#3135: Regorafenib response prediction in metastatic colorectal cancer by a novel genomic and transcriptomic model

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INTRODUCTION:

Regorafenib is a third-line option in metastatic CRC, often overshadowed by its limited efficacy and high toxicity. Yet, rare cases of deep and even complete responses hint at untapped potential. This study applies machine learning to transcriptomic and genetic data to identify those exceptional responders—aiming to turn regorafenib into a precision tool rather than a last resort.

Methods:

A predictive model for Rego-response was developed using transcriptomic and genetic data from 41 CRC cell lines. Cell lines were classified into Rego-sensitive and -resistant groups based on drug sensitivity data from the CTRP2 database. Several machine-learning algorithms were tested, with the Generalized Linear Model via Elastic Net (GLMNET) achieving the highest predictive performance. Model accuracy was assessed using leave-one-out cross-validation. Further validation was performed using transcriptomic (WTS) data from 24,384 real-world CRC patients assessed by Caris Life Sciences, which included 720 patients treated with Rego.

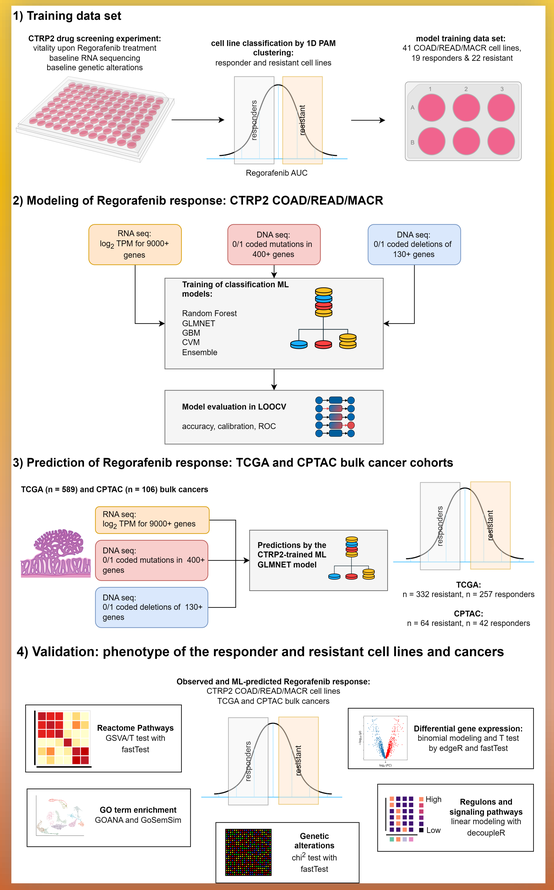

FIG.1: Strategy of modeling of regorafenib response and validation of the predictions in colorectal cancer cell lines and tumors.

Results:

The predictive model identified key features associated with Rego-response, including gene expression signatures (e.g., *ZNF441, CCDC82, ZFP69*) and specific mutations (e.g., *RALGAPA1, MORC1*). Transcriptome profiling showed that Rego responders exhibited enrichment in cell-cycle regulation and DNA-repair mechanisms, while non-responders showed a stroma-rich microenvironment with significant endothelial and fibroblast infiltration. External validation using molecular data from real-world Rego-treated CRC patients revealed that predicted responders had a prolonged time-on-treatment (p=0.02, HR=0.80) and overall survival (p=0.01, HR=0.76) compared to predicted non-responders. The prediction was specific to Rego-response, as there was no survival difference between predicted responders and non-responders among patients not treated with Rego (p=0.74, HR=1.0).

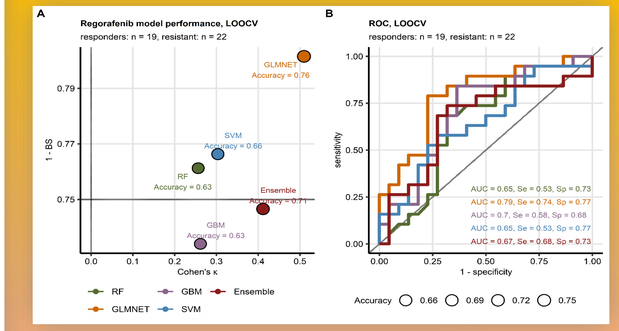

FIG.2: Evaluation of performance of the machine learning models of regorafenib response in cross-validation of the CTRP2 colorectal cancer cell line data set.

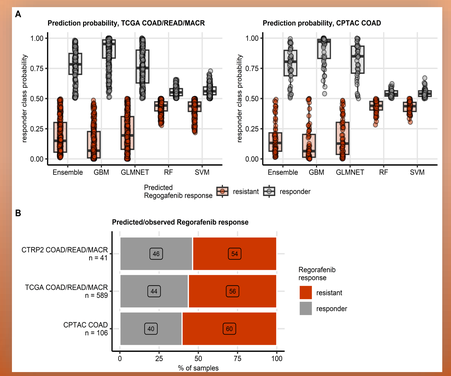

FIG.3: Prediction of the regorafenib response class assignment for bulk cancer samples in the TCGA and CPTAC collectives.

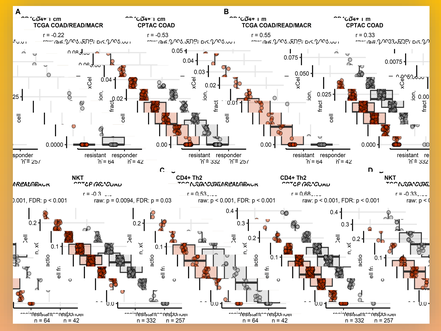

FIG.4: Differences in composition of T cell and NKT cell populations between cancers predicted to be responsive and refractory to Regorafenib.

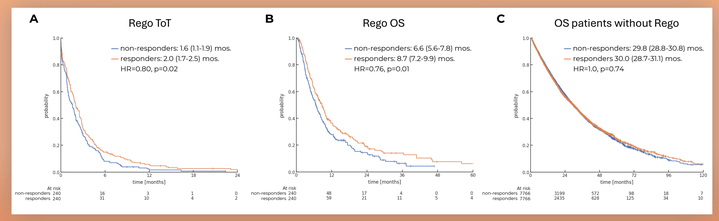

FIG.6: Survival outcomes for predicted Rego responders (top 33% model score) and non-responders (bottom 33% model score) in validation cohort. A) Rego time-on-treatment (ToT), quantified as first to last of Rego. B) Rego overall survival (OS) quantified as first of Rego to last contact. C) OS, quantified as collection to last contact, for patients not treated with Rego. Legend shows median ToT or OS and hazard ratio (HR).

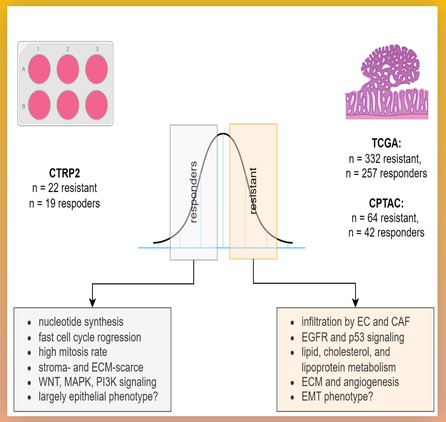

FIG.5: Summary of the analysis results.

Conclusion:

This novel predictive model successfully identified and validated molecular features associated with Rego-response in CRC. This transcriptomic and genetic signature holds significant potential for improving personalized treatment strategies by identifying patients most likely to benefit from Rego.

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