STUDY REPORT SYNOPSIS

D4194R00024 iDETECT

A Non Interventional Pilot Study on Machine Learning for ILD detection based on the patient data from digital devices in unresectable stage III Non-Small Cell Lung Cancer Patients receiving durvalumab

Milestones: Final Protocol: March 31, 2021
FSI: August 10, 2021
LSI: September 6, 2022
LSLV: March 3, 2023
Database Lock (EDC part): April 26, 2023
Development of AI models:
Analytics:
Final Result Tables:
Final Report:

Phase of development: not applicable

Sponsor: AstraZeneca

Author: [redacted]

The Observational Study was performed in accordance with ethical principles that were consistent with the Declaration of Helsinki, ICH GCPs, GPP, and Ethical Guidelines for Life Science, Medical and Health Research Involving Human Subjects (promulgated on March 23rd, 2021).

[redacted]

Background/rationale:
IMFINZI®(durvalumab) as consolidation therapy in patients with unresectable stage III non-small cell lung cancer (NSCLC) who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy has become popular, however, one of concerns is onset of pneumonitis and/or exacerbation of radiation pneumonitis. Once grade 3 and higher stage of interstitial lung disease including radiation pneumonitis (hereafter "ILD") is developed, patients have to terminate the durvalumab treatment, also physicians must make emergent medical care. In order to avoid such situation, early-warning indicators of ILD must be worthwhile for the patients. Recently we learned several wearable non-invasive devices could monitor patients physiological data which may be associated with ILD onset.
Therefore, we aimed to develop machine-leaning based model for the identification of future development of diagnosed Grade 2 or higher ILD in patients with unresectable Stage III NSCLC receiving durvalumab by using the clinical characteristics (patient characteristics, treatment information including radiation, biochemical test data) and continuous self-monitoring parameters from the wearable device and mobile application.
Although this study is a pilot one, our future goal is that the patients are served early-warning indicators of ILD and visit hospitals before having severe ILD so that they could take an appropriate medical measures to prevent for developing worse stage of ILD. This could enable the patients to take more intensive and longer duration of durvalumab treatment and may contribute to longer overall survival (OS).

Objectives:
Objective in this study was to investigate feasibility of developing machine-learning based model for the identification of future development of diagnosed Grade 2 or higher ILD and of disease progression in patients with unresectable Stage III NSCLC receiving durvalumab.

Study design:
This study was a multicentre, prospective, non-interventional pilot study conducted in Japan. The study population consisted of unresectable Stage III NSCLC patients treated with durvalumab following chemoradiation therapy (CRT).
Patients were followed up to 6 months after starting 1st dose of durvalumab or until the initiation of alternative cancer therapy (excepting durvalumab as a maintenance therapy), death, or withdrawal of consent, whichever firstly comes.

Data source:
All the data were collected prospectively. Data for this study population came from several different sources: electronic case report form (eCRF), a wearable device, and a mobile application.
Patients' clinical characteristics collection based on the medical records in the study sites were entered into the electronic data capture (EDC) system.
Patients' physiological data (heart rate, respiratory rate, oxygen saturation [SpO_2]) were measured by the wearable device and transferred to Quantum data server via smartphone.
Patients' cough data (numbers) were counted by ResApp application downloaded into the smartphone and its data were transferred to the Quantum data server.
The patient background data captured in the eCRF. And the data from wearable devices and mobile application were integrated and linked at the patient level via a common identifier.

Study population:
The study population consisted of stage III unresectable NSCLC patients treated with durvalumab following CRT in Japan from June 2021 to June 2022. They had to fulfil all the inclusion/exclusion criteria.

Inclusion criteria:
Patients meeting the following inclusion criteria were enrolled;
1. Patient who provided written signed informed consent prior to the first study-specific procedures
2. Patient who was going to receive durvalumab for unresectable stage III NSCLC at first time following CRT
3. Patient whose performance status showed 0 or 1 prior to durvalumab treatment
4. Patient aged ≥20 years
5. Patient who was able and willing to wear the devices daily for up to 6 months as instructed

Exclusion criteria:
The following patients were excluded from the study;
1. Patient was under immunotherapy treatment other than durvalumab
2. Patient had received prior immunotherapy
3. Patient was under the interventional clinical studies using unapproved drugs or off-label use of drugs
4. Patient who showed ILD (including radiation pneumonitis) of Grade 2 or higher, after consolidated CRT
5. Patient who was judged as not suitable for the study by the study site investigators, in terms of fitting wearable devices, presence of silicone or metallic allergy

Outcomes:
The primary outcome was probability of development of diagnosed Grade 2 or higher ILD. The secondary outcome was probability of development of diagnosed progression disease (PD). The exploratory outcome was probability of development of diagnosed Grade 3 or higher ILD.

Statistical methods:
1. model construction by Machine learning

All objective outcomes were binary positive/negative data, and machine learning based models were built using binary classification model to predict the labeled training data.
Each visit for a patient was considered as an observation unit. Post data after the occurrence of each endpoint were excluded from the analysis. Dose date was considered to be a visit date for all objectives, and date of diagnosed as Grade 2 or higher ILD, date of diagnosed as PD, and date of diagnosed as Grade 3 and higher ILD were also considered to be a visit date for primary objective, for secondary objective, and exploratory objective, respectively.
Multilayer Perception, Recurrent Neural Network, Extreme Gradient-Boosting (XGBoost), Decision Trees, Support Vector Machine (SVM), Random forest, and logistic regression model were used as binary classification models. From these models, a suitable model was selected by model performance.
K-fold cross validation (k=4) was used to evaluate the performance of the model. In validation, data were split into a training data and a testing data per patient, and the performance of the machine learning model trained in the training data was evaluated using the testing data.
Patient background information and physiological data collected from a wearable device and cough app were used as feature variables in the machine learning models. The receiver operator characteristics (ROC) curves were plotted for all models, and the area under the curves (AUCs) were estimated for those models to evaluate model performances. In order to clarify the nature of the selected model, thresholds for negative and positive predictions were set using Yoden's index and other parameters, and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated after binary classification.

2. Patient characteristics

Continuous variables were summarized by descriptive statistics including mean, median, Standard Deviation (SD), first quartile (Q1), third quartile (Q3), maximum, and minimum, and categorical variables were summarized by count and percentage. Ninety-five percent confidential intervals (CIs) were presented where appropriate.

3. ILD-related events

Time-to-event data for ILD with Grade 2 or higher, PD, Grade 3 or higher were analyzed using Kaplan-Meir method. Cumulative incidence and its 95% CIs were estimated based on the Nelson-Aalen estimator of the cumulative incidence function.

Results:

A total of 145 patients were enrolled from 27 investigational sites, excluding 22 patients who dropped out before data acquisition; the data of 123 patients were analyzed and used for the prediction models for ILD development as well as progressive disease.

The mean (SD) age was 65.9 (10.25) years, and the mean (SD) wearing time of the wearable device per day was 7.8 (2.1) hours. Among these 123 patients, regarding highest garde of ILD, 46 patients developed grade 2 or higher and six patients developed grade 3. Clinical prediction model was explored by several different machine-learning models indicated above using patient background information collected by eCRF, and the physiological data in three consecutive days collected by wearable device and cough app. Among the Receiver Operating Characteristic (ROC) curves obtained by each model, XGBoost exhibited the highest AUC for the prediction of grade 2 or higher ILD development, while the logistic regression model exhibited the highest AUC for the prediction of progressive disease as well as grade 3 or higher ILD development.

Conclusion: In this study, we constructed a prediction model for Grade 2 or higher ILD in patients receiving durvalumab consolidation therapy after chemoradiotherapy, using patient background information and physiological data collected from a wearable device and cough app as feature variables by the machine learning methods. The AUC of models by XGBoost are higher than those of other methods. The prediction models might be applied to detect ILD Grade 2 or higher in the clinical setting. Further research is warranted to determine the validity and generalizability of this model..