A large molecular model (LMM)-based predictor of clinical response to the WEE1 inhibitor Debio 0123 + carboplatin therapy

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SUMMARY

Debio 0123 is an investigational, orally available, highly selective, and brain-penetrant adenosine triphosphate (ATP)-competitive inhibitor of the WEE1 tyrosine kinase, currently in phase I/II clinical trials either as a monotherapy or in combination with various therapies[1]. Inhibition of WEE1 presents an opportunity as a therapeutic target in cancer therapy, either in cells relying on cell cycle checkpoints regulated by WEE1 or to potentiate DNA damaging agents.

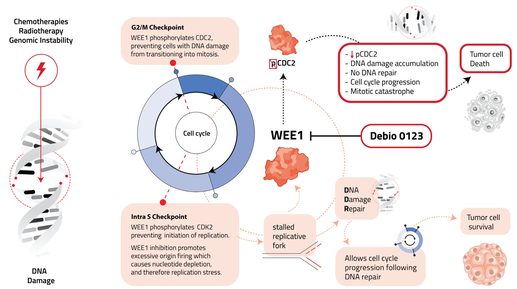
We previously described a first-generation digital biomarker that accurately predicted response to Debio 0123 in both patient-derived organoid and in vivo xenograft models. This biology-driven, machine learning–based classifier outperformed the baseline model, underscoring its potential for clinical application[2]. Building on that foundation, we now present a second-generation, clinically relevant, biology-informed machine learning predictor of response to Debio 0123 and carboplatin (CB) combination therapy. Developed using the Genialis ResponderID™ and Supermodel platforms, this model was built upon clinical data from patients enrolled in the Debio 0123-101 clinical trial (NCT03968653). Using a logistic regression model with ElasticNet regularization that was trained on diverse and biologically relevant features (biomodules) and their interactions, our predictor has shown excellent performance on the 24-week patient response in the Debio 0123-101 cohort, with robust AUROC (area under the receiver operating characteristic curve) (0.95), accuracy (0.80), and effective separation of patients with and without treatment benefit. This second generation model re-captures the same biological pathways as previously identified in preclinical models and uncovered additional biologies predictive for patient response.

These findings highlight the potential of a machine learning-driven approach to refine patient selection for WEE1 inhibitor therapies, providing a strong foundation for further clinical validation of Debio 0123.

1 BACKGROUND

The heterogeneity of cancer and the compensatory nature of DNA damage response (DDR) pathways pose significant challenges for therapies targeting DDR processes. Tumors often develop resistance to therapies through the engagement of alternative repair mechanisms. This limits the efficacy of current treatments, necessitating more refined approaches to predict and overcome therapeutic resistance.[3] As such, patients are typically suboptimally stratified and experience widely varying treatment outcomes. There is a critical need for robust, clinically relevant biomarkers that can accurately identify patients who will benefit from DDR-targeted therapies. Such predictive biomarkers not only improve patient outcomes but also optimize clinical trial designs, informing therapeutic strategies that significantly de-risk development and increase trial success rates.

WEE1 acts at both the Intra-S-phase and G2/M checkpoints making WEE1 inhibition, through agents like Debio 0123, amenable to combination with multiple chemotherapies with different mechanisms of actions ***(Figure 1)***. Our objective was to create a clinically meaningful, biology-driven machine learning model to predict response to the combination therapy of Debio 0123 and carboplatin (CB), using the Genialis ResponderID™ and Supermodel platforms and leveraging transcriptomic data from patient tumor biopsies.



▲ ***Figure 1.*** *In cancer cells, DDR pathways are often upregulated due to genomic instability. WEE1 is a key regulator of the Intra-S-phase and G2/M checkpoints where it leads to cell cycle arrest allowing DNA damage repair. Inhibition of WEE1 reduces the phosphorylation of CDC2 (CDK1) permitting cells to proceed through the cell cycle with an accumulation of DNA damage leading to mitotic catastrophe and ultimately cell death.*

2 METHODS

Data

Patient biopsies were performed in the scope of the Debio 0123-101 phase I clinical trial prior to the initiation of combination therapy with Debio 0123 and CB. Paired-end RNA sequencing (RNA-seq) libraries were prepared from 15 bulk primary and metastatic tumor tissue samples collected from patients with advanced cancer using either fresh or archival material. Library preparation was conducted using the Roche KAPA RNA HyperPrep Kit. Sequencing was performed on the Illumina NovaSeq 6000 platform, targeting a depth of 100 million reads per sample with a read length of 75 base pairs. Based on tumor assessments performed within the study according to RECIST, patients were designated as being progression-free (treatment benefit, here at least stable disease if not partial response) or as progressed (no treatment benefit, progressive disease) at 16 and 24 weeks after treatment initiation ***(Figure 2)***.

Genialis™ Supermodel

Genialis™ Supermodel is a large molecular model (LMM) which maps RNA-seq gene expression into the space of cancer biology. It computes scores of hundreds of biomodules that capture distinct biological processes and mechanisms, including but not limited to DNA damage repair, tumor suppressor and stress response pathways.

Modeling details

Biomodule features were computed from CPM (counts per million)-normalized gene expression data and were used as input to the model. Feature selection was performed through a combination of expert-curation of biomodules with stability-based filtering and ReliefF instance selection to ensure robust and informative feature identification.

A logistic regression model with ElasticNet regularization was trained accounting for interactions between selected features from the Genialis™ Supermodel. The model generated a binary classification for each sample, categorizing it as either with or without treatment benefit, along with the corresponding estimated probability of response.

The primary endpoint for this biomarker study was defined as the observed clinical response at the 24-week assessment following treatment initiation. For model training, patients exhibiting a response or stable disease were classified as patients with *"treatment benefit"*, while those with progressive disease were classified as patients with *"no-benefit"*.

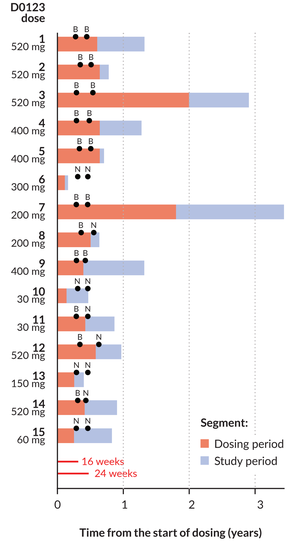
Performance of the model was estimated in nested cross-validation. The inner cross-validation loop included selection of optimal model type and the associated hyperparameters. The outer cross-validation loop was used for unbiased estimation of out-of-sample performance of the model. Leave-one-out cross-validation was used in both loops.

Performance of the model was compared to three baseline (dummy) models ***(Table 2)***. Dummy models generate predictions without using feature values, i.e., gene expression data, but may rely on the distribution of the target variable, i.e., patient response, in the training set. Predictions from the dummy models were obtained using the same cross-validation procedure as the digital biomarker model.

The prior strategy always predicts the majority class and assigns class probabilities according to the empirical class distribution in the training data. The random strategy predicts the treatment benefit of a randomly selected patient from the training data but does not estimate the probability of response. Finally, under the all-comer strategy, all patients are predicted to experience treatment benefit, with the probability of treatment benefit equal to one ***(Table 1)***.

Dummy model strategy	Predicted response	Predicted probability of treatment benefit
Prior	Majority class	Proportion of samples with treatment benefit
Random sample	Response of a random sample in the training data	N/A
All-comers	Treatment benefit	1

▲ ***Table 1.*** *Comparison of predicted response and treatment benefit probability across prior, random sample, and all-comers dummy model strategies.*



3 RESULTS

Model	Log loss	AUROC	AUPRC	ACC	F1-score	PPV	NPV	TPR	TNR	BA
ElasticNet with interaction terms	0.34	0.95	0.95	0.80	0.77	0.83	0.78	0.71	0.88	0.79
Dummy (prior)	0.77	0.00	0.47	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Dummy (random sample)	N/A	N/A	N/A	0.47	0.43	0.43	0.50	0.43	0.50	0.46
Dummy (all-comers)	19.22	0.50	0.47	0.47	0.64	0.47	N/A	1.00	0.00	0.50

Legend: AUROC (area under the receiver operating characteristic), **AUPRC** (area under the precision-recall curve), **ACC** (accuracy), **PPV** (positive predictive value), **NPV** (negative predictive value), **TPR** (true positive rate), **TNR** (true negative rate), and **BA** (balanced accuracy).

▲ ***Table 2.*** *Performance of the WEE1IDv2 predictor (colored gold) and dummy comparators on the Debio 0123-101 dataset at the 24 weeks time point of overall response assessment.*

Performance on Debio 0123-101 patient dataset

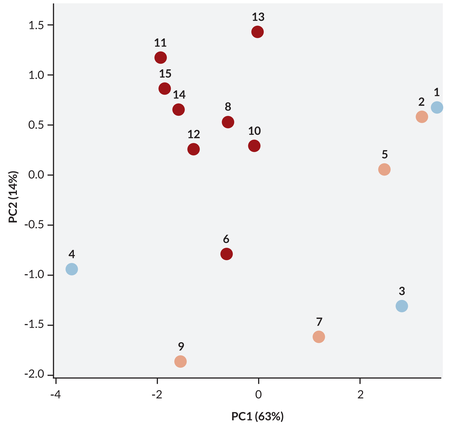
At the 24-week primary endpoint, model performance demonstrated strong predictive accuracy, with an AUROC of 0.95, overall accuracy of 0.80, F1-score of 0.77, and log loss of 0.34 ***(Table 2)***. The model correctly classified 7 of 8 samples from patients without treatment benefit and 5 of 7 samples from patients with treatment benefit. Of the three misclassifications, one was a false positive and two were false negatives.

Model interpretation

Principal component analysis (PCA) of biomodule features reveals clear biological stratification of patients ***(Figure 3)***. Samples from patients with and without treatment benefit aligned with high activity of different sets of biomodules out of the seven biomodules identified. Stable disease cases clustered between responders and non-responders.

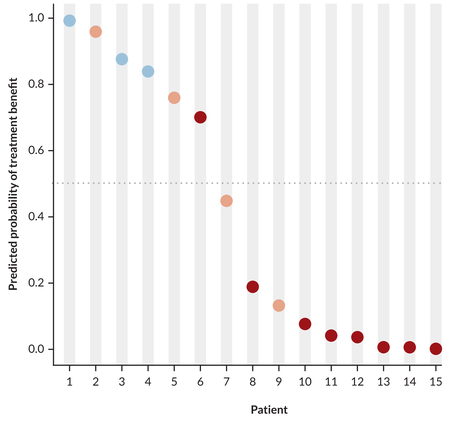
Classification capabilities are demonstrated in a rank plot of predicted probability of treatment benefit ***(Figure 4)***. The model effectively distinguishes between patients likely benefitting and not benefitting from Debio 0123+CB treatment. Most patients with partial response were assigned a high probability of treatment benefit in nested cross-validation. Progressive disease patients were predominantly assigned a low probability of treatment benefit. Samples with stable disease exhibited a broad range of predicted probabilities, reflecting the inherent clinical and molecular heterogeneity of this intermediate category. Cases near the decision boundary are examples of model predictions with low confidence.

◀ ***Figure 2.*** *Swimmer plot illustrating treatment benefit for the Debiopharm cohort at actual or imputed 16- and 24-week assessment time points and the corresponding D123 dose. Patients 6 and 13 who were withdrawn from the study due to documented disease progression before the scheduled assessment are classified as having no treatment benefit. Legend: B (treatment benefit), N (no treatment benefit).*



◀ ***Figure 3.*** *Principal component analysis (PCA) of Debio 0123-101 tumor samples using Z-score standardized WEE1IDv2 input modules.*

The input features showed separation between samples from patients with and without treatment benefit along the first two principal components.



◀ ***Figure 4.*** *Predicted treatment benefit probabilities based on the WEE1IDv2 model on Debio 0123-101 tumor samples in nested cross-validation. Each dot represents a single patient, ordered by predicted probability of treatment benefit in descending order.*

Points are colored by their actual overall response at 24 weeks post-treatment: PD (progressive disease), SD (stable disease), and PR (partial response). The horizontal dashed line indicates a decision threshold at 0.5. If the predicted treatment benefit probability is above 0.5, the patient is predicted as benefitting from treatment, below it as not benefitting.

CONCLUSIONS

This study demonstrates the potential of LMMs as a high-performance, interpretable, and biology-informed predictor of therapeutic response to Debio 0123 and CB combination therapy. By integrating diverse molecular features (biomodules) with mechanistic insights into DDR and related pathways, the model provides a high-performance framework for biomarker-driven precision oncology. It achieved strong predictive performance in nested cross-validation (AUROC 0.95, accuracy 0.80, F1-score 0.77, log loss 0.34), demonstrating generalizability and robustness of predicted probabilities on unseen samples.

A key limitation of this study is the small training cohort, comprising only 15 samples. This limited sample size constrains statistical power and the ability to capture the full spectrum of biological and clinical heterogeneity present in larger patient populations, allowing improvement of model robustness and generalizability in the future. Future work incorporating larger, multi-indication datasets will better align the model with relevant biological contexts and aim to improve its predictive performance across diverse cancer types and treatment regimens.

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