Abstract #3079: In silico approaches to patient selection: Credentialing elraglusib as a novel treatment in metastatic melanoma resistant to checkpoint inhibitors

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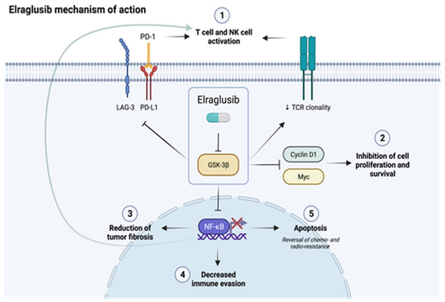
Background



- Elraglusib (9-ING-41), a novel inhibitor of GSK-3β, has been evaluated in >230 patients (pts) with advanced malignancies, including metastatic melanoma 1801 phase 1/2 trial (NCT03678883).
- 12 metastatic pts with advanced melanoma were treated elraglusib
- Elraglusib showed clinical benefit with multiple prior lines of therapy including checkpoint inhibitors (CPI)
  - 5 pts demonstrated durable clinical benefit with 1 CR (ongoing, >1400 days) and prolonged OS of 107, 256, 357, and 556 days.

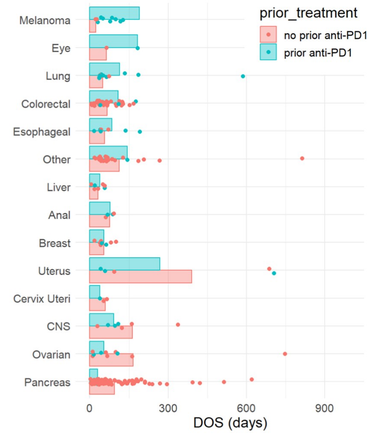


Figure 1. 1801 Patient Days on Study (DOS) Across Tumor Types and Prior Lines of Treatment.
Among tumor types with at least one patient having had anti-PD-1 and one not having had having αPD-1 in prior lines of treatment have DOS shown.

Methods

- We collected pt omic data from the 1801 trial to characterize markers of elraglusib response with bioinformatics and machine learning (ML).
- Pts were treated with elraglusib as a single agent or in combination with chemotherapy
- Genomic panels were available for 106 pts
  - The most frequent tumor types included colorectal cancer (n=35), pancreas (n=31), lung (n=15), and metastatic melanoma (n=12).
- Pathway-based features were generated by quantifying the percent of each Reactome pathway that was mutated
  - Pathway features were iteratively evaluated in a training set of 80 pts for performance in shallow neural networks predicting patient RECIST, with each model using 5-15 randomly suggested features at a time
- Publicly available genomics data from an αPD-1 trial in pts with metastatic melanoma (Hugo et al., *Cell* 2017) were transformed into pathway-based features and input into the final model to predict elraglusib response in this population
- RNA-seq of Pts given anti-PD-1 (without other CPI) was taken from public data (Hugo et al., *Cell* 2017; Gide et al., *Cancer Cell* 2019), with log2(fpkm+1) *GSK3B* values standardized before merging the datasets
  - Kaplain-Meier plots were made with the *survminer* and *survival* R packages

Results

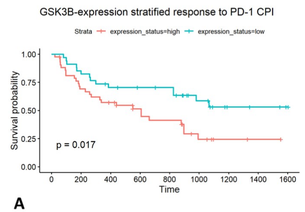


Figure 2. Higher GSK3B Expression is Associated with Poor Clinical Outcome in Melanoma Pts given αPD-1 Therapy.
Expression of *GSK3B* was used to stratify advanced melanoma patients who received αPD-1 therapy (n=77).

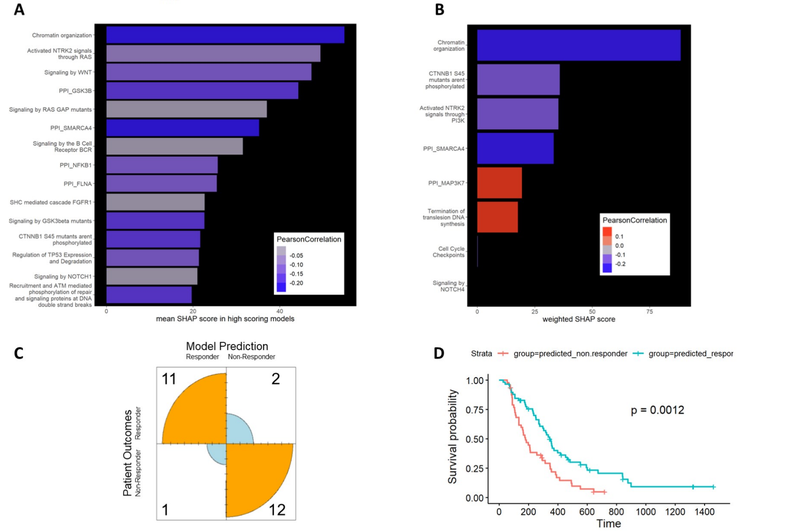
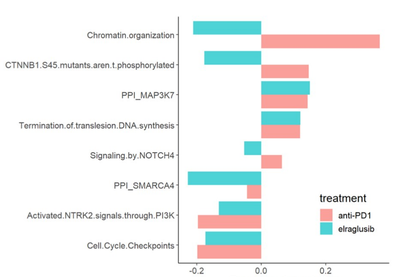


Figure 3. A) Feature impact on model prediction based on mean weighted SHAP scores of thousands of models. Red color indicates a positive feature association to Pt response, blue indicates a negative association. B) Feature SHAP contributions in a top-performing model. C) Confusion matrix of top model predictions on a test set of 26 pts with >88% accuracy. The upper left indicates true negatives, and the bottom right true positives.
D) Kaplain-Meier plot of 1801 patient overall survival days for predicted responder or non-responder groups.



	Elraglusib non-responder	Elraglusib responder
αPD-1 non-responder	3 (8.8%)	9 (26.4%)
αPD-1 responder	11 (33.3%)	11 (33.3%)

Figure 4. Predicted Elraglusib Response Analysis in Metastatic Melanoma Patients Treated with αPD-1
A) Comparison of feature associations to elraglusib response and αPD-1 response. B) Most Metastatic Melanoma Pts are Predicted Elra Responders (66%) with selectivity in αPD-1 non-Responders (78.5% of all αPD-1 non-responders).

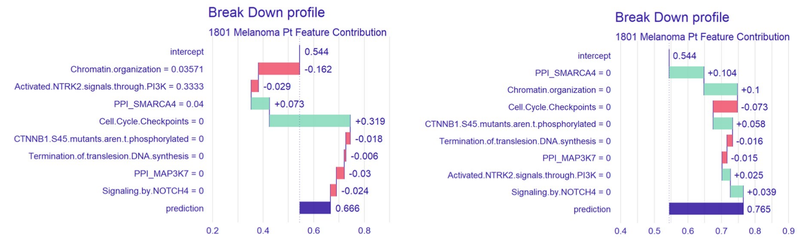


Figure 5. Explanation of Model Response Predictions on Individual Patients
SHAPley break-down plots calculate the importance of model input features by their contribution to model predictions at given values.

Major Take Aways

- Elraglusib showed strong responses in metastatic melanoma patients.
- AI modeling predicts that checkpoint resistant metastatic melanoma patients will benefit from elraglusib therapy, particularly CPI failures

Future Directions

- Exploration of Elraglusib and αPD-1 combination in select indications
  - Use ML model to select patient populations, such as advanced melanoma
- Develop clinical applications of ML model to inform clinical decision making