Study Protocol	
Study Code	D4194C00008
Version	V5.0
Date	2 December 2020

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

Effective date: 2 December 2020

Sponsor: AstraZeneca US, 1800 Concord Pike, Wilmington, DE 19803, USA

VERSION HISTORY

Version 5.0, 2 December 2020

Amendment 4

Key Protocol Amendment Changes

General Changes

- Revised date and version throughout
- Updated Table of Contents in alignment with section revisions
- Formatting, typographical, and other minor clarifications

Section 4.2 – Scientific Rationale for Study Design

- Removed track changes '~~, all~~'

Section 5.3 – Discontinuation and Withdrawal of Patients

- Added 'and Safety Follow-up visit' to the following sentence: 'The patient will be asked if information pertaining to the End-of-Study visit *and Safety Follow-up visit* can be collected from his/her medical records.'
- Added 'at the End-of Study visit' to the following sentence: 'The patient will also be asked to complete the final QoL and [redacted] *at the End-of-Study visit*.'

Section 6.1 – Patient characteristics

- Added 'date of diagnosis' to 'Disease characteristics, such as *date of diagnosis*, stage at diagnosis, current stage, etc.'

Section 6.2 – Exposure and Covariates

- Changed second sentence from '...., patients *will* initiate durvalumab treatment within 2 weeks of Baseline' to '..., patients *may* initiate durvalumab treatment within 2 weeks of Baseline'

Section 7.1.3 – Technical and Patient Support

- Added the word 'connected' in the following sentences: 'This study uses *connected* devices that will be paired to a mobile application, which needs to be installed on a tablet or smart phone. Site personnel will be suitably trained on the Current Wearable Health Monitoring System to onboard patients with all technology and study procedures. Designated site personnel will help the patients pair all *connected* devices, and train patients on how to use each *connected* device and the tablet application. '

Section 7.1.4 – Patient Compensation

- Changed the wording of the following sentence 'To recognize ....in *collecting daily variables*, patients ... in the study.' to 'To recognize...in *completing daily tasks*, patients ...in the study.'
- The word successfully was added to the following sentence: 'Patients who enroll in the study will be compensated for *successfully* completing the Day 1 Baseline visit and for each successful week on the study.

Section 7.4.1 – Medical Devices

- Removed 'Status cleared – 510(K) K191272

- Added the following after Manufacturer: Current Health Ltd: 'The product codes associated with FDA authorization of the device are shown in Table 2.'

Table 2 Product Codes associated with the Current Wearable Health Monitoring System

BZG	Spirometer, Diagnostic
BZQ	Monitor, Breathing Frequency
DQA	Oximeter
DRG	Transmitters And Receivers, Physiological Signal, Radiofrequency
MSX	System, Network And Communication, Physiological Monitors
FLL	Thermometer, Electronic, Clinical

- Added 'skin' to '*Skin* temperature (Multiparametric wearable device)'
- Added in the last section in the second sentence starting with 'Qualified site personnel' that qualified site personnel will be identified by the PI.
- Changed the following sentence: 'Qualified site personnel....collected by the *Current Wearable Health Monitoring System*...procedures.' to 'Qualified site personnel… collected by the *devices*…procedures.'
- Changed the following sentence: 'However, ...experiencing AE-related-symptoms.'to 'However, ...experiencing new or worsening of existing AE-related symptoms.'

8.3.1 – Management and Reporting of Adverse Events

- The first sentence was removed; the second sentence covers the message and supports the interventional nature of the study

8.4 – Non-Significant Risk Investigational Device Exemption

- Changed sentence: 'This study is not being conducted as a Non-Significant Risk Investigational Device *Exemption as all devices used in this study have 510K clearance*.' to 'This study is not being conducted as a Non-Significant Risk Investigational Device *as the device is not an investigational device. Previous versions of this device have obtained 510(k) clearance by FDA. While the version used in this study has been modified, it would not require submission to FDA because the modifications and product codes (Table 2) are within the scope of FDA's June 2020 (further revised in October 2020) guidance, "Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised)".*'

9.3.1 – Efficacy analyses

- The following paragraph:

  'Contributions to the identification/prediction of pneumonitis from PROs and variables collected by the devices *will* be assessed using *logistic* regression. The primary endpoint in these estimations will be the occurrence of pneumonitis. Lagged PRO values and values collected from the mobile technology incorporated as covariates in *logistic regression* model *for the detection of pneumonitis* will be specified in the SAP.'

  was changed to:

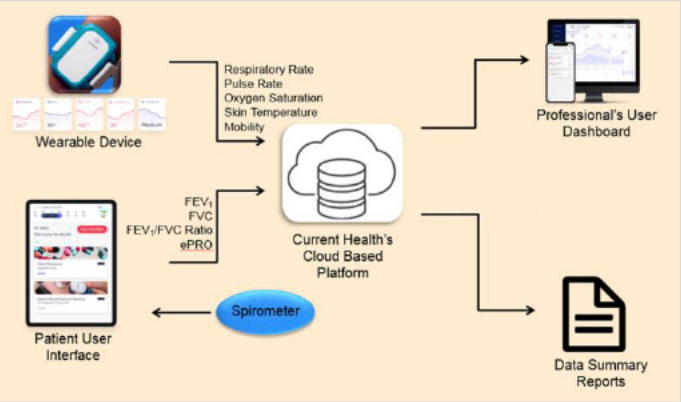
  '*PRO values and values from the mobile technology will be considered in connection with events of interest, specifically pneumonitis.* Contributions to the identification/prediction of pneumonitis from PROs and variables collected by the devices *may* be assessed using regression *models (e.g. logistic regression) depending on the number of events of interest that are observed in the study*; the primary endpoint in these estimations will be the occurrence of pneumonitis. Lagged PRO values and values collected from the mobile technology *may be* incorporated as covariates in *these* models; *more details* will be specified in the SAP.'

11 – References

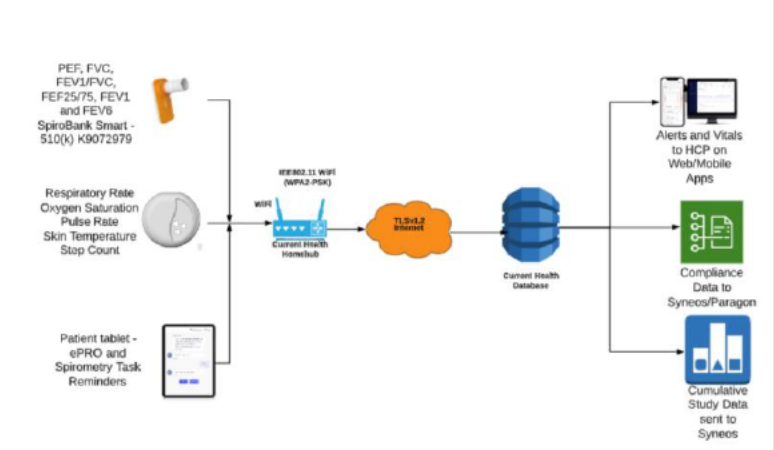
- The following reference was added based on the above changes to 8.4: 'United States Food and Drug Administration (US FDA). Guidance for Industry and Food and Drug Administration Staff. Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised). October 2020. Available from: https://www. https://www.fda.gov/media/136290/download.'

Appendix E - System Overview - Study Data Flow

- Changed figure from



  To:



Appendix F – Safety Medication guide

- Updated the medication guide to the version of November 2020

Version 4.0, 31 January 2020

Amendment 3

Key Protocol Amendment Changes

Section 4.1 – Study Design

- Figure 1 – Revised wording in arrow from "Data Collection Via Mobile Devices & Apps" to "Data Collection Via Current Wearable Health Monitoring System" and moved "EORTC PROs Completion (Q2 weeks for 3 months & monthly thereafter" from outside of the arrow to inside the arrow to clarify that the mobile devices and apps is referring to the Current Wearable Health Monitoring System .

Section 4.1.1 Data Sources

- Clarified that the multiparametric mobile technology used in the study is the Current Wearable Health Monitoring System.

Section 4.2 Scientific Rationale for Study Design

- Clarified that the PROs and other variables are collected using the Current Wearable Health Monitoring System.

Section 5.2 – Exclusion Criteria

- Added exclusion for pregnant women at the request of the central IRB.

Section 7.1.1 Enrollment

- Clarified that the devices and tablet application are part of the Current Wearable Health Monitoring System.

Section 7.1.2 Study Period

- Clarified that the multiparametric data is provided through the Current Wearable Health Monitoring System.

Section 7.1.3 Technical and Patient Support

- Clarified that the site personnel will be trained on the Current Wearable Health Monitoring System.

- Clarified that patients will not be installing any applications.

Section 7.2 Data Management

- Clarified that the Current Wearable Health Monitoring System will capture symptomatic and device data from patients.

Section 7.3 Data Collection Plan

- Table 1 – Clarified that training will be provided on the Current Wearable Health Monitoring System.
- Table 1 – Clarified that daily data collection will be via the Current Wearable Health Monitoring System.

Section 7.4.1 Mobile Application and Devices

- Changed section name to Medical Devices to identify that this section specifically speaks to the medical device used in the study.
- Added statement that the medical device used in the study is the Current Wearable Health Monitoring System, including the manufacturer and 510(K) number.
- Clarified how the electronic devices used by the patients are part of the Current Wearable Health Monitoring System.
- Added labeled intended use of the Current Wearable Health Monitoring System.
- Clarified that site personnel will review data collected by the Current Wearable Health Monitoring System.

Section 7.4.2 Symptom Assessments

- Table 2 – Clarified table name that data is collected via the Current Wearable Health Monitoring System.

General Changes

Revised date and version throughout
Updated Table of Contents in alignment with section revisions
Formatting, typographical, and other minor clarifications

Version 3.0, 27 November 2019

Amendment 2

Key Protocol Amendment Changes

Synopsis

- Updated to align with revised sections.

Section 2.3 – Benefit/Risk Assessment

- Added description of risks associated with the wearable device.

Section 3.1 – Study Objectives

- Removed blood pressure as variable to be collected by the mobile technology.
- Revised description of secondary objectives to focus on collection of pulmonary adverse events (AEs).

Section 3.2 – Study Endpoints

- Revised description of primary, secondary, and exploratory endpoints for alignment with objectives.

Section 4.2 – Scientific Rationale for Study Design

- Removed blood pressure as variable to be collected by the mobile technology.

Section 5.2 – Exclusion Criteria

- Removed the following Exclusion Criterion (#3): "Patient is currently taking relief medications or maintenance inhalers (bronchodilators) for asthma and/or chronic obstructive pulmonary disorder (COPD) and expectorants."

Section 5.3 – Discontinuation and Withdrawal of Patients

- Updated language to state that reasons for discontinuation will be noted in patient study records, not the Informed Consent Form (ICF).

Section 6.1 – Patient Characteristics

- Peak expiratory flow (PEF) added as pulmonary function test measurement to be collected.
- Added language specifying the time frame that should be used when collecting the patient's medical history.

Section 7.1.1 – Enrollment

- Added clarification that blood pressure will be collected as part of standard of care.

Section 7.1.2 – Study Period

- Added clarification that blood pressure will be collected as part of standard of care.

Section 7.3 – Data Collection Plan (Table 1)

- Table updated for consistency with body text.
- Blood pressure removed as variable to be collected by mobile technology, and added as separate variable to be collected at Baseline, Standard of Care, and End-of-Study visits.

Section 7.4.1 – Mobile Applications and Devices

- Added language clarifying the timeframe during which data collected by devices and applications will be reviewed by qualified site personnel.

Section 7.4.2 – Symptom Assessments

- Added language clarifying the timeframe during which study physicians will review pulmonary function test measurements.

Section 7.4.4 – User Experience Questionnaires

- CCI [redacted].

Section 8.3.1.1 – Definition of Adverse Event and Serious Adverse Event for Drugs

- Added language clarifying the timing of the AE collection.
- Added mandatory language regarding assessment of AEs of malignant tumors.

Section 8.3.1.2 – Definition of Adverse Event and Serious Adverse Event for Medical Devices

- Moved definition of Medical Device Deficiencies to new Section 8.3.2.

Section 8.3.2 – Medical Device Deficiencies

- New section created to incorporate medical device deficiency language in alignment with the current interventional protocol template.

General Changes
Revised date and version throughout
Updated Table of Contents in alignment with section revisions
Changed references to "Screening" to "Baseline" for consistency.
Formatting, typographical, and referencing revisions, as well as other minor clarifications

Version 2.0, 10 October 2019

Amendment 1

Key Protocol Amendment Changes

Title

- Removed the phrase "Causing Treatment Discontinuations" for clarity.

Synopsis

- Updated to align with revised sections.

Section 2.2 – Background

- Revised statement to confirm that multiparametric mobile technology is capable of automatically collecting data from patients.

Section 3.1 – Study Objectives

- Revised description of primary objective for clarity and to highlight the aim of identifying treatment-emergent cases of pneumonitis.
- Revised description of variables to be collected with the mobile technology for clarity.
- CCI [redacted]
- Added the following secondary objective: To describe the time to development of Grade 3 to 5 adverse events (AEs), including pneumonitis.

Section 3.2 – Study Endpoints

- Revised language for primary, secondary, and exploratory endpoints to reflect that description of study endpoints should refer to data collected in the study, as opposed to the transformation of data.
- Added the following secondary endpoint: Time (days) to development of Grade 3 to 5 AEs, including pneumonitis.
- CCI [redacted]

Section 4.1 – Study Design

- Removed the term "overlapping" in description of concurrent chemoradiotherapy (cCRT) cycle schedule for eligible patients.
- CCI [redacted]

Section 4.1.1 – Data Sources

- Updated description of timing for Quality of Life (QoL) assessment to align with revised study schedule.
- CCI [redacted]

Section 4.2 – Scientific Rationale for Study Design

- Updated to align with revisions to primary objective as described in Section 3.1.

Section 5 – Study Population

- Removed the term "overlapping" in description of cCRT cycle schedule for eligible patients.
- Number of sites at which the study will occur updated from 20 to 30.

Section 5.1 – Inclusion Criteria

- Revised Inclusion Criterion 3 to state that patient is eligible to receive durvalumab, rather than stating that the patient has already been prescribed the drug.
- Updated Inclusion Criterion 6 describing the timing of QoL assessments to align with revised study schedule.
- Removed Inclusion Criterion 7 requiring patient to understand written instructions in English only (Spanish instructions will be available).

Section 5.2 – Exclusion Criteria

- Added expectorants as class of medications excluded from use during the study.

Section 5.3 – Discontinuation and Withdrawal of Patients

- Revised language to state that patients who withdraw or are withdrawn may be replaced at the discretion of AZ.
- Updated to state that patients will be asked permission to collect data from his/her medical records pertaining to End-of-Study visit.
- CCI [redacted]

Section 6.1 – Patient Characteristics

- Physiological variables updated to include temperature, respiratory rate, and oxygen saturation.
- Sequential CRT included in list of previous treatments for NSCLC.

Section 7.1.2 – Study Period

- Description of End-of-Study visit added in alignment with study schedule.
- Added definitions for study completers and for End-of-Study.

Section 7.1.3 – Technical and Patient Support

- Revised statement with regard to the process patients will take in the event of study procedural issues, technical difficulties, and/or medical questions.

Section 7.1.4 – Call Center Operations

- This section was deleted as the information will be provided in a user guide for patients and investigators.

Section 7.1.5 – Patient Compensation

- Information regarding Call Center details were deleted.

Section 7.2 – Data Management

- Revised to clarify that multiparametric data will be combined with Baseline Plus data at the end of the study.

Section 7.3 – Data Collection Plan

- Revised to show that collection of NSCLC treatment history will include timing of most recent radiation.
- Revised description of adverse event collection to include all AEs and serious adverse events (SAEs), as well as durvalumab- and device-related events. Clarified timing of AE collection.
- Updated description of timing for QoL assessment to show that, after Day 1, assessments will occur once every 2 weeks for the first 3 months of the study, followed by once monthly until the End-of-Study visit.
- Added a column for safety follow-up occurring for up to 30 days following End-of-Study visit and associated AE/SAE collection.

Section 7.4.1 – Mobile Application and Devices

- Revised description of process by which data will be reviewed by study physicians.
- Added statement that patients will be advised to contact treating physicians directly with medical questions.

Section 7.4.2 – Symptom Assessments

- Peak Expiratory Flow added as variable to be collected (Table 3).
- Revised description of process by which values lower than normal will be reviewed by study physicians.
- Statement revised that patients will be advised to contact treating physicians, not study sites, directly with symptoms as described.

Section 7.4.3 – Quality of Life Assessment Questionnaires

- Updated description of timing for QoL assessment to align with revised study schedule.

Section 7.4.5 – NSCLC Disease History/Respiratory Disease History

- Revised to show that collection of NSCLC treatment history will include timing of most recent radiation.

Section 7.4.6 – Durvalumab Treatment

- Revised to include treatment holds, interruptions, discontinuations, and associated reasons for each, as data to be collected.
- Added statement specifying collection of concomitant medication.

Section 8.2.1 – Patient Informed Consent

- Statement regarding informed consent signature process updated to included United States Food and Drug Administration (FDA) Code of Federal Regulations (CFR) and Health Insurance Portability and Accountability Act (HIPAA) reference in alignment with current template.
- Added statement with regard to the process patients will take in the event of study procedural issues, technical difficulties, and/or medical questions.

Section 8.3.1 – Management and Reporting of Adverse Events

- Added clarification that the multiparametric technology will also seek to identify other pulmonary events (along with events of pneumonitis) in this study.

Section 8.3.1.1 – Definition of Adverse Event and Serious Adverse Event for Drugs

- Updated language to refer to “Screening” period as opposed to “run-in” period.

- Added definition of treatment-emergent AEs.
- Clarified timing of AE/SAE collection to reflect that any event meeting criteria after the patient signs the ICF may be considered an AE/SAE.

Section 8.3.1.2 – Definition of Adverse Event and Serious Adverse Event for Medical Devices

- Clarified timing of AE/SAE collection to reflect that any event meeting criteria after the patient signs the ICF may be considered an AE/SAE.

Section 8.3.1.3 – Adverse Events Information

- Added description of timing for AE/SAE collection in alignment with revised study schedule.
- Added statement that severity of AEs (and Baseline conditions, when available) will be documented.
- Added "Date AE met criteria for SAE" as variable to be collected.

Section 8.3.1.4 – Reporting of AEs/SAEs on Durvalumab and Device-Related Events

- Added statement regarding procedures for documenting and following-up on AEs unresolved at the end of study participation.
- Removed non-serious AEs and events related to study device from list of those to be reported promptly (ie, within 1 calendar day) to site physicians. Added the general category of "medication errors" to list of events to be reported promptly. Removed mentions of "spontaneous" reporting in alignment with AE/SAE collection procedures.

Section 8.3.1.5 – Reporting of Serious Adverse Events (SAEs)

- Added statement regarding procedures for documenting and following-up on SAEs unresolved at the end of study participation.
- Deleted 15-day expedited reporting requirement.

Section 8.3.2 – Reporting Patient Complaints about Devices or Mobile Applications

- Revised language with regard to the process patients will take in the event of study procedural issues and/or technical difficulties.

Section 9.2 – Populations for Analyses

- Revised definitions of the Full Analysis Set (FAS) and Safety Analysis Set (SAF) for clarity.

Appendices

- Updated abbreviations list.
- Revised figure in Appendix E (System Overview – Study Data Flow)
- CCI [redacted]

General Changes

Revised date and version throughout
Updated Table of Contents in alignment with section revisions
Removed table listing Responsible Parties and Proposed Milestones in alignment with current template.
Formatting, typographical, and referencing revisions, as well as other minor clarifications

Version 1.0, 31May2019

Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 SYNOPSIS

Title of Study:	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
Protocol Number:	D4194C00008
Background/Rationale:	The development of new multiparametric healthcare technologies has provided new sources of data collection for healthcare providers. This new form of data collection may improve healthcare delivery and outcomes. Given the potential impact of these new technologies, it is important to understand the utility of multiparametric mobile technology for patients and how information collected through these can be used to improve patient care. By analyzing disease characteristics and health status alongside a specific patient's history, it may be possible to predict changes in organ function and intervene earlier with the appropriate medical care. Previous studies have documented the ability of home spirometry devices to detect pulmonary adverse events (AEs) in lung transplant patients, establishing proof of principle in lung transplant and non-small cell lung cancer (NSCLC) populations. Multiparametric mobile technology devices and applications are non-invasive and simple to use, automatically collecting data from patients and/or allowing patients to report data in almost any location, whenever convenient. Multiparametric mobile technology has been used in previous studies, where large volumes of data were quickly and efficiently entered by a high proportion of patients who expressed their satisfaction with the technology. Patients undergoing treatment for lung cancer with durvalumab can experience pulmonary AEs that lead to treatment discontinuation and morbidity. This study, ON TRAX, is a pilot study to evaluate the potential benefit of multiparametric mobile applications and connected medical devices in collecting data to facilitate or improve early identification of pulmonary AEs in patients with unresectable Stage III NSCLC receiving durvalumab treatment. The data collected in this study will determine whether this multiparametric mobile technology will be progressed to a fully powered study for the early detection of pneumonitis and pulmonary AEs in patients with unresectable Stage III NSCLC. This project seeks to understand if the multiparametric mobile technology devices integrate well into a patient's daily life with minimal burden and to collect vital signs and respiratory data. These devices can then track and detect changes in a patient's vital signs and respiratory function and aid physicians in detection of pulmonary AEs.

Objectives:	Primary Objective: 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 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). Secondary Objectives: • To describe durvalumab treatment discontinuation due to pulmonary 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 Exploratory Objectives: CCI 
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.
Study Population:	The population will be comprised of 75 patients with unresectable Stage III NSCLC whose disease has not progressed following 2 or more cycles of cCRT who is eligible to receive durvalumab, as outlined in the package insert. Patients will be recruited in up to 30 sites in the United States.
Planned Sample Size:	This pilot study will enroll 75 patients and will provide descriptive outputs.
Primary, Secondary and Exploratory Endpoints:	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 discontinuations 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, including reasons 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 medications used to manage pulmonary AEs and the duration (days) of treatment • Change in QoL scores from baseline The endpoints used to addressed the exploratory objectives: CCI
Statistical Methods:	The occurrence of pulmonary AEs by type and grade will be summarized descriptively, using frequencies and percentages. A logistic regression will relate pneumonitis occurrence to PRO variables and variables collected from the mobile technology. Percentages will be presented with exact 95% Confidence Intervals (CIs). Aside from the logistic regression, data analyses using the primary, secondary, and exploratory endpoints will be descriptive, with no formal statistical testing, by overall patients in full analysis set. Continuous secondary and exploratory endpoint variables (eg, duration of durvalumab treatment, duration of pulmonary AE, absolute QoL and its change from baseline) will be summarized by the number of observations, mean, standard deviation, median, minimum, maximum, and 95% CIs. Categorical variables will be summarized by frequency counts, percentages, and 95% CIs for each category. Safety analysis will involve examination of the descriptive statistics and individual patient listings for clinical tolerability and safety by overall patients in safety analysis set (SAF). Summaries of treatment-emergent adverse events (TEAEs) will include the events by system organ class and preferred term, events by maximum intensity, event by relationship to study treatment, events leading to study discontinuation, and serious adverse events (SAEs).

2 INTRODUCTION

2.1 Study Rationale

Patients undergoing treatment with durvalumab for unresectable Stage III non-small cell lung cancer (NSCLC) after 2 or more cycles of concurrent platinum-based chemotherapy and radiation therapy (concurrent chemoradiotherapy [cCRT]) can experience pulmonary adverse events (AEs) that lead to treatment discontinuation and morbidity. This study, ON TRAX, is a pilot study to evaluate the potential benefit of multiparametric mobile applications and connected medical devices in collecting data to facilitate or improve early identification of pulmonary AEs in patients with unresectable Stage III NSCLC receiving durvalumab treatment. The outcomes of this study will determine whether this multiparametric mobile technology will be progressed to a fully powered study for the early detection of pneumonitis and pulmonary AEs in patients with unresectable Stage III NSCLC.

This project seeks to understand if the multiparametric mobile technology devices integrate well into a patient's daily life with minimal burden and to collect vital signs and respiratory data. These devices can then track and detect changes in a patient's vital signs and respiratory function and aid physicians in detection of pulmonary AEs.

2.2 Background

The PACIFIC study was a randomized, placebo-controlled, Phase 3 trial evaluating the immune checkpoint inhibitor durvalumab in patients with unresectable Stage III NSCLC who did not have disease progression after 2 or more concurrent cycles of platinum-based chemoradiotherapy. At the first planned interim analysis, the trial showed that durvalumab treatment significantly prolonged progression-free survival, as compared with placebo, with median durations of 16.8 months (95% confidence interval [CI], 13.0 to 18.1 months) and 5.6 months (95% CI, 4.6 to 7.8 months), respectively (Antonia et al. 2017). On the basis of these results, durvalumab treatment was approved by the United States Food and Drug Administration (US FDA) for the treatment of unresectable Stage III NSCLC in patients whose disease had not progressed after platinum-based chemoradiotherapy. In addition, overall survival was found to be significantly prolonged in durvalumab-treated patients compared with the placebo group (stratified hazard ratio for death, 0.68; 99.7% CI, 0.47 to 0.997; p=0.0025) (Antonia et al. 2018). During the PACIFIC trial, pneumonitis or radiation pneumonitis of any grade occurred in 33.9% and 24.8% and Grade 3 or 4 pneumonitis or radiation pneumonitis occurred in 3.4% and 2.6% of durvalumab and placebo patients, respectively (Antonia et al. 2017). A total of 15.4% of patients in the durvalumab arm discontinued study drug due to AEs, compared with 9.8% in the placebo arm (Antonia et al. 2018). The most frequent AEs leading to study drug discontinuation were pneumonitis (4.8% in the durvalumab group and 2.6% in the placebo group), radiation pneumonitis (1.3% in both groups), and pneumonia (1.1% in the durvalumab group and 1.3% in the placebo group). Immune checkpoint-inhibitor-related pneumonitis is a potentially serious and life-threatening toxicity. The reported incidence of pneumonitis in studies investigating anti-programmed cell death 1/programmed cell death-ligand 1 is variable and ranges from 0% to 10%, with an overall incidence of 2.7% reported in a recent meta-analysis of 20 studies with programmed cell death 1 (PD-1) inhibition; the incidence in patients with lung cancer as the underlying diagnosis is even higher (Nishino et al. 2016).

The development of new multiparametric healthcare technologies has provided new sources of data collection for healthcare providers. This new form of data collection may improve healthcare delivery and outcomes. Given the potential impact of these new technologies, it is important to understand the utility of multiparametric mobile technology for patients and how information collected through these can be used to improve patient care. By analyzing disease characteristics and health status alongside a specific patient's history, it may be possible to predict changes in organ function and intervene earlier with the appropriate medical care. Previous studies have documented the ability of home spirometry devices to detect pulmonary AEs in lung transplant patients, establishing proof of principle in lung transplant and NSCLC populations (Finkelstein et al. 1999; Finkelstein et al. 2013; Wang et al. 2013; Torre-Bouscoulet et al. 2018; Basch et al. 2017).

Multiparametric mobile technology devices and applications are non-invasive and simple to use, automatically collecting data from patients and/or allowing patients to report data in almost any location, whenever convenient. Multiparametric mobile technology has been used in previous studies (QUASAR 2; Cloudy with a Chance of Pain Study), where large volumes of data were quickly and efficiently entered by a high proportion of patients who expressed their satisfaction with the technology.

2.3 Benefit/Risk Assessment

All patients who participate in this study will receive standard of care appropriate for their lung cancer as determined by their treating physician.

The technology to be used in this study is non-invasive and has been used previously in other settings, including clinical studies; it is believed to pose an extremely low risk to study patients. Patients using the wearable arm device have reported minor events of skin irritation and discomfort during sleeping. In addition, patients undergoing concomitant anti-coagulation therapy have experienced ecchymosis near the device site. As part of their standard of care, patients will undergo routine assessment by their physician, who will decide when regular visits should take place. Due to the nature of the technology used and the fact that all other procedures are standard of care, study-related or multiparametric mobile technology-related AEs are expected to be rare. The study sponsor, AstraZeneca (AZ), has concluded that this study has a favorable benefit/risk ratio.

Data from this pilot study will be used by AZ to decide whether a larger comparative study of patients with and without the technology is warranted, which will potentially benefit other patients in the future.

3 OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

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 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).

The secondary objectives are:

- To describe durvalumab treatment discontinuation due to pulmonary 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

The exploratory objectives are:

CCI

3.2 Study Endpoints

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:

4 METHODOLOGY

4.1 Study Design

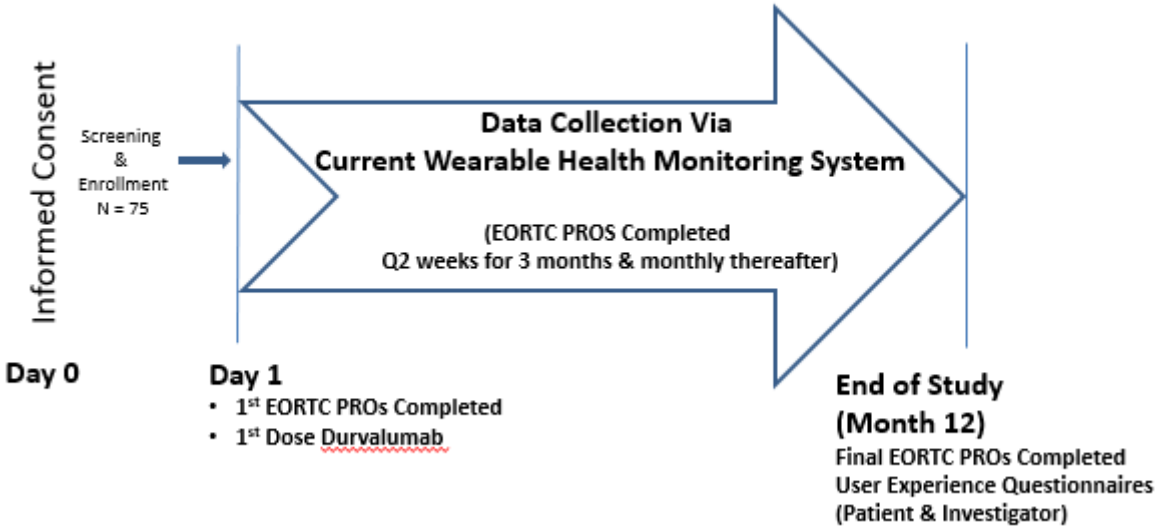
This is a multicenter, prospective, interventional pilot study conducted in the United States that will include patients with unresectable Stage III NSCLC whose disease has not progressed following 2 or more cycles of cCRT, and who will be treated with durvalumab for up to 12 months or until confirmed 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 be enrolled after their treating physician has prescribed durvalumab and before they start durvalumab treatment. Patients will receive mobile and wearable devices alongside their durvalumab treatment without any additional interventions. Patients will receive training on the mobile applications and supportive devices. Patients will return to their study site for routine visits and durvalumab infusions as guided by their physician over the duration of the study.

All patients will receive routine medical care as determined by their physician and will be instructed to contact the site with any new or worsening symptoms including, but not limited to: trouble breathing, chest pain, new or worsening cough, productive cough with purulent secretions, shortness of breath, fever, or tachycardia.

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

Figure 1 Study Design



4.1.1 Data Sources

Data will be collected prospectively using an integrated approach, where data from existing medical records will be combined with data collected via multiparametric mobile technology, called the Current Wearable Health Monitoring System.

Patients will complete QoL assessments via a tablet application at baseline on Day 1, once every 2 weeks for the first 3 months of the study followed by once per month thereafter, and at their End-of-Study visit.

CCI

4.2 Scientific Rationale for Study Design

The primary objective of the study is to describe the identification of treatment-emergent pneumonitis by grade in patients with unresectable Stage III NSCLC receiving durvalumab through the use of mobile technology which collects PROs, vital signs (temperature, heart rate, respiratory rate), spirometry (i.e., pulmonary function), pulse oximetry (i.e., oxygen saturation), and physical movement (number of steps per day). The multiparametric mobile technology being evaluated in this study does not involve administration of any medicinal product (other than durvalumab) or similar entity. Consequently, this study does not seek to evaluate any parameters related to dose, method of administration, or mode of action of any treatment patients receive per standard of care.

This is a descriptive pilot study with a sample size of 75 patients. The contributions of PRO variables and other variables collected via the Current Wearable Health Monitoring System to the identification of pneumonitis will be assessed using a logistic regression; addressing the question of whether there is an association between a pneumonitis event and variables collected prior to the event. Analyses of all secondary and exploratory endpoints will be descriptive only. Since this is a pilot study, a holistic multifaceted approach will be used to ascertain success and determine subsequent studies.

The decision to move from the pilot study to a larger trial will be determined using a number of factors. The study team will look to see a numerical trend in the primary endpoint as well as positive findings for the secondary and exploratory endpoints. Additional critical success factors are as follows:

- Treating physicians find the mobile technology to be useful/effective in the early detection of pneumonitis, and
- Patients are willing and able to effectively wear and use the devices for the full course of durvalumab.

An execution of retrospective clinical chart reviews of PACIFIC patients to evaluate/compare to real world pneumonitis data versus PACIFIC may also be considered to provide additional context before moving to a fully powered 2-armed trial. Also, supporting publications and to-be-published scientific literature of similar single-armed pilot studies will be used to guide

decision making to move to a larger trial. Additional details will be found in the statistical analysis plan (SAP).

5 STUDY POPULATION

The population will be comprised of 75 patients with unresectable Stage III NSCLC whose disease has not progressed following 2 or more cycles of cCRT, and who are eligible to receive durvalumab, as outlined in the package insert. Patients will be recruited in up to 30 sites.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1 Inclusion Criteria

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

1. Patient able to provide written signed informed consent prior to any study-specific procedures.
2. Patient must be ≥ 18 years except in the state of Alabama where the legal age is 19 years.
3. 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.
4. Patient will initiate durvalumab treatment within 2 weeks of Baseline and receive at least 1 dose of durvalumab.
5. Patient is able and willing to use the mobile application and connected devices on a daily basis for up to 12 months.
6. Patient is able to complete QoL assessments once every 2 weeks for the first 3 months of the study and monthly thereafter.

5.2 Exclusion Criteria

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

1. Patient is currently enrolled in an interventional research study or clinical trial.
2. Patient is currently oxygen dependent.
4. 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 [FEV_1/FVC] < 0.70 and FEV_1 < 50% predicted), severe asthma, congestive heart failure [CHF], interstitial lung disease [ILD], and others).
5. Patients on other immunotherapy or systemic immunosuppressants other than durvalumab.
6. 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.

7. 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.
8. For women only – currently pregnant.

5.3 Discontinuation and Withdrawal of Patients

As a patient's participation is voluntary, patients are free to discontinue their participation in this study at any time and without prejudice to his/her subsequent medical treatment. Patients who wish to discontinue must notify their study physician. Patients who discontinue should be asked about the reason(s) for their discontinuation, and this will be noted in the patient study records and the Data Capture Portal by the study site.

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.

If a patient is withdrawn prior to completing the study, any known reason for withdrawal should be documented by the study site (e.g., safety reason, change of address, death, voluntarily withdrawal, non-compliance). All information already collected as part of the study will be retained for analysis. The patient will be asked if information pertaining to the End-of-Study visit and Safety Follow-up visit can be collected from his/her medical records. The patient will also be asked to complete the final QoL and CCI [redacted] at the End-of-Study visit. However, no further efforts will be made to obtain or record additional information regarding the patient. The patient and sites will be provided instructions on how to return study equipment as required.

6 VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

6.1 Patient Characteristics

The following information will be obtained at Baseline:

- Demographic variables (as allowed by local regulations):
  - Age
  - Date of data collection
  - Sex
- Current physiological variables:
  - Height (inches)
  - Weight (pounds)
  - Temperature
  - Blood pressure
  - Heart rate (beats per minute)

    - Respiratory rate
    - Oxygen saturation (pulse oximetry)
    - Pulmonary function tests including: FEV_1, FVC, FEV_1/FVC ratio: obstructive versus restrictive, and peak expiratory flow (PEF)
- Comfort and familiarity with technology, including, but not limited to, internet use, ownership of smartphones, email use, etc.
- Relevant concomitant medications including, but not limited to, respiratory medications
- Abbreviated medical history (from birth to Baseline visit)
- Relevant previous respiratory medical history or procedures including, but not limited to, thoracentesis, subsequent radiation, etc.
- Disease characteristics, such as date of diagnosis, stage at diagnosis, current stage, etc.
- Previous treatments for NSCLC, including sequential CRT, cCRT regimen for unresectable Stage III NSCLC
- Time since most recent radiation

6.2 Exposure and Covariates

The primary exposure for this study will be multiparametric mobile technology in patients with unresectable Stage III NSCLC receiving durvalumab. As part of the inclusion criteria, patients may initiate durvalumab treatment within 2 weeks of Baseline. The decision to prescribe durvalumab will be made before enrollment, based on physician recommendation. The site physician or qualified site personnel will discuss the study with the patient after agreement to initiate durvalumab treatment, and the patient will be enrolled after consent and evaluation of eligibility using inclusion/exclusion criteria.

7 STUDY CONDUCT

7.1.1 Enrollment

Patients who are potentially eligible for enrollment will be contacted by qualified site personnel to gauge their interest in joining the study. Interested patients will be screened during their routine care visit, at which time they will be able to ask questions.

After explanation of the study by qualified site personnel, patients wishing to join the study will be asked to sign a study-specific ICF. Baseline information about the patient, including demographic data, relevant treatment and medical history, height, weight, vital signs (temperature, heart rate, respiratory rate, and blood pressure), oxygen saturation (pulse oximetry), pulmonary function (spirometry), and QoL measurements at time of visit, will be collected.

All patients enrolled will continue to receive routine standard of care treatment for NSCLC as per their treating physician's discretion. All patients will receive appropriate training on the devices and tablet application used in the Current Wearable Health Monitoring System. Patients will receive technology for home use and will otherwise continue to receive routine standard of care treatment for NSCLC as per their treating physician's discretion. Each site will be provided with appropriate training materials and support.

7.1.2 Study Period

All patients enrolled will be followed up to 12 months on durvalumab or until confirmed disease progression, permanent discontinuation of durvalumab treatment, the initiation of alternative cancer therapy, unacceptable toxic events, death, or withdrawal of consent, whichever is sooner.

At the End-of-Study visit (after 12 months of durvalumab dosing or upon withdrawal/discontinuation), information about the patient including height, weight, vital signs (temperature, heart rate, respiratory rate, and blood pressure), oxygen saturation, pulmonary-related concomitant medications and procedures, and information on AEs/SAEs (including pneumonitis), will be collected. The patient will also be prompted to take the QoL and CCI

A patient is considered to have completed the study when he/she has provided multiparametric data using the devices and installed application on a tablet in the Current Wearable Health Monitoring System through 12 months (or 26 cycles) of durvalumab treatment. In certain cases, a patient who does not complete all 26 cycles (i.e., durvalumab treatment prematurely discontinued due to an immune-related AE) may still be considered a study completer.

The end of study is defined as the date the last expected data will be collected.

7.1.3 Technical and Patient Support

This study uses connected devices that will be paired to a mobile application which needs to be installed on a tablet or smart phone. Site personnel will be suitably trained on the Current Wearable Health Monitoring System to onboard patients with all technology and study procedures. Designated site personnel will help the patients pair all connected devices, and train patients on how to use each connected device and the tablet application. Patients will be

asked to contact the study site for issues related to study procedures or for technical support. The study site will facilitate connection with the Current Health Call Center for assistance, as necessary. For medical questions or to report AE signs/symptoms, patients will be asked to contact their treating physicians directly.

7.1.4 Patient Compensation

To recognize the significant time commitment the patients will make in completing daily tasks, patients will be compensated for their participation in the study. Patients who enroll in the study will be compensated for successfully completing the Day 1 Baseline visit and for each successful week on the study.

7.2 Data Management

For this study Cisiv's Baseline Plus database platform will be used (Cisiv Baseline Plus).

Baseline Plus will be used to capture data from a patient's medical records. The Current Wearable Health Monitoring System will capture the symptomatic and specific device data from the patients. This data will be combined with the data in the Baseline Plus database at the end of the study.

High quality data standards will be maintained, and processes and procedures will be used to ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect missing or anomalous data. All the modifications to the data will be recorded in an audit trail.

7.3 Data Collection Plan

The data collection plan presented in Table 1 outlines all data points that will be obtained from patients' medical records, mobile devices, and QoL questionnaires, as collected in the tablet application, in the study. All patients in the study will attend routine visits, as recommended by the treating physician.

Table 1 Data Collection Plan for All Patients

Variables	Baseline (Day 1)	Daily Data Collection via Current Wearable Health Monitoring System	Data Collection via a Tablet Every 2 Weeks for First 3 Months and Once Monthly Thereafter	Standard of Care Visits	End-of-Study Visit	Safety Follow-Up (End-of-Study Visit +30 days)
Demographics: Age, gender; height	x					
Weight	x			x	x	
Blood pressure	x			x	x	
Vital Signs (temperature, heart rate, respiratory rate)	x	x		x	x	
NSCLC treatment and disease history, including time of most recent radiation	x					
Relevant medical and surgical history	x					
Pulmonary-related concomitant medication and procedures[a]	x			x	x	
All AEs/SAEs (including durvalumab-related and device-related AEs)[b]	x			x	x	x
If pneumonia or pneumonitis is diagnosed, details on pneumonitis and radiation pneumonitis if applicable	x			x	x	x
Quality of life questionnaires: EORTC QLQ C30, EORTC QLQ LC13	x		x		x	
CCI [redacted]					C	
Lung function measurements spirometry: FEV_1, FVC, FEV_1/FVC ratio, and PEF	x	x			x	
Pulse oximetry – oxygen saturation	x	x			x	
Activity step count		x				
Training on Current Wearable Health Monitoring System	x					
Durvalumab treatment[c]	x			x	x	

AE = adverse event; 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; FEV_1 = forced expiratory volume; FVC = forced vital capacity; NSCLC = non-small cell lung cancer; PEF = peak expiratory flow

[a] Information regarding concomitant medication (including over-the-counter medications) will include, when available: drug name, indication for treatment, route, and duration of drug administration.

[b] Adverse event collection (including event description, intensity/severity, outcome, action taken, etc.) will occur at Baseline (i.e., after the patient signs the ICF), during standard of care visits, at the End-of-Study visit, and for 30 days after the End-of-Study visit to capture late-onset symptoms.

[c] Information regarding durvalumab treatment will include, when available: start/stop date, treatment holds, interruptions, and/or permanent discontinuations (including reasons), as well as details of other treatments (ie, chemotherapy, radiation therapy, etc).

7.4 Study Procedures

7.4.1 Medical Devices

The medical device provided for use in this study is the Current Wearable Health Monitoring System.

- Manufacturer: Current Health Ltd.

The product codes associated with FDA authorization of the device are shown in Table 2.

Table 2 Product Codes associated with the Current Wearable Health Monitoring System

BZG	Spirometer, Diagnostic
BZQ	Monitor, Breathing Frequency
DQA	Oximeter
DRG	Transmitters And Receivers, Physiological Signal, Radiofrequency
MSX	System, Network And Communication, Physiological Monitors
FLL	Thermometer, Electronic, Clinical

Patients enrolled in the study will use the following electronic devices:

- Spirometer (Spirobank G as part of the Current Wearable Health Monitoring System)
- Multiparametric wearable device (as part of the Current Wearable Health Monitoring system)
- Tablet (application installed on tablet is part of the Current Wearable Health Monitoring system)

The Current Wearable Health Monitoring System is intended for:

- Continuous monitoring of the following parameters in adults:
  - Pulse rate *(Multiparametric wearable device)*
  - Oxygen saturation *(Multiparametric wearable device)*
  - Skin temperature *(Multiparametric wearable device)*
  - Movement *(Multiparametric wearable device)*
- Intermittent monitoring in adults of:
  - Respiration rate *(Multiparametric wearable device)*
  - Lung function & spirometry *(Spirobank G Spirometer)*
  - Non-invasive blood pressure *(feature not used in this study)*
  - Weight *(feature not used in this study)*

Training for the patients on the above devices and application will be provided by the investigative site personnel. Qualified site personnel as identified by the PI will review data collected by the devices once daily during business hours (exempting office closures, such as holidays, weekends, etc.), and will contact patients if a clinical intervention is necessary or if there are other issues related to study procedures. However, patients will be advised to contact their treating physicians directly if they are experiencing new or worsening of existing AE-related-symptoms. Technical support will be provided by the study site and Current Health Call Center as described in Section 7.1.3.

7.4.2 Symptom Assessments

Pulmonary function data collected via mobile applications and devices are described in Table 3.

Table 3 Data Collected via the Current Wearable Health Monitoring System

Pulmonary Function Parameters	Lowest Acceptable Value*
FEV_1	LLN
FVC	LLN
FEV_1/FVC ratio	LLN
Oxygen saturation	90%
PEF	LLN

FEV_1 = forced expiratory volume; FVC = forced vital capacity; LLN = lower limit of normal; PEF = peak expiratory flow

* Measurements less than the LLN indicate the presence of an abnormality

Study physicians should review values lower than normal on a daily basis in alignment with regular business hours (as noted above) and patients will be contacted if clinical intervention is necessary.

Patients will be advised to contact their treating physicians if they develop any of the following symptoms from either a change of baseline or a new worsening symptom that needs to be reported as a potential AE/serious adverse event (SAE): trouble breathing, chest pain, new or worsening cough, productive cough with purulent secretions, shortness of breath, fever, or tachycardia.

7.4.3 Quality of Life Assessment Questionnaires

Patients in the study will fill out QoL assessments using the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ C30) and the Lung Cancer Module (EORTC QLQ LC13) at the baseline visit prior to treatment being administered, at home every 2 weeks for the first 3 months and once monthly thereafter, and at their End-of-Study visit.

7.4.4 CCI

CCI

7.4.5 NSCLC Disease History/Respiratory Disease History

On Day 1, the patients' NSCLC disease history will be collected, including date of diagnosis, stage at diagnosis, and treatment history (including date of most recent radiation).

7.4.6 Durvalumab Treatment

Throughout the study, updated information on the patients' durvalumab treatment will be collected, including durvalumab start and stop date, treatment holds, interruptions, and permanent discontinuations (including reasons for each), as well as details regarding other treatments such as chemotherapy and radiation therapy (including doses and number of cycles).

Concomitant medication (including over-the-counter medication) details will also be collected. The indication for treatment must be recorded, including drug name, route, and duration of drug administration.

8 REGULATORY CONSIDERATIONS

8.1 Quality Control

8.1.1 Monitoring

AstraZeneca has delegated study monitoring to Syneos Health. Before the first patient is enrolled into the study, a Syneos Health designee will meet with the physicians (and other site personnel involved with the study) to discuss the joint responsibilities with regards to protocol compliance. The roles and responsibilities of Syneos Health and AZ or its representatives will be covered. This will be documented in a study Primary Agreement between the designated parties and the Primary Investigators (site physician) for each site.

During the study, a Syneos Health designee or AZ can implement various activities to assure compliance with AZ standards of quality. These activities could include but are not limited to:

Contacts with the sites to:

- Provide information and support to the physicians and other site personnel
- Ensure recruitment is meeting expectations for all sites
- Ensure that site personnel follow the appropriate process to ensure the patient ICFs are signed and stored at the site
- Ensure that site personnel follow the appropriate process to ensure patient's ON TRAX study participant identifiers are captured in the ICFs, as well as the contact details as required for the study

Monitoring activities (remotely, and before on site visit, if required) for:

- Checking a sample of ICFs at each site
- Checking a sample of patient data entry at each site

If there are any issues noted with ICFs or patient data entry that reflect a potential non-optimal level of protocol compliance by the site personnel, specific measures will be adopted by Syneos Health or AZ to evaluate the situation, identify the issue, and implement specific action plans to correct the situation.

8.1.2 Training of Study Site Personnel

The site physician will ensure that appropriate training relevant to the study is given to site personnel, and that any new information relevant to the performance of this study is forwarded to the staff involved.

Representatives of the AZ's quality assurance unit/monitoring team, AZ's delegate, and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site that support study data entry, including the Investigator Site File, the completed ICFs and the patients' medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

8.1.3 Storage and Retention

Following closure of the study, the site physician has the responsibility to ensure maintenance of all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records must be maintained to allow easy and timely retrieval, when needed (e.g., for AZ's or its representative's audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site personnel.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The site physician must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the site physician must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

AstraZeneca or its representatives will inform the site physician of the period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study with a minimum of 5 years, as dictated by any institutional requirements or local laws or regulations, AZ/delegate standards/procedures, and/or institutional requirements.

8.2 Protection of Human Patients

This study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), and applicable legislation for prospective studies.

The site physicians will perform data collection for the study in accordance with the regulations and guidelines governing medical practice and ethics in the United States.

The final protocol of the study, including the final version of the ICF, and submission of an Investigational Device Exemption must be approved or given a favorable opinion in writing by the appropriate Institutional Review Board (IRB) for each site.

The IRB must also approve amendments to the protocol and all advertising used to recruit patients for the study, according to local regulations.

8.2.1 Patient Informed Consent

The physician at each site will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study via the Informed Consent Process. Patients must also be notified that their participation is voluntary and they are free to discontinue from the study at any time. The patients should be given the opportunity to ask questions and allowed time to consider the information provided. The patients will be required to sign a statement of informed consent that meets the requirements of US FDA Code of Federal Regulations (CFR) 21CFR 50, local regulations, Health

Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study site.

Patients will be asked to contact the study site for issues related to study procedures or technical support. The study site will facilitate connection with the Current Health Call Center for assistance, as necessary. For medical questions or to report AE signs/symptoms, patients will be asked to contact their treating physicians directly.

It will be clearly explained to the patient that the study aims to collect data using certain devices, but that the use of these devices will not involve any additional risk for the patient. Patients will also be required to complete QoL and CCI pertaining to the devices. The frequency of those measurements, the methods to guarantee no personal data are disclosed, and the right of the patient to access his/her information at any time during the study will all be communicated to the patient in a clear and unambiguous way.

The signed and dated patient ICF must be obtained before device onboarding for the study is performed.

The physician or designated site personnel must store the original, signed ICF. A copy of the signed ICF must be given to the patient at the time of consent.

8.2.2 Confidentiality of Study/Patient Data

The patient's ICF will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorize the collection, use, and disclosure of their personal data by the physician to those persons who need that information for the purposes of the study.

The ICF will explain that study data will be stored in a web-based platform, maintaining confidentiality in accordance with local laws for data protection.

The ICF will also explain that for quality check purposes, a monitor from Syneos Health will require direct access to the signed ICFs. In case source data verification is planned as a quality check, the ICF will explain that for data verification purposes, a monitor from Syneos Health may require direct access to source documents relevant to the study.

8.3 Management and Reporting of Adverse Events and Device Complaints

8.3.1 Management and Reporting of Adverse Events

The focus of this study is to assess whether multiparametric mobile technology allows earlier detection and intervention of pneumonitis and other pulmonary events in the patient population.

8.3.1.1 Definition of Adverse Event and Serious Adverse Event for Drugs

An AE 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 undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings,

electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time after the Baseline visit (Day 1) once the patient signs the ICF, even if no study treatment has been administered. A treatment-emergent AE (TEAE) is an AE that starts or worsens at any time after initiation of a pharmaceutical product on the first day of treatment through the End-of-Study visit.

An SAE is an AE occurring during any study phase after the patient signs the ICF (i.e., at Baseline, treatment, washout, follow-up) that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent 1 of the outcomes listed above

Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a non-serious AE. For example, if the tumor is included as medical history and progression occurs during the study, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur.

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

8.3.1.2 Definition of Adverse Event and Serious Adverse Event for Medical Devices

An AE 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.

An SAE is an AE occurring during any study phase after the patient signs the ICF that fulfils 1 or more of the following criteria:

- Led to death

- Led to a serious deterioration in health of the patient, that either:
  - Resulted in a life-threatening illness or injury, or
  - Resulted in a permanent impairment of a body structure or a body function, or
  - Required in-patient hospitalization or prolongation of existing hospitalization, or
  - Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or
  - Led to fetal distress or a congenital abnormality or birth defect

Serious Injury is an injury or illness that:

- Is life-threatening
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure
- "Permanent" means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage
- A life-threatening injury meets the definition of serious injury, regardless of whether the threat was "temporary"

It should also be noted that a device does not have to malfunction for it to cause or contribute to a serious injury. Even though a device may function properly, it can still cause or contribute to a death or serious injury.

Medical Device Reporting (MDR) Reportable Event ("Reportable Event"): According to the US FDA 21CFR 803.3, a Reportable Event means:

(1) An event that user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury, or
(2) An event that manufacturers or importers become aware of that reasonably suggests that one of their marketed devices:
   i. May have caused or contributed to a death or serious injury, or
   ii. Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

8.3.1.3 Adverse Events Information

AE and SAE collection will occur at Baseline (i.e., after the patient signs the ICF), during standard of care visits, at the End-of-Study visit, and for 30 days after the End-of-Study visit. The following information should be collected for AEs and SAEs reported to AZ or its delegate, Syneos Health Pharmacovigilance:

- AE (verbatim)
- The date (and time) when the AE started and stopped
- Intensity rating scale (intensity, maximum intensity or changes in intensity)
  - Mild
  - Moderate

- Severe

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.3.1.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Section 8.3.1.1. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 8.3.1.1. The severity (i.e., grade) of all AEs will be documented at Baseline, during standard of care visits, and through final resolution (or other final outcome). When possible, the severity of Baseline conditions (i.e., AE-related signs/symptoms, laboratory measurements) will also be documented.

- Whether AE is serious or not
- Physician causality against durvalumab
- Action taken with regard to durvalumab
- Outcome

In addition, the following variables should be collected for SAEs reported to AZ (or its delegate, Syneos Health Pharmacovigilance, as described in Sections 8.3.1.4 and 8.3.1.5, as applicable):

- Date site physician became aware of SAE
- Date AE met criteria for SAE
- The reason AE is serious
- Date of hospitalization
- Date of discharge
- Date of death
- Autopsy performed

8.3.1.4 Reporting of AEs/SAEs on Durvalumab and Device-Related Events

The ON TRAX study is interventional in nature. Although information about past and current disease history will be collected, the study is not focused on any specific medicinal products. To participate in the study, patients will be treated with durvalumab.

Clinical practice and patient pathways should be as close as possible with routine practice.

All pulmonary AEs and other AEs will be collected regardless of causality, recorded by the study physician, and followed through final resolution (or other final outcome) during the standard of care visits. If an AE is not resolved by the end of study participation, the Investigator will determine whether to authorize additional follow-up, and will document this decision.

All pregnancies and medication errors (eg, overdose) associated with the AZ drug (durvalumab) must be promptly reported by the site physician or other site personnel quoting the study number **within 1 calendar day** of initial site awareness to the data entry site (DES) via the following e-mailbox:

CCI

In the event the secure email link is unavailable (eg, due to network issues), the following fax number should be used.

Fax number: CCI [redacted]

AstraZeneca will include in the documentation provided to the study physician a reminder of the importance of AE reporting. AstraZeneca representatives responsible for monitoring the study will continuously reinforce this process with the sites. Adverse Events reported will be closely monitored and evaluated in context of study continuation. A list of AEs will be forwarded to the IRB(s) at the end of the study.

Individual Case Safety Reports (ICSRs) related to any of AZ's medicinal products in the context of the present study will be treated per the company's Standard Operational Procedures.

8.3.1.5 Reporting of Serious Adverse Events (SAEs)

All SAEs should be reported to AZ's delegate for monitoring safety, Syneos Health Pharmacovigilance, within 24 hours of the study site's awareness of the information. Please complete the SAE Report Form and provide to Syneos Health Pharmacovigilance via:

CCI [redacted]

Fax number: CCI [redacted]

Syneos Health Pharmacovigilance will perform receipt and tracking of reported SAEs, and will pass through all reports to AZ for processing and generation of regulatory reporting forms.

Site personnel should follow all SAEs through to final resolution (or other explanation) and complete a follow-up SAE Report Form and provide to Syneos Health Pharmacovigilance within the same timeframe as the initial SAE Report (24 hours). If an SAE is not resolved by the end of study participation, the Investigator will determine whether to authorize additional follow-up and will document this decision.

Serious adverse events reporting to the respective IRB should be performed by the study site, in accordance with the site's policies.

For SAEs assessed as serious and unlisted (for durvalumab), or events assessed to meet MDR expedited reporting criteria, AZ or its designee will perform appropriate expedited reporting to the health authorities, ethics committees, and study sites, respectively in accordance with the US FDA CFR, 21CFR 314.80 for marketed products and, 21CFR 803.3 for marketed devices (if applicable).

8.3.2 Medical Device Deficiencies

Medical devices are being provided for use in this study as the study intervention. In order to fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

Definition of Device Deficiency

A device deficiency is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.1.

8.3.2.1 Time Period for Detecting Medical Device Deficiencies

Medical device incidents or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the Investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify AZ or its designee.

8.3.2.2 Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency. New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.3.2.3 Reporting Patient Complaints about Devices or Mobile Application to Sponsor

Patients will be asked to contact the study site with any technical complaints about their devices or applications (e.g., device is not working or pairing, application is not working properly). Detailed information about reporting complaints with devices or the mobile application will be included in the Patient Study Guide. The study site will facilitate connection with the Current Health Call Center for assistance, as necessary. If the Current Health Call Center cannot fix the technical complaint within 24 hours, the Current Health Call Center will send the patient a replacement device along with a prepaid return shipping label for patients to send the faulty device back to Current Health.

Device deficiencies will be reported to AZ or its designee within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency. A Medical Device Deficiency Report Form will be sent to AZ or its designee and reported to the appropriate device manufacturer as necessary. Any AEs/SAEs that occur as a result of the device complaint are to be sent to the AZ DES. Device malfunctions that do not result in an AE will be tracked separately.

8.3.2.4 Reporting Patient Complaints about Devices or Mobile Application to Regulatory Authorities

The Investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for AZ to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. Reported complaints will be closely monitored and evaluated in context of study continuation. The Investigator, or responsible person

according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB.

8.4 Non-Significant Risk Investigational Device Exemption

This study is not being conducted as a Non-Significant Risk Investigational Device as the device is not an investigational device. Previous versions of this device have obtained 510(k) clearance by FDA. While the version used in this study has been modified, it would not require submission to FDA because the modifications and product codes (Table 2) are within the scope of FDA's June 2020 (further revised in October 2020) guidance, "Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised)".

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

This is intended to be a pilot study. The study will enroll 75 patients, provide descriptive outputs, and a logistic estimation of whether variables collected in the study contribute to the detection of pneumonitis.

The estimated proportion of patients who experience an event and the precision (exact 95% CI) of the estimate if various numbers of patients are observed to have the event among a total of 75 patients is presented in Table 4 . If no patients are observed to experience a particular type of pulmonary AE, then there would be 95% confidence that the real incidence rate is no greater than 4.8% of patients.

Table 4 Estimated Proportion of Patients and 95% CI Expected to Experience an Event Based on Numbers of Observed Events

Number of observed events	Estimated proportion of patients with the event	95% Confidence Interval*
0	0.0%	(0.0% , 4.8%)
1	1.3%	(0.0% , 7.2%)
2	2.7%	(0.3% , 9.3%)
3	4.0%	(0.8% , 11.2%)
4	5.3%	(1.5% , 13.1%)
5	6.7%	(2.2% , 14.9%)
6	8.0%	(3.0% , 16.6%)
8	10.7%	(4.7% , 19.9%)
10	13.3%	(6.6% , 23.2%)
12	16.0%	(8.6% , 26.3%)
14	18.7%	(10.6% , 29.3%)
16	21.3%	(12.7% , 32.3%)

* Exact 95% Clopper-Pearson intervals

9.2 Populations for Analyses

Planned analysis population sets are described in Table 5 .

Table 5 Analysis Populations

Population	Description
Full Analysis Set (FAS)	All enrolled patients who take at least 1 dose of durvalumab and who have any post-baseline assessment (safety or otherwise).
Safety Analysis Set (SAF)	All enrolled patients who take at least 1 dose of durvalumab

9.3 Statistical Analyses

A comprehensive SAP will be developed and finalized before database lock and will describe the patient populations to be included in the analyses, as well as the procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. All analyses of the primary, secondary, and exploratory endpoints will be descriptive only with no formal statistical testing. Any deviations from this plan will be reported in the clinical study report.

9.3.1 Efficacy Analyses

PRO values and values from the mobile technology will be considered in connection with events of interest, specifically pneumonitis. Contributions to the identification/prediction of pneumonitis from PROs and variables collected by the devices may be assessed using regression models (e.g. logistic regression) depending on the number of events of interest that are observed in the study; the primary endpoint in these estimations will be the occurrence of pneumonitis. Lagged PRO values and values collected from the mobile technology may be incorporated as covariates in these models; more details will be specified in the SAP. The analyses of the primary endpoint will be conducted by overall patients in the full analysis set (FAS).

Continuous secondary and exploratory endpoints (e.g., duration of durvalumab treatment, duration of pulmonary AE, and absolute QoL and its change from baseline) will be summarized by the number of observations, mean, standard deviation, median, minimum, maximum, and 95% CIs. Categorical variables will be summarized by frequency counts, percentages, and 95% CIs for each category. All descriptive statistics of secondary and exploratory endpoints will be conducted by overall patients in the FAS.

9.3.2 Safety Analyses

Safety analyses will include all patients in the safety analysis set (SAF).

Safety analyses will involve examination of the descriptive statistics and individual patient listings for clinical tolerability and safety.

Summaries of TEAEs will include the events by system organ class and preferred term, events by maximum intensity, event by relationship to study treatment, events leading to study discontinuation, and SAEs.

9.4 Interim Analyses

An interim analysis is not planned for the study.

10 COMMUNICATION PLAN

10.1 Publication Plan

In alignment with AZ policies, a study report will be prepared by AZ's delegate, Syneos Health, within 12 months after completion of the study. Reports will be prepared for each of the major analysis steps specified in the protocol. The final report will encompass all planned analyses, including a description of the complete study population, as described above and in the corresponding data analysis plan.

The final results of the study will be disseminated through submission of manuscripts for publication and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE). Selected final results may also be disseminated through publication or presentation at scientific meetings.

All publications shall be developed in accordance with AZ Global Publications Policy, as well as ICMJE and Good Publications Practice 3 (GPP3) requirements for authorship and good publications practice. Publication decisions, including what, when, and where to publish, will be made jointly by AZ authors and study site authors.

Aggregate results will be published ahead of site-specific or subgroup analyses. AstraZeneca reserves the right to delay site-specific or subgroup analyses publications until overall aggregate results are published.

10.2 Compliance with Financial Disclosure Requirements

Financial compensation will be provided to cover all study procedures under the responsibility of the site physician. This compensation rate will be determined according to recommended fair market value for the corresponding study activities.

Financial disclosure of this compensation will fulfil applicable local laws, codes, and regulations.

10.3 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (ie, substantial, significant) amendments will be approved by the relevant regulatory authorities and will usually require submission or notification to the relevant IRB for approval or favorable opinion, if applicable. In such cases, the amendment will be implemented at the site only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating site and will be submitted to the relevant IRB or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

Amendments and updates to the protocol will be documented in a separate protocol section entitled "Version History".

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13 SIGNATURES

ASTRAZENECA SIGNATURES

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

This Study Protocol has been subjected to an internal AstraZeneca review.

I agree to the terms of this Study Protocol.

AstraZeneca representative

PPD

AstraZeneca PPD

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

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