Machine learning algorithm identifies key serum cytokines associated with evidence of clinical activity in patients treated with personalized immunotherapeutic platform (IGV-001)

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Background

IGV-001 is a novel immunotherapy that combines irradiated, patient-derived glioblastoma tumor cells and an antisense oligonucleotide against insulin-like growth factor type 1 receptor (IMV-001) in biodiffusion chambers (BDC). We recently reported [1] IGV-001-treated newly diagnosed glioblastoma patients had a median progression free survival of 17.1 months compared with 6.5 months in historical standard-of-care-treated patients (p=0.0025) at the highest exposure of the combination product. We have now identified key cytokines and other clinical measures that are predictive of patient outcome via serum profiling and machine learning classification.

Methodology

Cytokines in sera were assayed from the day of treatment (0d), 14, 28, 42, and 150d post-treatment. Cytokines quantified included IL-1β, IL-5, IL-6, IL-8, IL-10, IL-13, IL-15, IL-17A, IL-17F, IFNγ, and TNFα, among others. Methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter [1] was also input as a binary variable in the predictive algorithm. An overall survival cutoff point of 21.9 months was used to dichotomize 'good' vs. 'poor' outcomes. MATLAB® Classification Learner was used to train an "optimized tree" predictive model with a sub-population of samples. The trained model was subsequently used to predict survival classification for all patients based on cytokine and clinical data inputs.

Results

IL-8 sera analysis showed predictive potential discerning good vs. poor outcomes (Fig. 1). Median IL-8 sera concentrations from good (n=14) vs. poor (n=19) responders showed significant differences on 28d (good=5.68 pg/ml, poor=12.30 pg/ml, p=0.027) and 42d (good=4.25 pg/ml, poor=18.90 pg/ml, p=0.0025). No difference was observed on d0 (Fig. 2). The Classification Decision Tree Model (Fig. 3) placed IL8 at the first decision node, and IL13 and IL5 at the second one. Predictor Importance Analysis indicated key cytokines IL-8, IL-5, MCP-1, IL-10, IL-4, IL1β, and IL-6 (Fig. 4). MGMT methylation [1] also figured as an important predictor. The training set resulted in 100% correct classification of the training dataset (n=10, good=5, poor=5, data not shown). Applying the trained model on the full dataset (n=33, good=14, poor=19), resulted in 93.9% correct classification of patient's actual clinical outcomes (Fig. 5).

Fig. 1: IL-8 Sera Analysis: Good outcomes-green; poor outcomes-red

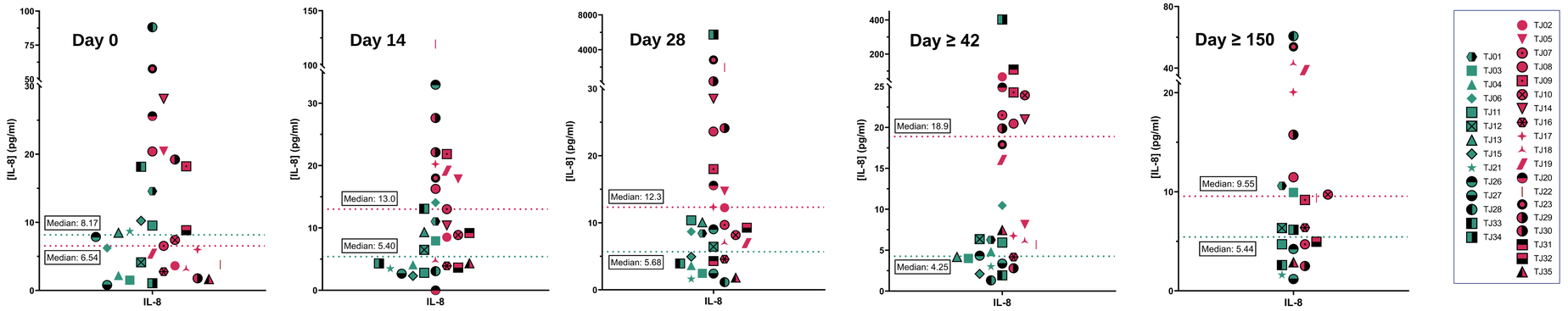


Fig. 2: Median IL-8 Time Course by Outcome

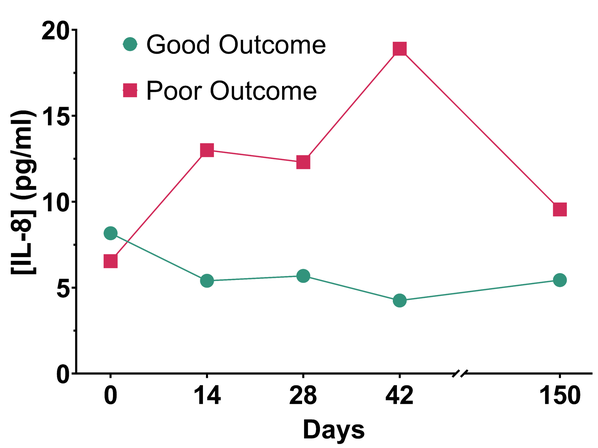


Fig. 3: Classification Decision Tree Model

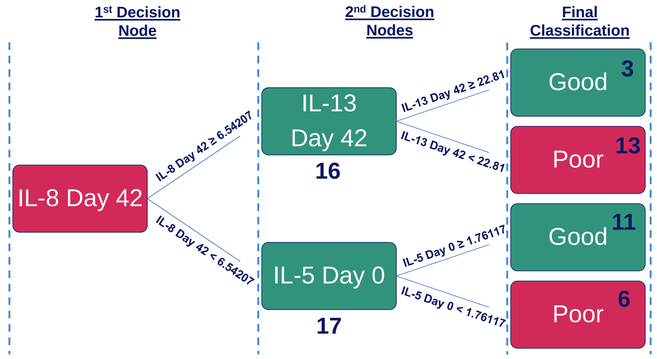


Fig. 4: Predictor Importance Analysis

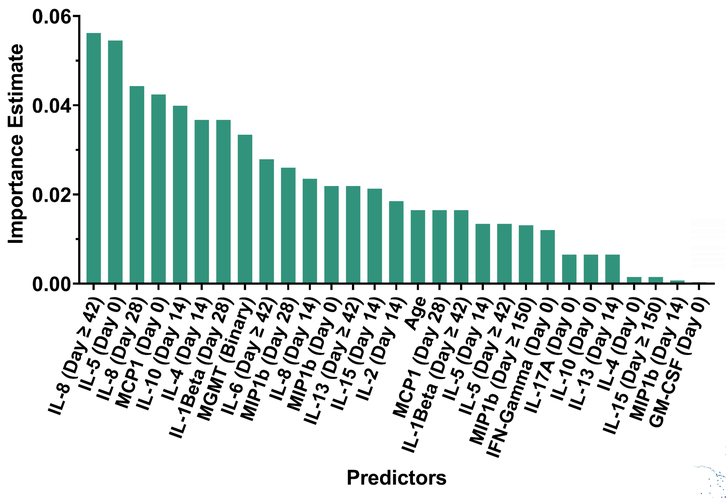
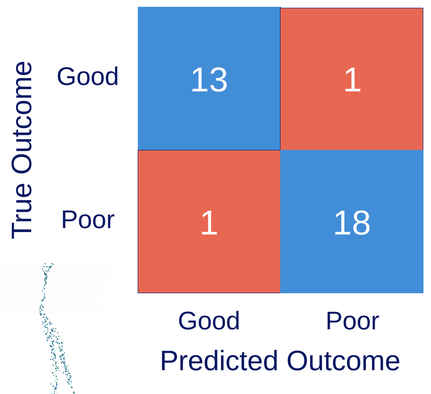


Fig. 5: Patient Outcome Classification



Classification Accuracy:
31 of 33 ~ 93.9%

Conclusions

- A classification decision tree model has been developed to predict long-term "good" vs. short-term "poor" outcomes of IGV-001-treated patients.
- GBM-associated cytokines **IL-8**, **IL-5**, **IL-6,** and **IL-13** are key immune-correlates of patient outcome in IGV-001 treated patients. These cytokines are known to correlate with tumor burden or prognosis, validating the utility of our model.
- Further inclusion of data from new patients from an upcoming Phase IIb (ClinicalTrials.gov Identifier: NCT04485949) will be utilized to strengthen the model's predictive capabilities and the potential identification of patient populations most likely to benefit from IGV-001 immunotherapy.

[1] Andrews, David W et al. "Phase Ib Clinical Trial of IGV-001 for Patients with Newly Diagnosed Glioblastoma." Clinical Cancer Research vol. 27,7 (2021): 1912-1922. doi:10.1158/1078-0432.CCR-20-3805l

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