depmap portal

PRISM
MULTIPLEXED CELL LINE SCREENING

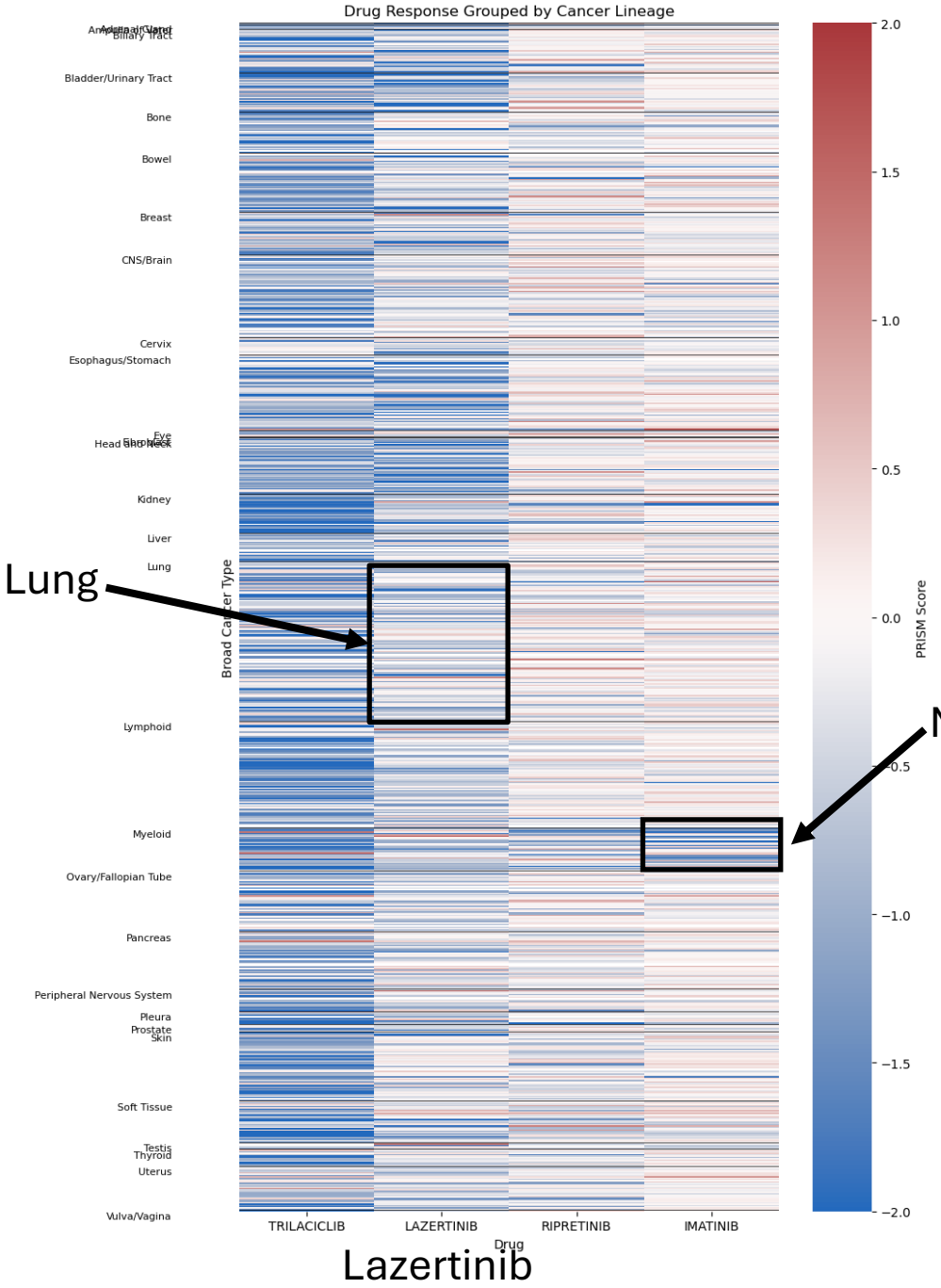
Mining PRISM Drug Response to Identify Predictive Features

Objective: Apply **machine learning** to PRISM drug response data to whether if predictive signals align with known or plausible biology

Approach: Select a representative drug and execute the full pipeline---from data wrangling to predictive feature prioritization

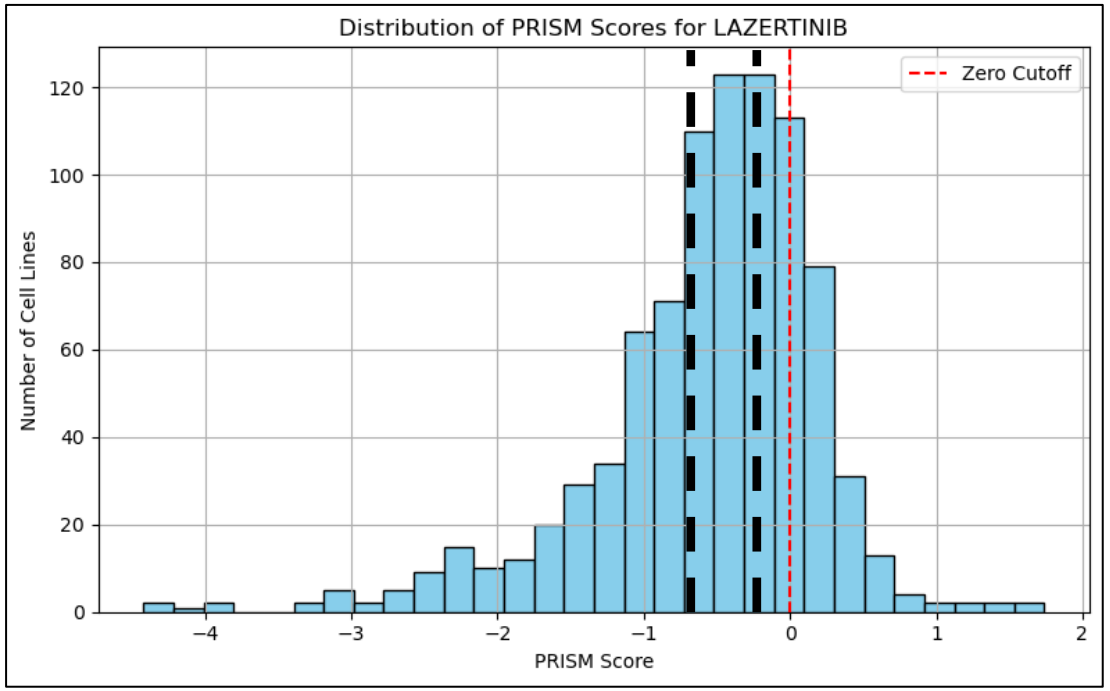
Initial goal: validate feasibility --- no assumptions made about signal strength or model success

https://github.com/mjtiv/Lazertinib_Response_Modeling



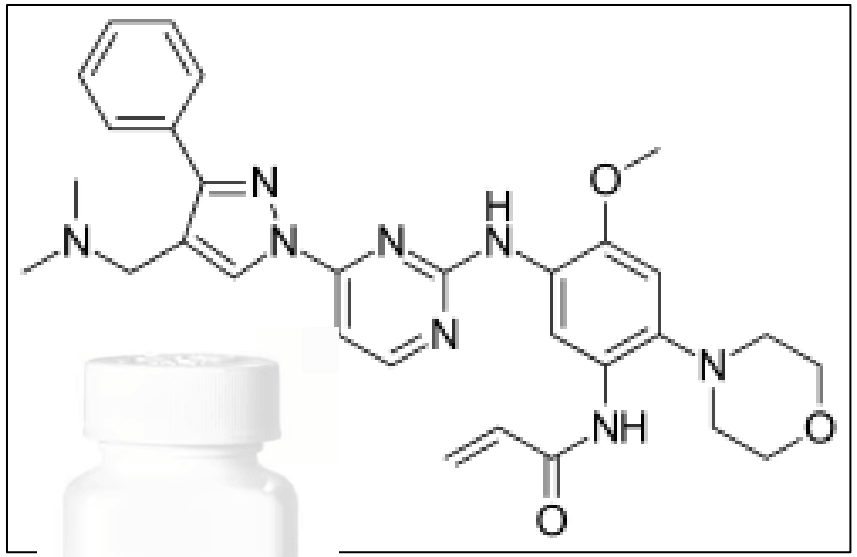
Selecting a Modeling Candidate from Public PRISM Drug Data

- DepMap has publicly available drug repurposing PRISM screen data (24Q2)
  - 1,514 Compounds and 859 Cell Lines
- Focused on four know inhibitor drugs (Trilaciclib, Lazertinib, Ripretinib and Imatinib) identified by "-ib" or "-tinib" naming convention
- Lazertinib was selected due to it's near-even distribution of responds and non-responders---ideal for model testing



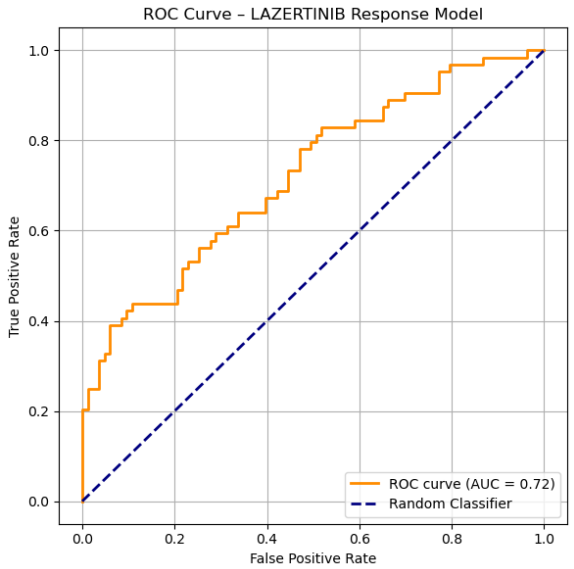
Lazertinib

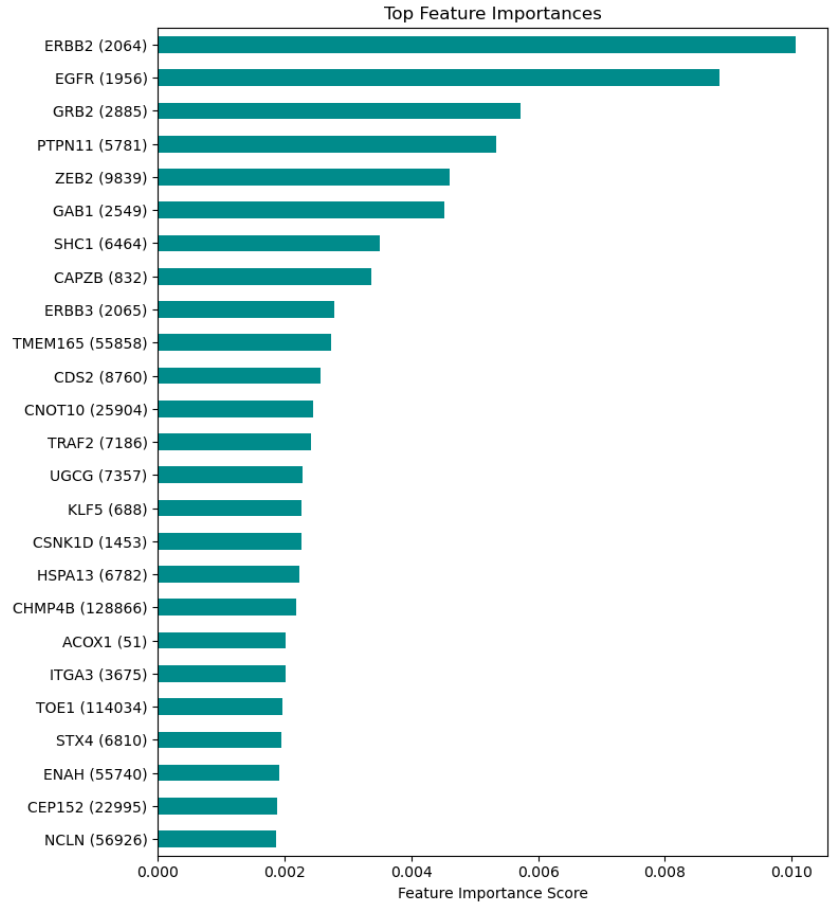
- Sold under the brand name **Lazcluze** (marketed by Janssen/J&J)
- Approved for treatment of **non-small cell lung cancer (NSCLC)**
- Mechanism of action: EGFR-targeting tyrosine kinase inhibitor
- Often used in combination with Rybrevant (amivantamab) to target target EGFR mutations, including exon 20 insertions

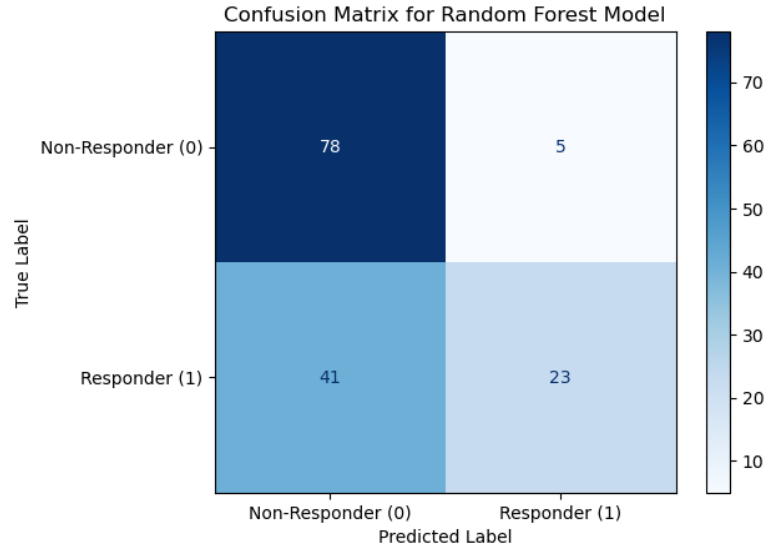


Examining PRISM and CRISPR Data

Model Shows Moderate Performance --- Limited Sensitivity for Responders



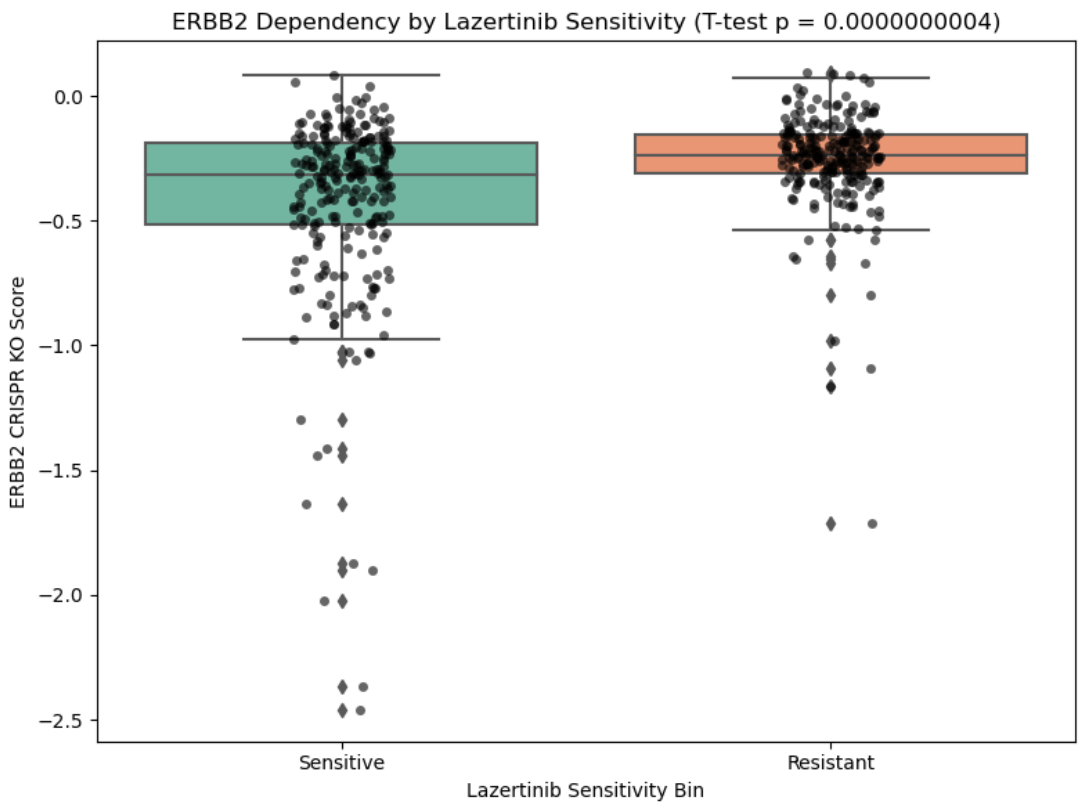




Sensitivity (Recall for Responders): 35.94%
Specificity (Correct Non-Responders): 93.98%

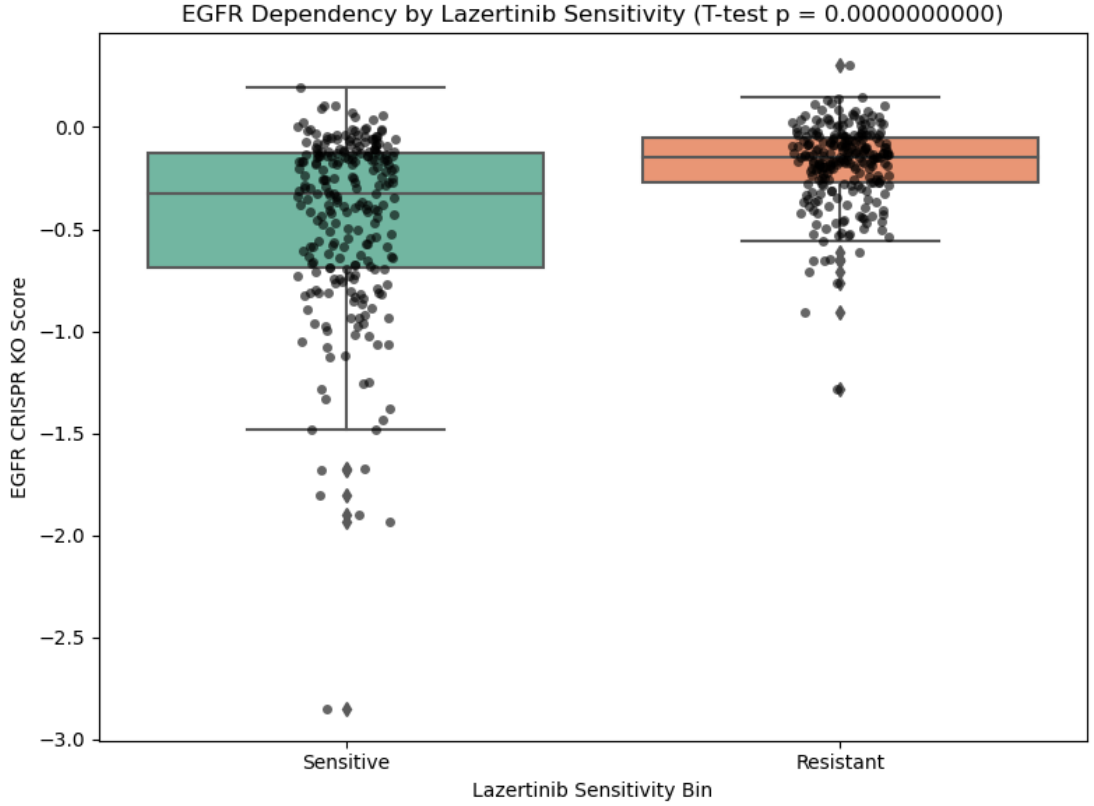
Key CRISPR K.O. Biomarkers Supporting Lazertinib Mechanism of Action

ERBB2



ERBB2 interacts with EGFR
-Knockout of ERBB2 mimics Lazertinib response, suggesting it acts through a shared pathway and supports the drug's MOA.

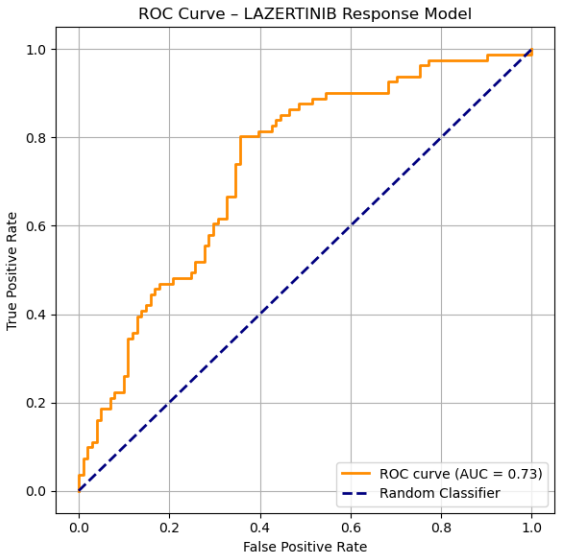
EGFR

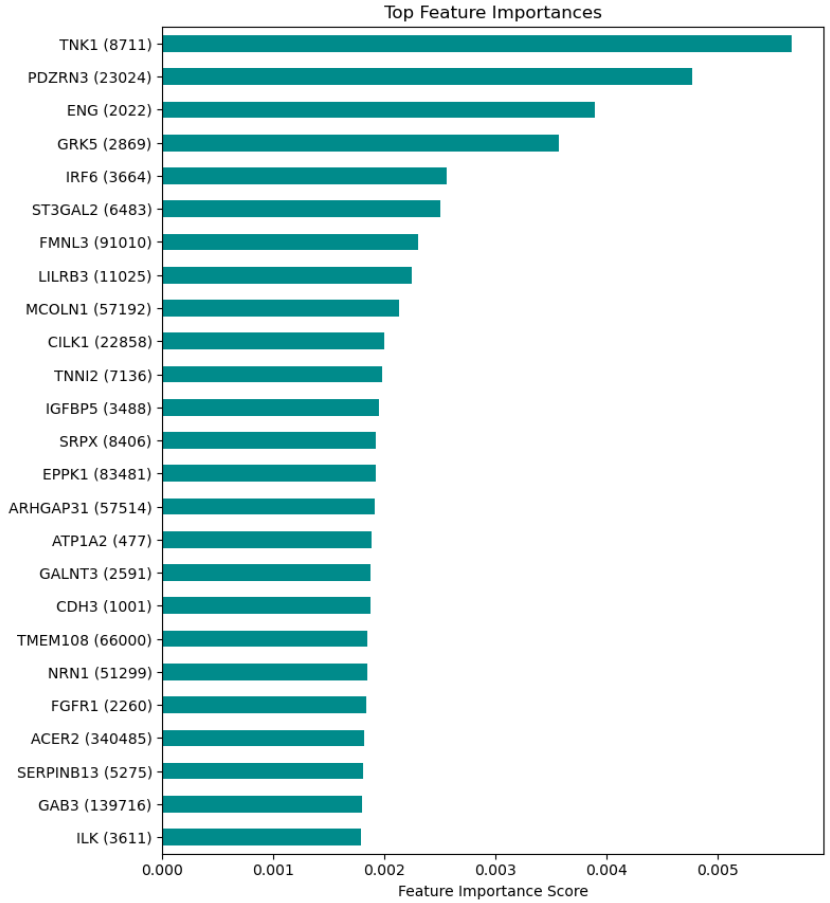


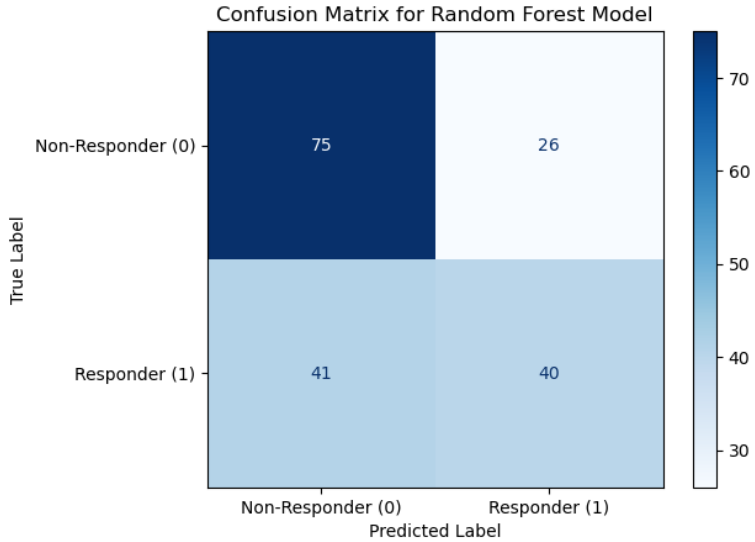
EGFR is the direct target of Lazertinib
- Its knockout fully recapitulates the drug effect, further validating the mechanism of action.

Examining PRISM and Expression Data

Model Shows Moderate Performance --- Limited Sensitivity for Responders



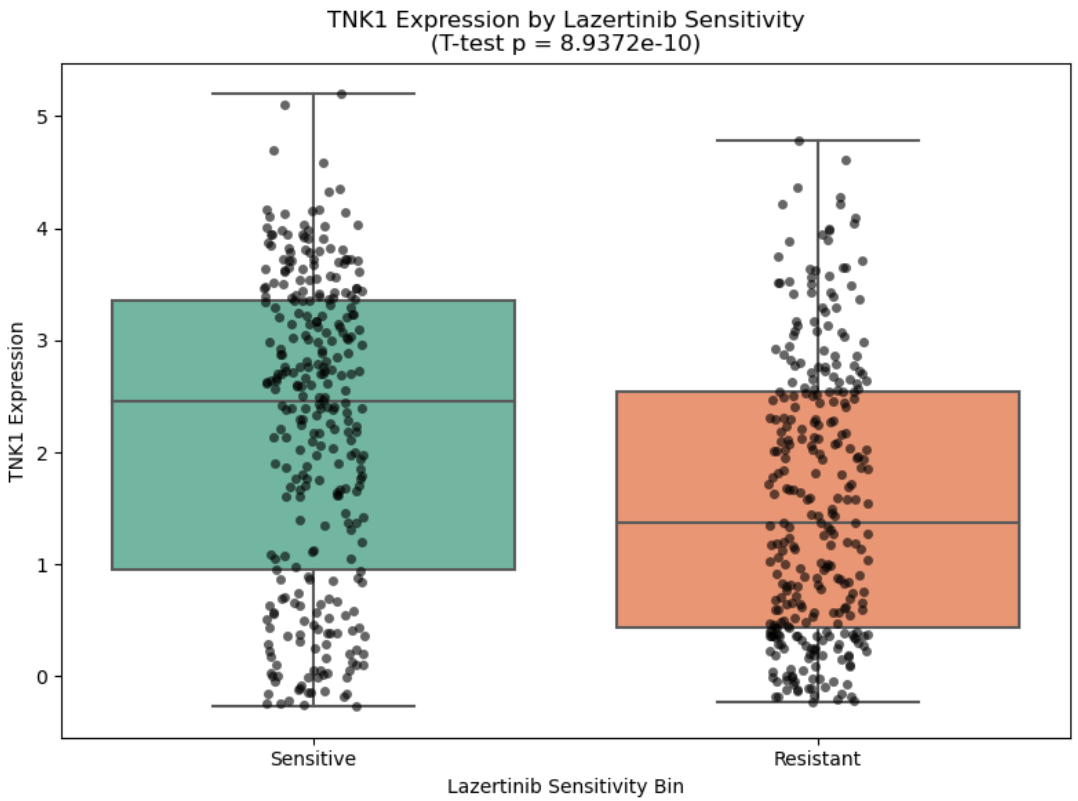




Sensitivity (Recall for Responders): 49.38%
Specificity (Correct Non-Responders): 74.26%

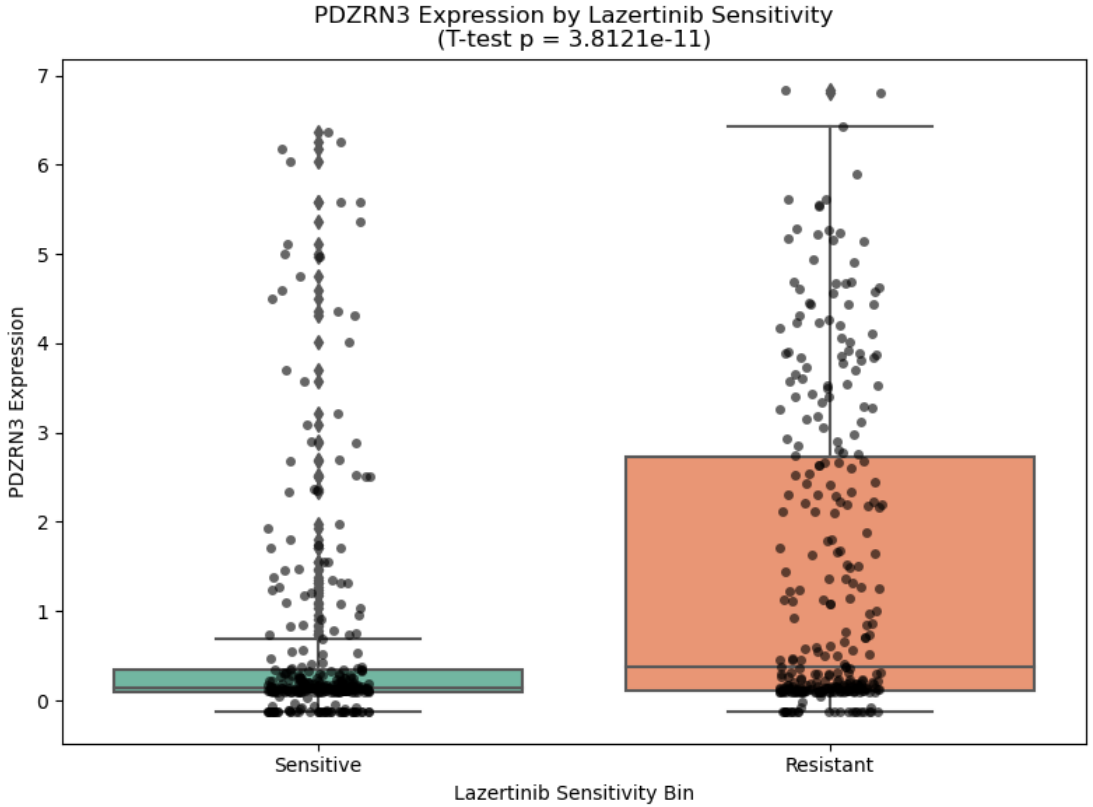
Top Expression Biomarkers Associated With Lazertinib Response

TNK1



TNK1 is known to interact with EGFR
-Higher TNK1 expression appears to sensitize cells to Lazertinib, possibly by enhancing EGFR inhibition.

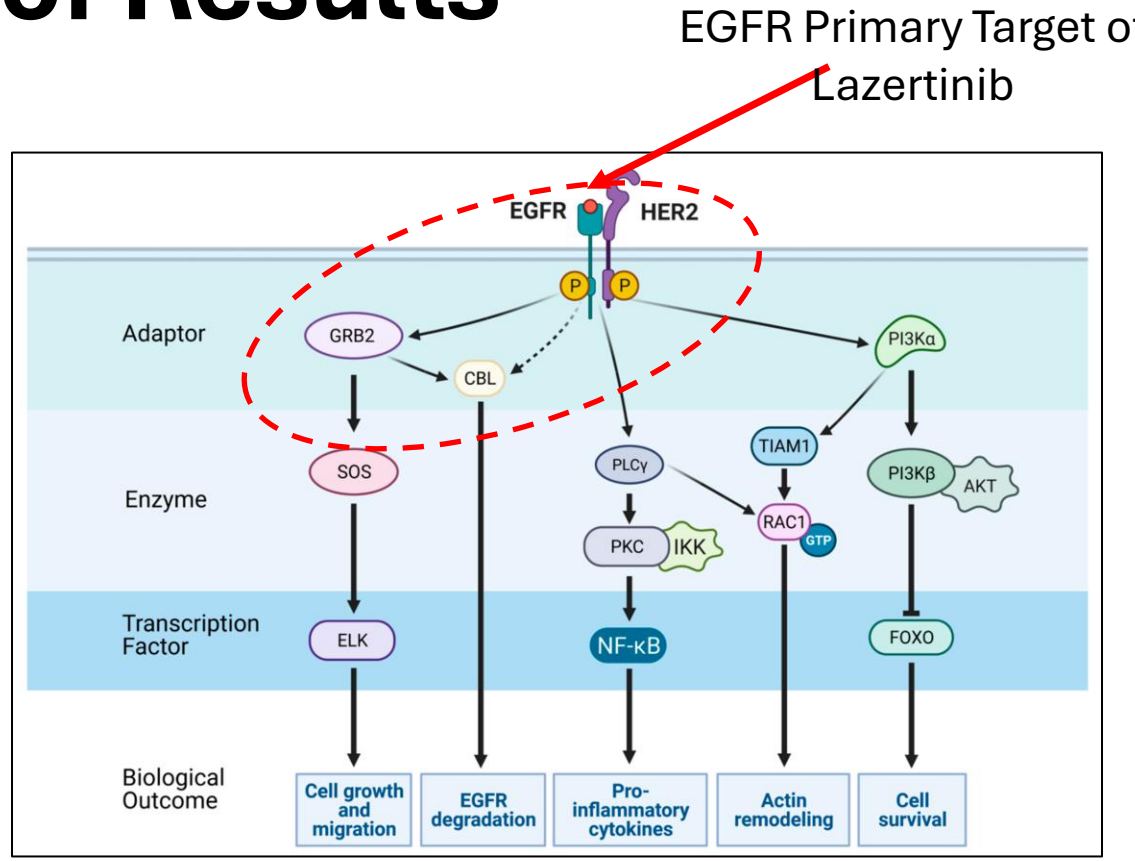
PDZRN3



PDZRN3 is know to form a PDZRN3-RAF1 Fusion Protein
- The elevated expression in resistant cells may reflect a proliferative advantage driven by this fusion.

Summary of Results

- The machine learning analysis successfully identified Lazertinib's mechanism of action (MOA) and surfaced potential biomarkers of susceptibility (e.g. TNK1, PDZRN3, ERBB2)
- However, model performance was limited by data noise and QC flags, particularly in predicting responders, an expected challenge in real-world biological datasets



https://www.mdpi.com/2072-6694/13/11/2748

Summary

- After compound has been thoroughly investigated (PRISM, toxicology, binding etc.) there are two options:
- 1. Compound moves onto the next stage of drug discovery for testing in clinical trials (still a long road ahead)
- 2. Compound gets redesigned, and the entire process repeated