AstraZeneca

Statistical Analysis Plan

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Prospective, Interventional Pilot Study of Mobile Devices and Digital Applications to Detect Early Pneumonitis and Other Pulmonary Adverse Events in Unresectable Stage III Non-Small Cell Lung Cancer Patients on Durvalumab

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Syneos Lead Statistician PPD

Syneos Health

Prospective, Interventional Pilot Study of Mobile Devices and Digital Applications to Detect Early Pneumonitis and Other Pulmonary Adverse Events in Unresectable Stage III Non-Small Cell Lung Cancer Patients on Durvalumab

AZ Study Statistician

PPD

Date
(Day Month Year)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
cCRT	Concurrent Chemoradiotherapy
CHF	Congestive Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disorder
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAP	Data Analysis Plan
DRM	Data Review Meeting
EORTC QLQ C30	European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire
EORTC QLQ LC13	European Organization for Research and Treatment of Cancer Quality of Life Lung Cancer Module
FDA	Food and Drug Administration
FEF25/75	Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity
FEV1	Forced Expiratory Volume
FEV6	Forced Expiratory Volume in 6 Seconds
FVC	Forced Vital Capacity
GHS	Global Health Status
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ILD	Interstitial Lung Disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
N/A	Not Applicable
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
PEF	Peak Expiratory Flow
PRO	Patient Reported Outcomes
PT	Preferred Term
QoL	Quality of Life
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event

AMENDMENT HISTORY

Version	Date	Brief description of change
1.0	02-Mar-2022	Update AZ Signatory & addition of new term defining pneumonitis in section 8.2.
0.6	03-Feb-2022	Update and finalize the SAP
0.5	06-Oct-2021	Added revisions based on sponsor comments on 24Aug2021 and 13SEP2021
0.4	27-Jul-2021	Added revisions based on sponsor comments on 29Jun2021
0.3	05-May-2021	Added revisions based on the Protocol Amendment 5.0 and AZ SAP template
0.2	02-Apr-2020	Added revisions based on sponsor comments on v0.1/29Jan
0.1	29-Jan-2020	N/A

1. STUDY DETAILS

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective of the study is to describe the identification of treatment-emergent pneumonitis by grade (regardless of radiation therapy and/or immune-related etiology) in patients with unresectable Stage III non-small cell lung cancer (NSCLC) receiving durvalumab through the use of mobile technology which collects patient reported outcomes (PROs), vital signs (temperature, heart rate, respiratory rate), oxygen saturation (pulse oximetry), pulmonary function tests (spirometry), and physical movement (number of steps per day).

1.1.2 Secondary Objectives

The secondary objectives are:

- To describe durvalumab treatment discontinuation due to pulmonary Adverse Events (AEs), including pneumonitis
- To describe the duration of durvalumab use
- To describe the incidence of pulmonary AEs by grade
- To describe the severity of pulmonary AEs (including pneumonitis) and use of medication to manage AEs
- To describe the time to development of Grade 3 to 5 AEs, including pneumonitis
- To describe health-related quality of life (QoL) during the study and its relationship with AEs

1.1.3 Exploratory Objectives

The exploratory objectives are:

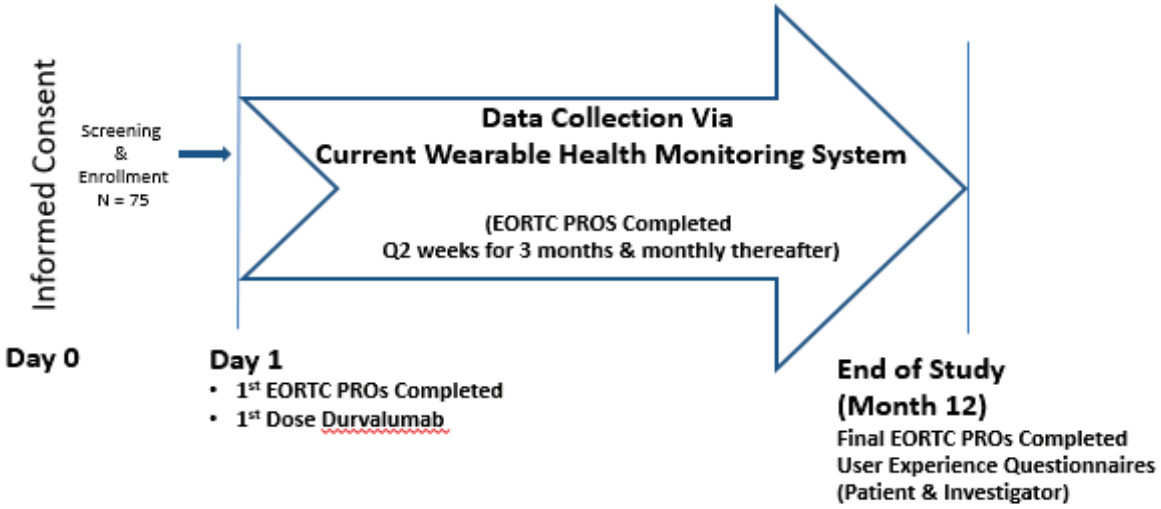
* The analysis of the two objectives above are covered in the attached Data Analysis Plan (DAP) in the appendix.

1.2 Study Design

This is a multicenter, prospective, interventional pilot study conducted in the United States that will include patients with unresectable Stage III NSCLC whose disease has not progressed following 2 or more cycles of platinum-based chemotherapy and radiation therapy (concurrent chemoradiotherapy [cCRT]), and who will be treated with durvalumab for up to 12 months or until confirmed disease progression, permanent discontinuation of durvalumab, the initiation of alternative cancer therapy, unacceptable toxic events, death, or withdrawal of consent, whichever is sooner. Patients will receive mobile and wearable devices alongside their durvalumab treatment without any additional interventions.

An overview of the study design is presented in Figure 1.

Figure 1 Study Design



1.3 Number of Subjects

The sample size of this pilot study is 75. A patient can be withdrawn from the study at the discretion of the site physician if they do not comply with study requirements. Patients who choose to withdraw or are withdrawn by the site physician may be replaced, at the discretion of AZ, by enrolling additional patients beyond the goal of 75. The sample size for this study was not chosen on the basis of statistical power calculations, but is regarded as sufficient to provide descriptive statistical data, and a logistic estimation of whether variables collected in the study contribute to the detection of pneumonitis.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

2.1.1 Safety Analysis Set

The Safety Analysis Set (SAF) will include all enrolled patients who take at least 1 dose of durvalumab.

2.2 Violations and Deviations

2.2.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria apply:

- Patient able provide written signed informed consent prior to any study-specific procedures.
- Patient must be ≥ 18 years except in the state of Alabama where the legal age is 19 years.
- Patient has unresectable Stage III NSCLC that has not progressed following concurrent platinum-based chemotherapy and radiation therapy and is eligible to receive durvalumab according to the US FDA approved package insert.
- Patient will initiate durvalumab treatment within 2 weeks of Baseline and receive at least 1 dose of durvalumab.
- Patient is able and willing to use the mobile application and connected devices on a daily basis for up to 12 months.
- Patient is able to complete QoL assessments once every 2 weeks for the first 3 months of the study and monthly thereafter.

2.2.2 Exclusion Criteria

Patients with any of the following criteria will be excluded from the study:

- Patient is currently enrolled in an interventional research study or clinical trial.
- Patient is currently oxygen dependent.

- Patient has comorbidities that will prevent consistent and reliable measurement assessments with multiparametric mobile technology including severe chronic obstructive pulmonary disorder (COPD) (defined as patients who, according to the Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2019 guidelines, have severe and very severe airflow limitation due to COPD; these are patients with forced expiratory volume/forced vital capacity [Forced Expiratory Volume (FEV_1) / Forced Vital Capacity (FVC)] < 0.70 and FEV_1 < 50% predicted), severe asthma, congestive heart failure (CHF), interstitial lung disease (ILD), and others).
- Patients on other immunotherapy or systemic immunosuppressants other than durvalumab.
- Patients with active or prior autoimmune disease or history of immunodeficiency, any unresolved toxicity Common Terminology Criteria for Adverse Events (CTCAE) > Grade 2 from the prior cCRT and patients with medical conditions that required systemic immunosuppression.
- In the opinion of the site physician, if the patient is unlikely to be able to complete the 12-month study period due to reasons that may include, but are not limited to, the following: difficulties with mobile literacy, unwillingness/inability to use devices or interact with an application, or treatment compliance.
- For women only – currently pregnant

2.2.3 Protocol Deviations

Protocol deviations will be captured by the clinical monitoring team on an ongoing basis throughout the study. All the deviations will be discussed on a case-by-case process, in a Data Review Meeting (DRM) and classified into important and unimportant deviations before the data base lock.

All-important protocol deviations will be listed.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Key Definitions

- The term 'baseline' is used to collectively refer to baseline visit or Day 1
    - Baseline visit is the date of informed consent.
        - This will apply to endpoints such as QoL, vital signs, spirometry, oximetry, etc.
            - For patient where there are multiple observations before the baseline visit, last non-missing observation will be used.
    - Day 1 is the date of first dose of Durvalumab. Day 1 can be up to 2 weeks after date of informed consent or may occur on the same date.
        - This will apply to endpoints related to pneumonitis, AEs, or durvalumab.
- Change from baseline will be calculated as follows:
    - Post-baseline value minus baseline value
    - If either the baseline value or post-baseline value is missing, the change from baseline is set to "missing".
- The last dose date is defined as the last non-missing date where a non-zero dose of durvalumab is given/administered.
- The Study Day is the day relative to the Day 1. Study day will be calculated from date on or after date of Day 1 as follows:
  Study day = date of assessment – date of first dose of durvalumab +1 if the date of assessment is on and after the date of first dose of durvalumab; Otherwise, Study day = date of assessment – date of first dose of durvalumab

3.2 Missing Data

For AEs and concomitant medications with missing start and/or end dates, the following rules will be applied:

For medication and AE, imputation of end date is not necessary if it is ongoing. If the ongoing flag is missing, then assume that AE is still present/medication is still being administered (i.e., do not impute a date).

Check the data captured in the following fields in the CRF:

- "Was this medication taken as a result of an adverse event"
  If the response is "yes", concomitant medication partial/missing start/end dates can be imputed by referring to related AE number, and vice versa.
- "Was this taken for a condition reported as medical history"
  If the response is "yes", concomitant medication partial/missing start/end dates can be imputed by referring to related medical history number.

If the responses to the above questions are "no" or do not allow imputed values, the following rules will be applied:

Partial/missing start date:

- Missing day - impute the first day of the month unless month is same as month of Day 1 then impute date of Day 1.
- Missing day and month – impute 1st January unless year is the same as Day 1 then impute date of Day 1.
- Completely missing – impute date of Day 1 unless the end date suggests it could have started prior to Day 1 in which case impute the 1st of January of the same year as the end date.
- When imputing a start date ensure that the new imputed date is sensible i.e., it is prior to the corresponding end date if known.

Partial/missing end date:

- Missing day - impute the last day of the month unless month is same as month of study exit then impute date of study exit.
- Missing day and month – impute 31st December unless year is the same as date of study exit then impute date of study exit.
- Completely Missing – For the concomitant medication, if start date is prior to Day 1 then impute date of Day 1, if it started on or after Day 1 then follow the above rule for missing day and month. For the adverse event, the end date will not be imputed.
- Note - for AE, duration would not be calculated.

These imputed dates will be used to determine whether the AEs are treatment emergent or if medications are concomitant. Missing safety data will be treated as missing. However, safety assessment values of the form of "< x" (i.e., below the lower limit of quantification) or > x

(i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

3.3 Study Endpoints

The definition and analysis of endpoints listed below are described in detail in section 4.2.

The endpoint used to address the primary objective is:

- Occurrence of pneumonitis (either radiation or immune-mediated, by grade).
    - Grade of pneumonitis at diagnosis and highest grade of pneumonitis

The endpoints used to address the secondary objectives are:

- Occurrence of pulmonary AEs, including diagnoses of events, by grade
- Duration (days) of pulmonary AEs by type and grade
- Permanent discontinuation of durvalumab due to pulmonary AEs, including pneumonitis
- Early discontinuation of durvalumab treatment for any reason
- Duration (days) of durvalumab treatment
- Treatment interruptions, duration (days) of interruptions, and the reason for interruptions that will be captured in a standard data management form with the site physician documenting reasons in patient charts
- Time (days) to development of Grade 3 to 5 AEs, including pneumonitis
- Prescription of medication used to manage pulmonary AEs and duration (days) of treatment
- Change in QoL scores from baseline

The endpoints used to address the exploratory objectives are:

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4. ANALYSIS METHODS

4.1 General principles

All analyses of the primary, secondary, and exploratory endpoints will be descriptive only with no formal statistical testing. Where appropriate, continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of patients for each category. The 95% CI will be calculated for means, percentages, rates, event-time endpoints by t-distribution/z-distribution, Clopper-Pearson exact method, chi-square distribution, and Kaplan-Meier method respectively where appropriate.

Table 1 Summary of outcome variables and analysis methods

Outcome variable	Analysis Method
Frequency of pneumonitis / pulmonary AEs by grade	Clopper-Pearson exact method
Duration (days) of pneumonitis / pulmonary AEs by type and grade	Kaplan Meier Method
Frequency of interruptions, duration (days) of interruptions, and the reason for treatment interruption	Summary Statistics
Time (days) to onset of Grade 3 to 5 AEs	Kaplan Meier Method
Change in QoL assessment scores from baseline	t-distribution / z-distribution

4.2 Analysis methods

4.2.1 Primary Endpoint and Analysis

The primary endpoint is occurrence of treatment-emergent pneumonitis by grade (grade of pneumonitis at diagnosis and highest grade of pneumonitis).

Definition of pneumonitis event:

- Pneumonitis is defined as a pneumonitis AE recorded in the CRF. An AE episode start from onset date of an AE record and stop at the date when AE is resolved. List of pneumonitis terms can be found in section 8.2.

- Pneumonitis at diagnosis is defined as the earliest onset of pneumonitis AE on or after Day 1, or onset of subsequent AE episode after previously resolved AE.
- Highest CTCAE grade of pneumonitis is defined as the pneumonitis AE with the highest CTCAE grade from on or after Day 1 per AE episode. Pneumonitis with the highest grade can occur on the same date or after the earliest pneumonitis.
- Patient with response "yes" to CRF question "Is this baseline condition suggestive of pneumonitis?" and the condition is on-going will not be included in this analysis.

Where there are only limited number of pneumonitis, listing will be provided including relevant dates, CTCAE grade, and duration (section 4.2.2.2), etc.
Where there are sufficient number of pneumonitis, frequency and percentage (95%CI) of patients with pneumonitis will be summarized by CTCAE grade for pneumonitis at diagnosis, and highest CTCAE grade of pneumonitis.

4.2.2 Secondary Endpoints and Analyses

4.2.2.1 Occurrence of pulmonary AEs, including diagnoses of events, by grade

Definition of pulmonary AE:

- Pulmonary AE is defined as pulmonary adverse event recorded in the CRF. For this study, pulmonary AE do not include pneumonitis event. An AE episode start from onset date of an AE record and stop at the date when AE is resolved. List of terms for pulmonary event can be found in section 8.3.
- Pulmonary AE at diagnosis is defined as the earliest onset of pulmonary AE on or after Day 1, or onset of subsequent AE episode after previously resolved pulmonary AE.
- Highest CTCAE grade of pulmonary AE is defined as the pulmonary AE with the highest CTCAE grade from on or after Day 1 per AE episode. Pulmonary AE with the highest grade can occur on the same date or after the earliest pulmonary AE.
- Patient with response "yes" to CRF question "Is this baseline condition suggestive of a respiratory disease?" and the condition is on-going will not be included in this analysis.

Where there are only limited number of pulmonary AE, listing will be provided including relevant dates, CTCAE grade, and duration, etc.
Where there are sufficient number of pulmonary AE, frequency and percentage (95%CI) of patients with pulmonary AE will be summarized by CTCAE grade for pulmonary AE at diagnosis, and highest CTCAE grade of pulmonary AE and by relationship with pneumonitis.

4.2.2.2 Duration (days) of pulmonary AEs by type and grade

The definition of pulmonary AE at diagnosis (excluding pneumonitis) is the same as defined section 4.2.2.1. The start and end dates of pulmonary AE duration are defined as follows:

- The onset date of each pulmonary AE will be the onset date in the CRF.
- The end date of a pulmonary AE will be the date when the AE is resolved as recorded in the CRF. The onset AE and AE with resolution could have different AE numbers.

The following censoring rules will be used:

- Death date for patient who died before AE being resolved.
- Date of study exit for patient who did not report end date of the AE or on-going beyond end of study.

The duration will be calculated as following:
Duration of a pulmonary AE = End date of pulmonary AE or date of censor – Onset date of pulmonary AE + 1
Where there are only limited number of pulmonary AE, listing will be provided as stated in section 4.2.2.1.

Where there are sufficient number of pulmonary AE, the duration will be summarized by CTCAE grade (defined as highest CTCAE grade per AE episode) using Kaplan-Meier method (Q1, median, Q3 along with 95% CI).

This analysis will be repeated for pneumonitis AEs (section 4.2.1).

4.2.2.3 Permanent discontinuation of durvalumab due to pulmonary AEs, including pneumonitis

This endpoint is fulfilled by section 4.2.4.1 patient disposition.

4.2.2.4 Early discontinuation of durvalumab treatment for any reason

This endpoint is fulfilled by section 4.2.4.1 patient disposition.

4.2.2.5 Duration (days) of durvalumab treatment

Overall and actual durations of durvalumab treatment will be reported.

Overall duration of durvalumab:

Overall duration of durvalumab is calculated using the start and stop dates of durvalumab and the intended dosing interval (2 weeks) defined as follows:

- Start date of durvalumab treatment will be date of first dose of durvalumab (Day 1) recorded in the CRF.
- End date of durvalumab treatment will be defined as the earliest of:
  - Death date for patient who died before date of study exit
  - Date of last non-zero dose administration of durvalumab plus 2 weeks minus 1.
  - Date of study exit for patient who had on-going durvalumab treatment beyond date of study exit.
- Patients are considered to be under durvalumab treatment during any interruption of any reasons. The duration will be calculated as:
- Duration of durvalumab treatment = End date of durvalumab treatment – Day 1 + 1

Actual duration of durvalumab:

Actual exposure will be calculated as the intended duration (as described above) minus the total duration of interruptions (section 4.2.2.6). The calculation of actual exposure makes no adjustment for any dose reductions that may have occurred.

Duration of durvalumab treatment will be summarized for patients in SAF using summary statistics as described in section 4.1.

4.2.2.6 Treatment interruptions, duration (days) of interruptions, and the reason for interruptions

Definition of treatment interruption:

- Short interruptions (defined as the durvalumab infusion interruption during the administration recorded in CRF in a single visit) are excluded from this analysis.
- Treatment withheld is defined as temporarily withheld of durvalumab recorded in CRF. It is possible that patients have durvalumab withheld in one visit and resumed in later visit and have multiple treatment withholds.

The duration of interruption will only include treatment withheld. Short interruption which resumed during the same visit will not be included in the calculation for duration of interruption. Start and end date of duration of interruption are defined as follows:

- Start date will be defined as the date of durvalumab withheld recorded in the CRF.
- End date will be defined as the earliest of:
    - Subsequent date of non-zero dose administration of durvalumab
    - Permanent discontinuation
    - Date of study exit
    - Death date

Since it is possible for patients to experience multiple treatment withholds/resumptions, the duration of interruption will be sum of the duration of each withheld/resumption.

The duration is calculated as:
Duration (days) of interruption = $\sum$ (End date as described above – Start date of treatment withheld + 1)

Where there are only limited number of treatment interruptions, listing will be provided as stated in section 4.2.4.6.

Where there are sufficient number of treatment interruptions, frequency and percentage of patients with treatment withheld, reason of treatment withheld, and duration of interruption will be summarized.

4.2.2.7 Time (days) to development of Grade 3 to 5 AEs, including pneumonitis

Time (days) to development of Grade 3 to 5 pneumonitis AEs is defined as the period from Day 1 to earliest of each grade of pneumonitis AE (grade 3, grade 4, and grade 5) or censoring date using the following rules:

- Date of study exit for patient who did not experience the event and left the study during the period of follow-up.
- End of the period of follow-up for patient who did not experience the event and remained in the study after the period of follow-up.

Where there are only limited number of pneumonitis AEs, listing will be provided as stated in section 4.2.1.

Where there are sufficient number of pneumonitis AEs, time to development of Grade 3 to 5 pneumonitis AEs will be summarized using Kaplan-Meier summary statistics including 1st quartile and 3rd quartile time to event, median time to events with 95% CIs, the number of events, the number of censored.

This analysis will be repeated for pulmonary AEs (section 4.2.2.1).

4.2.2.8 Prescription of medication used to manage pulmonary AEs and duration (days) of treatment

This endpoint is fulfilled by section 4.2.4.5.

4.2.2.9 Change in QoL assessment scores from baseline

Quality of life assessment questionnaires will be conducted at Baseline visit, every 2 weeks for the first 3 months and once monthly thereafter, and at End-of-Study visit. The questionnaires will include European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ C30) and Lung Cancer Module (EORTC QLQ LC13). EORTC QLQ C30 will be separated into 3 parts, function scales, symptoms scales and global health status (GHS) [1]. EORTC QLQ LC13 will be measured by 3 parts including lung cancer associated symptoms (cough, haemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication [2].

Therefore, the assessment scores by these two QoL questionnaires will be summarized by 6 parts as following:
Part 1: Function scales from EORTC QLQ C30; Higher score signifies higher functional ability (i.e. better quality of life); Item 1-7 and Item 20-27
Part 2: Symptom scales from EORTC QLQ C30; Higher score signifies stronger symptoms (i.e. worse quality of life); Item 8-19 and Item 28
Part 3: GHS from EORTC QLQ C30; Higher score signifies higher GHS (i.e. better quality of life); Item 29-30
Part 4: Lung cancer associated symptoms from EORTC QLQ LC13; Higher score signifies stronger symptoms (i.e. worse quality of life); Item 31-35 and Item 40-42
Part 5: treatment-related side effects from EORTC QLQ LC13; Higher score signifies stronger side effects (i.e. worse quality of life); Item 36-39
Part 6: Pain medication from EORTC QLQ LC13; Higher score signifies better pain relief from medication; Item 43

Time windows below will be used to summarize scores by planned data collection time points:

Week	Day	Statistical Analysis Window
Baseline	Day 0	Low – <1
Week 2	Day 11	1 - 21

Week 4	Day 28	22 - 35
Week 6	Day 42	36 - 49
Week 8	Day 56	50 - 63
Week 10	Day 70	64 - 77
Week 12	Day 91	78 - 105
Month 4	Day 120	106 - 135
Month 5	Day 150	136 - 165
Month 6	Day 180	166 - 195
Month 7	Day 210	196 - 225
Month 8	Day 240	226 - 255
Month 9	Day 270	256 - 285
Month 10	Day 300	286 - 315
Month 11	Day 330	316 - 345
Month 12	Day 360	346 - 375

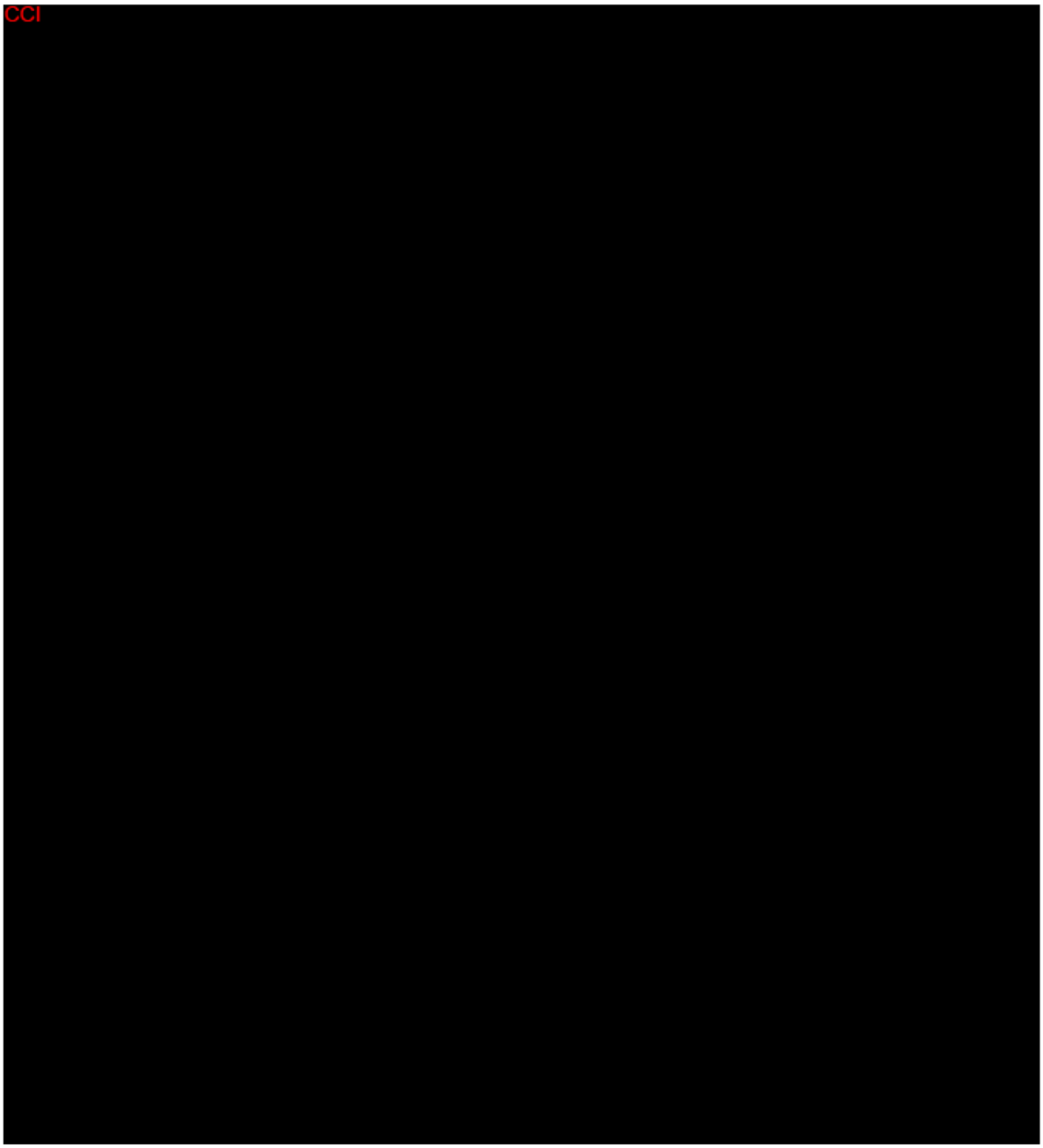
- Inclusion within the time window will be based on the actual date and not the intended data collection time point.
- If there are two scores recorded on the same day, the average of the two records will be used.

If there are limited number of patients with AE events, figure will be produced to show the score change through all time windows with 1 line per patient along with the following labels for AE groups: pneumonitis AEs, other pulmonary AEs.
Where there are sufficient number of patients with AE events, the score change from baseline for the scores within time windows at specified time points will be summarized by part and by CTCAE grade (only AEs which has causal relation with durvalumab), mean score change, standard deviation, median, minimum, maximum, and along with the number of patients. The time points are:

- Time Point 1: Prior to the time window which initial pulmonary AE occurred.
- Time Point 2: At the same time window which initial pulmonary AE occurred.
- Or other time point(s) if necessary.

The 95% CI of mean score change will be calculated by one-sample t distribution / z distribution depending on sample size. This analysis will be repeated for pneumonitis AEs

4.2.3 Exploratory Endpoint(s) and Analyses



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4.2.4 Safety

The population used for safety analyses will be the safety analysis set (SAF).

4.2.4.1 Patient Disposition

Patient disposition will be presented overall. Tabulation will include the number of patients screened, number of patient's screen failed, number of patients with inclusion criteria not met, number of patients with exclusion criteria met, number of patients enrolled, number and percentage of patients in safety analysis sets, as well as the number and percentage of patients discontinuing study treatment and the reason for treatment discontinuation. In addition, this table will summarize the number and percentage of patients discontinuing the study and the primary reason for study discontinuation. The number of patients enrolled will be used as denominator for calculating the percentages.

Listings will be provided for patient disposition, and patients with inclusion criteria not met and exclusion criteria met.

4.2.4.2 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be standardized and summarized. Descriptive statistics will be presented for variables including age, age group, sex, height, weight, body mass index (BMI), oxygen saturation (SPO2 median from Current Health), etc. at baseline. All demographic and physiological data at baseline will be listed.
The following conventions will be used to standardize measurements for reporting purposes:

- Height (in cm) = height (in inches) * 2.54
- Weight (in kg) = weight (in lbs) * 0.4536
- BMI (kg/m2) = weight (kg)/ [height (m)2]
- Temperature (in °C) = 5/9 (Temperature [in °F] - 32).

4.2.4.3 NSCLC Disease History/Respiratory Disease History

NSCLC disease history will be listed including stages at diagnosis, referral, prior to treatment and study entry, histological grade and date of diagnosis.
Prior NSCLC treatment including radiation therapy with the time since last prior radiation and chemotherapy will be listed. In the radiation therapy, regimen, anatomical site, nodal station, duration of dose (days), total number of fractions, total doses, time since last prior radiation

and time since last prior radiation by intervals (< 14 days, 14 – 28 days, 29 – 42 days, 43 – 60 days, > 60 days) will be summarized.
Duration of Dose (day) = date of last dose – date of first dose +1.
Time since last prior radiation (day) = date of last dose of prior radiation – date of Day 1.
Surgical history and relevant previous respiratory procedures collected in CRF will be also presented in the listing.

4.2.4.4 Medical History and Concomitant Diseases

Medical History as recorded at baseline will be summarized overall using the number and percentages of patients reporting each system organ class (SOC) and preferred term (PT). Medical history will be sorted by international order for SOC and in alphabetical order for PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 22.1 or later in the summary table.

4.2.4.5 Prior and Concomitant Medications

Prior medications are medications taken before baseline and include medications ongoing at the start of durvalumab. Concomitant medications are medications taken on or after baseline. For medications with incomplete end dates, the imputed dates will be used to determine if the medications are concomitant. If a patient has taken a medication more than once, the patient will be counted only once in the total.
The summary of medications taken during the course of the study will be presented in tabular form using Anatomical Therapeutic Chemical (ATC) classification level 2 and generic drug name via the WHO Drug Global B3 Sep 2019 or later. All medications will be sorted alphabetically by ATC level 2 class and generic drug name A listing of concomitant medications will be presented.
Concomitant procedures collected in CRF will be also presented in the listing.

4.2.4.6 Extent of Exposure

Durvalumab administration, dose assigned date, total dose and the reason for dose not taken will be presented in the listing.

4.2.4.7 Compliance Rates for PROs, spirometry, and wearable device

Summary measures of overall compliance and compliance over time will be derived for the spirometry, oximetry (referred to as measurement below) from the wearable device, EORTC-QLQ-C30 and LC13 (referred to as questionnaire below) respectively. These will be based upon:

- Expected measurement/questionnaire = a measurement/questionnaire that is expected to be completed at a scheduled assessment time e.g., a measurement /questionnaire from a patient who has not withdrawn from the study at the scheduled assessment time. Date of study exit will be mapped to the nearest visit date to define the number of expected forms. The schedule assessment time points for spirometry and oximetry are daily from Day 1 until date of study exit. The schedule assessment time for EORTC-QLQ-C30 and LC13 are described in 4.2.2.9.
- CCI [redacted]
- Overall PRO compliance rate is defined as: Total number of evaluable measurement/questionnaires across all scheduled assessment time, divided by total number of measurement/questionnaires expected to be received across all scheduled assessment time points multiplied by 100.

- Overall patient compliance rate is defined as: Total number of patients with an evaluable baseline and at least one evaluable follow-up measurement/questionnaire (as defined above), divided by the total number of patients expected to have completed at least a baseline measurement/questionnaire multiplied by100.

- If feasible, compliance over time will be calculated separately for each scheduled assessment time, including baseline, as the number of patients with an evaluable questionnaire at the scheduled assessment time point (as defined above), divided

by number of patients still expected to complete questionnaires. Similarly, the evaluability rate over time will be calculated separately for each scheduled assessment, including baseline, as the number of evaluable questionnaires (per definition above), divided by the number of received questionnaires. For spirometry and oximetry, the scheduled assessments are collected daily by wearable device. Therefore, the daily compliance and daily evaluability rate will be calculated first and summarize as average over each time point defined in the Time Window in section 4.2.2.9.

4.2.4.8 Adverse Events

An AE for drugs is the occurrence of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product or device, whether or not considered causally related to the product or device. An AE for medical devices is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in patients, users, or other persons whether or not considered related to the medical device. This includes events considered related to the medical device and events considered related to the study procedures involved. AEs will be collected throughout the study, from informed consent until 30 days after the End-of-Study visit.

Treatment-emergent adverse events (TEAEs) are defined as any AEs that occur or worsen at any time after the start of administration of the first dose of durvalumab and through 30 days after the last dose of durvalumab. Treatment-emergent AEs will be characterized based on the onset date relative to each patient's first dose date. For adverse events with incomplete start dates, the imputed dates will be used to determine whether the adverse events are treatment emergent.

Adverse events will be summarized by the SOC and PT based on the MedDRA dictionary version 22.1 or later. The CTCAE grades will be summarized by SOC and PT, using the current version of National Cancer Institute (NCI) CTCAE. For summaries by SOC and PT, a patient will be counted once at the SOC level and once at each PT within the SOC level. For

summaries by SOC, PT, and CTCAE Grade, a patient will be counted once at the highest grade for which the event occurred at the SOC level and the highest grade for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level. The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following AE tables will be provided:

- TEAEs, overall and by SOC and PT
- TEAEs related to pneumonitis by maximum relationship, overall and by SOC and PT
- TEAEs related to medical devices by maximum relationship, overall SOC and PT

With the exception of the overall summary AE table, only the TEAEs will be included in the summary tables; however, all AEs will be included in the listings. Any AE occurring before the first dose of durvalumab will be included in the data listings but will not be included in the summary tables of AEs.

Additional listings will be provided for deaths, AEs with an outcome of death, SAEs, AEs leading to discontinuation of durvalumab, study procedure and other significant AEs. TEAEs will be flagged in the listings. The death data will be listed in a separate listing.

5. INTERIM ANALYSES

No interim analyses are planned for this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The primary analysis will be descriptive summary of occurrence of pneumonitis by grade. The primary analyses of logistic regression models used for identifying pneumonitis were changed and will be applied to exploratory endpoints which are not covered in this SAP.

CCI [redacted].

Full analysis set specified in the protocol will not be used in the analysis covered in this SAP.

The analysis of change in QoL will only be applied to the pulmonary AE which has causal relation with durvalumab.

7. REFERENCES

[1] Caroline BM, Florence C & David A, et al. EORTC QLQ-C30 Descriptive Analysis with the QLQC30 Command. Stata Journal, StataCorp LP. 2017; 15(4):1060-1074.
[2] Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: A modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. European Journal of Cancer. 30A: 635-42, 1994.

8. APPENDIX

8.1 General Changes

- Update SAP based on Protocol Amendment 5.0, 2 December 2020
- Updated Table of Contents in alignment with section revisions
- Changed from SYNH SAP template to AZ SAP template

8.2 List of pneumonitis terms

The following six terms are interchangeably used to identify pneumonitis in this study. They are drawn from a previous study of durvalumab treatment of NSCLC (N Engl J Med 2017; 377:1919-1929) and/or reviewed by study physician:

1. Pneumonitis
2. Radiation pneumonitis
3. Acute interstitial pneumonitis
4. Interstitial lung disease (ILD)
5. Pulmonary fibrosis

6. Immune-mediated pneumonitis

8.3 List of pulmonary event terms

The following list of terms are drawn from MedDRA (version 23.1) and defined by the AstraZeneca ILD Task Force as associated with identification/suspicion of ILD. These are used in this study as a wider class of pulmonary events:

1. Alveolar lung disease
2. Alveolar proteinosis
3. Alveolitis
4. Alveolitis allergic
5. Alveolitis necrotizing
6. Autoimmune lung disease
7. Bronchiolitis
8. Combined pulmonary fibrosis and emphysema
9. Diffuse alveolar damage
10. Eosinophilia myalgia syndrome
11. Eosinophilic granulomatosis with polyangiitis
12. Eosinophilic pneumonia
13. Eosinophilic pneumonia acute
14. Eosinophilic pneumonia chronic
15. Idiopathic interstitial pneumonia
16. Idiopathic pneumonia syndrome
17. Idiopathic pulmonary fibrosis
18. Lung infiltration
19. Necrotising bronchiolitis
20. Obliterative bronchiolitis
21. Progressive massive fibrosis
22. Pulmonary necrosis
23. Pulmonary radiation injury
24. Pulmonary toxicity
25. Pulmonary vasculitis
26. Radiation alveolitis
27. Radiation fibrosis – lung
28. Small airways disease
29. Transfusion-related acute lung injury
30. Acute respiratory distress syndrome
31. Allergic eosinophilia
32. Granulomatous pneumonitis
33. Organising pneumonia
34. Pulmonary sarcoidosis
35. Restrictive pulmonary disease
36. Rheumatoid lung

37. Sarcoidosis

8.4 Data Analysis Plan

AZ_D4194C00008_SAP_V1.0

Interim Agreement Report 2022-03-14

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2022-03-08 - 8:36:44 PM GMT- IP address: PPD

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