PACIFIC-Real World

First real-world data on unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy

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<td>EAP</td>
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<td>ECOG</td>
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<td>Epidermal Growth Factor Receptor</td>
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<td>Global Medical Development</td>
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<td>ICF</td>
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<td>IEC</td>
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<td>ILD</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>MA</td>
<td>Market Authorisation</td>
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<tr>
<td>MC</td>
<td>Marketing Company</td>
</tr>
<tr>
<td>MDT</td>
<td>Multi-Disciplinary Team</td>
</tr>
<tr>
<td>MEOR</td>
<td>Medical Evidence Observational Research</td>
</tr>
<tr>
<td>MPEAP</td>
<td>Multiple Patient Early Access Programme</td>
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<tr>
<td>NPS</td>
<td>Named Patient Supply</td>
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<td>NSCLC</td>
<td>Non-Small Cell Lung Cancer</td>
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<tr>
<td>OBU</td>
<td>Oncology Business Unit</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
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A subgroup of this global study. The PACIFIC-LIKE cohort will be as similar as possible to the PACIFIC trial population in a real world setting, based on available data, and will be further defined in the SAP once study enrolment has completed. The PACIFIC trial included unresectable stage III NSCLC patients with a performance status (0, 1) who had not progressed following a platinum-based concurrent chemoradiotherapy and who were treated with durvalumab within 42 days after end of chemoradiotherapy.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<td>PACIFIC-LIKE</td>
<td>A subgroup of this global study. The PACIFIC-LIKE cohort will be as similar as possible to the PACIFIC trial population in a real world setting, based on available data, and will be further defined in the SAP once study enrolment has completed. The PACIFIC trial included unresectable stage III NSCLC patients with a performance status (0, 1) who had not progressed following a platinum-based concurrent chemoradiotherapy and who were treated with durvalumab within 42 days after end of chemoradiotherapy.</td>
</tr>
<tr>
<td>PD-R</td>
<td>PACIFIC-Real World</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive Disease</td>
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<tr>
<td>PD-1</td>
<td>Programmed Cell Death Protein 1</td>
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<tr>
<td>PD-L1</td>
<td>Programmed Cell Death Ligand 1</td>
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<td>PFS</td>
<td>Progression-Free Survival</td>
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<tr>
<td>PS</td>
<td>Performance Status</td>
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<tr>
<td>QC</td>
<td>Quality Control</td>
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<tr>
<td>RT</td>
<td>RadioTherapy</td>
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<tr>
<td>RWE</td>
<td>Real World Evidence</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<tr>
<td>sCRT</td>
<td>Sequential ChemoRadioTherapy</td>
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<tr>
<td>TNM</td>
<td>Tumour Node Metastasis</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>WBDC</td>
<td>Web Based Data Capture</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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### RESPONSIBLE PARTIES

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<tr>
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<tr>
<td>Alyssa Klein</td>
<td>Director, Epidemiology and Real World Evidence</td>
<td>Epidemiologist</td>
<td>OBU</td>
<td><a href="mailto:Alyssa.Klein@astrazeneca.com">Alyssa.Klein@astrazeneca.com</a></td>
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PROTOCOL SYNOPSIS

PACIFIC-Real World

First real-world data on unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy

Background/Rationale:

Following the presentation of PACIFIC results, AstraZeneca decided to open an early access programme (EAP) and provide ethical access to durvalumab for patients who have completed chemoradiotherapy (CRT) for unresectable stage III non-small cell lung cancer (NSCLC) and who, in their treating physicians’ opinion, have an unmet clinical need which cannot be treated with approved and commercially available drugs.

The EAP is a prospective, open-label, expanded clinical access programme which was designed to provide treatment access to durvalumab (IMFINZI) for patients with locally advanced, unresectable NSCLC (stage III) who have not progressed following chemoradiation.
To further understand the rapidly changing real-world treatment and clinical outcomes in this unresectable stage III NSCLC patient population, we designed PACIFIC-Real World (abbreviated in PACIFIC-R) study to enrol patients who have received durvalumab as part of the EAP. Country participation and patient recruitment to the study will be when the EAP enrolment period has closed within that country.

This study is aimed to provide the first real-world data on the use of durvalumab in this NSCLC patient population treated outside a clinical trial.

**Primary Objectives:**

To assess the effectiveness of durvalumab in a real-world setting by evaluating the following:

- Progression-free survival (PFS) following initiation of durvalumab received from the index date (date of the first dose of durvalumab) to the date of investigator-determined disease progression or death (if no progression) or the end of follow-up

- Overall survival (OS) following durvalumab received from the index date to death or end of follow-up.

**Secondary Objectives:**

- To describe adverse events of special interest (AESIs) leading to temporary treatment interruption, permanent discontinuation of durvalumab or which require interventions of concomitant use of corticosteroids, immunosuppressants and/or endocrine therapies

- To evaluate the time to endpoint outcomes (OS and PFS) in patient subset populations including a population similar to that enrolled in the PACIFIC trial (PACIFIC-LIKE cohort), as the real-world population of patients treated in the EAP may actually be different. PACIFIC-LIKE will be a subgroup of this global study. The PACIFIC-LIKE cohort will be defined as a population similar to the PACIFIC trial population in a real-world setting and will be further defined in the statistical analysis plan (SAP) once study enrolment has completed. The PACIFIC trial included unresectable stage III NSCLC patients with a performance status (PS) (0, 1) who have not progressed following a concurrent platinum-based chemoradiotherapy (cCRT) and who were treated with durvalumab within 42 days after end of CRT.

- To describe patients’ clinical characteristics, details on durvalumab treatment, previous and subsequent treatment strategies, healthcare resource utilisation and other intermediate time to event outcomes.

**Methods:**
Observational Study Protocol  
Study Code D4194R00005  
Version 1  
Date 7 September 2018

**Study Design:** The study is an observational review of medical records of patients diagnosed with unresectable stage III NSCLC in Australia, Belgium, France, Germany, Italy, Israel, the Netherlands, Switzerland and the United Kingdom (UK). Physicians having treated patients in the EAP will be asked to recruit these patients to have their data abstracted from their medical records. Data will only be collected from routine clinical care.

**Data Source(s):** Centre staff will extract de-identified data from patient’s medical charts. All collected data will be retrospective at time of extractions.

**Study Population:** Patients diagnosed with an unresectable stage III NSCLC, having not progressed after a CRT and who have received at least one dose of durvalumab following the CRT within the EAP will be the target population.

**Exposure(s):** Clinical characteristics, details of treatments (previous therapies, subsequent therapies), durvalumab exposure and serious AESIs.

**Primary Outcome(s):** PFS and OS.

**Sample Size Estimations:** A target of 1000 to 1200 patients is requested in the study.

**Statistical Analysis:** All analyses will be descriptive; they will be summarised by displaying mean values, medians ranges and standard deviations for continuous variables, frequency distributions for categorical variables. Time to event outcomes will be described using the Kaplan-Meier method. Medians, event rates and 95% confidence intervals will be displayed. Results will be presented globally, regionally and at country level where feasible.

**AMENDMENT HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Section of study protocol</th>
<th>Amendment or update</th>
<th>Reason</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
Observational Study Protocol
Study Code D4194R00005
Version 1
Date 7 September 2018

MILESTONES

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Planned date</th>
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<tbody>
<tr>
<td>Protocol final</td>
<td>14 August 2018</td>
</tr>
<tr>
<td>First data extraction</td>
<td>Q4 2018 to Q2 2019</td>
</tr>
<tr>
<td>Last data extraction</td>
<td>Q2-Q3 2023</td>
</tr>
<tr>
<td>Database lock final</td>
<td>Q4 2023</td>
</tr>
<tr>
<td>Final manuscript</td>
<td>Mid 2024</td>
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1. BACKGROUND AND RATIONALE

1.1 Background

Lung cancer is the leading cause of cancer deaths in men and the second after breast cancer in women. In 2012, there were an estimated incidence of 312,600 (Globocan 2012) cases diagnosed in Europe of which 68% were men and with a total of 267,700 deaths. Lung cancer incidence in women is steadily increasing whereas it has been stable in men since 1980. The characteristics of lung cancer have changed in the last 15 years (sex, age, histological subtypes). Tobacco is still the leading cause but pollution and asbestos are other causes which are now better known.

Diagnosis of lung cancer has also improved with the use of positron emission tomography (PET) and computed tomography (CT) scans in routine practice for the staging, and the development of molecular methods to detect gene mutations.

Lung cancer is classified in different categories and non-small cell lung cancer (NSCLC) represents between 80-85% of lung cancer diagnoses. Almost two-thirds of NSCLCs are diagnosed initially at metastatic stage and around 40% of those at early stage relapse to a metastatic stage.

Stage III represents between 25-30% of NSCLCs and the majority of them are unresectable. The role of curative intent radiotherapy (RT) is well established in this stage (ESMO 2017). Currently, the standard treatment is concurrent chemoradiotherapy (cCRT); this strategy is especially beneficial for patients with good performance status (PS), without important comorbidities and younger than 70 years. Platinum-based chemotherapy is administered at cytotoxic doses. For other patients, sequential CRT (sCRT), chemotherapy or RT alone, as palliative treatment, are the alternative strategies, and according to some countries these strategies are at least as often prescribed as cCRT.

There remain also a lot of questions for those patients with cCRT: the benefit of induction chemotherapy before the CRT phase is not proven, the modalities of radiation in terms of doses and fractionations are not either.
Recent improved results in this setting appear to be partially linked to better patient selection through optimisation of diagnostic imaging, new radiation modalities, and subsequent lines of treatment. Despite the progress in therapeutic strategies, overall survival (OS) of stage III NSCLC is poor.

AstraZeneca is currently developing an anti-programmed cell death ligand 1 (PD-L1) compound, durvalumab (IMFINZI®), in multiple tumour types, including unresectable stage III NSCLC. The PACIFIC study (NCT02125461) is an ongoing, randomised, double-blind, placebo-controlled, multi-centre, Phase 3 study to evaluate the efficacy and safety of durvalumab compared with placebo, as sequential therapy in patients with locally advanced, unresectable stage III NSCLC who have not progressed following definitive, concurrent platinum-based chemotherapy and thoracic RT. The planned interim analysis of progression-free survival (PFS) was conducted after 371 events (80%) of the target 458 events were observed. Based on the review of the interim analysis, the study was unblinded for PFS and safety. Since the study achieved statistical significance based on this analysis, this will now be considered as the final PFS analysis. The first interim analysis of OS has recently been announced as positive. However, currently, results are not public and patient follow-up for OS continues for further data maturity.

The PACIFIC (Antonia 2017) study enrolled a total of 713 patients randomised in a 2:1 ratio to receive either durvalumab 10 mg/kg every two weeks (476 patients) or placebo (237 patients). At the time of the data cut-off date of 13 February 2017 for this interim dataset, treatment was ongoing in 30 (6.3%) patients in the durvalumab group and 12 (5.1%) patients in the placebo group. In this pre-planned interim analysis of PFS, durvalumab treatment demonstrated a statistically significant PFS benefit compared with placebo (hazard ratio [HR]: 0.52; p-value less than 0.0001). Durvalumab treatment resulted in a 48% reduction in the overall risk of progression or death. Median PFS was 16.8 months in the durvalumab group and 5.6 months in the placebo group. The magnitude of PFS improvement, 11.2 months with durvalumab treatment, was substantial and clinically meaningful. The early separation of Kaplan-Meier estimates favouring durvalumab indicates the potential for an early PFS benefit with durvalumab treatment. The Kaplan-Meier estimates at 12 months and 18 months indicated that the PFS benefit with durvalumab is sustained over time.

The PACIFIC study findings represent a landmark change in the treatment strategy of locally advanced, unresectable stage III NSCLC patients whose disease had not progressed after platinum-based CRT. The data demonstrate that durvalumab therapy results in a statistically significant and clinically meaningful prolongation of PFS compared with placebo. Durvalumab is a promising new therapeutic option in this setting.

Following the presentation of PACIFIC results, AstraZeneca decided to open a clinical access programme and provide ethical access to durvalumab for patients who meet the eligibility criteria, and who, in their treating physicians’ opinion, have an unmet clinical need which cannot be treated with approved and commercially available drugs.

The early access programme (EAP) is a prospective, open-label, expanded clinical access programme which was designed to provide treatment access to durvalumab (IMFINZI) for patients with locally advanced, unresectable NSCLC (stage III) who have not progressed following platinum-based CRT.
According to the participating countries and local regulations, the EAP uses different names which includes the Named Patient Supply (NPS) programme and the local Multiple Patient Early Access Programme (MPEAP) such as the Authorisation for Temporary Use (ATU), Early Access to Medicines Scheme (EAMS), and the Cohort Compassionate-Use Programme (CUP).

Patients are treated globally as part of this programme with durvalumab 10 mg/kg via intravenous (IV) infusion every two weeks until disease progression or unacceptable toxicities, except for French patients in ATU where durvalumab is prescribed up to 12 months.

As in the PACIFIC trial, patients must have completed a platinum-based chemotherapy concurrently or sequentially with radiation therapy without evidence of disease progression. It was preferred that treatment starts within approximately three months from end of radiation in order for patients to recover from treatment-related toxicities and/or for treating physicians to have adequate time to perform the baseline disease assessment.

There was no fixed maximum duration for durvalumab treatment. Treatment with durvalumab continues until the physician determines that it is in the patient’s best interest to stop therapy. Programme drug should be discontinued if there is progression of disease (PD) (unless the physician considers the patient is receiving clinical benefit from programme drug), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue programme drug occur.

No specific efficacy endpoints or other information about participants are collected within this programme. The treating physician was responsible for informing the Ethics Committee and/or the Regulatory Authority of the serious adverse events (SAEs) as per local requirements. The programme has been opened and completed in a staggered fashion, country by country, ending when durvalumab becomes commercially available in each country.

1.2 Rationale

Due to the prognosis of these patients and the great variability in the real-world multidisciplinary treatment approaches, there remains an important need to continue further observational research on the durvalumab immunotherapy outcomes and resources used for these population.

The EAP constitutes the first and unique subset of patients with cancer in whom use of durvalumab in a non-clinical trial, in conditions close to “real-world” setting can be studied.

In order to further understand the treatment landscape of unresectable stage III NSCLC patients in a real-world setting, the study will include patients who have been treated within the durvalumab in the EAP. This study is aimed to provide the first real-world data for the use of durvalumab in this NSCLC patient population treated outside a clinical trial.

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objectives

To assess effectiveness of durvalumab in patients treated in real-life settings by evaluating:
• PFS defined as time from the index date (date of the first dose of durvalumab) to the date of investigator-determined disease progression or death (if no progression) or the end of follow-up

• OS following durvalumab regimen received from the index date to death or end of followup.

2.2 Secondary Objectives

• To describe adverse events of special interest (AESIs) leading to treatment temporary interruption or permanent discontinuation of durvalumab, or which require interventions of concomitant use of corticosteroids, immunosuppressants and/or endocrine therapies

• To evaluate the time to endpoint outcomes (OS and PFS) in patient subset populations# including a population similar to that defined by the PACIFIC trial (PACIFIC-LIKE cohort*), as the real-world population of patients treated in the EAP may actually be different.

*PACIFIC-LIKE will be a subgroup explored in this global study. The PACIFIC-LIKE cohort will be as similar as possible to the PACIFIC trial population in a real-world setting, based on available data. The characteristics will be further defined in the statistical analysis plan (SAP). The PACIFIC trial included unresectable stage III NSCLC patients with a PS of 0, 1 who have not progressed following a platinum-based cCRT and who are treated with durvalumab within 42 days after end of CRT.

#Subgroup definitions are described in section 4 and will be presented in detail in the final SAP, once patient enrolment has been completed and feasibility has been determined.

• To estimate time and sites of disease progression or relapse in metastatic setting, i.e., time to relapse in brain

• To describe details on durvalumab treatment including: duration of treatment, time to start durvalumab after completion of CRT, temporary treatment interruptions for AESIs, reasons for treatment discontinuation (prior to 12 months versus after 12 months), concomitant use of corticosteroids, immunosuppressants, endocrine therapies and antibiotics

• To describe demographic (age, sex, smoking status) and clinical (stage, World Health Organisation [WHO] PS, NSCLC histology, response [or non-progression] to CRT, immuno-histochemistry molecular testing) characteristics of stage III unresectable NSCLC patients treated with durvalumab

• To describe previous cCRT strategy including duration of chemotherapy, number of cycles and type of chemotherapy, and details of RT (total dose, number of fractions, type of RT, chest organ doses)
• To describe the baseline staging status (‘de novo’ versus ‘relapse’ patients), diagnostic Tumour Node Metastasis (TNM) classification edition used, staging, testing characteristics of these patients in this setting and physicians’ and hospitals’ characteristics

• To further assess subsequent treatments pattern at the time of disease progression including duration of therapy, type of therapy (targeted therapy, chemotherapy, immunotherapy)

• To explore healthcare resource utilisation while on durvalumab treatment.

2.3 Exploratory Objectives

• To assess the impact of previous RT on study outcomes and on occurrence of pneumonitis where applicable. Details of previous RT that is recorded mainly by radiation oncologists and not the physician who prescribed durvalumab in the EAP will be collected locally in some countries.

The RT data collection and analysis will be handled either via an ancillary study or a collaborative study. It is not part of this protocol. However, data from the main study will be merged with the RT data where this collection is performed.

Additional country-specific exploratory objectives may be included in the SAP, pending study recruitment and feasibility.

3. METHODOLOGY

3.1 Study Design – General Aspects

This is a non-interventional/observational cohort of NSCLC unresectable stage III patients treated with durvalumab.

The study will be carried out as a retrospective review of established medical records for a subset of unresectable stage III patients treated with durvalumab within the EAP.

The EAP includes the NPS programme and the local MPEAP such as the ATU, EAMS, and the CUP. Patients will be eligible to enter in the study if they were included in the EAP between September 2017 (start of EAP) and the end date of EAP enrolment (national reimbursement or market authorisation [MA]).

As per regulatory requirements, once a country has closed EAP enrolment, it will be eligible to participate in this study. It is recommended that the study sites start the enrolment in this study as close to the end date of EAP enrolment as possible to minimise loss to follow-up.

France, Germany, Italy, Switzerland and UK have their EAP programmes end within a period of zero to three months after MA and will enter in the study first. Australia, Belgium, Israel and the Netherlands will be eligible to participate as well and are expected to enter in the study in mid-end 2019 (at their planned end of EAP) (see Table 1 and Figure 1).
For Spain, data collection will be performed in a separate study conducted by the local marketing company (MC). Due to regulatory restrictions on data collection which allows one extraction only, the data will be merged into the study dataset at time of analysis and included in the PFS analysis (planned analysis date Q3 2020).

Other countries participating in the EAP could join the study if applicable.

**Table 1. List of planned end dates of EAP enrolment.**

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<thead>
<tr>
<th>Country</th>
<th>Planned EAP Enrolment End Dates*</th>
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<tr>
<td>France</td>
<td>December 2018</td>
</tr>
<tr>
<td>Germany</td>
<td>November 2018</td>
</tr>
<tr>
<td>Italy</td>
<td>December 2018</td>
</tr>
<tr>
<td>UK</td>
<td>May 2019</td>
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<td>Australia</td>
<td>December 2019</td>
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<td>Belgium</td>
<td>March 2019</td>
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<td>Israel</td>
<td>September 2019</td>
</tr>
<tr>
<td>Netherlands</td>
<td>May 2019</td>
</tr>
<tr>
<td>Switzerland</td>
<td>September 2018</td>
</tr>
</tbody>
</table>

MA: Market Authorisation.
*Estimates, actual dates determined by the actual MA that are dictated by local health regulatory authorities.

**Figure 1. Study Design.**

The proposed timelines for countries are based on the closing the EAP due to end of enrolment or due to MA. End of EAP enrolment or MA will serve as the trigger for this study and all attempts will be made to enrol patients in this study as soon as possible of the EAP enrolment ending.

The chart abstractions will occur at specified intervals up to five years after the patient has enrolled in the EAP/first dose of durvalumab. A target of four (maximum five) chart extractions is anticipated for each participant. Dates may be adjusted based on local market ethics processes or patient enrolment.

- First chart extraction will be used to determine which patients meet the inclusion/exclusion criteria for the study and will retrospectively collect all data from diagnosis of stage III unresectable NSCLC and the durvalumab start date (index date). Planned dates are Q4 2018-Q2 2019
- The second chart extraction will be triggered at time of estimated maturity of PFS data to provide an accurate measure of the PFS outcome. Planned dates are between Q1-Q2 2020
- The third chart extraction will be triggered at time of estimated maturity of OS data to provide an accurate measure of the OS outcome. Planned dates are around Q4 2021
- The fourth and fifth chart extractions will occur approximately 3-years and 5-years after enrolment in the EAP, planned for Q2 2022, and Q3 2023
- The dates for the second through fifth chart abstractions may be adjusted, pending data availability.
The estimated PFS and OS maturity will be calculated from the actual patient index dates (date of first dose of durvalumab) and any available data on PFS and OS observed in the first extraction together with the distribution of PFS and OS observed in the PACIFIC trial. See statistical section (section 5) for details.

For countries with an EAP enrolment end date in 2019, the chart extractions will be adjusted accordingly. It is possible that first extraction may overlap with the planned extraction at PFS for these countries. In that case, the chart extractions could be combined (e.g., chart abstraction 1 and 2).

3.2 Data Source(s)

The study is designed for collection of secondary data. All clinical data will be extracted from medical records of eligible patients, and collected retrospectively. However, not all extracted data will be available at time of regulatory submission.

Any physicians and their affiliated sites who previously participated in the EAP, will be invited to participate in the PACIFIC-R study. Representativeness of each type of hospitals (academic, community, city, rural) will be checked to ensure correct participation of all prescribers of stage III NSCLC patients. To ensure that participants in PACIFIC-R mirror the general characteristics of their corresponding market, weighting (or some other analytical measure) may be used to ensure that participants in this study are representative of the stage III unresectable NSCLC population.

If the physician agrees to participate in the study, s/he will invite any patient who has been treated with at least one dose of durvalumab in the EAP, within the selection period. Patients who have discontinued treatment with durvalumab during the EAP will still be eligible for inclusion in the study. All participating patients will provide informed consent. Patients who die during the EAP are eligible to enter in the study when local laws allow for a consent waiver.

Once the physician has the patient’s (or next of kin’s, if requested by local regulation) signed consent form, s/he will be able to abstract from medical dossier the requested information and enter the data in the electronic case report form (eCRF).

At least four chart abstractions are planned:

- The first extraction, at time of the patient consents to participate in this study. Data collected, depending on availability, will include as minimum: previous diagnosis and treatment, staging and completion of CRT information, clinical characteristics and the start date of durvalumab (index date). Healthcare resource utilisation may also be included.

- The second extraction, triggered at a time when it is expected that median PFS can be estimated with an acceptable precision, with all data from previous extraction including durvalumab administration details, interruption, discontinuation, AESIs and PFS data.
• The third extraction, triggered at a time when it is expected that median OS can be estimated with an acceptable precision, with all data from second extraction with subsequent treatments prescription and OS data

• The fourth and fifth extractions will be triggered at the time of 3-years and 5-years after enrolment in the EAP.

3.3 Study Population

The study will include all patients who have participated in the EAP between 1 September 2017 up to end of EAP enrolment or MA + a maximum of three months (estimated as maximum to 30 December 2018) (whichever occurs earlier), and have received at least 1 dose of durvalumab prior to the study start. Patients may participate in other clinical trials during this follow-up period.

To enter in the EAP, patients must have completed a platinum-based chemotherapy concurrently or sequentially with radiation therapy without evidence of disease progression. It is preferred that treatment starts within approximately three months from end of radiation for patients to recover from treatment-related toxicities and/or for treating physicians to have adequate time to perform the baseline disease assessment. There is no fixed maximum duration for durvalumab treatment. Treatment with durvalumab continues until the physician determines that it is in the patient’s best interest to stop therapy.

It is to note that France has had a different selection process for entering patients in their EAP called ATU:

• With a treatment duration of maximum 12 months whereas other countries could continue up to progression of the disease

• Previous sequential therapy was not allowed in the ATU

• Patients with Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) PS equal to 2 were not allowed in the ATU.

A non-inclusion register recording information on patients who refuse to participate in the study or on sites who are not contacted for participating in the study will be kept during the inclusion period. This register will ensure the representativeness of the patients included, by comparing their main characteristics with those of patients not included.

Non-inclusion register will list all patients who have received durvalumab within the selection period from 01 September 2017 up to end of EAP enrolment or MA + a maximum of three months (whichever occurs earlier) and have received at least 1 dose of durvalumab but who are not included in the study, whether or not they are still treated with durvalumab. The register will include the following information: age, sex, treatment with durvalumab ongoing (yes/no). This register will be constituted from a line listing of patients who received durvalumab within the EAP provided by AstraZeneca records during the EAP. Additionally, reason for nonparticipation and PS status will be collected by the site if possible.

It is estimated that around 400 sites enrol patients from the following countries: Australia, Belgium, France, Germany, Italy, Israel, the Netherlands, Switzerland and the UK. Any
physicians and their affiliated sites who previously participated in the EAP, will be invited to participate in the PACIFIC-R study. The list of all physicians who participated within the EAP will be shared with the study scientific committee. For sites not willing to participate in the study, the reason why will be requested.

Based on the current recruitment and enrolment in the EAP for the above countries, an estimated 1500 to 2000 patients are expected to be enrolled in the EAP during the patients’ selection period. A 30% attrition rate from the EAP has been used to estimate the sample size for this study, meaning 30% of patients from the EAP may not enter in Pacific-R. AstraZeneca expects a reasonable sample size of 1400 patients enrolled in the study and 1000 to 1200 patients evaluable for the two primary study objectives. If the target of 1000 to 1200 patients is not reached, discussion will take place to decide if the current patients’ selection period could be extended in order to attain the requested target.

### 3.4 Inclusion Criteria

Patients should fulfil the following criteria:

1. Written informed consent or any locally required authorisation obtained from the patient prior to performing any protocol-related procedures
2. Age \( \geq 18 \) years at time of study entry or adult according to each country regulations for age of majority
3. Patients must have histologically or cytologically documented diagnosis of NSCLC with a locally advanced, or locally recurrent, unresectable (stage III) disease (according to American Joint Committee on Cancer [AJCC] lung cancer edition 7 or 8)
4. Patients must have been enrolled in one of the durvalumab EAPs

Patients must have been treated with at least one dose of durvalumab within the EAP prior to the study entry and between start of EAP in the country, from September 2017 or later up to end of EAP enrolment or MA + three months (estimated as maximum to 30 December 2018) (whichever occurs earlier).

Patients who die during the EAP are eligible to enter in the study when local laws allow for a consent waiver, if all other inclusion/exclusion criteria are met.

### 3.5 Exclusion Criteria

Patients should not be enrolled if the exclusion criterion as follows is fulfilled.

1. Patients treated with durvalumab in clinical studies prior to the index date (first dose of durvalumab received within the EAP).
3.6 Participant Follow-up

Patients will be followed from the index date (first dose of durvalumab received within the EAP) to the end of follow-up (date of death for patients, withdrawal from study, loss to follow-up, or end of study period).

In the event a patient is lost to follow-up in the medical records, his/her vital status at index date and date of death should be obtained by the site personnel from publicly available resources.

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

The PFS date will be based on the investigator’s judgment and the documentation of progression according to Response Evaluation Criteria In Solid Tumors (RECIST) is not required. During the course of routine clinical practice, progression can be based on radiological evaluation or clinical judgement, or other measure. As such, the progression date may not always be included in the medical charts; in that case, the date of next subsequent systemic treatment, information which should be present in all dossiers, is used as a ‘proxy’ to replace the missing information. This approach is typically used in and as for other retrospective studies, though it could introduce a measurement bias in the analysis due to heterogeneity.

Only specific concurrent therapies (e.g., steroids, immunosuppressant and/or hormone replacement therapy) that are prescribed during the occurrence of an AESI will be collected, antibiotics will also be collected as medications which could decrease the efficacy of immune check point inhibitors.

The definitions are the following (to be further detailed in the SAP):

- cCRT is defined as radiation administered while a patient is receiving chemotherapy. A patient may complete radiation therapy before, during or after the platinum-based chemotherapy

- sCRT is defined as radiation administered within 3 months of the last dose of platinum-based chemotherapy. Given the potential permutations of treatment algorithms in a realworld setting, additional definitions may be considered and explored using sensitivity analyses

- Induction chemotherapy is any chemotherapy administered prior to start of radiotherapy
- Consolidation chemotherapy is a chemotherapy administered after end of radiotherapy
- Local recurrence can be defined as a recurrence in the thorax radiation field
- Distant relapse or distant metastatic relapse is defined as a relapse with a new metastatic site outside of radiation field.

Whether an unresectable stage III patient receives cCRT or sCRT, depends on health, age, PS, tumour volume and comorbidities. The proposed categories for each of the variables listed below may be adjusted or pooled as needed, pending data availability and requested analyses. The categories will be described in detail in the SAP.
• Age: The threshold of 70 or 75 years is used to define the elderly population (Colle 2012, De Ruyscher 2009). Age will be displayed as a continuous variable and by the following categories as well: ≤ 70 years, > 70 years and ≤ 75 years, > 75 years

• ECOG/WHO PS: The threshold of PS 2 is used to define the frail population and to take the decision to prescribe sCRT in several European countries. PS will be displayed for each category (0,1,2,3,4) and pooled as (0,1), and (≥2)
• The crossway of age * PS is used also to determine if the patient can benefit from previous cCRT or sCRT and will be displayed as follows: ≤ 70 years, [70, 75] years, >75 years) * PS in categories (0,1), (≥2)

• Longest dimension of primary tumour and lymph nodes involvement will be displayed as a continuous variable and by the following categories:<30 mm, [30,50] mm, [50,70] mm, >70 mm

• Comorbidities: patients with at least one comorbidity and/or another cancer history will be considered as a group

• External factors or hospitals characteristics could also influence the management of treatment strategy in this setting and will be reported as follows:
  o Multi-Disciplinary Team involved: pneumologist/oncologist/radiation oncologist
  o Hospital characteristics: general hospital, university hospital, private centre, specialised cancer centre
  o In-house RT, external RT facility (public, private)

• For RT, the total dose in Gray (Gy) will be displayed as a continuous variable and by categories as follows: <54, [54, 60], [60, 66], [66, 70], [70, 74], >74 Gy.

4.1 Exposures
Durvalumab treatment is the exposure of interest. Durvalumab prescription is based on the unsolicited participation in the EAP and is clearly separated from the decision to include the patient in this non-interventional/observational study protocol.

Treatment with durvalumab will be determined from pharmacy dispensing records or issued dispensing/prescriptions in electronic medical records.

Previous treatment strategies and subsequent treatment patterns are considered as standard of care treatments and will be displayed descriptively.

Time to start durvalumab after completion of CRT will be assessed as continuous variable and also in categories (≤ 42 days, > 42 days) and is defined as the date between the last dose of RT and the initiation date of durvalumab, irrespective of any chemotherapy overlapping the RT.

4.2 Outcomes
Clinical outcomes include disease progression and OS with intermediate endpoints as local recurrence, time to relapse in metastatic setting or time to relapse with distant brain metastasis. These outcomes are physician reported clinical outcomes.

Progression free survival (PFS)
• Defined as the time from initiation of the durvalumab therapy (index date) until earliest record of disease progression (including metastatic disease) determined by physicians’ assessment,
• metastatic recurrence or death (if no progression) or end of follow-up (for censored observations).

**Overall survival (OS)**

Defined as the time from durvalumab initiation date up to death or last date the patient was known to be alive (for censored observations).

The two outcomes will be described for the overall population, and for subgroups of interest which may include:

• PACIFIC-LIKE cohort
• Elderly patients (no/yes)
• Frail patients (no/yes)
• Disease stage (IIIA, stage IIIB/C)
• Initiation of durvalumab relative to end of radiotherapy (≤ 42 days, > 42 days)
• Previous type of CRT (concurrent and sequential)
• RT total dose (≤ 54, >54 Gy)
• Type of histology (squamous and non-squamous).

PACIFIC-LIKE will be a subgroup explored in this global study. The PACIFIC-LIKE cohort will be as similar as possible to the PACIFIC trial population in a real-world setting, based on available data. The characteristics will be further defined in the final SAP once study enrolment has completed. The PACIFIC trial included unresectable stage III NSCLC patients with a performance status of 0,1 who have not progressed following a platinumbased cCRT and who were treated with durvalumab within 42 days after end of CRT.

**Safety measures** with retrospective collection of AESIs, when:

• Require concomitant use of systemic corticoids, immunosuppressants and/or endocrine therapies, or
• Leading to durvalumab temporary interruption, or
• Leading to durvalumab permanent discontinuation.

The AESIs considered in the study are the following:

• Diarrhoea / colitis and intestinal perforation
• Pneumonitis / Interstitial Lung Disease (ILD)
• Hepatitis / transaminase increases
• Endocrinopathies (i.e. events of hypophysitis / hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I Diabetes Mellitus)
• Rash / dermatitis
• Nephritis / blood creatinine increases
• Pancreatitis / serum lipase and amylase increases
  Myocarditis
• Myositis / polymyositis
• Neuropathy / neuromuscular toxicity (Guillain-Barré, and myasthenia gravis).

Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

Other time to event outcome measures
• Time to relapse in metastatic setting defined as having a first distant metastasis after durvalumab initiation
• Time to brain metastasis relapse defined as having a first distant brain metastasis only after first durvalumab initiation
• Local recurrence rate versus distant relapse rate will be displayed if available.

Other potential study measures of interest
• Durvalumab details ○ Time to start durvalumab after completion of RT, duration of treatment  ○ Temporary interruptions for AESIs  ○ Concurrent therapies (steroids, immunosuppressant and/or hormone replacement therapy) during AESIs
  ○ Percent of patients who end treatment after 12 months compared to patients who end treatment at the time of disease progression when after 12 months
  ○ The reasons for treatment discontinuation.
• Patient demographic and clinical characteristics ○ Age, sex, date of diagnosis, stage at diagnosis, and especially: Age in categories (≤ 75 years, > 75 years (and <70years, ]70, 75] years, >75 years). PS in categories (0,1) (≥2),
  ○ Longest dimension of primary tumour and lymph nodes involvement, ○ Comorbidities.
• Physician and hospital characteristics  ○ Multi-Disciplinary Team involved: pneumologist/oncologist/radiation oncologist ○ Hospital characteristics: general hospital, university hospital, private centre, specialised cancer centre
  ○ In-house RT, external RT (public, private).
• **Patient molecular testing patterns** • Epidermal Growth Factor Receptor (EGFR) mutation test, anaplastic lymphoma kinase (ALK) mutation test, PD-L1 expression performed as part of routine clinical care,
Results of testing EGFR/ALK, PD-L1 expression in tumour cells (% and in categories).

- **Previous treatment strategies** Details of cCRT or sCRT including duration of chemotherapy, number of cycles and type of chemotherapy received, total dose of RT, number of fractions, mean organ radiation dosing, response at end of the strategy, and where CRT was administered (inside versus outside the centre).

- Class and type of chemotherapy in monotherapy and in combination, dates of administration of each agent, total number of cycles, duration of each type of chemotherapy, percentage of chemotherapy in induction with number of cycles, type of association of chemotherapies received and for induction

- For RT as minimum:\ duration of radiotherapy continuous, total dose in Gy, continuous and by categories. The proposed categories may include: <54, [54, 60], [60, 66], [66, 70], [70, 74], >74 Gy

- Toxicities during CRT (maximum toxicity occurring) and at end of CRT when not resolved.

$ Further details on radiotherapies will be collected at local level if possible.

- **Subsequent therapies after durvalumab** Subsequent therapy: target therapy, chemotherapy, immuno-oncology agent, treatment duration by class of therapies and/or by molecules.

- **Healthcare resource utilisation** Number of emergency visits, hospitalisations (different from perfusion visits), duration of hospitalisation, diagnostic procedures during durvalumab prescription.

The above list of variables is not exhaustive. Additional details will be provided in the data collection forms and SAP.

### 4.3 Other Variables and Covariates

Potential covariates that could affect the outcomes:

- Demographics (age, sex)
- Tumour characteristics at stage III diagnostic (TNM stage, histology)
- Performance status (ECOG/WHO or Karnofsky score)
- Smoking status (yes/no)
- Initiation time of durvalumab relative to last dose of radiotherapy
- Previous type of CRT (concurrent, sequential)
- PS is not always recorded in the dossier source, especially when patient is in good condition, therefore the ECOG/WHO or the Karnofsky scores (as available) will be collected in order to evaluate patient’s health status.
5. STATISTICAL ANALYSIS PLAN

5.1 Statistical Methods – General Aspects

All statistical analyses will be performed by AstraZeneca or its representatives.

A detailed SAP will be created with details on tables of interest and related statistics. The definitions of derived variables will be described.

The analyses will be descriptive with summary statistics for continuous variables (mean, median, minimum, maximum) or number and frequency for calculation of categorical variables.

Graphs, such as bar charts, histograms, curves over time by Kaplan-Meier plots, age ranges will be used as complementary ways to display the data.

Missing values will be displayed. The frequency of missing values for each variable will be examined and evaluated whether or not data are missing at random in the data source. Imputation will be considered whenever data appear to be missing at random within subgroups of the study population. Rules will be defined in the SAP with distinct methods depending of the frequency of missing variables (≤10%, >10%).

For time to event analyses, data will be censored for patients when lost to follow-up (i.e., still alive as of their last visit/contact prior to data cut-off).

5.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest

PFS is calculated from the index date (date of the first dose of durvalumab) to the date of investigator-determined disease progression or death (if no progression) or the end of follow-up for censored patients.

OS is calculated following durvalumab regimen received from the index date to death or end of follow-up for censored patients.

PFS and OS will be estimated and plotted using the Kaplan-Meier method. The median and associated 95% confidence interval will be estimated. The percentage of patients remaining event free at specific timepoints will be displayed: PFS at 12, 18 months, OS at 2-years, 3-years and 5-years.

Except for the first chart extraction, all will be triggered at time of estimated maturity in outcomes.

The timing of the second extraction will be based on an estimate of when there will be a sufficient number of observed progression events to determine the median PFS and its 95% confidence interval for the total sample. This estimation will be based upon the dates of first dose of durvalumab and any available data of PFS already obtained in the first extraction together with the distribution of PFS previously estimated for the PACIFIC study.

The timing of the third extraction will be based on an estimate of when there will be a sufficient number of observed deaths to determine the median OS and its 95% confidence interval for the
total sample. This estimation will be based upon the dates of first dose of durvalumab and any available data on PFS and OS already obtained in the previous extractions together with the distributions of OS, PFS, and time from progression to death estimated for the PACIFIC study. The fourth and fifth chart extractions will be planned within the same process to determine OS rate at 3-years and 5-years and its 95% confidence interval.

5.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest

Other time to event measure outcomes will be displayed in the same way that primary objectives. Clinical characteristics, previous and subsequent treatment patterns will be displayed descriptively.

Regimen use by line of therapy will be summarised.

5.2 Subgroups Analyses

Additional sensitivity analyses may be conducted and will be described in the SAP, e.g. stratification by covariates and comparison of subgroups where sample size allows.

5.3 Bias

5.3.1 Methods to Minimise Bias

Information bias

The present study will be carried out using data recorded during routine clinical care. Some records are expected to be incomplete. For example, previous treatment information (e.g., RT treatment may be given in a treatment setting separate from the hospital where the patient received durvalumab as part of the EAP).

In addition, the availability of the information in a patient’s health record may depend on the study site and/or countries. Given that the primary purpose of the study is to describe the efficacy of durvalumab in the real-world, and the oncologist participating in the study is the one to treat the patient, these potential sources of bias should be a relatively minor concern for the PFS outcome. For the OS outcome, all efforts will be put in place to reduce the loss of follow-up patients. In the event a patient is lost to follow-up in the medical records, his/her vital status at index date and date of death should be obtained by the site personnel from publicly available resources. Additionally, the decision to have chart extractions at regular intervals can help to minimise information bias. Allowing for a subsequent abstraction can help to capture any information that may have been missed during the previous abstraction due to lag time inherent to the electronic health record systems, as well as reduce the amount of time the physician is expected to ‘look back’ in the dossiers. Selection bias

The EAP comprises sites whose investigators are aware that this programme is running. Participating investigators may be more likely to adopt new treatment options and may somehow differ from physicians that elect not to participate in an EAP. However, there is a
large number of participating physicians and sites in these countries, with additional site requests currently being addressed. Based on the current number of sites in the EAP, we anticipate that participating sites will be representative of physicians treating stage III unresectable NSCLC in each country. By including most of sites and centres from the EAP in this observational study, the representativeness should still be assured and selection bias should be minimised. Information regarding physician and hospital characteristics will be collected and analytical approaches, such as weighting (according to the weight of each hospital type), could be applied in the analyses if there are marked differences in the study population.

Patients will be eligible to enter PACIFIC-R as soon as the EAP enrolment ends, in order to minimise the number of EAP patients declining to participate in the PACIFIC-R study. The narrow window between end of EAP enrolment and start of the observational study, as well as involvement of the study working group will help to minimise patient attrition between the studies. Efforts have been put in place to ascertain the reasons of non-participation. Such a register will ensure the representativeness of the patients included versus the source population, by comparing the baseline characteristics of patients that choose to participate with those who do not. Additional sensitivity analyses can be conducted to account for any differences between participants and non-participants. **Measurement bias**

The data are collected retroactively from the patients’ medical charts, which should bias in measurements obtained in other ways. Despite the efforts taken to define algorithms specific to each health outcome of interest, some of the data sources utilised in this study are subject to underreporting; hence, non-differential misclassification of health outcomes may occur. Sensitivity analyses could be performed on subset of population.

**5.3.2 Adjustment for Multiple Comparisons**

There is no testing of hypothesis, therefore no adjustments among multiple outcomes is needed.

**5.3.3 Strengths and Limitations**

This protocol presents a certain number of limitations that need to be discussed and that must be taken into account when setting up the study and analysing its results.

The study is not fully representative of all patients treated for locally advanced, stage III lung cancer in this setting, as this study includes only patients enrolled in the EAP. All participants in PACIFIC-R are early adopters of the new therapy and should be considered as such.

Due to these selection process, some heterogeneity could persist at global or regional level and results at the local level will also be described if sufficient sample size requirements are met. For example, the French ATU has selection criteria that mimic the PACIFIC trial:

- Treatment duration of maximum 12 months whereas other countries could continue up to progression of the disease
- Previous sequential therapy was not allowed in the ATU
- Patients with PS equal to 2 were not allowed in the ATU
This is the reason why we plan to study endpoints in the PACIFIC-LIKE population.

The participation of EAP sites is key to ensure study completeness and there is a high reliance on physicians to make updates to the study at several time periods. Both global and local scientific committees will be set up to maintain and motivate sites participation during the full data collection period. Sites contacts were established for the EAP in providing training in the management of immune-mediated adverse events (AEs) for patients on durvalumab. Such actions should continue to maintain interest in scientific data collection.

Safety events, except events of special interest (which lead to treatment interruption or permanent discontinuation or those which require use of specific treatments) are not collected as part of the EAP. Therefore, the study will provide limited evidence to evaluate the BenefitRisk profile of the durvalumab treatment. Furthermore, the reporting of such AEs will not follow the similar process that in the PACIFIC trial with target questionnaire and steps for characterising immune-mediated AEs through suspected AESIs after a central medical review. Therefore, no comparison with the PACIFIC trial can be made on the AE reporting in this study.

This large, observational study will provide the first real-world evidence of patients treated with durvalumab and will uniquely deliver robust, global findings.

### 5.4 Interim Analyses

Several interim analyses will be performed per below:

- At time of first chart extraction finalised, a baseline report will be produced
- At times of PFS and OS median maturity, separate analysis could be performed on these endpoints
- The final analysis will present the OS rate at 5-years. Additional interim analyses may be performed based on local regulatory requests.

### 5.5 Sample Size and Power Calculations

The sample of patients identified for the current study will be based on a portion of patients enrolled into the durvalumab EAP and no hypothesis and power analysis will be conducted.

However, for the planned data extraction periods, more than 500 patients among France, Germany, Italy, UK should be included in data collection. A target study size of 100 to 200 patients per country is expected, allowing reporting of results at individual country level. Spain will participate in a separate study and data is planned to be merged with this study data.

Additional countries are expected to enter in the study with a total participation of more than 1000-1200 patients.

PFS and OS are the effectiveness endpoints of interest for this study. Considering median PFS of 16.8 months in PACIFIC trial, median PFS in the study is assumed to be approximately 14-18 months. Median OS has not been reached in the PACIFIC trial and the assumption is to have an OS of 30 months. For the time being, it is assumed to be 25-35 months.
While the sample size is not known a priori, illustrations of the precision with which PFS and OS could be calculated from this real-world study are given in the table below. These illustrations have been based on actual take-up numbers for the EAP from September 2017 through to May 2018 and with recruitment assumed to remain uniform from June 2018 through to the end of December 2018. It is also assumed that PFS and OS are exponentially distributed with no lag time and that there are no drop-outs.

If data extraction for PFS were triggered at 28 months after the first patient was enrolled in the EAP, there is a high risk that too few patients will have progressed for median PFS and its 95% confidence interval to be estimated. If it were triggered at 34 months, we would expect 60.9% of patients to have progressed under the assumption of a median PFS of 18 months, and 65.2% of patients to have progressed under the assumption of a median PFS of 16 months. 

Table 2. Expected percentage of patients with progression at different extractions times.

<table>
<thead>
<tr>
<th>Extraction Time (months)</th>
<th>Median Progression-Free Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14</td>
</tr>
<tr>
<td>28</td>
<td>59.61%</td>
</tr>
<tr>
<td>30</td>
<td>63.41%</td>
</tr>
<tr>
<td>32</td>
<td>66.86%</td>
</tr>
<tr>
<td>34</td>
<td>69.99%</td>
</tr>
<tr>
<td>36</td>
<td>72.82%</td>
</tr>
</tbody>
</table>

This calculation will be revised after the first chart extraction in all countries has been realized. At that time, the index date will be known for all patients and also the date of progression for some patients. Comparing this with the PFS data seen in PACIFIC will allow an update of the estimate of the date when there is sufficient maturity in the PFS data for the second chart extraction in all countries. Similarly, data from the first and second chart extractions will enable updates in the estimate of when the OS data may be expected to be mature enough for the third extraction.

Based on the estimates below, if approximately 1000 patients enter the study, the median PFS is 16 months as observed in PACIFIC, and data for PFS is extracted at 34 months, the corresponding 95% confidence interval for PFS would be approximately 14.9 – 17.2 months. If an additional PFS data extraction is made at 50 months (at the time of the OS data extraction), the 95% CI will be approximately 15.0 – 17.1 months and PFS data would be more mature (83% maturity). With the assumed sample size of 1000 patients, a data extraction at 60 months and an assumed median OS of 30 months, the corresponding 95% confidence interval would be approximately 27.9 – 32.2 months.
### Table 3 Sample size estimation assuming varying median PFS.

<table>
<thead>
<tr>
<th>Time to data extraction (months)</th>
<th>N</th>
<th>14 months mPFS</th>
<th>16 months mPFS</th>
<th>18 months mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Events</td>
<td>CI for mPFS</td>
<td>Events</td>
</tr>
<tr>
<td>&lt;34 months</td>
<td>100</td>
<td>69 11.1 - 17.7</td>
<td>65 12.6 - 20.3</td>
<td>60 14.2 - 22.8</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>139 11.9 - 16.5</td>
<td>130 13.5 - 18.9</td>
<td>121 15.2 - 21.3</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>349 12.6 - 15.5</td>
<td>325 14.4 - 17.8</td>
<td>304 16.2 - 20.0</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>419 12.7 - 15.4</td>
<td>391 14.5 - 17.6</td>
<td>365 16.4 - 19.8</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>559 12.9 - 15.2</td>
<td>521 14.7 - 17.4</td>
<td>487 16.6 - 19.6</td>
</tr>
<tr>
<td></td>
<td>900</td>
<td>629 12.9 - 15.1</td>
<td>586 14.8 - 17.3</td>
<td>548 16.6 - 19.5</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>699 13.0 - 15.1</td>
<td>651 14.9 - 17.2</td>
<td>608 16.7 - 19.4</td>
</tr>
<tr>
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<td>782 15.0 - 17.1</td>
<td>730 16.8 - 19.3</td>
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<td>852 16.9 - 19.2</td>
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<td>473 16.5 - 19.6</td>
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<td>631 16.7 - 19.4</td>
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<td>777 13.0 - 15.0</td>
<td>743 14.9 - 17.2</td>
<td>709 16.8 - 19.3</td>
</tr>
<tr>
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<td>864 13.1 - 15.0</td>
<td>825 15.0 - 17.1</td>
<td>788 16.8 - 19.2</td>
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</tbody>
</table>

* A high risk of insufficient events

**50**
Table.

<table>
<thead>
<tr>
<th>Extraction Time (months)</th>
<th>Median Overall Survival</th>
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</thead>
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<tr>
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<td>25</td>
</tr>
<tr>
<td>48</td>
<td>65.57%</td>
</tr>
<tr>
<td>50</td>
<td>67.42%</td>
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<td>52</td>
<td>69.18%</td>
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<tr>
<td>54</td>
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<tr>
<td>56</td>
<td>72.42%</td>
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<tr>
<td>58</td>
<td>73.90%</td>
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<tr>
<td>60</td>
<td>75.31%</td>
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### Table 5 Sample size estimation assuming varying median OS.

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<th>Time to data extraction (months)</th>
<th>N</th>
<th>25 months mOS</th>
<th>30 months mOS</th>
<th>35 months mOS</th>
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<tr>
<td></td>
<td></td>
<td>Events</td>
<td>CI for mOS</td>
<td>Events</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<td>&lt;50 months</td>
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<td>100</td>
<td>67</td>
<td>19.7 - 31.8</td>
<td>60</td>
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<td>134</td>
<td>21.1 - 29.6</td>
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<td>674</td>
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<td>75</td>
<td>19.9 - 31.3</td>
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<td>21.3 - 29.3</td>
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<td>413</td>
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<td>800</td>
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<td>602</td>
<td>23.1 - 27.1</td>
<td>550</td>
</tr>
<tr>
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<td>900</td>
<td>677</td>
<td>23.2 - 27.0</td>
<td>619</td>
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<tr>
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<td>1000</td>
<td>753</td>
<td>23.3 - 26.9</td>
<td>688</td>
</tr>
</tbody>
</table>

A high risk of insufficient events
Table.

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1200</td>
<td>903</td>
<td>23.4</td>
<td>26.7</td>
<td>826</td>
<td>28.1</td>
<td>32.0</td>
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<tr>
<td>1400</td>
<td>1054</td>
<td>23.5</td>
<td>26.6</td>
<td>963</td>
<td>28.2</td>
<td>31.9</td>
</tr>
</tbody>
</table>

CI: Confidence Interval, *mOS: median Overall Survival based on the formula in Collett 1994 (*Collett 1994*).
6. STUDY CONDUCT AND REGULATORY DETAILS

6.1 Study Conduct

6.1.1 Study Flow Chart and Plan

A global Scientific Committee, including oncologists and radiation oncologists from the main European countries, has been set up and will provide guidance to the study set up and conduct, contribute to the interpretation of results and to the publications.

The Scientific committee will validate the study design concept, the case report form (CRF), will make significant contributions to the analyses and interpretation of the data. This committee will also decide on any interventions during the study likely to impact on the methodology described in this protocol.

The proposed timelines are suggested below and may be adjusted based on MA date, end of EAP enrolment in each country and local market ethics process.

Estimated dates for:

- MA + three months: ≤30 December 2018
- First extraction: from October-December 2018 to May 2019 or from September 2019 to March 2020
- Second extraction: Q1-Q2 2020
- Third extraction: Q4 2021
- Final extraction: Q2-Q3 2023
- Database lock: Q4 2023.

For patient chart extraction, the CRO will ensure data completeness and will call the physician to request data entry as planned. In some centres, there could be the request to have on-site monitoring.

Within the eCRF, internal validity checks will appear during data entry. External checks will be set up by the CRO to ensure data accuracy.

6.1.2 Procedures

The patient can withdraw from the study at any time without giving a reason.

6.1.3 Quality Control

Data will be entered in the web based data capture (WBDC) system at the Investigator’s site. The Investigator will be responsible for entering data into the WBDC system and according to the Investigator Instructions Manual. The Investigator Instructions Manual will also provide the site with data entry instructions.
Data queries will be edited in case of discrepancies in the recorded data. The Investigator will be responsible for handling the data query and answering appropriately.

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed and edited, the Investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be locked to prevent further editing. A copy of the eCRF will be archived at the Investigator’s site

**Monitoring**

Before the first subject is recruited into the study, the local MC, Oncology Business Unit (OBU) Delivery Director, Medical Evidence Observational Research (MEOR) Operations Lead or CRO Representative will:

- Establish the adequacy of the facilities and the investigator’s capability to appropriately select the sample
- Discuss with the investigator(s) (and other personnel involved in the study) their responsibilities with regards to protocol compliance, and the responsibilities of AstraZeneca or its representatives. This will be documented in an Observational Study Primary Agreement between AstraZeneca/delegate and the investigator

During the study the local MC representative or delegate can implement different activities to assure compliance with AstraZeneca standards of quality. These activities could include but are not limited to:

**Contacts with the sites to:**

- Provide information and support to the investigator(s)
- Confirm that the research team is complying with the protocol and that data are being accurately recorded in the CRFs
- Ensure that the subject informed consent forms (ICFs) are signed and stored at the investigator’s site
- Ensure that the CRFs are completed properly and with adequate quality.

**Monitoring activities for:**

- Checking of ICFs
- Checking that subjects exist in medical records.

The extent and nature of monitoring will be decided during the study planning based on design, complexity, number of subjects, number of sites, etc. Observational Research Centre (multi country) / MC will give some recommendations that could be locally adapted.

Different signals (e.g., high rejection rate at a site) should be used as potential identification of low protocol compliance by investigators.
If these or any other signal occurs or if the local coordinator is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

**Operating procedures**

Standard operating procedures for each research partner will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

**Programming**

Implementation of this protocol will be laid out in a global quality control (QC) document. Local modifications by the research partners will ensure that each local QC document is sufficiently detailed to trace data manipulations from the original database files through study files to final analyses and tabulations. The QC document will be the basis for checking all analytic computer programs by a second team member. Original data files, intermediate files, study files, and the programs that link them will be maintained by each research partner in a secure archive for 5 years following submission of the final study report.

All work will be subject to QC and documentation procedures to make certain that the final report is accurate and thorough and the analyses can be reproduced. If the data do not permit an analysis as planned or if clarifying analyses are required, then the missing or the additional information and results will be included in the report(s) and the corresponding explanation made. All key study documents, such as the protocol, SAP, abstraction forms, and study reports, will undergo QC review, senior scientific review, and editorial review.

**Training of Study Site Personnel**

The Principal Investigator will ensure that appropriate training relevant to the Observational Study is given to investigational staff, and that any new information relevant to the performance of this Observational Study is forwarded to the staff involved.

**6.2 Protection of Human Subjects**

The Observational Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Council for Harmonisation (ICH) Guideline to Good Clinical Practice (GCP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and the applicable legislation on Non-Interventional Studies and/or Observational Studies.

The Investigator will perform the Observational Study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the Observational Study and in accordance with currently acceptable techniques and know-how.
The final protocol of the Observational Study, including the final version of the Subject Informed Consent Form, must be approved or given a favourable opinion in writing by the Ethics Committee/Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
The Ethics Committee/IRB/IEC must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

6.2.1 Subject Informed Consent

The Investigator at each site will ensure that the subject (or close relatives for deceased patients if requested by local regulation) is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the Observational Study. Subjects must also be notified that they are free to discontinue from the Observational Study at any time. The subjects should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated subject informed consent must be obtained before any specific procedure for the Observational Study is performed.

The Investigator must store the original, signed Subject Informed Consent Form in the corresponding section of the Investigator Site File. A copy of the signed Subject Informed Consent Form must be given to the subject or close relative.

6.2.2 Confidentiality of Study/Subject Data

The Subject Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects or close relatives will authorise the collection, use and disclosure of their personal data by the Investigator and by those persons who need that information for the purposes of the Observational Study.

The Subject (or next to kin) Informed Consent Form will explain that Observational Study data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

The Subject Informed Consent Form will also explain that for quality check purposes, a monitor of AstraZeneca or a monitor of company representing AstraZeneca, will require direct access to the signed subject informed consent forms. In case source data verification is planned as quality check, the Subject Informed Consent Form will explain that for data verification purposes, a monitor of AstraZeneca or a monitor of company representing AstraZeneca may require direct access to source documents that are part of the hospital or practice records relevant to the Observational Study.

6.3 Collection and Reporting of Adverse Events/Adverse Drug Reactions

Collection and reporting of AE data is required for primary data studies but not for secondary data studies. The relevant SAEs of study patients within durvalumab treatment have already been reported according to local regulations in place.
Therefore, the study will only collect AESIs which lead to durvalumab temporary interruption or permanent discontinuation and/or those who require use of systemic steroids, immunosuppressants or endocrine therapies.

### 6.3.1 Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject 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, 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.

### 6.3.2 Definition of Serious Adverse Events (SAE)

An SAE 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 life-threatening (life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event that may jeopardise the subject or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether other situations should be considered an SAE
- Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

### 6.3.3 Definition of Adverse Drug Reactions (ADR)

An Adverse Drug Reaction (ADR) is an AE suspected to be causally related to the medicinal product.

An ADR is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure.
6.3.4 Collection of Adverse Events of Special interest (AESIs)

In this study, only AESIs potentially attributable as immune-mediated AEs, and reported in association of anti PD-L1 / anti programmed cell death protein 1 (PD-1) antibodies, will be collected, when they:

- Require the use of systemic corticoids, immunosuppressants and/or endocrine therapies, or
- Lead to durvalumab temporary interruption, or
- Lead to durvalumab permanent discontinuation.

The AESIs considered in the study are the following:

- Diarrhoea / colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis / hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / dermatitis
- Nephritis / blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / polymyositis
- Neuropathy / neuromuscular toxicity (Guillain-Barre, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

Because of the expected incidence of AEs of radiation pneumonitis, due to the previous definitive RT received by patients prior to entering the study, and because of the inherent difficulties for sites in determining whether imaging changes are true radiation pneumonitis or immune-mediated pneumonitis, or a combination of both, a group term of the pneumonitis including acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis will be used whereas radiation pneumonitis will be reported separately. **Time period for collection of adverse events**

AEs will be collected from the time of starting the medicinal product(s) under study throughout the durvalumab treatment period up to 90 days after last durvalumab infusion or at time of next subsequent therapy initiation (whichever occurs earlier).

7. LIST OF REFERENCES


8. APPENDICES

Not applicable.
9. ATTACHMENTS
Not applicable.
10. SIGNATURES

ASTRAZENECA SIGNATURE(S)

First real-world data on unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy

This Observational Study Protocol has been subjected to an internal AstraZeneca review I agree to the terms of this Study protocol.

MARCO chair / AstraZeneca representatives:

MARCO chair: [Signature] 10 September 2018

GMAL: [Signature] (Senior Global Medical Affairs Leader) 10 September 2018

GPS/Study Statistician: [Signature] 10 September 2018
This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.