Clinical Study Report Synopsis

Drug Substance	Durvalumab
Study Code	D4191R00028
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RELEVANCE

A Retrospective Observational, Multi-Centre, Cohort Study to Understand Real-World Treatment Patterns and Clinical Outcomes of Adult Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) in Canada

Study Dates:	First subject enrolled: November 19, 2021 Last subject last visit: August 31, 2022
Phase of Development:	Phase IV
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This study was performed in compliance with International Council for Harmonization Good Clinical Practice, including the archiving of essential documents.

Study Centers

This study was conducted at five participating sites — BC Cancer Agency (Vancouver, British Columbia [BC]), Tom Baker Cancer Centre (Calgary, Alberta), The Ottawa Hospital, CHUM (Centre Hospitalier de l'Université de Montréal; Montréal, Quebec), and Queen Elizabeth II Health Sciences Centre (Halifax, Nova Scotia) — across Canada.

Publications

As of August 30, 2023, the study results will be presented at the 2023 World Conference on Lung Cancer (Singapore) in the format of a mini oral presentation (MA16.06).

Objectives and Criteria for Evaluation

Table 1 describes all study objectives and endpoints.

Table 1: Primary objectives and outcome measures of the real-world study

Objective		Outcome Variable
Type	**Description**	**Description**
Primary	To describe treatment patterns and estimate OS	Descriptive counts — treatments and their proportions, by line of therapy. OS for the overall population, as well as subgroups of interest.
Secondary	To describe rate and type of resection performed among stage III NSCLC patients	Descriptive count — proportions of patients by type of resection.
Secondary	To characterize treatments received including rates of cCRT and sCRT use	Descriptive count— proportions of patients by treatment received.
Secondary	For patients who received CRT, to describe proportion of uptake of those who went onto initiate subsequent durvalumab	Descriptive count — proportions of patients that initiated durvalumab consolidation.
Secondary	To describe reasons for treatment drop-off over the treatment journey from diagnosis with stage III NSCLC	Reason for treatment drop-off (descriptive summary of reason for discontinuation/drop-off).
Secondary	To estimate time-to-treatment discontinuation	Time-to-treatment discontinuation for all treatments.

Secondary	To estimate time to durvalumab initiation following CRT	Time from last dose of chemotherapy/radiation therapy to date of durvalumab initiation.
Secondary	To describe type and dose of radiation received	Descriptive count — proportions of patients by type of radiation prescription received and type of technique used. Descriptive count — proportions of patients by type of radiation prescription received and by dosing categories.
Secondary	To describe rates and types of adverse events of special interest (AESI) among patients who received durvalumab	Descriptive count — proportion of patients with adverse events of special interest (AESI) among those who received durvalumab.
Exploratory	To estimate rwPFS	rwPFS (physician-assessed) for the overall population, as well as subgroups of interest.
Exploratory	To estimate time to TTNT-D	TTNT-D for the overall population, as well as subgroups of interest.
Exploratory	To evaluate factors associated with OS and rwPFS among patients who received durvalumab	Associations between patient factors and clinical outcomes (OS and rwPFS) evaluated using multivariable regression.
Exploratory	To evaluate the impact of durvalumab status on OS and rwPFS	Associations between durvalumab treatment status (completed treatment, ongoing treatment, treatment discontinuation due to AEs, treatment discontinuation due to progression, and treatment discontinuation due to reasons other than progression and AEs) and clinical outcomes (OS and rwPFS)

Abbreviations: Adverse events, AEs; Adverse events of special interest, AESI; Curative chemoradiotherapy, CRT; Concurrent curative chemoradiotherapy, cCRT; Non-small cell lung cancer, NSCLC; Overall survival, OS; Real-world progression-free survival, rwPFS; Sequential curative chemoradiotherapy, sCRT,; Time to next treatment or death, TTNT-D.

Study Design

Multicenter, retrospective, phase IV observational cohort chart review study in Canadian patients with locally advanced stage III NSCLC. Data were collected from eligible stage III NSCLC patients from five sites across Canada.

Target Subject Population and Sample Size

The target population was adult (≥18 years) patients with histologically or cytologically documented diagnosis of NSCLC with locally advanced (stage III) disease (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology) or locally recurrent

(stage III) disease between November 1, 2017 and December 31, 2019 (inclusive). Patients who received durvalumab in clinical studies prior to the study start date and patients enrolled in clinical trials were excluded.

The planned number of patients for enrollment was 800 patients, with approximately half comprising patients who received durvalumab. The completed number of patients enrolled in the study was 662 patients, of which 342 patients received initial CRT + durvalumab and 320 patients received other treatments for initial treatment.

Investigational Product and Comparator: Dosage, Mode of Administration and Batch Numbers

Durvalumab (Imfinzi) and other stage III treatments such as curative chemoradiation, palliative radiation therapy alone, and surgery were administered at the discretion of the treating physician given that this was a retrospective, observational, chart review study.

Duration of Treatment

No limit to duration of treatment was specified. Duration was based on the discretion of the treating physician.

Statistical Methods

Descriptive statistics were used to summarize the baseline characteristics, treatment patterns, reasons for treatment discontinuation, and durvalumab adverse events of special interest. Time to event outcomes including OS, rwPFS, time to durvalumab initiation following CRT, time to discontinuation, and time to next treatment or death were estimated using Kaplan-Meier methods. Exploratory analyses evaluating patient factors associated with OS and rwPFS were performed using multivariable Cox proportional hazards model.

Counts of patients were reported by treatment type, line of therapy, resection status, durvalumab initiation, reason for treatment discontinuation and durvalumab adverse events of special interest. Time to event outcomes including OS, PFS, time to treatment initiation in the durvalumab cohort and TTD were estimated using Kaplan-Meier methods. Exploratory analyses evaluating patient factors associated with clinical outcomes (PFS and OS) were performed using multivariable Cox proportional hazards model, with the proportional hazards assumption assessed via log-cumulative hazard plots and Schoenfeld residuals (continuous variables were discretized).

Subject Population

A total of 662 patients diagnosed with Stage III NSCLC (overall population) were included across Canada from five participating centers. Of these, 343 patients received CRT and durvalumab as the initial stage III treatment, whereas 319 patients underwent alternative initial stage III treatments such as CRT alone, palliative radiation therapy alone, or surgery, among others.

In the full population, the median age at stage III diagnosis was 68 years (range: 29-89) and the median age at stage III treatment initiation was 68 (range: 29-89). The majority of patients were males (54%), had adenocarcinoma histology (58%), and were ever smokers (current or former) (90%). Most patients (75%) reported ECOG performance score of 1 or 0, while ECOG PS was unknown in 9.5% of the population. EGFR mutation information was reported in 5.4% of the population, of which 43% reported

wildtype and 52% reported unknown EGFR status. ALK rearrangement status were reported in 0.3% of patients, of which 51% reported wild-type and 48% reported unknown ALK status. High PD-L1 expression (≥50%) was reported in 31%, low expression reported in 19%, negative expression (< 1%) reported in 21%, and no record of PD-L1 testing was reported in 30% of patients. At the time of the initial NSCLC diagnosis, majority of patients were recorded as having stage IIIA disease (50%), followed by IIIB (35%), IIIC (6.6%), II (3.5%), I (3.2%), III NOS/other (1.4%), and unknown (0.3%).

Summary of Effectiveness Results

- CRT + durvalumab treatment was associated with numerically longer mOS (44.6 months, 95%CI: 36.9 – NR) relative to other initial stage III treatments: resection (33.6 months, 95%CI: 25.0 – NR), CRT alone (21.3 months, 95%CI: 17.5 – 28.1), curative RT alone (26.6 months, 95%CI: 21.2 – NR), palliative RT alone (9.7 months, 95%CI: 7.6 – 14.0), and palliative chemotherapy (14.3 months, 95%CI: 10.3 – 25.8).
- CRT + durvalumab exhibited numerically longer median rwPFS (24.6 months, 95%CI: 21.3 – 30.0) than other initial stage III treatments: resection (11.2 months, 95%CI: 7.8 – 28.2), CRT alone (9.6 months, 95%CI: 7.4 – 11.8), curative RT alone (9.7 months, 95%CI: 6.4 – 21.2), palliative RT alone (5.5 months, 95%CI: 3.9 – 8.3), and palliative chemotherapy (5.3 months, 95%CI: 2.6 – 7.5).
- Similar trends were exhibited for results pertaining to assessment of time to next treatment or death (TTNT-D). CRT + durvalumab had numerically longer TTNT-D (28.6 months, 95%CI: 24.9 – 34.9) relative to other initial stage III treatment groups: CRT alone (11.7 months, 95%CI: 9.0 – 13.9), curative RT alone (13.7 months, 95%CI: 9.6 – NR), palliative RT alone (6.7 months, 95%CI: 4.1 – 9.7), and palliative chemotherapy (6.2 months, 95%CI: 3.9 – 12.9).
- Subgroups that trended to having improved median OS among patients who received CRT + durvalumab were:
    - Age <65 years
    - Female
    - Adenocarcinoma histology
    - Ever smoker
    - ECOG 0
    - PD-L1 high (>=50%)
- Subgroups that trended to having improved median rwPFS among patients who received CRT + durvalumab were:
    - Age <65 years
    - Female
    - Adenocarcinoma histology
    - Ever smoker
    - EGFR wildtype
    - PD-L1 high (>=50%)
- For patients who received CRT + durvalumab or CRT alone as the initial stage III treatment, subgroup analyses were carried out by applying further restrictions on eligibility criteria to replicate the phase III PACIFIC trial (denoted as “PACIFIC-eligible CRT alone” group and “PACIFIC-eligible CRT + durvalumab” group). The following exclusion criteria were applied to both groups:
    - Progression or receipt of next treatment or death during CRT or within 42 days after CRT completion

    - Receipt of sequential CRT
    - ECOG 2+
    - PACIFIC-eligible CRT + durvalumab cohort was associated with numerically longer mOS (43.7 months, 95%CI: 35.7 – NR) relative to the PACIFIC-eligible CRT alone cohort (22.4 months, 95%CI: 20.3 – 30.9)
- Patients who completed the full 12 months of maintenance durvalumab had improved OS and rwPFS than patients who discontinued treatment early due to adverse events, progression, or other reasons.

Summary of Safety Results

- Overall, durvalumab was well tolerated and had a manageable safety profile aligned with the phase III PACIFIC trial results.
- The most common adverse events of special interest among patients who received CRT + durvalumab were:
    - Respiratory (pneumonitis / interstitial lung disease): 20.1%
    - Dermatological (rash / dermatitis): 10.5%
    - Endocrinopathies (events of hypophysitis / hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, and type I diabetes mellitus): 9.0%

Conclusions

- CRT + durvalumab treatment was associated with longer OS, rwPFS, and TTNT-D relative to other initial stage III treatments.
    - Similar results favoring CRT + durvalumab was observed through assessment of PACIFIC-eligible cohorts (PACIFIC-eligible CRT alone group and PACIFIC-eligible CRT + durvalumab group) with restricted eligibility criteria.
- Subgroups with observed improved OS and rwPFS were:
    - Age <65 years
    - Female
    - Adenocarcinoma
    - Ever smoker
    - ECOG 0,
    - EGFR wildtype
    - PD-L1 high (≥ 50%)
- Durvalumab treatment demonstrated a well-tolerated and manageable safety profile. The safety profile observed in this study was consistent with the established safety profile to date and is in alignment with the phase III PACIFIC trial, with the most common AESI being pneumonitis / ILD.
- Taken together, the overall benefit/risk of durvalumab treatment is highly favorable in the indicated patient population.