Clinical Study Protocol	
Drug Substance	DURVALUMAB
Study Code	D133HC00003
Version	4.1
Date	12/10/2022

A prospective, multicenter, Phase-IV clinical trial to assess safety of Durvalumab in Indian adult patients with locally advanced, unresectable non-small cell lung cancer (NSCLC).

Sponsor:

AstraZeneca Pharma India Limited

Block N1, 12th Floor, Manyata Embassy Business Park

Rachenahalli, Outer Ring Road, Bangalore-560045.

VERSION HISTORY

Version 1.0 Date 26.11.2018
Initial Document Creation
Version 2.0 Date 02.03.2020
Table 1: Schedule of Activities: Added Urine Pregnancy Test and Physical Examination at baseline **Section 2.1**: Study Timelines **Section 6.1**: Study Treatments: Dosage Formulation changes **Section 6.5.3**: Clarity on Rescue medication **Section 8:** Changes in the quantity of blood to be withdrawn to approximately 10 mL/visit **Section 9.2:** Sample Size Determination now changed to 200 as mandated by the Indian HA **Section 9.4:** Simplified Statistical Analysis, PK analysis will not be done **Appendix D:** Removed Hy's law and added Recommended Treatment Modifications for Durvalumab and Management Recommendations
Version 3.0 Date 07.04.2020
Table 1: Schedule of Activities: Added Urine Routine and microscopy test .End of Evaluation visit timeline corrected to last day of Week 20 and follow up time lines updated to 15 days after EoE visit. **Section 4.2.2 :** Removed Justification for follow up period. **Appendix A :** Schedule Y changed to New Drug & Clinical Trial Rules, 2019
Clinical Study Protocol V3 - Addendum 1.0 21 June 2021
Protocol Section 1: (Follow Up Phase ,End-Of-Study, Schema, Table 1 -Schedule of Activities) telephonic follow-up will be conducted 90 days after the EOE Visit. **Protocol Section – 1 & 6.7:** Post-Trial Access. **Protocol Section 7.1:** Discontinuation of study treatment.
Version 4.0 Date 04.04.2022
Title : Urothelial Cancer Indication removed from the study . **Post-Trial access:** Post trial access duration updated with reference to change in Prescribing Information. **Sample size:** Study sample size updated to 100 patients.
Version 4.1 Date 12.10.2022
Post-Trial access: Post trial access duration updated as until unacceptable toxicity/disease progression or as per the decision of the treating physician **Section 7.1**: 'Patient has completed maximum of 12 months of drug treatment from treatment initiation' removed form Discontinuation criteria.

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. PROTOCOL SUMMARY

1.1 Table 1: Schedule of Activities (SoA)

Dose		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Days (± 3 days of windows period)	**-7 to 0**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**230**
Week (1st day of week)		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**Last day of week 20**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
	Screening Period	**Evaluation Phase**											**Follow-up period**
	Screening Visit	**Evaluation Visit (2-11)**										**End of Evaluation Visit**	**End of Study Visit**
Informed Consent Form	X												
Eligibility Criteria	X	X											
Demography and history of tobacco and alcohol use	X												
Medical and surgical history (including all treatments for NSCLC/mUC)	X												
Physical examination	X	X	Targeted physical exam (based on symptoms)									X	
Vital signs (pre and post-infusion vital signs assessments; see Section 6.4.8)		X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test	X												
Weight		X		X		X		X		X			
World Health Organization performance status	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Disease Characteristics Assessment		X			X			X			X	X	
Adverse event/serious adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (before dosing of IP)		X				X				X			
Haematology		X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry (LFT, RFT, Electrolytes)		X	X	X	X	X	X	X	X	X	X	X	
Urine Routine and microscopy		X	X	X	X	X	X	X	X	X	X	X	
Thyroid function tests (TSH, T3 and T4)[a]		X				X				X		X	
IP Administration		X	X	X	X	X	X	X	X	X	X		

a. Except screening visit, free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

1.2 Synopsis

Protocol Title: A prospective, multicenter, Phase-IV clinical trial to assess safety of Durvalumab in Indian adult patients with locally advanced, unresectable non-small cell lung cancer (NSCLC).

Version: 4.1 Date: 12 October 2022

Study site(s) and number of patients planned

No. of total screened patients: Approximately 120

No. of total enrolled patients: Approximately 100

No. of study sites ~10

Total planned Study period	
Estimated date of first patient in	Q4 – 2021
Estimated date of last patient in	Q4 – 2022
Estimated date of last patient last visit	Q3 – 2023
Estimated date of data base lock	Q3 – 2023
Clinical study report	Q4 – 2023

Rationale

The present study is a Phase IV safety study of durvalumab to be conducted in compliance with a condition of approval specified by the Health Authorities of India. Approval in India has been granted for the use of durvalumab for the treatment of patients with locally advanced, unresectable non-small cell lung carcinoma (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy. As a condition of approval, AstraZeneca is required to conduct a Phase IV clinical trial so that adverse reactions related to treatment with durvalumab are reported to the Health Authorities in India and subsequently, any regulatory action resulting from the review of reported adverse reactions should be complied with by the Sponsor.

The present study will provide information on the safety profile of durvalumab for the treatment of locally advanced NSCLC in Indian patients in accordance with the requirements of the Health Authorities of India.

Objectives and Endpoints

Primary objective:	**Primary Outcome Measure:**
To assess the safety of durvalumab among locally advanced unresectable non-small cell lung carcinoma in Indian patients	Number, frequency and proportion of patients with adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI) including interstitial lung disease/pneumonitis-like events, and on-study deaths.

Overall design:

This is a Phase IV, open-label, single arm, multi-center, prospective study to be conducted in India. Two cohorts of patients will be included in the current study patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy (N= 100). Potential patients will undergo eligibility determination within 7 days prior to first dose. Patients who meet the protocol-defined inclusion/exclusion criteria will be prospectively enrolled in a sequential manner at 10 centres in India. All enrolled patients will be treated with durvalumab administered intravenously over 60 minutes at 10 mg/kg every 2 weeks. The treatment period for this study is 20 weeks, which corresponds to 10 doses of study drug administration. Treatment will continue as long as clinical benefit is observed for a maximum of 20 weeks or either of the criteria defined in section 7 are met, whichever is earlier. Patients who are observed to continue to receive clinical benefit from durvalumab at end of Week 20 (as defined in SoA) will continue treatment in post-trial phase (defined in section 6.7). Any patient who discontinues treatment with durvalumab before end of Week 20 on study will be followed for 90 days after discontinuation of study drug or until the start of alternate treatment intervention, whichever is earlier.

Safety will be evaluated throughout the evaluation phase and during the follow up of patients who discontinue treatment before end of Week 20 by physical exams including vital signs, AE/SAE monitoring, laboratory evaluations and recording of concomitant medications.

Screening Phase (Visit 1)

Patients, or their legally acceptable representative, will provide written informed consent before any trial-specific procedures are performed. During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Event Schedule. Screening procedures will be performed 7 days before first dose (week 0, day 1). All baseline disease characteristics will be captured based evaluation performed as a part of routine clinical practice. The documented tests that are required before consideration of patient for durvalumab treatment based on the local prescribing information by investigator must have been performed 28 days before first dose (week 0, Day 1).

Evaluation Phase (Visit 2 To 11)

The Evaluation Phase will extend from first dose (Week 0, Day 1) to end of Week 20; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons whichever occurs first, as listed in Section 7. Details of the procedures performed during the Evaluation Phase are outlined in the Time and Events Schedules. Patients will be closely monitored for adverse events and other safety evaluations including laboratory investigations, concomitant medications. If disease progression is diagnosed before end of week 20 then the patient will discontinue study drug with completion of the End-of-Evaluation Visits on the day of progression, and will enter the safety Follow-up Phase.

End-Of– Evaluation Visit (EoE)

An End-of- Evaluation Visit is to be scheduled on end of week 20 (Day 141) of the study. In a case where patient discontinues the study treatment for any reason listed in Section 7.1 before 20

weeks, last visit of the patient will be considered as End-of- Evaluation visit. Every effort should be made to conduct the telephonic End-of-Study Visit before the patient starts subsequent treatment.

Follow Up Phase (End-Of-Study)

A telephonic follow-up will be conducted 90 days after the EOE Visit. This will be considered as End-of-Study visit.

The observation period including the Evaluation Phase and safety Follow-up phase will be up to a maximum duration of approximately 230days for each patient.

PATIENT POPULATION

Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

1. Provision of signed, written and dated informed consent prior to any study specific Procedures
2. Male or female aged 18 years or older
3. As per local prescribing information and in view of positive benefit-risk assessment, patient prescribed Durvalumab treatment as per independent clinical judgment of treating physician for either treatment for locally advanced, unresectable non-small cell lung carcinoma whose disease has not progressed following platinum-based chemoradiation therapy (N= 100)

The ICF process is described in Appendix A 3.

Exclusion criteria

1. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study
2. Current or prior use of immunosuppressive medication within 14 days before the first dose of study drug, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. Systemic steroid administration required to manage toxicities arising from radiation therapy delivered as part of the chemoradiation therapy for locally advanced NSCLC is allowed.
3. Prior exposure to any anti-PD-1 or anti-PD-L1 antibody including durvalumab.
4. For NSCLC cohort only:
    a. Mixed small cell and non-small cell lung cancer histology
    b. Any unresolved toxicity CTCAE >Grade 2 from the prior chemoradiation therapy.
    c. Patients with ≥Grade 2 pneumonitis from prior chemoradiation therapy

5. Active or prior documented autoimmune disease within the past 2 years, inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis), primary immunodeficiency, organ transplant that requires therapeutic immunosuppression, hypersensitivity to study drug or any excipient, leptomeningeal carcinomatosis, tuberculosis.

   NOTE: Patients with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
6. Female patients who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control
7. Any condition that, in the opinion of the investigator, would interfere with evaluation of the study drug or interpretation of patient safety or study results.

Study Drug, dosage and mode of administration

The recommended dose of Durvalumab is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, until disease progression or unacceptable toxicity. Dose escalation or reduction is not recommended. Dose withholding, or discontinuation may be required based on individual safety and tolerability.

Durvalumab will be supplied as either 500 mg (500mg/10mL) or 120 mg (120 mg/2.4mL) single-dose vial and does not contain any preservatives, aseptic technique must be observed. Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

Duration of treatment

The Treatment Phase will extend from start of Week 0 to end of week 20, Day 141; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons whichever occurs earlier, as listed in Section 7.1. Patients may continue to receive durvalumab as long they are continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria.

Post-trial access

Patients who are observed to receive clinical benefit from durvalumab at the end of week 20 may continue get the drug free of cost (provided by AstraZeneca) to all the responding patients until unacceptable toxicity/disease progression or as per the decision of the treating physician

Safety Evaluations

Safety evaluations will include adverse event monitoring, physical examinations, ECG monitoring, clinical laboratory parameters (hematology and biochemistry), vital sign measurements, and WHO performance status and death as observed by the investigator. Based on the previous human experience with durvalumab, in vitro studies, and animal toxicological

findings, immune mediated pneumonitis, hepatitis, colitis and endocrinopathies will be closely monitored. Any of the safety monitoring assessments may be performed more frequently, and adverse events should be evaluated by the investigator according to the standard practice if clinically indicated.

Statistical methods

Sample Size Justification

The primary endpoint of the trial is to demonstrate the safety profile of durvalumab in routine clinical practice as assessed by the incidence of adverse events (AEs) (Serious and Non-serious AEs) observed during trial. Based on the Durvalumab historic data, estimated proportion of 31% for adverse events prevalence rate. With a sample size of 83, would be able to achieve the 10% precision of the estimates with the 95% level of confidence. Approximately 120 participants will be screened to achieve around 100 participants enrolled in the study.

Scenario#	estimated proportion	Precision	Confidence level	Required sample size
1	31%	.15	95%	37
2	31%	.14	95%	42
3	31%	.13	95%	49
4	31%	.12	95%	58
5	31%	.11	95%	68
6	31%	.10	95%	83

Hypothesis

No formal hypothesis testing will be conducted.

Statistical Analysis

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

The safety analysis population will include all patients who sign the ICF and receive at least one dose of durvalumab.

Adverse Events (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. Any AE occurring before treatment with durvalumab will be included in the data listings but will not be included in the summary tables of AEs.

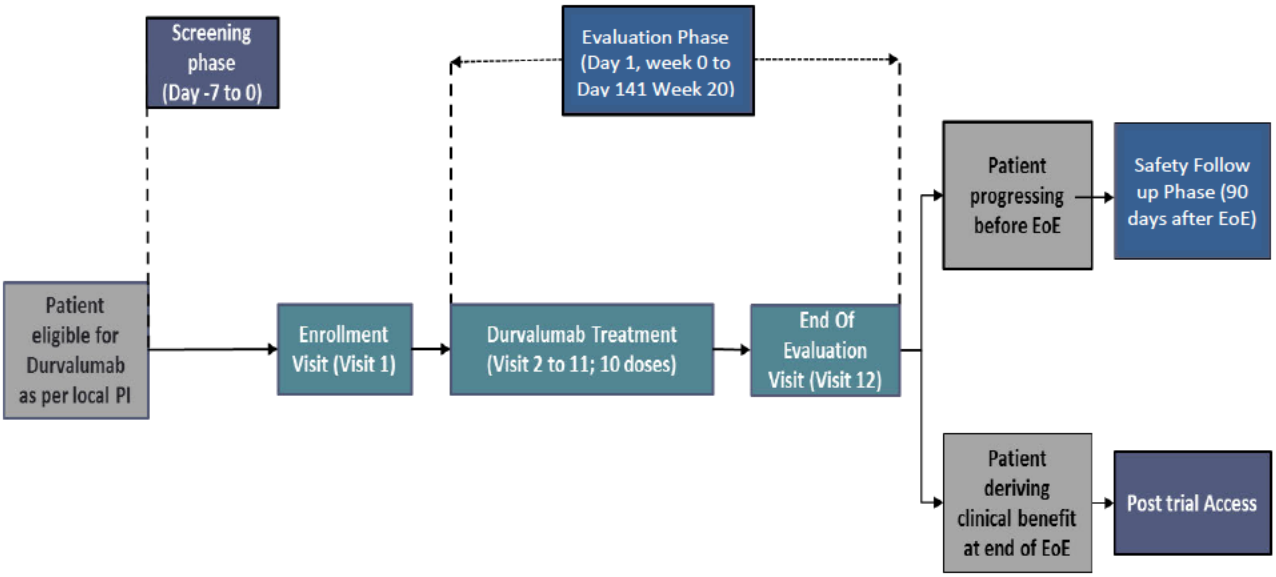
Any AE occurring within 90 days of discontinuation of investigational product (ie, the last dose of durvalumab) will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of durvalumab) will be flagged in the data listings.

The study is designed in accordance with the Health Authority requirements in India. It is intended to provide information regarding the safety profile for patients in India and will contribute additional information to the overall safety profile of durvalumab. Due to the small sample size, this study should not be directly compared to the data from any other country.

1.3 Schema

The general study design is summarised in

Figure 1. Study design



2. INTRODUCTION

2.1 Study rationale

This is a Phase IV safety study of durvalumab to be conducted in compliance with a condition of approval specified by the Health Authorities of India.Approval in India has been granted for the use of durvalumab for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy. As a condition of approval, AstraZeneca is required to conduct a Phase IV clinical trial so that adverse reactions related to treatment with durvalumab are reported to the Health Authorities in India and subsequently, any regulatory action resulting from the review of reported adverse reactions should be complied with by the Sponsor. This Phase IV clinical trial is required in addition to the Periodic Safety Update Report, which must be submitted every 6 months for the first 2 years after approval, and annually thereafter.

The present study will provide information on the safety profile of durvalumab for the treatment of locally advanced NSCLC in Indian patients in accordance with the requirements of the Health Authorities of India.

2.2 Background

2.2.1 Durvalumab

Immune responses directed against tumours are one of the body's natural defences against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T-cells. PD-L1 is one such protein and is expressed in a broad range of cancers.

The inhibitory mechanism described above is co-opted by tumours that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on ICs. This activity overcomes PD-L1-mediated inhibition of antitumour immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

Durvalumab is a human mAb of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 on immune cells. The proposed mechanism of action for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon gamma (IFNγ). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response

Stimulating an antitumour immune response is a mechanism employed successfully by a number of approved cancer therapies. Blocking the PD-1/PD-L1 pathway is an approach that has been successfully employed with therapies such as pembrolizumab (KEYTRUDA™), nivolumab (OPDIVO™), atezolizumab (TECENTRIQ™) and durvalumab (IMFINZI™), which have been approved by a number of various Regulatory Agencies, including the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency, as a treatment for a number of oncology indications including malignant melanoma, NSCLC, renal cell carcinoma, bladder cancer, HNSCC and classical Hodgkin lymphoma.

2.2.2 Non-small cell Lung Cancer

Lung cancer is the leading cause of cancer related mortality world-wide and amongst males in India. About 85% of lung cancers are non-small cell lung cancers (NSCLC). Stage III disease comprises approximately 30% of the NSCLC diagnoses. It comprises a heterogeneous patient population with 2 subsets: Stage IIIA and IIIB. Approximately, one-third of the patients with Stage IIIA disease are considered operable. However, majority of patients with Stage IIIA/B have inoperable (unresectable) disease and are amenable to receiving curative intention chemoradiation treatment.

Lung cancer in India is detected at relatively advanced stage compared to western data. Multiple reasons have been proposed for the late presentation including access to healthcare, misdiagnosis due to high prevalence of tuberculosis and limited modern infrastructure to diagnose the patient early.

The current standard-of-care for patients with locally advanced, unresectable, NSCLC is concurrent chemoradiation administered with a curative intent While chemoradiation can achieve initial disease control, majority of patients eventually progress. More than 50% of patients develop distant metastasis, and up to 40% can experience local recurrence. The prognosis remains poor, and the 5-year survival rate is approximately 15%.

The PACIFIC study has demonstrated the efficacy of durvalumab versus placebo in patients with locally advanced, unresectable Stage III NSCLC who had completed treatment with at least 2 cycles of platinum-based chemotherapy concurrent with radiation therapy within 1 to 42 days. Durvalumab demonstrated a statistically significant (HR: 0.52; 95% CI: 0.42, 0.65; p-value <0.0001) and a median PFS improvement of 11.2 months when compared with placebo.

As per recommendation, current phase-IV study is planned with the aim to assess the safety of durvalumab in Indian patients as a post-marketing requirement. The data obtained from the present study will help to understand the safety profile of durvalumab in Indian patients with locally-advanced, unresectable NSCLC.

2.3 Benefit/risk assessment

Patients with locally advanced, unresectable NSCLC who have progressed during or after chemoradiotherapy enrolled in this study will be treated with durvalumab at the dose level and with the frequency approved in India (10mg/kg IV over 60 minutes every 2 weeks) throughout the 20 week treatment period or until unacceptable toxicity. During this time patients will be monitored for safety according to the assessment frequency presented in Table 1, and those patients who discontinue treatment before the end of the 20 week treatment period will be monitored for 90days or until the start of subsequent interventional treatment whichever is

earliest. Those patients who continue to receive benefit from durvalumab at the end of the week 20 treatment phase, may continue treatment via drug supplied by AstraZeneca.

Overall, the safety profile of durvalumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose reached at any dose tested up to 20 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to durvalumab dose level.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these will be provided to the study sites as a separate document. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of durvalumab may be found in the Durvalumab India Prescribing Information.

3. OBJECTIVES AND ENDPOINTS

Table: 2 Study objectives

Primary Objective:	*Endpoint/Variable:*
To assess the safety of durvalumab among locally advanced unresectable NSCLC	Number, frequency and proportion of patients with adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI) including interstitial lung disease/pneumonitis-like events, and on-study deaths.

4. STUDY DESIGN

4.1 Overall design

For an overview of the study design see Section 1.3. For details on treatments given during the s tudy, see Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.2 Scientific rationale for study design

Justification for Study duration:

In the combined safety database with Durvalumab monotherapy, the median time to onset of select adverse events is summarised in the Table below. The current phase IV study includes a

treatment phase of 141 days (20 weeks) which would enable us to detect the incidence of adverse events in eligible Indian patient population.

Table 3: Median time to onset of Immune-mediated Adverse Events

S. No.	Immune-mediated adverse event	Median time to onset (days)
1	Pneumonitis	55
2	Hepatitis	70
3	Diarrhoea/colitis	74
4	Hypothyroidism	85
5	Immune mediated nephritis	91
6	Dermatitis	36
7	Hyperthyroidism	41

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving Durvalumab. Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging and managed as recommended by local guidelines.

Radiation pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar. In the PACIFIC Study, in patients who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the trial, pneumonitis including both immune-mediated pneumonitis and radiation pneumonitis, occurred in patients receiving Durvalumab. Pneumonitis or radiation pneumonitis occurred in 161 (33.9%) patients in the Durvalumab -treated group and 58 (24.8%) in the placebo group; including Grade 3 in 16 (3.4%) patients on Durvalumab vs. 7 (3.0%) patients on placebo and Grade 5 in 5 (1.1%) patients on Durvalumab vs. 4 (1.7%) patients on placebo. The median time to onset in the Durvalumab -treated group was 55 days (range: 1-406 days) vs. 55 days (range: 1-255 days) in the placebo group.

Refer to section Appendix D for recommended treatment modifications and management of immune-mediated adverse reactions.

4.3 Justification for dose

The dose used in the current study is based on the locally approved prescribing information.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled visit or last scheduled procedure shown in the SoA

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

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

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

1. Provision of signed, written and dated informed consent prior to any study specific Procedures

2. Male or female aged 18 years or older

3. As per local prescribing information and in view of positive benefit- risk assessment, patient prescribed Durvalumab treatment as per independent clinical judgment of treating physician for either treatment for locally advanced, unresectable non-small cell lung carcinoma whose disease has not progressed following platinum-based chemoradiation therapy (N=100)

The ICF process is described in Appendix A 3.

5.2 Exclusion criteria

1. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study

2. Current or prior use of immunosuppressive medication within 14 days before the first dose of study drug, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. Systemic steroid administration required to manage toxicities arising from radiation therapy delivered as part of the chemoradiation therapy for locally advanced NSCLC is allowed.

3. Prior exposure to any anti-PD-1 or anti-PD-L1 antibody including durvalumab.

4. For NSCLC cohort only:

   a. Mixed small cell and non-small cell lung cancer histology

   b. Any unresolved toxicity CTCAE >Grade 2 from the prior chemoradiation therapy.

   c. Patients with ≥Grade 2 pneumonitis from prior chemoradiation therapy

5. Active or prior documented autoimmune disease within the past 2 years, inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis), primary immunodeficiency, organ transplant that requires therapeutic immunosuppression, hypersensitivity to study drug or any excipient, leptomeningeal carcinomatosis, tuberculosis.

NOTE: Patients with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

6. Female patients who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control

7. Any condition that, in the opinion of the investigator, would interfere with evaluation of the study drug or interpretation of patient safety or study results.

5.3 Lifestyle restrictions

Not Applicable

5.4 Screen failures

Screen failures are defined as patients who signed the informed consent form to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

These patients should have the reason for study withdrawal recorded in the CRF (electronic or paper).

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to durvalumab.

6.1 Treatments administered

Table 4: Study Treatments

	Treatment
Study treatment name:	Durvalumab

Dosage formulation:	Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg/120-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% w/v polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL.IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.
Route of administration	Intra-venous infusion over 60 min.
Dosing instructions:	Following preparation of study drug the entire contents of the iv bag should be administered as an iv infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm in-line filter.
Packaging and labelling	Study treatment will be provided and labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.
Provider	AstraZeneca/ delegate will be providing the IP to site.

6.2 Preparation/handling/storage/accountability

6.2.1 Preparation of solution

Durvalumab is supplied as a single-dose vial and does not contain any preservatives, aseptic technique must be observed.

- Visually inspect drug product for particulate matter and discolouration. Durvalumab is clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.
- Withdraw the required volume from the vial(s) of Durvalumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL. Do not freeze or shake the solution.
- Care must be taken to ensure the sterility of prepared solutions.
- Do not re-enter the vial after withdrawal of drug; only administer one dose per vial.
- Discard any unused portion left in the vial.

6.2.2 Administration

- Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

- Do not co-administer other drugs through the same infusion line.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.2.3 Dose calculation

The volume of reconstituted Durvalumab (mL) to add to the iv bag is calculated as follows:

10 mg/kg × Patient Weight (kg) ÷ durvalumab concentration (nominal 50 mg/mL)

Example: For a patient weighing 80 kg, dosed at 10 mg/kg, 16 mL [10 mg/kg × 80 kg divided by 50 mg/mL] of durvalumab is to be diluted in a 250 mL iv bag containing 0.9% (weight/volume) saline. First, 16 mL of saline is removed from the iv bag, and then 16 mL of durvalumab is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted durvalumab is administered as described above

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

6.3 Measures to minimise bias: randomisation and blinding

Since the present study is an open label phase IV trial, blinding and randomisation is not applicable.

6.4 Treatment compliance

Any change from the dosing schedule, does interruptions, dose reductions, dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager(Investigator/delegate) is responsible for managing the IMP from receipt by the study site until the destruction or return of all unused IMP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IMP.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Investigators may prescribe concomitant medications or treatments (eg, acetaminophen , diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed below:

- Any investigational anticancer therapy
- Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for non cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.

  NOTE: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy).
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent; methotrexate, azathioprine, and tumour necrosis factor alpha blockers. Use of immunosuppressive medications in patients for the management of study drug-related AEs or their use in patients with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.
- Live attenuated vaccines within 30 days of dosing. Inactivated viruses such as those in the influenza vaccine are permitted.

6.5.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

6.5.2 Rescue medication

Rescue Medication, if required will be provided by the investigator as per the Standard of Care. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication will be recorded

6.6 Dose modification

All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which study drug should be permanently discontinued (Section 7).

Following the first infusion of study drug, subsequent administration of study drug can be modified based on toxicities observed. All toxicities will be graded according to CTCAE Version 4.03. Dose reductions are not permitted.

Dose modifications will not be required for AEs that are clearly not attributed to study drug (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Dosing may continue despite concurrent vitiligo of any AE grade. Based on the mechanism of action of Durvalumab leading to T-cell activation and proliferation, there is the possibility of observing irAEs (immune related Adverse Events) during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab and nivolumab including immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies (Brahmer et al 2010, Hodi et al 2010). Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate aetiology (eg, infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

6.7 Post-trial Access

Patients who are observed to receive clinical benefit from durvalumab at the end of week 20 may continue get the drug free of cost (provided by AstraZeneca) to all the responding patients until unacceptable toxicity/disease progression or as per the decision of the treating physician

7. DISCONTINUATION OF STUDY DRUG

7.1 Discontinuation of study treatment

Patients may be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event, that in the opinion of the investigator or the sponsor, contraindicates further dosing
- Severe non-compliance to study protocol that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits.
- Any AE that meets criteria for discontinuation, as defined in Appendix D
- An AE related to study drug that is ≥Grade 3, with the exception of toxicities that do not meet criteria for discontinuation as defined Section 5.2
- ≥Grade 3 infusion reaction
- Initiation of alternative anticancer therapy including another investigational agent
- Disease progression as per investigator's clinical and imaging assessment.
- Pregnancy or intent to become pregnant.

If the patient is discontinued from study drug, the patient will be followed up until the start of subsequent anti-cancer intervention or up to a duration of 90 days whichever is earlier.

7.2 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time (investigational product and assessments) at his/her own request, without prejudice to further treatment.

A patient who considers withdrawing from the study must be informed by the Investigator that the day of withdrawal will be considered as the end of study phase for the patient. However, the patient will still have the provision of spontaneous AE reporting.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up patients as medically indicated.

AstraZeneca or its delegate will request investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patient is crucial for the integrity of the study.

See SoA, Table 1, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

The investigator will ensure that data are recorded on the paper or electronic Case Report Forms.

The investigator ensures the accuracy, completeness for CRFs (electronic or paper) include: legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed paper/electronic Case Report Forms. A copy of the completed paper/electronic Case Report Forms will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue Study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided

the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each patient will not exceed approximately 10 mL/visit. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

8.1.1 Clinical safety laboratory assessments

See Table 6 & 7 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.2.6.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate CRF.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Table : 5 Haematology

Haematocrit
Haemoglobin
Basophils
Eosinophils
Monocytes
Absolute Neutrophil Count
Platelet count
Total Lymphocyte count including differential

Table : 6 Clinical chemistry (serum or plasma)

Albumin
Glucose
Alkaline phosphatase[a]
Lactate dehydrogenase
Alanine aminotransferase[a]
Lipase[b]
Aspartate aminotransferase[a]
Magnesium[b]
Amylase[b]
Potassium
Bicarbonate
Sodium
Calcium
Total bilirubin[a]
Chloride
Total protein
Creatinine (creatinine clearance)[b]
Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase
Uric acid[b]
TSH
Urine Routine and microscopy

a Tests for aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin must be conducted concurrently and assessed concurrently.

b Creatinine clearance, magnesium, amylase, lipase, and uric acid tested at Screening Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1) and every 4 weeks thereafter.

c Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated. Clinical chemistry assessments to be performed at each visit and when clinically indicated.

NB. All patients with an AST, ALT or bilirubin value (the latter ≥1.5 x ULN) at the time of the last dose of study drug should have a further liver chemistry profile (AST, ALT, bilirubin and alkaline phosphatase) performed 30 days (±7days) after permanent discontinuation of study drug.

Haematology and clinical chemistry tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. See Section 6.4.3 for when abnormal laboratory values should be reported as AEs.

All patients who have any Common Toxicity Criteria (CTC) Grade 3 or 4 laboratory values at the time of completion or discontinuation from study drug must have further tests performed

until the laboratory values have returned to CTC Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.1.2 Physical examinations

For timing of individual measurements refer to the study schedules (Table 1 [Screening and the Treatment Period]

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), genital/rectal and neurological systems.

Performance status will be assessed using WHO performance status.

8.1.3 Vital signs

- For timings of assessments refer to the study plans in Table 1 (Screening and the Treatment Period).
- Patients will be monitored with assessment of vital signs (BP, pulse, respiratory rate, temperature and oxygen saturation) at Screening and on the day of each infusion and in the follow-up period. On infusion days vital signs will all be taken before the infusion.
- Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.
- Additional recording of vital signs may be captured on an unscheduled vital signs eCRF and on the eCRF for AE/SAE where applicable. The date and time of collection and measurement will be recorded on the appropriate eCRF.
- The date and time of collection and measurement will be recorded on the appropriate eCRF.
- Temperature, respiratory rate and oxygen saturation: On infusion days, temperature, respiratory rate and oxygen saturation should be collected before the infusion.

8.1.4 Electrocardiograms

Clinical interpretation and management of patients for all ECGs will be done locally. The same method of assessment should be used throughout. Electrocardiograms will be recorded at 25 mm/sec. Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been rested in a supine position for at least 5 minutes and recorded while the patient remains in that position. In case of clinically significant ECG abnormalities, including a QTc value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

All ECGs should be assessed by the Investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically

significant abnormal finding, the Investigator will record it as an AE on the eCRF (see Section 6.4.3).

At Screening, mean QTc with Bazett's correction (QTc = QT/√R) must be <470 msec.

8.1.5 Weight

Weight of the patient will be measurement at alternate visits .Dose calculation will be as per weight of the patient.

8.2 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see section 8.3.3.

8.2.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.2.2 Time period and frequency for collecting AE and SAE information

Adverse events and SAEs will be collected from time of signature of informed consent, throughout the treatment period (20 weeks) and including the follow-up period (90 days after the last dose of study drug) in patients who discontinue before 20 weeks.

If a patient discontinues from study drug for reasons other than disease progression, drug-related SAEs must be captured until the patient is initiated on an alternate intervention or upto 90 days whichever is earlier.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.2.3 Follow-up of AEs and SAEs

During the course of the study all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary. Adverse event data collection

'The following variables will be collect for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- CTCAE grade 3 or more /Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- Select the appropriate as required: AE caused patient's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication'

8.2.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.2.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.2.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see sections 8.3.9 and 8.310.

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study drug and have been identified after the patient's inclusion in this study.

Deaths

All deaths that occur during the study, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as a SAE.
- Where death is not due (or not clearly due) to PD under study, the AE causing the death must be reported to the study monitor as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca/MedImmune Drug Safety or its representative within the usual timeframes.

8.3 Safety reporting and medical management

8.3.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.3.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study drug
- Pregnancies in the partner of male patients.

  If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

  Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.2.1 Maternal exposure

If any pregnancy occurs in course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 9.2.5) and within 30 days for all other pregnancies.The same timelines apply when outcome information is available.

8.3.3 Overdose

Use of durvalumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab and possible symptoms of overdose are not established.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose Case Report Form module.
- An overdose without associated symptoms is only reported on the Overdose CRF module

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.2.2. For other overdoses, reporting must occur within 30 days.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

No formal hypothesis testing will be conducted.

9.2 Sample size determination

The primary endpoint of the trial is to demonstrate the safety profile of durvalumab in routine clinical practice as assessed by the incidence of adverse events (AEs) (Serious and Non-serious AEs) observed during trial.

The study is intended to provide information regarding the safety profile for patients in India, and will contribute additional information to the overall safety profile of durvalumab. Due to the small sample size, this study should not be directly compared to the data from any other country. In this study, we expect to recruit 100 patients from Stage III unresectable NSCLC patients as per the Indian HA approved indication to satisfy the Imfinzi MA conditional approval.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All patients who sign the ICF
Safety analysis set	All patients assigned to Study treatment and who take at least 1 dose of IMP.

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalised before database lock and will describe the patient populations to be included in the analyses, and 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. Any deviations from this plan will be reported in the clinical study report.

10. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Agarwal JP, Hotwani C, Prabhash K, Munshi A, Misra S, Mathew A, et al. Optimizing treatment and analysis of prognostic factors for locally advanced nonsmall cell lung cancer in resource-limited population. Indian J. Cancer. 2016 Jan 1;53(1):96.

Baburao A, Narayanswamy H. Clinico-Pathological Profile and Haematological Abnormalities Associated with Lung Cancer in Bangalore, India. Asian Pac. J. Cancer Prev. 2016 Jan 11;16(18):8235–8.

Badwe R, D'Cruz A, Budrukkar A, editors. Treatment of Algorithms in Cancer.pdf [Internet]. Tata Memorial Centre, Mumbai; 2012 [cited 2018 Feb 28]. Available from: https://tmc.gov.in/tmh/PDF/Treatment%20of%20Algorithms.pdf

Bayman N, Blackhall F, McCloskey P, Taylor P, Faivre-Finn C. How can we optimise concurrent chemoradiotherapy for inoperable stage III non-small cell lung cancer? Lung Cancer Amst. Neth. 2014 Feb;83(2):117–25.

Blank C, Kuball J, Voelkl S, Wiendl H, Becker B, Walter B, et al. Blockade of PD-L1 (B7-H1) augments human tumor-specific T cell responses in vitro. Int. J. Cancer. 2006 Jul 15;119(2):317–27.

Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N. Engl. J. Med. 1985 Jun 20;312(25):1604–8.

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer. 2015 Mar 1;136(5):E359-386.

Jiwnani S, Laskar SG, Joshi A, editors. Evidence-Based mangement of Cancers in India-Guidelines for Lung and Esophagogastric Cancers [Internet]. Tata Memorial Centre, Mumbai; 2013 [cited 2018 Feb 28]. Available from: https://tmc.gov.in/tmh/PDF/Lung-Gastric.pdf

Kaur H, Sehgal IS, Bal A, Gupta N, Behera D, Das A, et al. Evolving epidemiology of lung cancer in India: Reducing non-small cell lung cancer-not otherwise specified and quantifying tobacco smoke exposure are the key. Indian J. Cancer. 2017 Jan 1;54(1):285.

Keegan P. Supplement Approval [Internet]. 2018 [cited 2018 Feb 28]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/761069Orig1s002ltr.pdf

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu. Rev. Immunol. 2008;26:677–704.

Malik PS, Malik A, Deo SV, Mohan A, Mohanti BK, Raina V. Underutilization of curative treatment among patients with non small cell lung cancer: experience from a tertiary care centre in India. Asian Pac. J. Cancer Prev. APJCP. 2014;15(6):2875–8.

Malik PS, Sharma MC, Mohanti BK, Shukla NK, Deo S, Mohan A, et al. Clinico-pathological profile of lung cancer at AIIMS: a changing paradigm in India. Asian Pac. J. Cancer Prev. APJCP. 2013;14(1):489–94.

Mandal SK, Singh TT, Sharma TD, Amrithalingam V. Clinico-pathology of lung cancer in a regional cancer center in Northeastern India. Asian Pac. J. Cancer Prev. APJCP. 2013;14(12):7277–81.

Ministry of Health & Family Welfare, Government of India. The Drugs and Cosmetics Rules, 1945 [Internet]. Dec 21, 1945. Available from: http://cdsco.nic.in/writereaddata/Drugs&CosmeticAct.pdf

Mohan A, Latifi AN, Guleria R. Increasing incidence of adenocarcinoma lung in India: Following the global trend? Indian J. Cancer. 2016 Jan 1;53(1):92.

Murali AN, Radhakrishnan V, Ganesan TS, Rajendranath R, Ganesan P, Selvaluxmy G, et al. Outcomes in Lung Cancer: 9-Year Experience From a Tertiary Cancer Center in India. J. Glob. Oncol. 2017 Jan 11;3(5):459–68.

National Cancer Registry Programme. Consolidated Report of Hospital Based Cancer Registries : 2007-2011 [Internet]. Bangalore, India: Indian Council of Medical Research; 2013 Sep. Available from: http://www.ncrpindia.org/ALL_NCRP_REPORTS/HBCR_REPORT_2007_2011/

National Cancer Registry Programme. Trends over time for all sites and on selected sites of cancer & projection of burden of cancer. Bengaluru, India.: Indian Council of Medical Research; 2016a Mar. Report No.: Three-Year Report of Population Based Cancer Registries 2012-2014.

National Cancer Registry Programme. Consolidated Report of Hospital Based Cancer Registries : 2012-2014 [Internet]. Bangalore, India: Indian Council of Medical Research; 2016b Mar. Available from: http://www.ncrpindia.org/ALL_NCRP_REPORTS/HBCR_REPORT_2012_2014/

National Comprehensive Cancer Network. NCCN Guidelines®- Non-Small Cell Lung Cancer, Version 3.2018 [Internet]. 2018 [cited 2018 Feb 28]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Noronha V, Dikshit R, Raut N, Joshi A, Pramesh CS, George K, et al. Epidemiology of lung cancer in India: Focus on the differences between non-smokers and smokers: A single-centre experience. Indian J. Cancer. 2012 Jan 1;49(1):74.

Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int. Immunol. 2007 Jul;19(7):813–24.

Pazdur R. BLA Approval [Internet]. 2017 [cited 2018 Feb 28]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/761069Orig1s000ltr.pdf

Rajappa S, Gundeti S, Talluri MR, Digumarti R. Chemotherapy for advanced lung cancer: A 5-year experience. Indian J. Cancer. 2008 Jan 1;45(1):20.

Singh N, Aggarwal AN, Gupta D, Behera D, Jindal SK. Quantified smoking status and non-small cell lung cancer stage at presentation: Analysis of a North Indian cohort and a systematic review of literature. J. Thorac. Dis. 2012 Jan 8;4(5):474–84.

Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and Characterization of MEDI4736, an Antagonistic Anti-PD-L1 Monoclonal Antibody. Cancer Immunol. Res. 2015 Sep;3(9):1052–62.

Subramanian J, Velcheti V, Gao F, Govindan R. Presentation and Stage-Specific Outcomes of Lifelong Never-smokers with Non-small Cell Lung Cancer (NSCLC). J. Thorac. Oncol. 2007 Sep 1;2(9):827–30.

Tiwana MS, Lee HN, Saini S, Verma SK, Gupta M, Gupta M, et al. Outcomes of patients with unresected stage III and stage IV non-small cell lung cancer&58; A single institution experience. Lung India. 2013 Jan 1;30(3):187–92.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH-GCP guidelines and New Drug & Clinical Trial Rules, 2019where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date and time the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorised representative.

A 4 Data protection

Each patient will be assigned a unique identifier by the sponsor. Any patient records or data sets transferred to the sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com, http://www.clinicaltrials.gov and CTRI (http://ctri.nic.in/Clinicaltrials) as will the summary of the study results when they are available. The clinical trial summary of study results may also be available on other websites according to the regulations of India in which the study is conducted.

A 7 Data quality assurance

All patient data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for

verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in- patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 For oncology studies, the following may be used instead:

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. 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 a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same

pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not stored as instructed
- Examples of events that **do not** require reporting as medication errors in clinical studies:
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

C 2 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

This section is not applicable as no biological samples shall be transported out of the study sites during the course of study.

Appendix D: Recommended Treatment Modifications for Durvalumab and Management Recommendations

Adverse Reactions	Severity[a]	DURVALUMAB Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified
Immune-mediated pneumonitis	Grade 2	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	1 to 4 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated hepatitis	Grade 2 with ALT or AST >3-5xULN and/or total bilirubin >1.5-3xULN	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with AST or ALT ≤8xULN or total bilirubin ≤5xULN		
	Grade 3 with AST or ALT >8xULN or total bilirubin >5xULN	Permanently discontinue	
	Concurrent ALT or AST >3xULN and total bilirubin >2xULN with no other cause		
Immune-mediated colitis or diarrhea	Grade 2	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or

Adverse Reactions	Severity[a]	DURVALUMAB Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified
	Grade 3 or 4	Permanently discontinue	equivalent followed by a taper
Immune-mediated endocrinopathies: Hyperthyroidism	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Immune-mediated endocrinopathies: Hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated endocrinopathies: Adrenal insufficiency, Hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated endocrinopathies: Type 1 diabetes mellitus	Grade 2-4	Withhold dose until clinically stable	Initiate treatment with insulin as clinically indicated
Immune-mediated nephritis	Grade 2 with serum creatinine >1.5-3x (ULN or baseline)	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with serum creatinine >3x baseline or >3-6xULN; Grade 4 with serum creatinine >6xULN	Permanently discontinue	
Immune-mediated rash or dermatitis	Grade 2 for >1 week	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Immune-mediated myocarditis	Grade 2	Withold dose[c]	Initiate 2 to 4 mg/kg/day prednisone

Adverse Reactions	Severity[a]	DURVALUMAB Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified
	Grade 3 or 4, or any Grade with positive biopsy	Permanently discontinue	or equivalent followed by a taper
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose[d]	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	May consider pre-medications for prophylaxis of subsequent infusion reactions
	Grade 3 or 4	Permanently discontinue	

[a]Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
[b] Based on severity of the adverse reactions, Durvalumab should be withheld and corticosteroids administered. Consider increasing dose of corticosteroids and/or using other systemic immunosuppressants if there is worsening or no improvement. Upon improvement to ≤Grade 1, corticosteroid taper should be initiated and continued over at least 1 month.
After withhold, Durvalumab can be resumed if the adverse reactions improved to ≤Grade 1 and the corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day.
[c] If no improvement within 3 to 5 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month, after which Durvalumab can be resumed based on clinical judgment.
[d] Permanently discontinue Durvalumab if adverse reaction does not resolve to ≤Grade 1 within 30 days or if there are signs of respiratory insufficiency.

Appendix E: Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
CRF	case report form (electronic/paper)
CSA	clinical study agreement
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	discontinuation of investigational product due to adverse event
DNA	deoxyribonucleic acid
EC	ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IVRS	interactive voice response system
IWRS	interactive web response system
LSLV	last subject last visit
LIMS	laboratory information management system
OAE	other significant adverse event
PI	principal investigator
SAE	serious adverse event
SAP	statistical analysis plan
WBDC	web based data capture

ASTRAZENECA SIGNATURE(S)

A prospective, multicenter, Phase-IV clinical trial to assess safety Durvalumab in Indian adult patients with locally advanced, unresectat non-small cell lung cancer (NSCLC)

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

I agree to the terms of this Study protocol.

AstraZeneca representative

Oct 12, 2022

Date (Day Month Year)

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