Predicting Glioblastoma Clinical Trial Success

Transforming Trial Design Through AI-Powered Patient Response Prediction

Executive Summary: The pharmaceutical industry faces a critical challenge: over the past two decades, completion rates for adult neuro-oncology trials have dropped from ~88% to ~64%, stemming from difficulties with patient accrual. Annually, an estimated $50-60 billion is spent on oncology drug development trials that ultimately fail.

The SATGBM predictive framework offers a solution. By identifying which patients are most likely to respond to specific therapies *before* trial enrollment, this AI-powered platform enables precision patient selection, reduces trial sizes through response enrichment, and significantly de-risks clinical programs. Developed and trained on over 500 glioblastoma patients and documented across over 80 clinical trials, our predictions consistently align with real-world clinical trial response rates. In contrast to traditional precision oncology based approaches that rely solely on genetic biomarkers of responsive, SATGBM leverages multiomic data to derive network based biomarkers of response thereby expanding the application of precision oncology beyond the <10% of patients with actionable mutations.

The Challenge

Clinical trial development in oncology faces significant challenges. An estimated $50-60 billion is spent annually on oncology drug development trials that ultimately fail. In adult neuro-oncology specifically, completion rates have declined from ~88% to ~64% over the past two decades, primarily due to patient accrual difficulties.

The core issue is an inability to identify which patients will respond to treatment before trial development or enrollment, leading to diluted efficacy signals and higher failure rates.

The SATGBM Solution

How It Works: SATGBM is a systems biology-based AI-powered analytics approach that leverages three critical data sources:

- **Historical clinical trial data** documented across over 80 clinical trials
- **Multi-omic tumor profiles** from over 500 glioblastoma patients
- **Disease-gene network models** based on mechanistic disease biology

The key innovation: A curated disease-gene network model based on the causal and mechanistic underpinnings of disease biology enables explainable individualized predictions of disease progression risk and responsiveness to treatments. This model was developed using systems biology to mine and integrate a large variety of data types including mutations, chromosomal structural variations, gene function annotations, transcriptome, chromatin accessibility, protein-DNA interaction, miRNA target interactions, protein-protein interactions, protein-drug interactions, and clinical outcomes.

The Predictive Process

The framework learns from real-world outcomes by:

1. **Screening clinical outcomes data** to understand real-world patient response to a given treatment
2. **Developing response profiles** based on metrics such as predicted drug activity, drug target expression levels, epigenetic biomarker characteristics, (e.g., MGMT promoter methylation status of GBM patients), and chromosomal aberrations (e.g., mutations and complex chromosomal structural variations)
3. **Simulating clinical trials** with 1000s of synthetic patient cohorts of defined characteristics to understand expected outcomes of running real-world trials
4. **Comparing simulated outcomes** to real-world trial outcomes of response

This strategy provides an innovative means of learning from past clinical trial successes and failures to better guide the development and execution of trials in the future.

Validation: Proven Accuracy Across Multiple Drug Classes

Response probabilities have been *predicted* for many drugs, including three major drug classes not commonly associated with glioblastoma. While there has been suggested evidence for these drug classes in GBM, no trials have generated sufficiently high response rates to warrant consistent clinical use. Our *predictions* have successfully reproduced the range of objective response rates *observed* in clinical trials for each drug class (Fig. 1A).

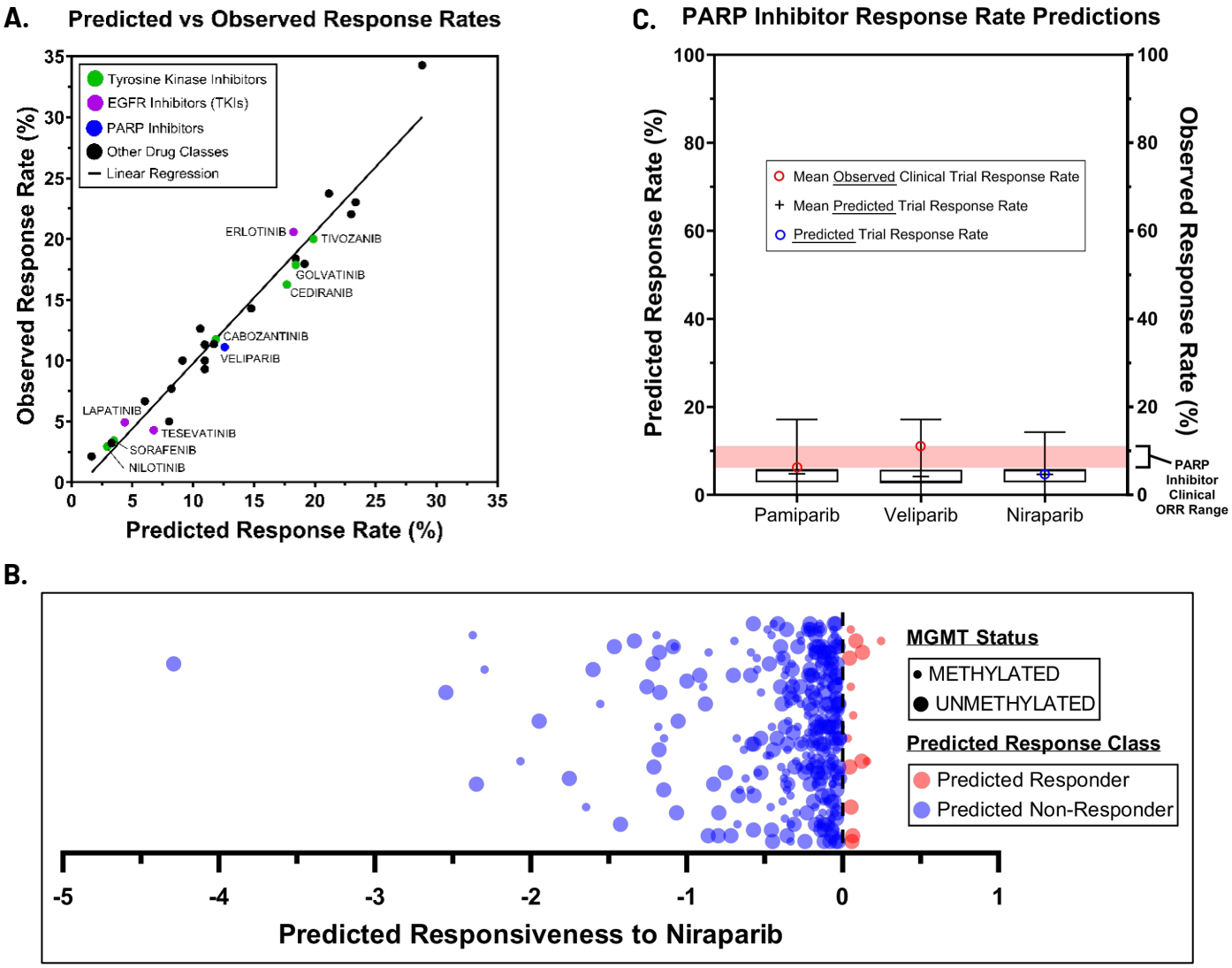

Figure 1. Response Prediction Outcomes. A. Correlation analysis of *predicted* and *observed* GBM clinical trial response rates for major drug classes, including PARP, EGFR, and Tyrosine Kinase Inhibitors. (Spearman r value: 0.9710, P value: <0.0001, **** highly significant correlation). **B.** Responders (red) and non-responders (blue) to Niraparib across a cohort of 321 TCGA GBM patients, *predicted* based on SATGBM uncovered characteristics of response to Niraparib. **C.** Box plots indicate *predicted* range of response rates for Pamiparib, Veliparib and Niraparib based on 1000 simulations on synthetic cohorts of randomly sampled TCGA patients of similar numbers and characteristics as the actual corresponding clinical trials. *Observed* range of response rates across trials is shown as a red band, and red circles denote *observed* mean response rates for each drug trial. *Predicted* average response rate for on-going Niraparib trial is indicated as a blue circle.

PARP Inhibitors

Predicted response rate: ~ 0 - 15%
Actual clinical trial range: ~ 6 - 12%

Simulations for PARP inhibitors, such as Pamiparib and Veliparib, showed response rates consistent with clinical trial outcomes (Fig. 1C).

Key finding: Use of MGMT methylation status as a predictor of response to PARP inhibitors has been shown to be ineffective based on the prediction simulations. Approximately half of all potential PARP inhibitor responders are predicted to have a methylated MGMT promoter status.

EGFR Inhibitors

Predicted response rate: ~ 0 - 50%
Actual clinical trial range: ~ 0 - 35%

Simulations for targeted therapies such as EGFR inhibitors have shown similarly favorable results, with predictions consistent with clinical trial outcomes.

Tyrosine Kinase Inhibitors (TKIs)

Predicted response rate: ~ 0 - 50% (across 15 different inhibitors from independent trials)
Actual clinical trial range: ~ **0 - 35%** (across independent trials)

Even in a drug class as diverse as TKIs, simulation results show consistency with clinical trial outcomes data across 15 different TKIs, targeting 34 distinct targets, all from independent trials.

Real-World Application: Niraparib Case Study

To demonstrate practical utility, we applied SATGBM to **Niraparib**, a PARP inhibitor being trialed in newly diagnosed adult GBM patients with unmethylated MGMT promoters and no IDH mutation (NCT06388733).

Our Predictions:

- **Expected response rate based on patient eligibility criteria for NCT06388733:** ~4.6% average (range: 0-15%)
- **Estimated U.S. responders based on SATGBM delineated eligibility criteria:** ~900 patients
- **Estimated global responders based on SATGBM delineated eligibility criteria:** ~3,300 patients

Validation Against Similar Trials:

These predictions align well with real-world trial outcomes observed in clinical trials on other PARP inhibitors:

- Pamiparib (NCT03150862): ORR = 6.17%
- Veliparib (NCT03581292): ORR = 11.11%

Actionable Insights:

Our simulations suggest that based on the patient eligibility criteria for the Niraparib trial, response rates are likely to be in the 0-15% range.

Key finding: Our simulations show that methylation status has no effect on patient response to PARP inhibitors. Given the accuracy of our simulations in recapitulating observed response rates for previously conducted Pamiparib and Veliparib trials, future trials on PARP inhibitors should consider SATGBM derived network biomarkers as eligibility criteria for patient selection.

Value Proposition for Pharmaceutical Partners

The SATGBM framework offers the ability to:

- **Overcome Historical Trial Failures**
  - Learn from over 80 clinical trials to understand what drives success and failure in glioblastoma trials.
- **De-Risk Prospective Clinical Programs**
  - Predict response rates before investing in full trial development, enabling data-driven decisions.
- **Reduce Trial Sizes Through Patient Response Enrichment**
  - Guide precision patient selection to enrich for likely responders, improving success probability.
- **Estimate Population-Level Impact**
  - Determine the number of patients likely to respond on both national and global scales.
- **Optimize Recruitment Criteria**
  - Identify which inclusion/exclusion criteria impact outcomes versus those that unnecessarily limit responder enrollment.

Conclusion

The insights provided by the SATGBM predictive framework can be leveraged in the process of developing eligibility criteria for patient recruitment and selection for proposed trials. The ability to guide precision patient selection constitutes an enormous opportunity to overcome historical trial failures, de-risk new prospective clinical programs, and reduce trial sizes through patient response enrichment.