Elraglusib (9-ING-41) response prediction and mechanistic discovery using iterative machine learning

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Abstract: #5355

ABSTRACT

Elraglusib (9-ING-41) is a selective GSK-3 inhibitor that has demonstrated preliminary signs of activity on a broad array of neoplasms as well as their immune microenvironment. However the determinants of tumor response in patients have not been elucidated. Here, we use genomic panels of cancer driver genes to predict patient response to elraglusib therapy as measured by RECIST criteria. Patient response in the Phase I 1801 trial (NCT03678883) was matched to genomic data from patient tumors, with 80 cases used to train Machine Learning models and 26 cases reserved as a test set for model evaluation. When predicting response from mutation status alone our models reached a modest accuracy of 65% in the test set, which we attributed to the sparsity of genomic data. To remedy this, we engineered pathway-based features to provide combinatorial information while ensuring feature stability. To select the optimal combination of features, we designed an iterative design process that first randomized feature combinations and then created refined models from the highest performing pathway features. This resulted in several final models with greater than 88% accuracy. We retained several models of similar accuracy to more comprehensively identify potential biomarkers and combinatorial relationships. These models were then interpreted using SHapley Additive exPlanations (SHAP) where we were able to identify highly predictive features for both the entire pan-cancer cohort and specific histologies. We found the feature constructed from the Reactome pathway "Chromatin Modifying Enzymes" frequently occurred in high performing models with a high-ranking SHAP value. This feature included genes such as ***SMARCA4***, ***HDAC2***, and ***KDM5A***, and was negatively associated with patient response. Another frequently observed high-ranking pathway feature with a negative response association was based on the "Innate Immune System" Reactome pathway. Many of the features highlighted in our models were negatively associated with elraglusib response and thus could be general markers of poor prognosis unrelated to drug effect. To address this, we altered our pipeline to test only positively associated features which substantially reduced our feature pool to only 285 features but still produced models with accuracies of up to 81%. Analysis of key features used by these models identified several positive markers of elraglusib including mutations in the ***POLE*** gene, which previously has been linked to DNA-damage response deficiency and anti-tumor immune response. In sum, we forecast elraglusib response for a variety of tumor histologies and simultaneously reveal potential mechanisms of elraglusib sensitivity and biological action. In future work we will investigate the utility of using ***POLE*** and other identified biomarker candidates to predict the likelihood of patient response to elraglusib, as well as whether our machine learning models will be an effective tool to guide patient enrichment or stratification.

RESULTS

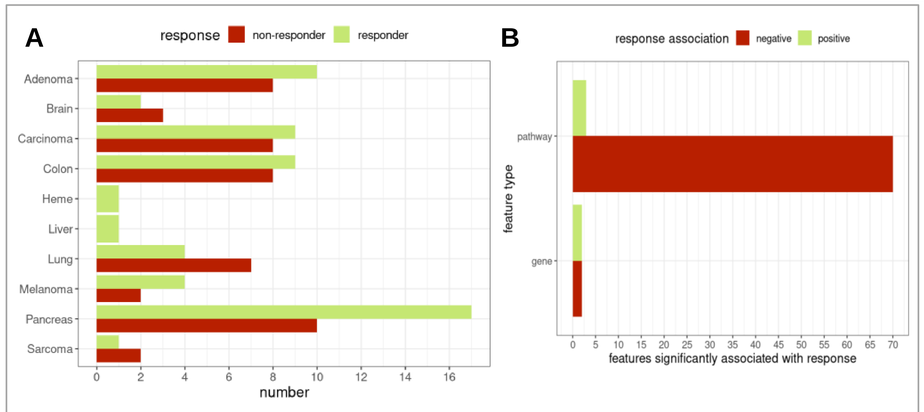


Figure 1. A) The number of responders (Stable Disease or better) or non-responders (Progressive Disease) per each histology class. **B)** The number of significant features across different models as determined by unpaired two-sided t-tests

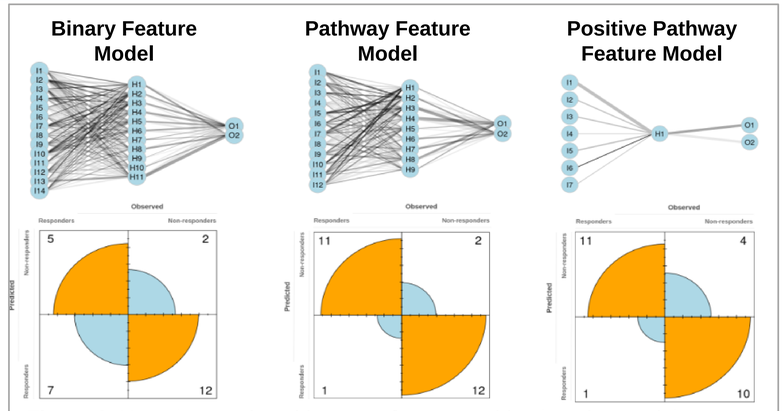


Figure 2. Neural network architectures for top machine learning models

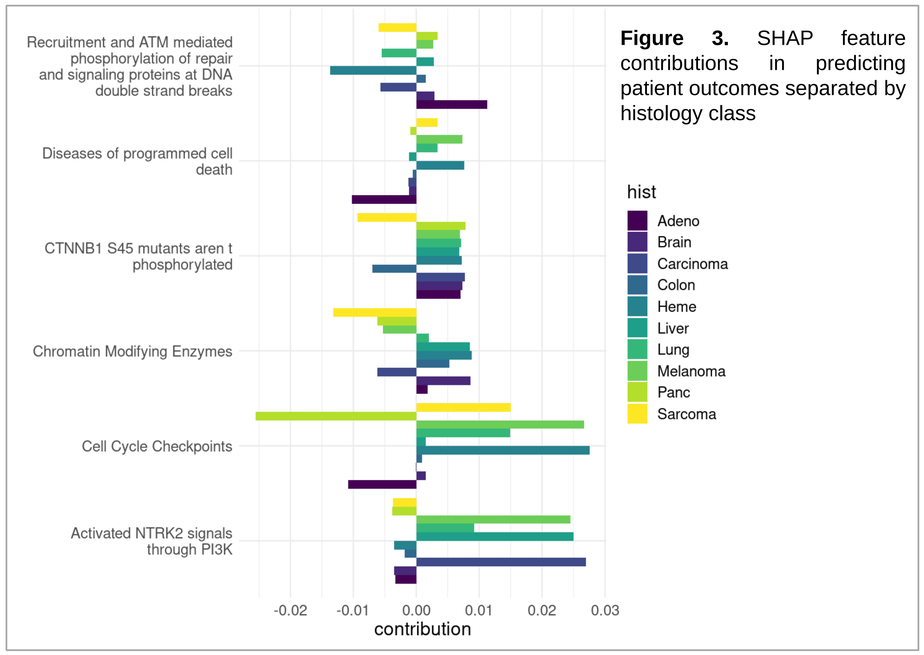


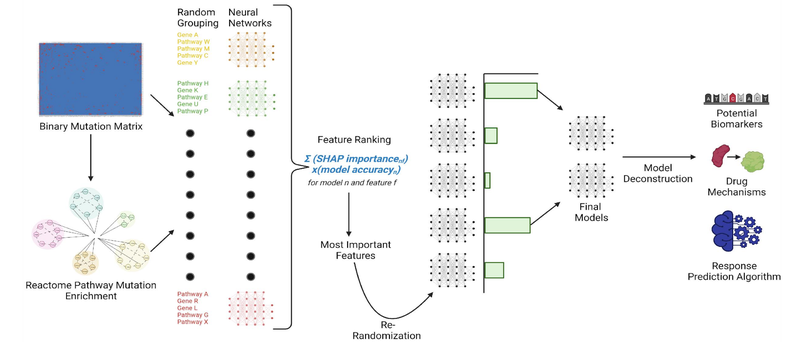
Figure 3. SHAP feature contributions in predicting patient outcomes separated by histology class

Feature	General Feature Association to Response	Genes in Feature	Relevance
Chromatin modifying enzymes	Mutations in feature negatively associated with patient response	SMARCA4, KMT2D, MLL2, KMT2A, MLL, KMT2C, MLL3, PRDM16, EZH2, EED, WHSC1, SETD2, DOT1L, NSD1, KDM6A, KDM5A, CDK4, CCND1, ARID2, PBRM1, ARID1B, ARID1A, DNMT3A, JAK2, YEATS4, EP300, CREBBP, HDAC2	GSK3B phosphorylation is reported to regulate chromatin factors (Shinde, 2017), and dual GSK3B/HDAC inhibition is reported to enhance anti-tumor effects in Pancreatic Cancer mouse models (Edderkaoui, 2018).
Innate Immune System	Mutations in feature negatively associated with patient response	TP53, NFKBIA, NOD1, MAP2K4, PPP2R1A, JUN, MAP2K1, MAP3K1, BIRC3, BTK, SOCS1, PLCG2, APOB, SLC2A3, TMEM173, IDH1, B2M, NRAS, BCL2L1, TNFAIP3, CYLD, EP300, CREBBP, PIK3R1, PIK3R2, PIK3CA, ABL1, NF2, CARD11, KRAS, HRAS, PAK3, CTNNB1, PRKDC, ITK	GSK3B is known to regulate the immune system (Huntington, 2022; Carneiro, 2020), and we hypothesize that Elraglusib acts by enhancing anti-tumor immune response.
Termination of translesion DNA synthesis	Mutations in feature positively associated with patient response	POLE, POLD1	Mutations in POLE and POLD1 have been associated with increased tumor mutational burden and neoantigen load, which enhances response to anti-PD-1 CPI (Rivzi, 2016)

CONCLUSIONS

- Generation of pathway features can increase the information content of genomic data, leading to more significant associations with drug response, and features better suited to machine learning.
- Patient genomics can be converted into input for machine learning models that accurately predict whether a patient will benefit from elraglusib.
- *POLE* is proposed as a positive marker for elraglusib response, which is consistent with the hypothesized role of GSK-3 inhibition in damaged DNA response deficiency and activation of immune response.
- Mutations in Chromatin Modifying Enzymes appear to negatively impact response.

COMPUTATIONAL PIPELINE



Input Data: Patients in the Phase I 1801 trial were given Elraglusib injection and patient response was measured by RECIST 1.1. 106 patients had tumor biopsies prior to treatment that was analyzed in a mutation panel of ~400 alterations, including SNVs and amplifications, in cancer related genes.

Modeling: Genetic alterations were converted to binary representations and converted into feature representations that pooled multiple genes into a normalized score. Genetic pathways and protein interaction lists were used to group genes, which were scored by the fraction of genes present out of the total number of pathway genes that were available in a panel. Pathway features increased significance of associations with patient response. Features were compared for performance in machine learning. A training set of 80 patients was used for iterative feature reduction, and evaluated by performance in a test set of 26 patients. Feature contributions were evaluated by SHAPley values calculated from 25 random orderings.

OTHER WORK FROM ACTUATE:

Exploring Mechanisms of Resistance to Elraglusib in Pancreatic Cancer and PDX Models

Section 15 Poster 7 April 18th 9-12 AM

Immunomodulation in Elra Phase 1/2 Trials

Section 47 Poster 12 April 18th 9-12 AM

Carneiro BA, et al., "Phase I study of 9-ing-41, a small molecule selective glycogen synthase kinase-3 beta (GSK-3β) inhibitor, as a single agent and combined with chemotherapy, in patients with refractory tumors." *Journal of Clinical Oncology,* 2020.

Edderkaoui M, et al., "An Inhibitor of GSK3B and HDACs Kills Pancreatic Cancer Cells and Slows Pancreatic Tumor Growth and Metastasis in Mice." Gastroenterology, 2018.

Huntington KE, et al., "Small-molecule inhibition of glycogen synthase kinase-3 (GSK-3) increases the efficacy of anti-PD-L1 therapy in a murine model of microsatellite stable colorectal cancer (CRC); Therapeutic response correlates with T cell ratios and serum cytokine profiles in mice.", *Cancer Research*, 2022.

Rivzi NA, et al., "Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer." *Science*, 2016.