Predictive Modeling as an OHDSI Network Study: Treatment Non-Response in NSCLC patients treated with ALK Inhibitors

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Abstract
In this study, we determine the role of non-response to treatment with ALK inhibitors in patients of Non-Small Cell Lung Cancer (NSCLC). We also develop a predictive algorithm for identifying patients at high risk of treatment non-response to these agents. Both investigations are conducted as an OHDSI network study, i.e. a R developed on a local database is distributed for execution against a suite of US database assets remotely, using the ARACHNE study execution tool.

Introduction
Targeted therapy is now standard-of-care (SOC) for subsets of patients whose tumors harbor oncogenic alterations, exemplified by Non-Small Cell Lung Cancer (NSCLC) mutations. EGFR mutations are the most ‘common’ de novo mutations and are effectively treated using TKI inhibitors, with patients routinely achieving a significant response rate (ORR 60-70%) and a median progression free survival (mPFS) of 8.5 months. At the same time, variation of ALK mutations (amplification, fusions: D34E-ALK, RANBP2-ALK, NPM-ALK, STTR-ALK, KIF5B-ALK) are still not fully investigated. These patients have significantly lower response rates on TKI therapy. As an area of current need, Takeda is interested in developing novel therapeutics intended to benefit NSCLC patients with less common mutations. To support these efforts, Takeda is interested in developing novel therapeutic approaches to NSCLC patients with less common mutations. To support these efforts, Takeda is interested in developing novel therapeutic approaches to NSCLC patients with less common mutations. As an area of current need, Takeda is interested in developing novel therapeutics intended to benefit NSCLC patients with less common mutations. This information is used to develop a predictive modeling algorithm for identifying patients at higher risk of treatment non-response to these agents. The goal of the algorithm would be to aid in identifying patients likely to benefit from novel therapeutics through clinical parameters, thereby complementing germline/breast-based approaches. Such an approach has potential applications to characterizing population needs, clinical study recruitment, and treatment decision-making for patients with NSCLC.

Study overview
This study developed a new model and used this model to predict health outcome for patients with locally advanced and metastatic NSCLC, constituting a retrospective, observational, new-user cohort study. We used OHDSI PatientLevelPrediction package to develop risk model and used this model to predict health outcome for patients with locally advanced and metastatic NSCLC, constituting a retrospective, observational, new-user cohort study. This study developed a risk model and used this model to predict health outcome for patients with locally advanced and metastatic NSCLC, constituting a retrospective, observational, new-user cohort study.

Study Design
All subjects in the database were included who meet the following criteria (Fig. 1):

Inclusion criteria:
- Exposure to at least 1 of ALK inhibitors (crizotinib, ceritinib or alectinib)
- At least 182 days of observation time prior to the index date
- At least 90 days of observation time at the first diagnosis date (diagnosis is locally advanced or metastatic NSCLC)
- Presence of other cancer during the wash-out period
- At least 3-month gap in treatment after the previous regimen was allowed prior to the index date.

Outcome definition
The primary outcome for each treated patient in response or nonresponse to treatment. Patients were assumed to be a non-responder if:
- A new line of therapy started after at least 60 days gap
- Treatment with another standard chemotherapeutic was initiated
- Surgical or radiological procedures were administered.

If none of these occurred within a window of observation the patient was considered a responder. As the data set had privacy limitations on death information, mortality could not be considered.

Results
We are planning to execute the study and demonstrate results for a number of US-data assets derived from payer-based claims, provider-based claims and EHR systems.

Study Design
The ARACHNE Research Network platform has been developed by Odysseus Data Services (Odysseus) to perform this task and used to conduct this study e.g. collaborate on study protocol between multiple parties, share analytical code and analysis results, annotate and share final insights.

Results
The following shows the preliminary results of generated from the database used for development:

- observation window 1: 267 responders vs 206 non-responders
- observation window 2: 296 responders vs 177 non-responders
- observation window 3: 323 responders vs 240 non-responders

Models used:
- Naive Bayes, Gradient Boosting Machine, Random Forest and Neural Network were trained for each observation window. The preliminary results for the predictive models were as follows:

Fig. 3. The preliminary accuracy of predictive models

Conclusion
It is possible to predict treatment outcome for NSCLC patients, but the sample size was rather small to reach conclusions. In particular, the fact that different methods generated exactly the same accuracy (Fig. 3) can be attributed to them probably generating the same effective model. We therefore want to expand the study using the larger OHDSI network. We also intend to expand our modeling efforts to include other targeted therapies, such as EGFR inhibitors.