Observational Study Report Synopsis

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MEDI-APEX
A Retrospective Non-Interventional Study of PD L1 Prevalence and Clinical Outcomes for Non-Small Cell Lung Cancer in Asia-Pacific

Milestones: Study Final Protocol version 1.0, 11 July 2015
Study Final Protocol version 2.0, 16 February 2016
First Patient In, 15 October 2015
Last Patient In, 27 February 2017
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Phase of development: Not Applicable – Observational study

Sponsor: [redacted]

Author: [redacted]

This study was performed in compliance with Good Clinical Practice and Good Pharmacoepidemiology Practice, including the archiving of essential documents.

Background/Rationale:

Lung cancer, the leading cause of cancer-related deaths worldwide, is characterized at the molecular level by the underlying mutation, which plays a crucial role in targeted treatment selection. Durvalumab is a human immunoglobulin G1 monoclonal antibody directed against the programmed cell death 1/programmed cell death-ligand 1 (PD-1/PD-L1) pathway. The proposed study was designed to support AstraZeneca programs by characterizing PD-L1 expression in the tumour cells (TCs), using the Ventana PD-L1 SP263 IHC assay, among non-small cell lung cancer (NSCLC) patients in Asia-Pacific and by assessing the clinical characteristics and outcomes of these patients, with specific attention to epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations. In particular, this non-interventional study (NIS) aimed to determine whether PD-L1 is a prognostic factor in the Asia-Pacific population, in an effort to improve targeted therapy utilization in standard practice for lung cancer treatments.

Objectives:

The **primary objective** of MEDI-APEX was to characterize PD-L1 expression among locally advanced, unresectable NSCLC patients (Stage III) and newly diagnosed Stage IV or recurrent metastatic NSCLC patients who received 1st, 2nd, 3rd line therapy or greater, stratified by histological subtype (squamous cell lung cancer [SqCLC] and non-SqCLC) and by EGFR, ALK, or KRAS mutation status where available.

The **secondary objectives** were:

1. To examine the overall survival (OS) by PD-L1 expression among locally advanced, unresectable NSCLC patients (Stage III) and newly diagnosed Stage IV or recurrent metastatic NSCLC patients by line of therapy and stratified by histological subtype and by EGFR, ALK, or KRAS mutation status where available;
2. To examine disease-free survival (DFS), relapse-free survival (RFS), and progression-free survival (PFS) by PD-L1 expression among locally advanced, unresectable NSCLC patients (Stage III) and newly diagnosed Stage IV or recurrent metastatic NSCLC patients by line of therapy and stratified by histological subtype and by EGFR, ALK, or KRAS mutation status where available;
3. To describe patient characteristics by PD-L1 expression among locally advanced, unresectable NSCLC patients (Stage III) and newly diagnosed Stage IV or recurrent metastatic NSCLC patients by line of therapy and stratified by histological subtype and by EGFR, ALK, or KRAS mutation status where available;
4. To describe the overlap between PD-L1 expression and presence of EGFR, ALK or KRAS mutations among locally advanced, unresectable NSCLC patients (Stage III) and Stage IV/recurrent metastatic NSCLC patients overall and by line of therapy and stratified by histological subtype.

[redacted]

Study design:

The study design was a non-interventional, retrospective, cohort study to characterize PD-L1 expression in the TCs among NSCLC patients, including SqCLC patients. If unavailable from the patient medical records, EGFR, ALK, and KRAS mutation status were tested from archival tumour tissue.

Data source:

All clinical data were collected retrospectively from medical records. Archival tumour tissue samples were used to determine PD-L1 expression. Existing biomarker test results for EGFR, ALK, and KRAS mutations were used for study purposes. When unavailable from the patient medical records, EGFR, ALK, and KRAS mutation status were tested from the archival tumour tissue.

Study population:

A total of 692 patients from one site in China, two sites in Japan and one site in South Korea had been screened to enter MEDI-APEX. The study enrolled 562 (81.2%) patients with NSCLC, including SqCLC, diagnosed between 01 January 2010 and 31 December 2014: 28.8% were dead and 71.2% were alive. Patients must have had initiated 1st line palliative chemotherapy by 31 December 2014, and had sufficient archival tumour tissue sample available for PD-L1 testing, as defined in the eligibility criteria. Of the 562 patients included in the Full Analysis Set (FAS), 506 (90.0%) were enrolled in the Evaluable Population (EP) (defined as patients with PD-L1 expression level known): 137 from China, 154 from Japan, and 215 from South Korea.

Inclusion criteria:

1. Adult male or female (according to age of majority as defined in local regulations).
2. NSCLC diagnosis between 01 January 2010 and 31 December 2014.
3. Fixed Paraffin-Embedded Tissue (FFPET) collected via core needle biopsy or resection and available in sufficient amount to complete PD-L1 testing.
4. FFPET tissue samples collected for NSCLC original diagnosis determination or for further analysis (e.g. research or treatment purposes) until the index date.
5. Patients with locally advanced or metastatic NSCLC who have initiated 1st line palliative chemotherapy by 31 December 2014.

Exclusion criteria:

1. Patients with locally advanced NSCLC with resectable disease and treated with curative intent.

Statistical methods:

Continuous variables were reported as mean, median, standard deviation (SD), maximum (max), and minimum (min). Categorical variables were summarised as absolute frequency and percentage of patients in each category. Percentages were calculated over the number of patients with non-missing data.

Levels of PD-L1 expression in the TCs were summarized descriptively according to PD-L1 expression cut offs TC≥25%, [redacted]
PD-L1 levels were presented for the overall study population and for the different patient segments as defined in the study objectives.

DFS, RFS, PFS, and OS were evaluated descriptively by Kaplan-Meier curves, and patient characteristics were presented by PD-L1 expression overall and by different patient segments as defined in the study objectives. Cox proportional hazards model was used for OS.

PD-L1 expression and survival measures were compared among countries, and stratified by NSCLC patient segment and histological subtype.

Sensitivity analyses were conducted to determine the optimal cut-off points of PD-L1 expression on TCs predictive of prognosis in standard of care.

Results:

The 562 patients included in the FAS had a mean age at diagnosis of 60.9 (SD 11.16) years, and comprised 341 males (60.7%). Two-hundred and sixty-five (n/N=265/533, 49.7%) were never smokers, and most patients reported to be in paid/self-employment (n/N=141/363, 38.8%) or to be retired (n/N=95/363, 26.2%).

A total of 269 patients (n/N=269/540, 49.8%) reported, at least, one medical condition at diagnosis, with vascular disorders as the most frequently observed medical condition, reported by 42.9% of patients (n/N=115/268), followed by respiratory, thoracic and mediastinal disorders (n/N=81/268, 30.2%).

Non-SqCLC was the most frequent histologic type, reported by 87.7% of patients (n/N=493/562), and adenocarcinoma not otherwise specified (NOS) was the most frequent histologic sub-type (n/N=399/562, 71.0%). Most patients were diagnosed with Stage IV NSCLC (n/N=289/560, 51.6%) or Stage IIIA (n/N=100/560, 17.9%).

Primary objective

Among the 506 patients included in the EP, 25.7% (95% CI: 21.9, 29.7) presented with PD-L1 expression level TC≥25%, and 74.3% (95% CI: 70.3, 78.1) with PD-L1 expression level TC<25%. Considering the exploratory cut-off point, the EP was evenly distributed, with 51.2% (95% CI: 46.7, 55.6) and 48.8% (95%CI: 44.4, 53.3) of patients expressing PD-L1 TC≥1% and TC<1%, respectively.

Among the different disease stages, 23.2% (95% CI: 16.7, 30.7) of Stage III patients (n/N=35/151) and 26.6% (95% CI: 22.0, 31.5) of Stage IV patients (n/N=94/354) presented with PD-L1 TC≥25%. Considering the exploratory cut-off point, 55.0% (95% CI: 46.7, 63.1) of Stage III patients (n/N=83/151) and 49.4% (95% CI: 44.1, 54.8) of Stage IV patients presented with PD-L1 TC≥1%.

In non-SqCLC and SqCLC patients, 25.8% (95% CI: 21.8, 30.1; n/N=116/449) and 24.6% (95% CI: 14.1, 37.8; n/N=14/57) of patients expressed PD-L1 TC≥25%, respectively. A higher proportion of SqCLC patients expressed PD-L1 TC≥1% (63.2% [95% CI: 49.3, 75.6]) compared with non-SqCLC patients (49.7% [95% CI: 44.9, 54.4]).

PD-L1 TC≥25% was seen in 16.7% (95% CI: 12.0, 22.5) of EGFR+ (N=209) and 30.7% (95% CI: 24.8, 37.1) of EGFR- (N=228) patients. PD-L1 TC≥25% was quite similar among ALK+ (N=19) and ALK- (N=235) patients: 26.3% (95% CI: 9.1, 51.2) and 22.1% (95% CI: 17.0, 28.0), respectively. PD-L1 TC≥25% was more prevalent among KRAS+ (N=20) than KRAS- (N=193) patients: 30.0% (95% CI: 11.9, 54.3) and 21.2% (95% CI: 15.7, 27.7), respectively. Nonetheless, the low number of ALK+ and KRAS+ patients limits the ability to drawn meaningful conclusions on the distribution of PD-L1 TC≥25% across the mutation status.

The prevalence of biomarker mutations was 47.8% EGFR+ (n/N=209/437), and 8.0% EGFR+ and PD-L1 TC≥25% (n/N=35/437); 7.5% ALK+ (n/N=19/254), and 2.0% ALK+ and PD-L1 TC≥25% (n/N=5/254); 9.4% KRAS+ (n/N=20/213), and 2.8% KRAS+ and PD-L1 TC≥25% (n/N=6/213).

Secondary objectives

The low number of patients presenting with ALK+ and KRAS+ limited the ability to establish meaningful comparisons with ALK- and KRAS- patients, respectively.

Overall survival LOT1

Of the 116 patients with PD-L1 TC≥25% and the 356 patients with PD-L1 TC<25% initially at risk, 30.2% and 25.8% of patients died after LOT1 initiation, respectively. Differences in the survival experience between the two groups became apparent from 12 months after LOT1

initiation, with PD-L1 TC<25% patients presenting a higher cumulative survival rate than PD-L1 TC≥25% patients, until the end of follow-up.

Among non-SqCLC patients, 22.3% of PD-L1 TC≥25% patients (N=103) and 21.1% of PD-L1 TC<25% (N=317) died during follow-up. Both groups displayed a similar survival experience during the first 10 months of follow-up, after which PD-L1 TC<25% patients had a slightly higher cumulative survival rate until 48 months.

Among SqCLC patients, a larger proportion of events was seen in PD-L1 TC≥25% (N=13) compared to PD-L1 TC<25% (N=39) patients: 92.3% versus 64.1%, respectively. The last PD-L1 TC≥25% patient alive died at 33 months, whereas the last event among PD-L1 TC<25% patients was observed at 49 months.

Among EGFR+ patients, 23.3% and 18.1% of PD-L1 TC≥25% (N=30) and PD-L1 TC<25% (N=166) patients initially at risk died during follow-up, respectively. From four months, PD-L1 TC<25% patients presented with a consistently higher cumulative survival rate compared to PD-L1 TC≥25% patients.

Among EGFR- patients, PD-L1 TC≥25% (N=64) patients recorded a lower mortality compared to PD-L1 TC<25% (N=151) patients, 26.6% versus 35.1%, respectively. PD-L1 TC≥25% patients registered a higher cumulative survival rate for the most part of the follow-up period compared to PD-L1 TC<25% patients.

Disease-free survival LOT1

The analysis of DFS after LOT1 yielded the exact same number of events as the OS analysis after LOT1.

Relapse-free survival LOT1

There were no events of disease recurrence during the observation period; therefore RFS estimates could not be computed.

Progression-free survival LOT1

Of the 116 PD-L1 TC≥25% patients and the 357 PD-L1 TC<25% patients initially at risk, 37.9% and 34.7% of patients progressed or died during follow-up. PD-L1 TC≥25% patients recorded a shorter median PFS time after LOT1 initiation, 25.1 (95% CI: 17.3, not defined [ND]) months versus 39.9 (95% CI: 29.3, 49.6) months in PD-L1 TC<25%. The survival curves started diverging at 3 months after LOT1 initiation.

Among non-SqCLC patients, PD-L1 TC≥25% (N=103) and PD-L1 TC<25% (N=318) patients recorded the same proportion of events after LOT1 initiation, 31.1%. PD-L1 TC≥25% patients exhibited, however, a shorter median PFS time compared to PD-L1 TC<25%: 37.3 (95% CI: 23.7, ND) and 43.7 (95% CI: 35.2, ND) months, respectively.

Among SqCLC patients, PD-L1 TC≥25% (N=13) patients recorded a higher proportion of events compared to PD-L1 TC<25% (N=39) patients: 92.3% and 64.1%, respectively. The median PFS time was estimated at 6.1 (95% CI: 3.0, 16.1) months in PD-L1 TC≥25% patients, and at 8.7 (95% CI: 4.1, 14.6) months in PD-L1 TC<25%. PD-L1 TC<25% patients exhibited a higher cumulative PFS rate compared to PD-L1 TC≥25% for the most part of the follow-up period.

Among EGFR+ patients, PD-L1 TC≥25% patients (N=30) recorded a higher proportion of events after LOT1 initiation compared to PD-L1 TC<25% patients (N=167), 43.3% and 26.3%, respectively; and a shorter median PFS time, 24.9 (95% CI: 17.3, ND) and 49.6 (95% CI: 41.4, ND) months, respectively. The PFS curves separated shortly after the beginning of the observation period, with PD-L1 TC<25% patients registering a persistently higher cumulative PFS rate.

In EGFR- patients, 31.3% and 44.4% of PD-L1 TC≥25% (N=64) and PD-L1 TC<25% patients (N=151) progressed or died after LOT1 initiation, respectively. The median PFS time in PD-L1 TC≥25% patients was twice that of PD-L1 TC<25%, 34.0 (95% CI: 12.6, ND) and 16.5 (95% CI: 10.9, 32.7) months, respectively. Contrary to that observed in EGFR+ patients, PD-L1 TC≥25% patients exhibited a higher cumulative PFS rate compared to PD-L1 TC<25% patients from seven months after LOT1 initiation until the end of follow-up.

Overall survival LOT2

Among the 56 PD-L1 TC≥25% patients at risk, 35.7% died during follow-up yielding a median survival time of 22.0 (95% CI: 9.5, ND) months after LOT2 initiation.
PD-L1 TC<25% patients recorded an identical proportion of events (35.6%), however, exhibited a longer median OS time, 28.0 (95% CI: 21.9, ND) months.

The low number of patients at LOT2 limits the ability to establish meaningful comparisons between non-SqCLC and SqCLC patients, EGFR+ and EGFR- patients, ALK+ and ALK- patients, and between KRAS+ and KRAS- patients.

Disease-free survival LOT2

The analysis of DFS after LOT2 yielded the exact same number of events as the OS analysis after LOT2.

Relapse-free survival LOT2

There were no events of disease recurrence during the observation period; therefore, RFS estimates could not be computed.

Progression-free survival LOT2

Among the 56 PD-L1 TC≥25% patients at risk, 46.4% progressed or died after LOT2. In PD-L1 TC<25% patients (N=149), the proportion of patients progressing or dying after LOT2

was similar to that seen among PD-L1 TC≥25% patients (48.3%), however, a longer median PFS time was recorded in this group, 17.3 (95% CI: 8.4, 22.2) months versus 10.6 (95% CI: 5.6, 16.1) months in PD-L1 TC≥25% patients.

In EGFR+ patients, the proportion of patients progressing or dying after LOT2 was similar in PD-L1 TC≥25% (N=20) and PD-L1 TC<25% (N=66) patients, 40.0% and 39.4%, respectively. PD-L1 TC≥25% patients recorded a shorter median PFS time, 13.5 (95% CI: 8.5, ND) months versus 22.2 (95% CI: 16.2, ND) months in PD-L1 TC<25% patients.

In EGFR- patients, PD-L1 TC≥25% (N=28) and PD-L1 TC<1% (N=68) patients registered a similar proportion of patients progressing or dying after LOT2 initiation, 53.6% and 55.9%, respectively. PD-L1 TC≥25% patients had a longer median PFS time compared to PD-L1 TC<1%, 10.6 (95% CI: 4.2, 19.8) and 6.5 (95% CI: 3.1, 23.9) months, respectively.

The low number of patients at LOT2 limits the ability to establish meaningful comparisons between ALK+ and ALK- patients, and between KRAS+ and KRAS- patients.

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