STUDY REPORT SYNOPSIS

CODAK: A retrospective observational research study to describe the characteristics and real-world clinical outcomes of patients with locally advanced, unresectable Stage III non-small cell lung cancer receiving durvalumab in the United Kingdom

A multicentre retrospective observational research study in patients with locally advanced, unresectable Stage III non-small cell lung cancer receiving durvalumab as part of the UK Early Access Programme or post-reimbursement

Milestones:

Milestone	Date
Study protocol approved	October 2020
Ethics approval	December 2020
Database start date	June 2021
Data analysis and tables interim	April 2022
Database end date	June 2022
Final database lock	September 2022
Data analysis and tables final	August 2023
Clinical study report to commence	October 2022

Sponsor: AstraZeneca

This study was performed in compliance with Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale

Durvalumab was granted marketing authorisation by the European Commission in September 2018 for the treatment of locally advanced, unresectable Stage III non-small cell lung cancer (NSCLC) in adults whose tumours express programmed cell death ligand-1 (PD-L1) on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (CRT) (European Medicines Agency, 2023). Subsequently, in May 2019 the National Institute for Health and Care Excellence (NICE) approved durvalumab monotherapy "for use within the Cancer Drugs Fund (CDF) as an option for treating locally advanced unresectable NSCLC in adults whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after platinum-based chemoradiation only if: they have had concurrent platinum-based chemoradiation; and the conditions in the managed access agreement are followed" (NICE, 2019). Durvalumab is approved for use by the Scottish Medicines Consortium (SMC) in Scotland (SMC, 2019), and recommended by NICE in Wales, Northern Ireland and England (NICE, 2022).

Prior to reimbursement, durvalumab was made available to patients in the United Kingdom (UK) through an Early Access Programme (EAP) from September 2017 to March 2019. Whilst a number of patients enrolled in the EAP were subsequently enrolled in the ongoing real-world study PACIFICR (PACIFIC-R, NCT03798535) (ClinicalTrials.gov, 2023), the inclusion criteria for PACIFIC-R required patients to begin treatment with durvalumab by 16th December 2018. Therefore, there was a cohort of patients who initiated treatment with durvalumab from 17th December 2018 onwards (either through the EAP or post-reimbursement) who remain uncharacterised. Currently, published studies on durvalumab treatment in patients with locally advanced, unresectable Stage III NSCLC in real-world settings are in small groups of patients outside of the UK, including in Taiwan (31 patients) (Chu et al., 2020) and Japan (41 patients) (Miura et al., 2020) and from the ongoing multi-country PACIFIC-R study (1399 patients (54 from the UK)) (ClinicalTrials.gov, 2023; Girard, 2022, 2021; Girard et al., 2023, 2020; McDonald, 2021). In addition, whilst patient characteristics and outcomes with durvalumab were characterised through the PACIFIC trial including its interim data (Antonia et al., 2017), subsequent 3-year data (Antonia et al., 2018, 2017; Gray et al., 2020) and recently published 5-year data (Spigel et al., 2022), there is a lack of real-world data to describe the effectiveness of durvalumab in the UK routine clinical practice setting.

The purpose of this study was to describe the clinical outcomes, demographics, and clinical characteristics in patients with locally advanced, unresectable Stage III NSCLC treated with durvalumab as part of the UK EAP or post-reimbursement.

Objectives:

Primary objectives

The primary study objectives, in patients with locally advanced, unresectable Stage III NSCLC treated with durvalumab as part of the UK EAP or non-EAP (i.e. post-reimbursement), were:

- To describe the clinical outcomes
- To describe the patient demographic and clinical characteristics

Secondary objective

The secondary objective was to describe treatment patterns of durvalumab in patients with locally advanced, unresectable Stage III NSCLC treated with durvalumab as part of the UK EAP or non-EAP (i.e. post-reimbursement).

Study design

This was a multicentre, non-interventional cohort study involving retrospective data collection with a prospective observational period of patients with locally advanced, unresectable Stage III NSCLC treated with durvalumab following platinum-based CRT as part of the UK EAP or non-EAP (i.e. post-reimbursement). The study included patients treated in 10 UK secondary care hospitals, who were initiated on durvalumab between 1st September 2017 and 31st December 2019. The 10 centres were selected as they had participated in the EAP and had large number of patients treated with durvalumab; centre selection also aimed to maximise the geographical spread and range of sizes of centres to increase the representativeness of UK practice.

Data were collected retrospectively for each participant at baseline and for a minimum of 24 months from the date of the first dose of durvalumab received (index date) to the date of death, withdrawal from study, loss to follow-up or the end of study period, whichever was earliest.

Key definitions for study timepoints included:

- Index event: Defined as the date of first dose of durvalumab
- Baseline: Baseline data were the closest observation recorded no more than 6 months prior to the index event date
- Observation period: A minimum of 24-month period from index to date of death, withdrawal from study, loss to follow-up or the end of study period, whichever was sooner

Data source

Data were collected retrospectively from hospital medical records, pharmacy, and hospital databases (paper-based and/or electronic) from 10 clinical sites across the UK. De-identified data were collected using a standardised electronic case report form (eCRF) designed specifically for the study. Participants were assigned a unique participant identification number to link multiple study records for each participant (where applicable) and allow data management queries to be resolved with reference to source medical records while preserving patient confidentiality.

Study population

The study population was adult patients with locally advanced, unresectable Stage III NSCLC treated with durvalumab following platinum-based CRT between 1st September 2017 and 31st December 2019. Patients who were enrolled on the ongoing PACIFIC-R study (ClinicalTrials.gov, 2023) were excluded. Inclusion in the study was independent of treatment decision making and patient care was not influenced by inclusion in this study. Patients who met all the inclusion and exclusion criteria were considered for participation in the study.

Inclusion criteria were:

- Patient had documented diagnosis of locally advanced, unresectable Stage III NSCLC
- Patient received platinum-based CRT and received ≥1 dose of durvalumab
- Patient was initiated on durvalumab (index event) between 1st September 2017 and 31st December 2019 via the EAP or non-EAP (i.e. post-reimbursement)
- Patient was aged ≥18 years at durvalumab initiation

Exclusion criteria were:

- Patients who participated in the PACIFIC-R study
- Participation in any clinical study with an investigational product at the time of durvalumab initiation or during the observational period

Statistical methods

The demographics, characteristics and clinical outcomes of the study participants were analysed with descriptive statistics. Distributions and descriptive statistics of central tendency (medians and arithmetic or geometric means) and dispersion (standard deviation [SD], interquartile range [IQR], range) were presented for quantitative variables. Categorical variables were described with frequencies and percentages; where appropriate, distributions, modes, medians, IQR and range were reported. Where appropriate, 95% confidence intervals (CIs) were also presented for means and estimates of proportions.

Time-to-event analyses were presented as Kaplan–Meier plots of the probability of real-word overall survival (rwOS), real-world progression-free survival (rwPFS), real-world second progression free survival (rwPFS2), time to treatment discontinuation (TTD), and time to first subsequent therapy (TFST) over time. The rwOS was defined as the time from durvalumab initiation date up to death or last date the patient was known to be alive. The rwPFS was 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. The rwPFS2 was defined as time from index date to objective tumour progression on next-line treatment or death from any cause. For these outcomes analyses (rwOS, rwPFS, rwPFS2, TTD, TFST), the median (95% CI) time and/or restricted mean time (months; 95% CI) to the event were presented based on the Kaplan–Meier based analyses.

The survival rates were summarised as the proportion of patients (median [95% CI] and restricted mean [95% CI]) alive (for rwOS), alive and not progressing (for rwPFS), and alive and had not progressed on subsequent treatment (for rwPFS2) at 12 and 24 months post durvalumab initiation. TFST was described as the proportion of patients without subsequent treatment and alive at 12 and 24 months after discontinuation of durvalumab using life tables, presented as a proportion (median, restricted mean) with 95% CI.

Time to durvalumab treatment discontinuation (or overall treatment duration), estimated as the time from index date until the date of last durvalumab infusion, was summarised as mean, SD, median, range, and IQR.

Subject to sufficient group size (n≥25), the primary and secondary objectives were subject to subgroup analyses, stratified according to: PD-L1 status (<1%, 1%–49% inclusive, ≥50%, unknown); World Health Organisation (WHO) performance status/Eastern Cooperative Oncology Group (ECOG) score (0, 1, 2); time from last day of CRT to durvalumab (≤14 days, >14 days, ≤42 days, >42 days, ≥14 to ≤42); type of CRT (concurrent CRT, sequential CRT); method of treatment access (EAP, non-EAP); disease stage (IIIA, IIIB/C); and age (<70 years, ≥70 years).

Statistical analyses were carried out using R statistical software (version 4.2.1) and Microsoft Excel.

Results:

Primary objective

Survival and progression outcomes

- In the overall cohort (n=114), the median duration of rwOS (95% CI) was 35.9 (35.9–not reached) months, and the median (95% CI) rates of rwOS were 80.2% (73.1%–

88.0%) at 12 months and 63.0% (54.1%–73.4%) at 24 months post durvalumab initiation.

- In the overall cohort (n=114), the median (95% CI) rwPFS was 28.5 (16.4–not reached) months, and the median (95% CI) rates of rwPFS were 61.1% (52.6%–70.9%) at 12 months and 54.2% (45.3%–64.7%) at 24 months post durvalumab initiation.
- In the overall cohort (n=114), the median (95% CI) rwPFS2 was 35.9 (35.9–not reached) months, and the median (95% CI) rates of rwPFS2 were 76.2% (68.6%–84.6%) at 12 months and 62.6% (53.7%–73.1%) at 24 months post durvalumab initiation.
- For best overall response to durvalumab, 3% (3/114) achieved a complete response, 39% (44/114) of patients achieved a partial response, 34% (39/114) achieved stable disease and 12% (14/114) had progressive disease, while 12% (14/114) had no response recorded.
- Amongst 113 patients with data available, 33% (37/113) were recorded to have at least 1 progression site. Of these 37 patients with at least one progression site recorded, 54% (20/37) were recorded to have locally recurring progression, 14% (5/37) had regional progression, 3% (1/37) had nodal progression, 16% (6/37) had oligometastases, 30% (11/37) had distant progression.

Time to treatment discontinuation

- In the overall cohort (n=114), the median (95% CI) duration of durvalumab treatment was 8.7 (6.2–11.2) months.

Time to first subsequent therapy

- In the overall cohort (n=114), the median (95% CI) time to first subsequent therapy (TFST) was 34.9 (21.0–not reached) months. The median (95% CI) proportion of patients who had received first subsequent treatment at 12 and 24 months post durvalumab was 69.4% (61.3%–78.5%) and 55.8% (46.9%–66.3%) at 12 and 24 months, respectively.

Demographic and diagnosis characteristics

- In this UK real-world cohort, there was a large proportion of patients aged between 60–69 years (36%; 41/114) and 70–79 years (35%; 40/114) at index, and more men (59%; 67/114) than women. Most patients (64%; 73/144) reported that they were not smoking within 6 months prior to index, whereas 33% (38/114) reported that they did smoke within this time period. Smoking status during baseline period was not recorded for 3/114 (3%) patients.
- Most patients received durvalumab treatment in England (96%; 109/114) and 4% (5/114) received treatment in Wales.
- The median (IQR) time from diagnosis of NSCLC to initiation of durvalumab was 135.5 (113.0–168.0) days.

Clinical characteristics at baseline

- Most patients were at stages IIIA (49%; 56/114) and IIIB (37%; 42/114), and 9% (10/114) were at stage IIIC, while disease stage was unavailable for 6/114 (5%) patients.
- Most patients (60%; 68/114) were in the performance status of WHO/ECOG 1, 30% (34/114) were in WHO/ECOG 0, and 3% (3/114) were in WHO/ECOG 2. Performance status was not recorded for 9/114 (8%) patients.
- Squamous cell carcinoma (54%; 61/114) was the most common histological type at diagnosis followed by non-squamous cell carcinoma (37%; 42/114), while histological subtype at diagnosis was not recorded for 11/114 (10%) patients.
- Of the 90 patients with records of PD-L1 status at baseline, 51% (46/90) of patients had a PD-L1 expression ≥50%, 40% (36/90) had a PD-L1 expression 1% to 49% inclusive, and 9% (8/90) showed a PD-L1 expression <1%. Baseline PD-L1 status was not recorded or unavailable for 24/114 patients.
- The epidermal growth factor receptor (EGFR) mutation status at baseline was recorded as: 34% (39/114) of patients with wild-type EGFR, 4% (5/114) with mutant EGFR, 1% (1/114) with inconclusive data, and 61% (69/114) with no records.

CRT regimen prior to durvalumab

- Prior to durvalumab initiation, 85% (97/114) of patients were treated with concurrent CRT, while 13% (15/114) of patients were treated with sequential CRT (2 unknown).
- The median (IQR) total radiotherapy dose per patient was 64.0 (56.0–66.0) Gy; the median (IQR) number of fractions per patient was 32.0 (24.0–33.0) fractions.
- Of the 143 records of chemotherapy reported for the CRT, the top three most common types of platinum-based chemotherapy regimen were cisplatin and vinorelbine (27%; 39/143), cisplatin and etoposide (20%; 28/143), and carboplatin and vinorelbine (17%; 24/143).
- Considering best overall response to prior treatment: 3% (3/114) achieved a complete response, 61% (69/114) of patients achieved a partial response, 29% (33/114) achieved stable disease, and 2% (2/114) had disease progression. The best overall response to prior treatment was not recorded for 6/114 (5%) patients and was not evaluated for 1/114 (1%) patients.

Method of durvalumab treatment access (EAP, non-EAP)

- In this study cohort (n=114), 67% (76/114) and 33% (38/114) of patients initiated durvalumab through EAP and non-EAP (i.e. post-reimbursement), respectively.

Secondary objective

Durvalumab treatment pattern

- The median (IQR) time from last day of chemoradiotherapy to initiation of durvalumab was 41.0 (33.0–54.8) days.
- The median (IQR) number of infusions of durvalumab per patient during the observation period was 15.0 (5.0–22.0) infusions.
- All patients (100%; 114/114) received a starting dose of durvalumab at 10.0 mg/kg. The mean (SD) dose of durvalumab per patient during the study period was 10.3 (1.6) mg/kg across all infusions.
- The median (IQR) length of follow-up from durvalumab initiation was 22.0 (12.9–27.5) months.

Treatment discontinuation

- All patients (n=114) had discontinued durvalumab at the end of the study period. The majority of patients (86/114) discontinued durvalumab prior to 12 months, while 28/114 patients discontinued after 12 months.
- The top four reasons for treatment discontinuation were end of treatment (34%; 39/114), toxicity/AE (29%; 33/114), progression (24%; 27/114) and patient choice (4%; 5/114).
- Of the 33 patients where the reason for discontinuation was due to AE, the top three types of AEs were ‘pneumonitis or interstitial lung disease’ (58%; 19/33), ‘diarrhoea/colitis and intestinal perforation’ (9%; 3/33), and ‘hepatitis or transaminase increases’ (9%; 3/33).

Treatment interruption

- During the study period, a total of 258 treatment interruptions were reported amongst the 114 patients, equivalent to an average of 2.3 (SD: 2.7) interruptions per patient and a median of 1.0 (IQR: 0.0–4.0) interruption per patient.
- An interruption was defined as a delay of ≥1 week of planned dose. Within the 63 patients with at least one interruption recorded, the median (IQR) duration of interruption per patient was 28.0 (27.0–29.0) days calculated as days between the two consecutive doses.
- The top three most common reasons recorded for treatment interruptions were ‘change in frequency of cycles due to COVID-19 (e.g. switch to 4-weekly cycle)’ (47%; 121/258), toxicity/AE (33%; 86/258), and patient choice (8%; 20/258).
- Of the 86 interruptions due to AE, 33 of these AE interruptions reported type of AE with the most common being ‘pneumonitis or interstitial lung disease’ (36%; 12/33) followed by ‘diarrhoea/colitis and intestinal perforation’ (21%; 7/33) and ‘endocrinopathies’ (15%; 5/33).
- During durvalumab treatment, the majority of reported types of AE that led to either discontinuation (n=33/66 records) or interruptions (n=33/66 records) were managed by prescription of a concomitant medication (76%; 50/66). Of the total 78 issued

prescriptions for the AE management, prednisolone (47%; 37/78) was the most common concomitant medication prescribed followed by amoxicillin (5%; 4/78) and co-amoxiclav (5%; 4/78). Prednisolone was used for treatment of several types of AEs and primarily for 'pneumonitis or interstitial lung disease'.

Treatment received post durvalumab discontinuation

- In this study cohort, 19% (22/114) received at least one systemic therapy post durvalumab discontinuation.
- A total of 34 systemic therapy prescriptions were issued for 22 patients post durvalumab discontinuation, with chemotherapy (82%; 28/34) being the most common type of systematic therapy prescribed, followed by immunotherapy (15%; 5/34) and targeted therapy (3%; 1/34).
- Of the 28 chemotherapy prescriptions issued post-durvalumab, the top three most common chemotherapies were carboplatin and gemcitabine (21%; 6/28), pemetrexed (14%; 4/28), and carboplatin (14%; 4/28).

Conclusion:

- Overall, the clinical outcomes including OS, progression-survival, best overall response, and TFST in this study cohort were generally more favourable than those reported in the PACIFIC trial, PACIFIC-R trial and currently available real-world studies, except that the 12 and 24 months OS rates were approximately 3 percentage points lower than the PACIFIC trial where the 12 and 24 months OS rates were 83.1% (95% CI, 79.4 to 86.2) and 66.3% (61.8 to 70.4), respectively (Spigel et al., 2022).
- Toxicities and AEs of durvalumab were tolerable and manageable in this study cohort, consistent with those reported in the PACIFIC trial, PACIFIC-R trial and other real-world studies.
- Treatment discontinuation was mainly associated with end of treatment, toxicity/AEs and patient choice. Treatment interruption was primarily caused by COVID-19 (e.g. switch to 4-weekly cycle), toxicity/AE, and patient choice. As expected, pneumonitis or interstitial lung disease was the most common AE resulting in treatment discontinuation or interruption. Prednisolone was primarily used for the treatment of pneumonitis or interstitial lung disease, and was prescribed for management of several other AEs.
- In this UK real-world cohort, most patients were in the older age group (60–79 years), men, and did not smoke within 6 months prior to durvalumab initiation. Most patients in this cohort were diagnosed with IIIA/IIIB stage NSCLC, squamous cell carcinoma, >50% PD-L1 expression and wild-type EGFR; had WHO/ECOG score 1 (restricted activity); and were previously treated with concurrent CRT. These patients are likely to represent the target population who may be prescribed with durvalumab as a consolidation treatment after CRT in the UK real-world practice.
- This study provides additional evidence relating to effectiveness and safety profile of durvalumab in patients with locally advanced, unresectable Stage III NSCLC who had received CRT in the UK real-world setting.

Publications

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