Prediction of Response to Immunotherapy using Machine Learning and Tumor Kinetic Modeling incorporating CD8 ImmunoPET Imaging Analysis

1281

Agnish Dey,[1] Michael Ferris,[2] Ian Wilson,[2] William Le,[2] Kristin Schmiedehausen,[2] Kevin P. Maresca,[3] Edmund J. Keliher,[3] Jayant Narang,[4] Ganesh M. Mugundu,[1] Aman P. Singh[1]

[1]Oncology Cell Therapy Precision and Translation Medicine, Takeda Pharmaceuticals, Cambridge, MA, USA; [2]ImaginAb, Inglewood, CA, USA; [3]Worldwide Research, Development, and Medicine, Pfizer Inc, NY, USA;[4]Clinical Imaginag, Preclinical Translational Sciences Center of Excellence for Imaging, Takeda Pharmaceuticals, Cambridge, MA, USA

Question Can we predict response to immunotherapy using baseline characteristics of patients including CD8 cell density from biopsied samples and CD8 ImmunoPET imaging derived SUV (Standardized Uptake Value) and early tumor kinetic data?

Study design

- Green arrow head: Dose of 89Zr-Df-Crefmirlimab.
- Blue arrow head: Start of immunotherapy.
- 89Zr-Df-Crefmirlimab is a humanized, engineered, 80-kDa minibody (an antibody fragment), with high affinity to human CD8 (kd of 0.4 nM)
- Upto 1 week prior to initiation of immunotherapy, patients will receive an injection of 89Zr-Df-Crefmirlimab and will undergo PET/CT scan to determine baseline uptake of the tracer in tumor lesions and reference tissues.
- Patients received an additional injection of 89Zr-Df-Crefmirlimab and undergo PET/CT scan 4-6 weeks after commencement of immunotherapy to evaluate uptake of tracer in tumor lesions and reference tissues (NCT03802123).

Dose of CD8 Minibody: 1.5 mg
Immunotherapy Treatment: Nivolumab, Ipi-Nivo, Pembrolizumab

- Lung cancer: 8 patients
- Melanoma: 14 patients
- Renal cancer: 16 patients
- Gastric cancer: 2 patients
- Head and Neck cancer: 1 patient
- Bladder cancer: 1 patient
- Spindle cell carcinoma: 1 patient

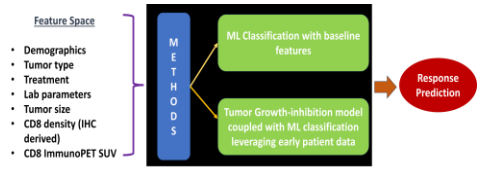
Key Take-aways

- Supervised machine learning model leveraging various baseline patient characteristics including CD8 ImmunoPET imaging derived SUV data was able to successfully predict clinical response to immunotherapy across different tumor types.
- Tumor growth-inhibition (TGI) model developed using early tumor kinetic data was coupled with supervised machine learning leveraging baseline CD8 density from biopsied samples, CD8 ImmunoPET imaging derived SUV and TGI model estimated parameters to predict clinical outcome as measured by Best Overall Response to immunotherapy.
- Various explainable machine learning techniques were further explored to study relative/marginal contribution of features of interest towards model prediction– thus showcasing the impact of different features utilized in the developed model on the desired outcome.

Background

- Immunotherapy (IO) has changed the landscape of oncology care and drug development, however not all patients respond or benefit from IO therapy. Accurate prediction of patient response to IO therapy is both critical and challenging.
- In this post-hoc analysis, A novel approach combining mixed effects modeling of longitudinal tumor size data and supervised machine learning (ML) was developed to predict patient response with good accuracy based on early tumor size assessments, baseline CD8 cell density from biopsied samples and CD8 ImmunoPET imaging derived SUV. Possibility of prediction of response using baseline patient characteristics alone was also explored.
- Early prediction of response could help optimize IO therapy for individual patients.

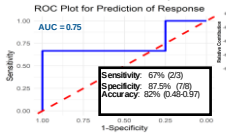
Methods



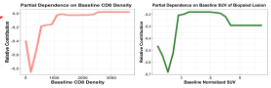
- Data source: Phase IIA BOT Study of 89Zr-Df-Crefmirlimab from ImaginAb.
- Input parameters considered in the model development are listed in Feature Space.
- Primary outcome of interest: prediction of Best Overall Response.
- Machine Learning Problem Statement: Patient Classification based on clinical outcome.

Prediction of Response using Baseline Patient Characteristics

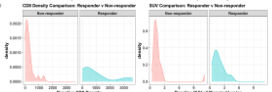
Random Forest Model: Accuracy of Prediction



Partial Dependence of Model Output on: CD8 Density and SUV of Biopsied Lesion



Observed Distribution of CD8 Density and SUV of Biopsied Lesion: Stratified by Response

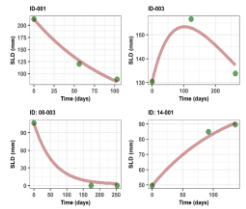


Data	Non-responder	Responder	Total
Train	14	7	21
Test	8	3	11

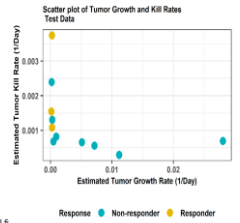
- Increase in the likelihood of patient response was associated with increase in baseline CD8 density and CD8 ImmunoPET SUV of biopsied lesion except when the feature values were very small.
- Model prediction was further verified by observed distribution of the two predictive markers across patient response.

Prediction of Response using Early Tumor Size Data

Tumor Growth Inhibition (TGI) Model: Individual Fits for Selected Subjects

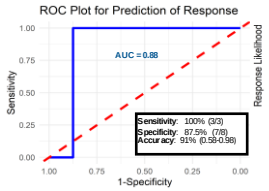


Distribution of TGI Model Parameters: Color Coded by Response in Test Data

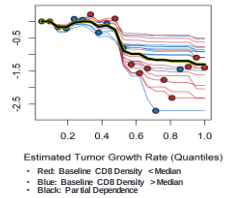


Green Circle: Observed data **Red Curve**: Model fi

Random Forest Model: Accuracy of Prediction



ICE Plot for rate of tumor growth: Color coded by Baseline CD8 Density



- Red: Baseline CD8 Density <Median
- Blue: Baseline CD8 Density >Median
- Black: Partial Dependence

- Baseline CD8 density and CD8 ImmunoPET SUV data were used in addition to TGI model estimated parameters (rate of tumor growth and kill) to develop the final supervised ML model to predict clinical outcome.
- Marginal contribution of TGI model estimated rate of tumor growth towards prediction of response was further explored using explainable machine learning (partial dependence + individual conditional expectation (ICE)).
- Decrease in likelihood of response was associated with increase in estimated rate of tumor growth and smaller baseline CD8 density.

Conclusions

- CD8 cell density from biopsied samples and CD8 ImmunoPET imaging derived SUV data were used along with other baseline patient characteristics to predict patient response to immunotherapy across different tumor types with reasonable degree of accuracy.
- Contribution of features of interest towards model outcome was studied using explainable machine learning techniques.
- A modelling platform using a combined approach of tumor growth inhibition modelling and supervised machine learning was developed to predict clinical outcome leveraging early patient data.
- Future Work: Developed model will be further refined to predict signal of activity (change in CD8 ImmunoPET SUV from baseline to post-treatment) and duration of response.
- Limitation: Small sample size.

Acknowledgments and Funding
Patient level data was shared by Imaginab.
This work was funded by Takeda Development Center Americas, Inc.

Disclosures
Agnish Dey, Aman P. Singh, Jayant Narang And Ganesh M. Mugundu are employees and stockholders of Takeda Pharmaceuticals. All authors declare no competing interests for this work.

Disclaimer
This poster is intended for healthcare professionals