutations to gain more insights to progress towards personalized therapy.
- ❖ To study the interaction network of the mutated genes and the drug targets to infer insights of different cancer treatments.

### Questions

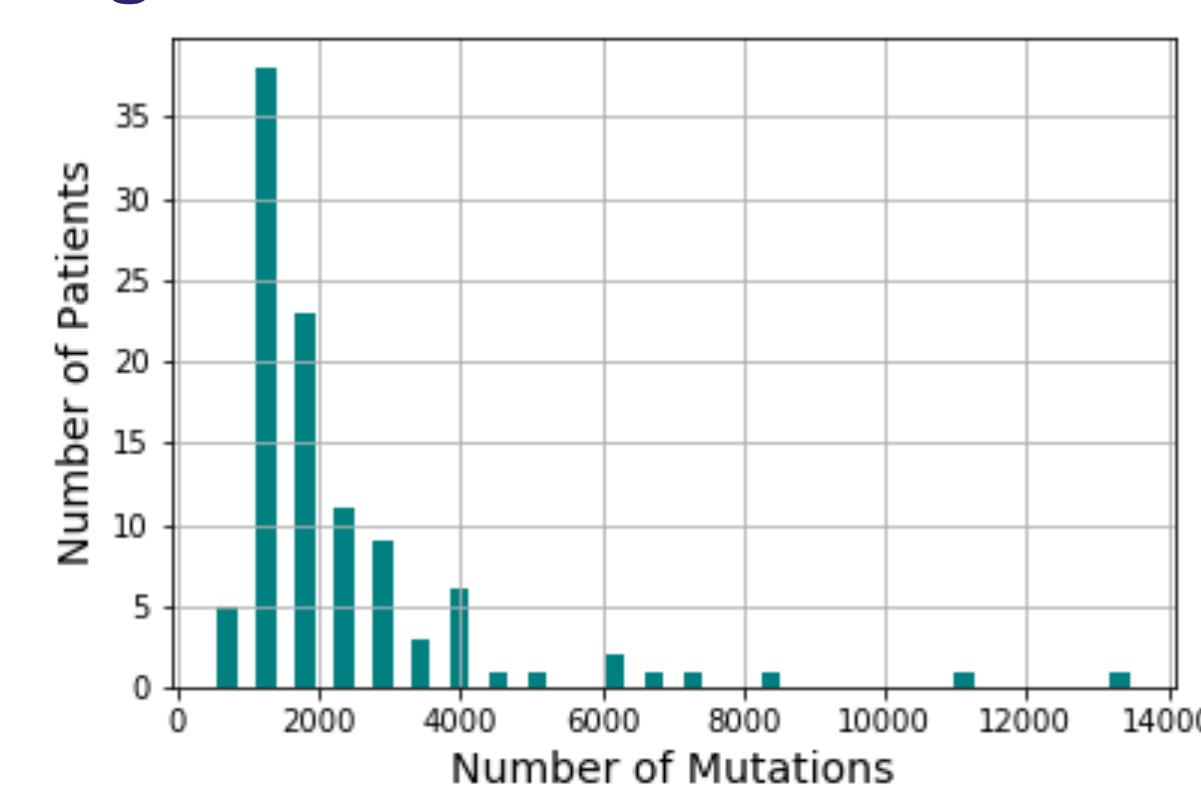
- ❖ What are the subnetworks of genes involved in a drug’s mechanism of action?
- ❖ How does the response to cancer treatment vary based on the different mutational profiles of patients?

## Background Information

### Drug therapy used in breast cancer and their target genes



### Histogram of Patients' Mutations Count



Relates the number of genes somatic mutations that each patient has and the frequency of patients having such number of genes mutations

## Methods

### Collection of data

- ❖ Publicly available databases are compiled to construct the network graph of drug-gene interactions focusing on the BRCA-EU patients’ dataset.



> Cancer genome database: ICGC

- To collect the somatic mutations dataset of 560 breast cancer patients. (104 selected)



> Genome-wide Interaction network database: String Network

- To construct PPI network.



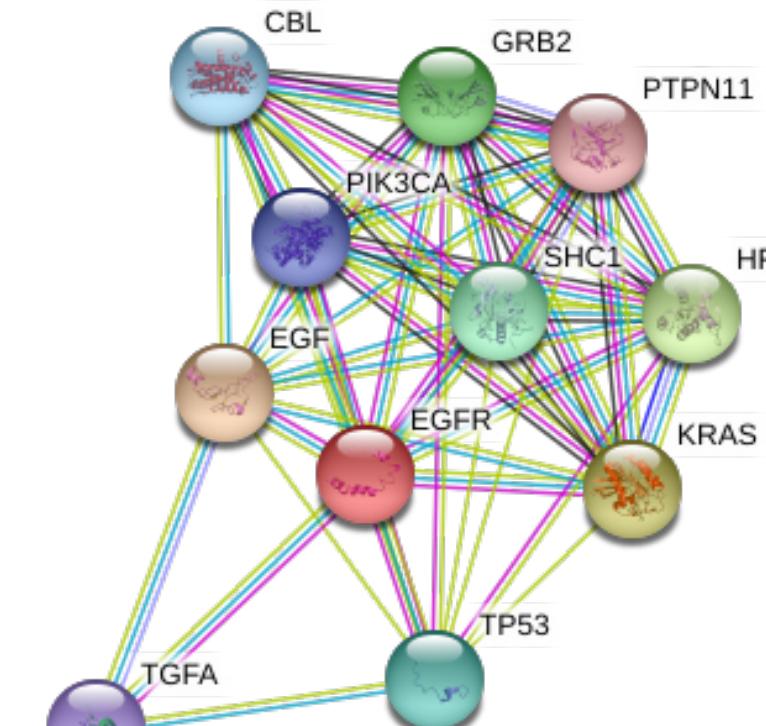
> Drug-Gene Interaction network database: Drugbank

- To construct the network interaction of the drugs and their targeted genes and to gather information about breast cancer therapy treatment.



> Network visualization: Cytoscape

- Bioinformatics software platform for visualizing interaction networks.



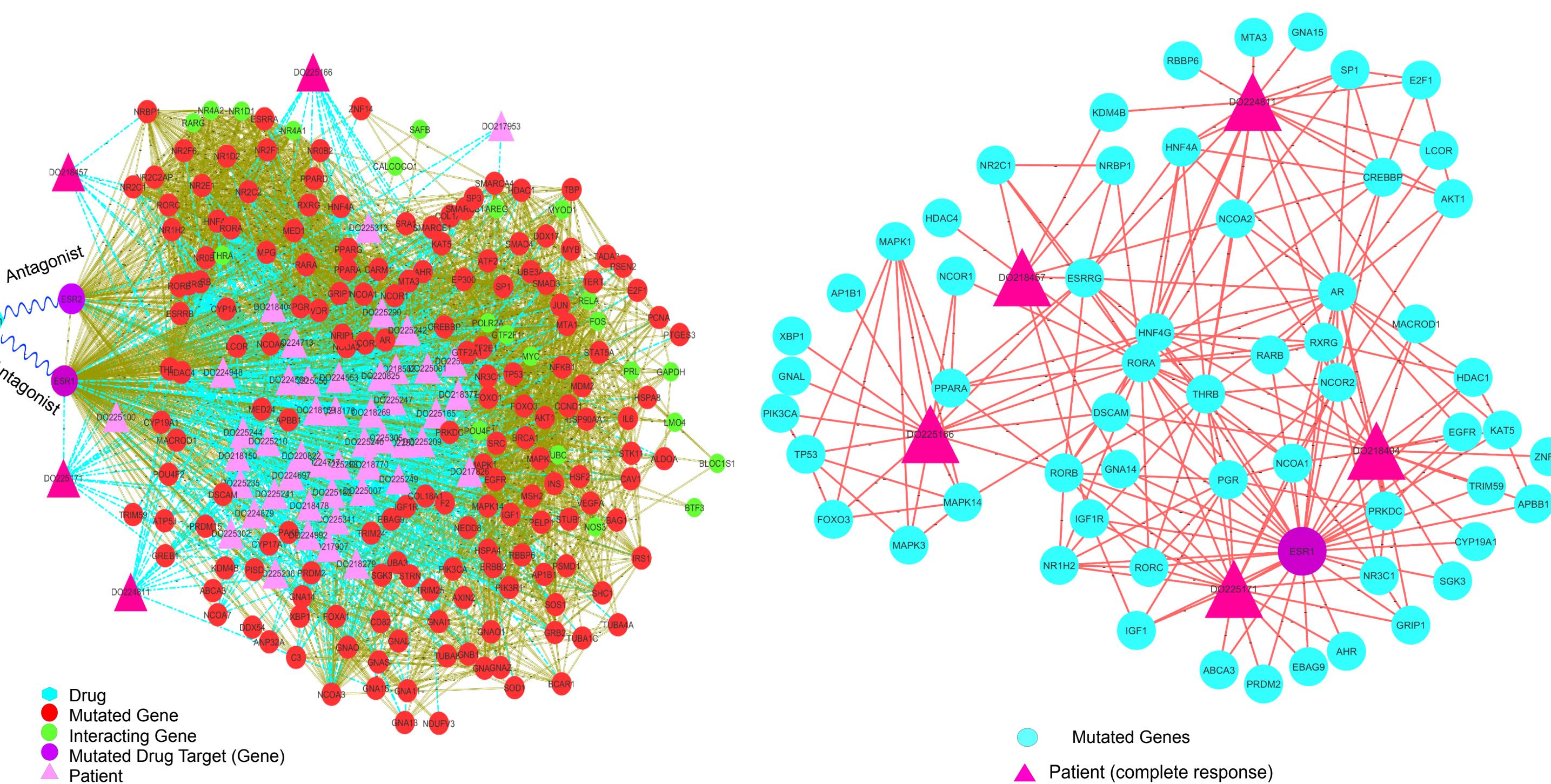
### Construction of the drug-gene-patient network

- ❖ Drug therapies received by the BRCA-EU patients and those corresponding drugs’ direct targets are used by incorporating the PPI from string network.
- ❖ N-hop neighbors of those drugs are also included and combined with the mutation data for each patients to identify how many mutated genes are within the n-hop neighbors of the drug-targets.

## Initial Analysis

### Tamoxifen(most commonly used treatment)

- ❖ A selective estrogen receptor modulators (SERM) with tissue-specific activities for the treatment and prevention of estrogen receptor positive breast cancer.[DrugBank]
- ❖ 51 out of total patients received this treatment, 5 had complete responses. These mutated genes are found within 1-hop neighbors from the drug target.



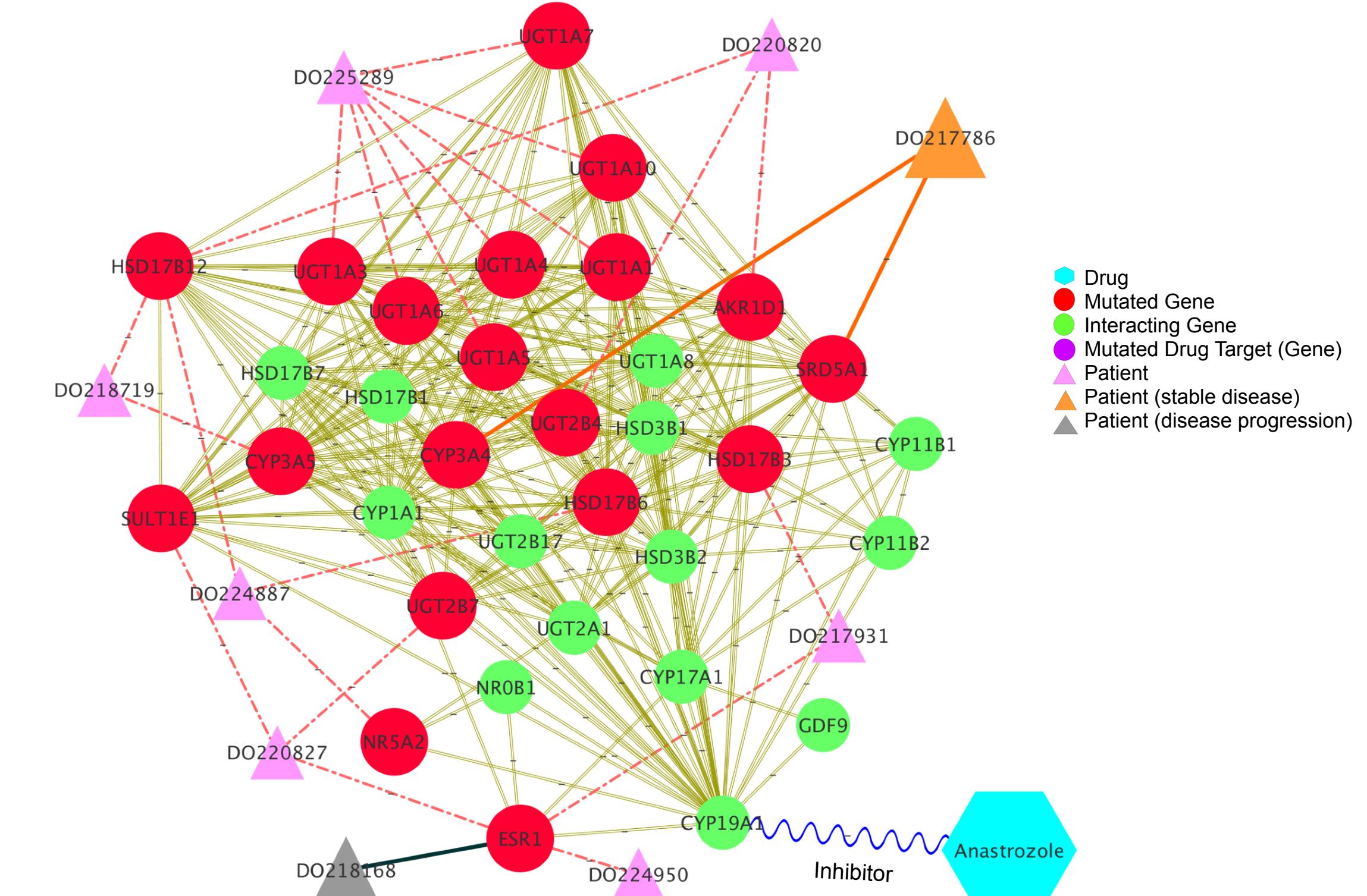
## References

Nik-Zainal, S. et al., Landscape of somatic mutations in 560 breast cancer whole-genome sequences. *Nature*. May 2016.

## Initial Analysis

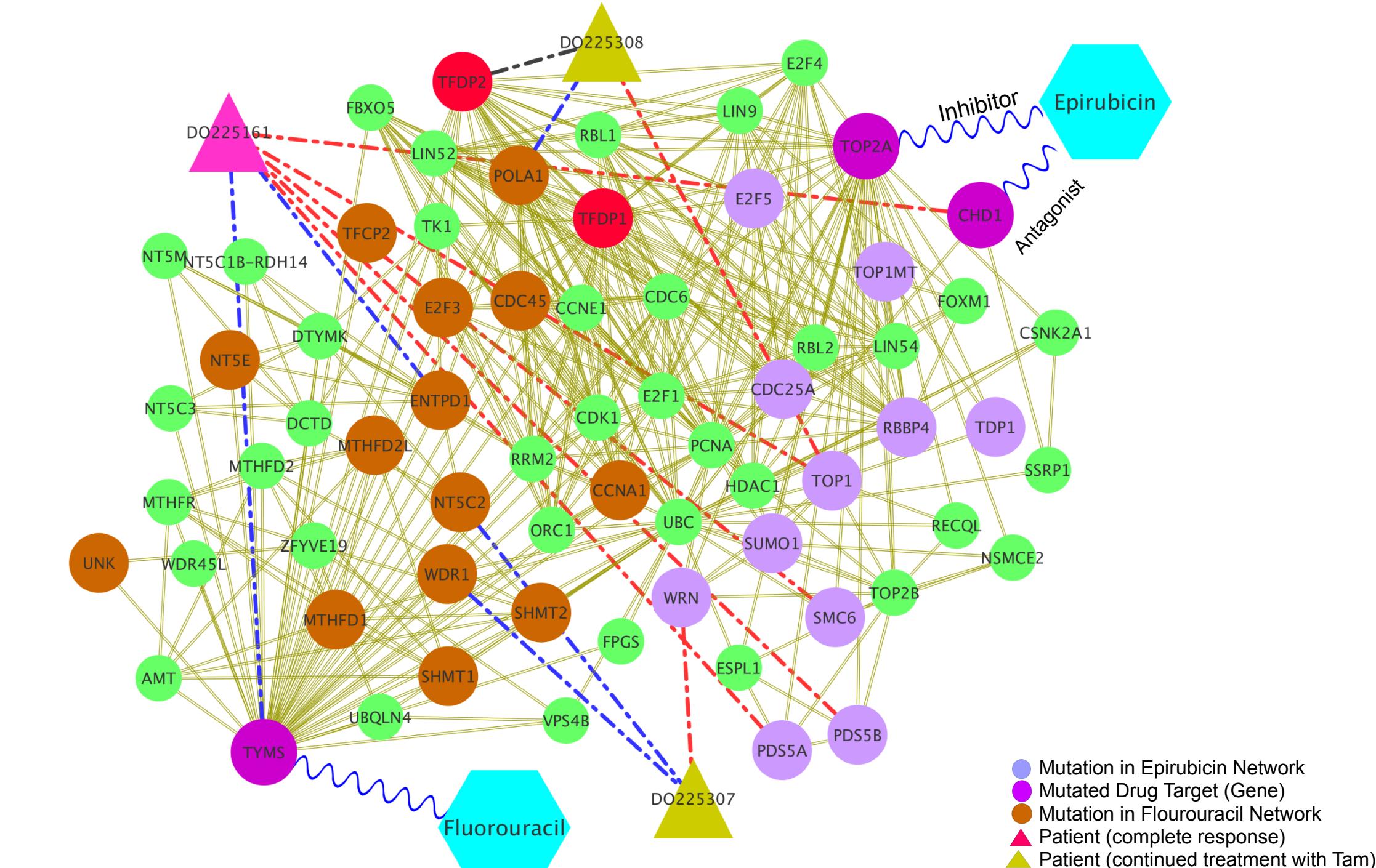
### Anastrozole(Aromatase Inhibitor)

- ❖ Used both in adjuvant therapy for hormone receptor positive breast cancer and in metastatic breast cancer. [DrugBank]
- ❖ 3 out of 14 patients (who received said drug) that have known responses, two have stable disease response and one have progression response.



### Fluorouracil, Epirubicin, Cyclophosphamide

- ❖ 1 out of 3 patients had complete response (pink triangle), and 2 continued treatment with Tamoxifen afterwards.



## Summary & Future Directions

- ▶ Constructed Drug-Gene-Patient networks using
  - DrugBank
  - String database
  - ICGC BRCA somatic mutation dataset
- ▶ Heterogeneous mutation patterns among the patients treated with the same drug
  - Different drug responses
- ▶ Drug response data is limited so incorporating drug screening projects for drug response prediction
  - the Genomics of Drug Sensitivity in Cancer (GDSC)
  - the Cancer Cell Line Encyclopedia (CCLE)
- ▶ Investigate the role of mutations in drug response
  - mutual exclusivity and co-occurrences
  - mutational signatures