# 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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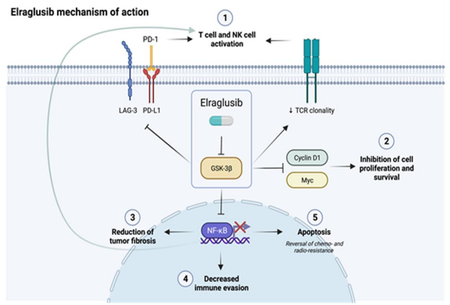
## Background




- 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)
- Emerging pre-clinical and early clinical data suggests activation and expansion of CTL and NK cells, modulation of cytokine dynamics, and increased neoantigen presentation as novel aspects of elraglusib mechanism of action[1]
- Metastatic melanoma pts (n=12) were heavily pretreated (mean of 3 prior lines of treatment) including one or more checkpoint inhibitors
- These pts received single agent elraglusib at doses ranging from 5-15 mg/kg IV 2X/week
- 5 pts demonstrated durable clinical benefit with 1 CR (ongoing, >1400 days) and prolonged OS of 107, 256, 357, and 556 days.

**1801 Trial Days on Study Across Tumor Type and Prior CPI**

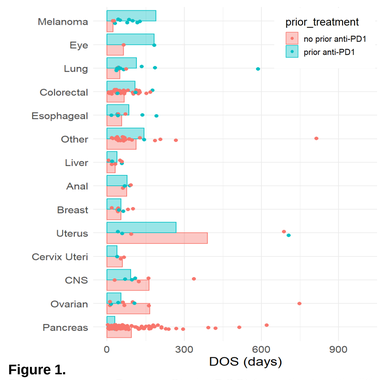



**Figure 1.**
Bars show mean Days on Study (DOS) for patients with different tumor types that had at least one pt having had prior αPD-1 and at least one not having had αPD-1.

## Methods

**Development of a Machine Learning Model to Predict Patient Elraglusib Response with Genomics Input**

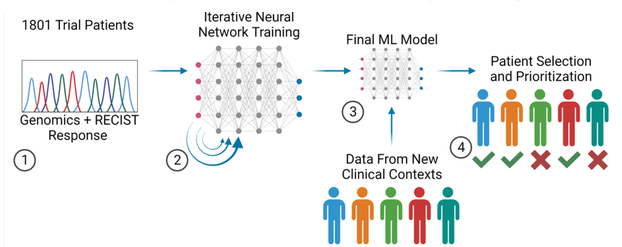



**Figure 2.**
1) Genomics data from a mutation panel of pre-treatment tumor biopsy with 106 patients from the 1801 trial was used with patient outcome to develop neural network models that predict patient response. After generation of pathway-based genomics features, models were trained to predict patients as responders or non-responders, with response defined by RECIST criteria. A test set of 26 patients was used to evaluate performance. 2) Models were improved by an iterative feature reduction process. 3) The best performing model was used to predict Elraglusib response in patient data outside of the training set, including with public genomics data. 4) The ML model is being developed to inform patient decisions, based on predicted likelihood of patient response based on a pre-treatment mutation status. Model predictions for individuals explained through calculations of feature impact on outcome, using SHAP force ("break down") plots.

## Results

**Tumor GSK3B Expression is Associated with Poor Survival in Melanoma Pts given αPD-1 Therapy**

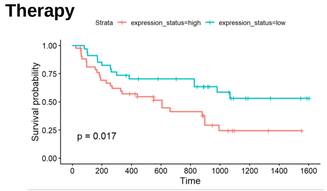



**Figure 3.**
Expression of *GSK3B* was used to stratify advanced melanoma pts who received αPD-1 therapy (n=77)[2,3]. RNA-seq data from two separate studies of patients with advanced melanoma were taken from pre-treatment tumor samples and standardized before combining for stratification analysis. Strata were separated if having above-average *GSK3B* expression.

**Machine Learning Modeling of Elraglusib Response**

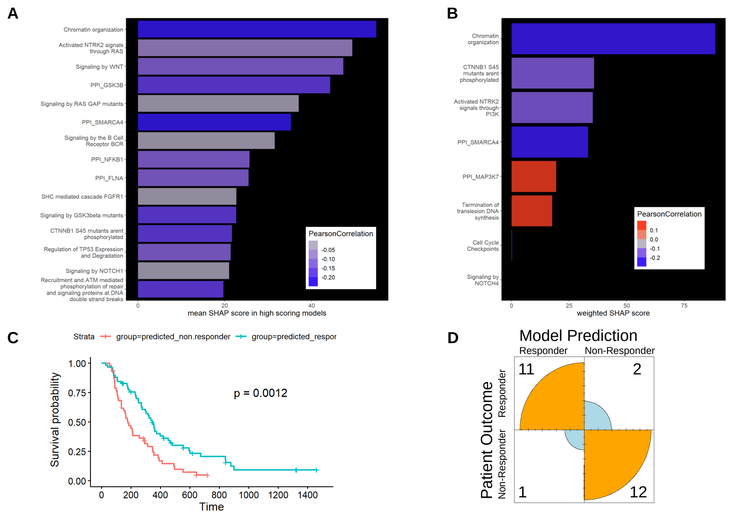
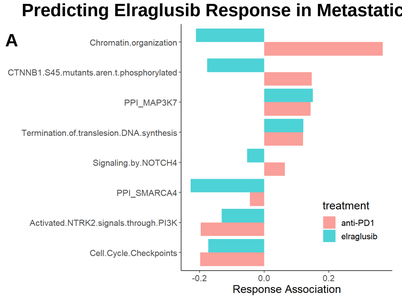



**Figure 4.** A) The most important features for model performance were ranked after calculating their mean SHAPley values[4,5], which were weighted by model performance in thousands of models; Color indicates Pearson correlation of feature to response; B) Feature SHAP contributions in the best-performing model; C) Kaplan-Meier plot of 1801 patient overall survival days with groups of the model's predicted responders or non-responders; D) Confusion matrix of the top model's predictions on the test set of 26 Pts. The upper left indicates true negatives, and the bottom right true positives.

**Predicting Elraglusib Response in Metastatic Melanoma Patients Treated with αPD-1**




B

| | Elraglusib non-responder | Elraglusib responder |
|---|---|---|
| **αPD-1 non-responder** | 3 (8.8%) | 9 (26.4%) |
| **αPD-1 responder** | 11 (32.3%) | 11 (32.3%) |

**Figure 5.**
Metastatic melanoma Pts[2] with pre-treatment WES data had pathway features processed through scoring the same mutations assayed in the 1801 genomics panel which were used to generate original pathway features.
A) Model feature response associations to either elraglusib response or αPD-1 response; B) Percentage and number of metastatic melanoma Pts that were responders/non-responders to αPD-1 therapy with their predicted Elraglusib response groups. The majority of metastatic melanoma Pts were predicted Elraglusib responders, with a selectivity in αPD-1 non-responders.

**Explanation of Machine Learning Model Response Prediction on Individual Patients**

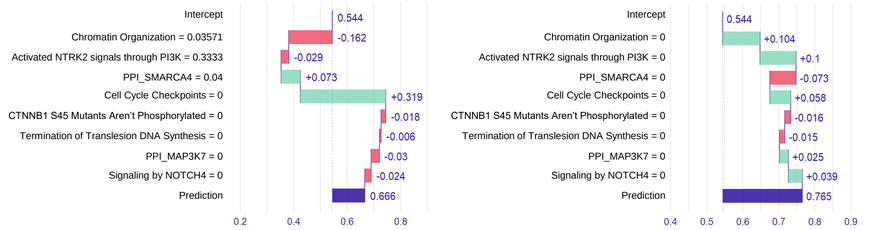



**Figure 6.** Two Melanoma Pts from the 1801 trial were taken as examples to explain the genomic basis of the ML model's prediction of Pt response. Genomics-based pathway features were scored and then used as input for the model to predict outcome. The contribution of features to individual predictions was estimated by calculating SHAPley values. The x-axis represents the probability of response, with values over 0.5 being predicted responders.

## Major Take Aways

- Single agent elraglusib demonstrated signs of clinical activity in heavily pre-treated pts with metastatic melanoma including one CR and prolonged OS in 5 pts.
- AI modeling predicts that checkpoint resistant metastatic melanoma patients may benefit from elraglusib therapy

## Future Directions

- Future clinical studies of elraglusib and αPD-1 combination in histologies selected based on clinical data from 1801 and ML modeling
- Further evaluation of ML models to select patient populations for elraglusib as well as more broadly for other cancer drugs
- Develop clinical applications of the ML model to inform clinical decision making

## References

[1]Sahin I, et al. *Cancer Biol Ther.* 2019.
[2]Hugo W, et al. *Cell* 2016.
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[4]Shapley LS. *Contributions to the Theory of Games* 1953.
[5]Biecek P. *Journal of Machine Learning Research* 2018.