STUDY REPORT SYNOPSIS

THASSOS-International

A Multicountry, Multicentre, Non-interventional, Retrospective Study to Determine the Real-world Treatment Patterns and Associated Outcomes in Patients With Resectable Early-stage (IA to IIIB) Non-small Cell Lung Cancer

Lung cancer is among the most prevalent malignancies and is the leading cause of cancer death. 85% of cases of lung cancer are Non-small Cell Lung Cancer (NSCLC). According to reports, the five-year survival rate for stage IA disease ranged between 80% and 90%, dropping to 19% to 23% in stage IIIB disease.

This retrospective study was carried out in 7 countries on patients with resectable, early-stage (IA to IIIB) NSCLC in order to understand real-world treatment patterns, 3-years survival rates, and different factors assoc1iated with NSCLC, such as demographic, clinico-pathological characteristics, adjuvant and neo-adjuvant treatment, surgical outcome, prevalence of EGFR mutation and PD-L1 expression, and its variations by region.

Milestones:

Milestone	Planned date
Study protocol	August 2021
First patient in	November 2021
Last patient in	September 2022
Database lock	April 2023

Phase of development: Retrospective Study

Sponsor: AstraZeneca

Author: [redacted]

This study was performed in compliance with Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice (ICH GCP), Good Pharmacovigilance Practices (GPP), and the applicable legislation on non-interventional studies.

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Background/rationale:

Early detection and treatment of resectable NSCLC is crucial for prolonging life, as it is a leading cause of cancer mortality worldwide. Resectable NSCLC refers to cases where the tumor can be completely removed by surgery. Despite advancements in treatment, recurrence rates remain high and overall survival with adjuvant chemotherapy is poor. To potentially cure patients, delay recurrence, and improve survival, a multimodal approach combining surgery, chemotherapy, and radiotherapy is necessary. The focus of this study was solely on resectable NSCLC patients, who had tumors suitable for surgical removal. Immunotherapy has rapidly changed the management paradigm of advanced NSCLC over the past 5 years. Durvalumab, a monoclonal antibody against programmed cell death ligand-1 (PD-L1) has shown significant improvement in overall survival (OS) in patients with unresectable stage III disease. In recent years, the management of advanced NSCLC has been revolutionized by immunotherapy, specifically Immune-Checkpoint Inhibitors (ICIs). However, the efficacy and safety of ICIs in resectable early-stage NSCLC are still being evaluated in ongoing studies. Screening for EGFR mutations has demonstrated significant clinical implications in the treatment of NSCLC, but further research is needed.

The management landscape of patients with epidermal growth factor receptor (EGFR) mutant advanced NSCLC has also changed significantly with the advent of targeted therapies like tyrosine kinase inhibitors (TKIs). There are EGFR-TKIs currently approved for neo-adjuvant and adjuvant use in resectable early-stage NSCLC (I to III), such as Osimertinib which is a third-generation EGFR TKI. Osimertinib has been shown to significantly prolong DFS and OS in resectable NSCLC patients, as demonstrated in the ADAURA trial.

This retrospective study aims to collect data from established patients' medical records to consolidate the available information on treatment patterns, survival rates and associated treatment effectiveness outcomes in patients with resectable early-stage (IA to IIIB) NSCLC. Results from this study will support other studies like ADAURA, NeoADAURA, AEGEAN, and BR.31 to better understand the receipt of neo-adjuvant/adjuvant therapies and associated clinical outcomes.

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Objectives:

Primary objective:

To describe the treatment patterns and determine their associated 3-year survival rate according to clinical and pathologic staging in patients with resectable early-stage (IA to IIIB as per AJCC seventh edition) NSCLC

Secondary objectives:

• To describe the demographic and clinico-pathological characteristics of patients with resectable early-stage (IA to IIIB) NSCLC

• To determine the real-world OS and survival rates in resectable early-stage (IA to IIIB) NSCLC according to treatment patterns

• To determine the prevalence of EGFR mutations and PD-L1 expression in patients with resectable early-stage (IA to IIIB) NSCLC

• To determine the relationship between OS and age, stage, EGFR mutation status, and PD-L1 status

• To describe the biomarker testing strategies such as type of samples and antibodies used in patients with resectable early-stage (IA to IIIB) NSCLC

• To determine the factors associated with receipt of neo-adjuvant and/or adjuvant treatments for resectable early-stage (IA to IIIB) NSCLC

• To describe the type of surgical resection and associated outcomes

• To determine the compliance to neo-adjuvant and/or adjuvant treatment and the reason(s) for discontinuation (if available).

Exploratory objectives:

• To determine the real-world effectiveness of the treatment patterns in terms of disease-free survival (rwDFS) and event-free survival (rwEFS) as per treatment patterns

• To determine the effectiveness of the post-progression treatment in terms of progression-free survival (rwPFS) as per the first-line of therapy (LOT) in relapsed NSCLC.

Study design: Non-interventional, multi-country, multicentre, retrospective study.

Data source: Data from 755 patients with primary stage IA to IIIB NSCLC was collected from index date until end of follow-up.

Study population: The study population included patients diagnosed with primary stage IA to IIIB NSCLC and followed up from 01 January 2013 until at least 31 December 2020.

Inclusion criteria:

1. Adult female and male patients aged ≥18 years or ‘adults’ according to age of majority as defined by the local regulations on index date

2. Patient or next of kin/legal representative (for deceased patients at study entry, unless a waiver is granted) who provided written or electronic informed consent according to the local regulations, where applicable

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3. Patients diagnosed with primary stage IA to IIIB NSCLC as per seventh edition AJCC whose tumor was deemed resectable between 01 January 2013 and 31 December 2017 and followed up until at least 31 December 2020, as per the medical records with availability of at least 12 months of follow up data from the index date (date of diagnosis of early-stage [IA to stage IIIB] resectable NSCLC), unless patient died within 12 months of diagnosis.

Exclusion criteria:

1. Patients with a concomitant cancer at the time of diagnosis of NSCLC, except for nonmetastatic nonmelanoma skin cancers, or in situ or benign neoplasms; a cancer was considered concomitant if it occurs within 5 years of NSCLC diagnosis

2. Patients diagnosed with stage IV NSCLC

3. Histology of the tumor is small cell lung cancer, neuroendocrine in origin, or a mixed histologic type with small cell and non-small cell lung cancers.

Statistical methods:

Statistical analyzes were primarily descriptive in nature. All tabulations, figures and listings were produced using the SAS System (Version 9.2 or higher). Data from all participating centres were pooled for analysis and where applicable, data was presented by cohort, as well as by country and/or region in pre-defined subgroups of interest. The comprehensive statistical analysis of the data collected in this study was documented in the Statistical Analysis Plan (SAP), which was dated and maintained by the sponsor. The SAP might have modified the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses was reflected in a protocol amendment. All analyzes were performed using Full Analysis Set (FAS) that comprised of all the participants who fulfil all the eligibility criteria and were included into the study. According to the objectives, the relevant parameters were summarized descriptively with appropriate statistical methods: categorical variables were presented using frequencies, percentages and corresponding 95% Confidence Intervals (CIs) using Clopper-Pearson exact method (subject to availability of adequate data) and continuous variables using number of observations, arithmetic mean, Standard Deviation (SD), median, 25th and 75th percentiles, minimum and maximum values. Standard imputation methods were used to handle missing/partially entered dates. Where other types of data were missing from the original medical record, the affected analyzes were conducted using only the results of those patients with data available. The percentage of patients with data missing were reported for each outcome variable. Counts of missing observations were presented in summary of each outcome. Tabular and graphical representation of the time-to-event data was prepared using KM method.

Results:

Primary objective:

The following were the results as per treatment patterns:

‘Surgery’ only was performed on 32.5% of the patients, with the highest proportion (64.1%) in stage I and the lowest proportion (12.8%) in stage III. A small percentage (4.8%) of patients received both surgery and neo-adjuvant systemic cancer therapy, with the highest proportion (7.4%) in stage III and the lowest proportions in Stages IA and IIB. Similarly, a small percentage (4.9%) of patients underwent neo-adjuvant therapy, surgery, and adjuvant therapy, with the highest proportion (9.3%) in stage III and the lowest proportions in stage I (1.3%). The majority of patients (35.5%) received surgery and systemic cancer therapy as adjuvant treatment, with the highest proportion (50.8%) in stage II and the lowest proportion (22.5%) in stage I. A moderate percentage (12.6%) of patients

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received surgery, systemic cancer therapy, and radiation therapy as adjuvant therapy, with the highest proportion (26.7%) in stage III and the lowest proportion (3.0%) in Stage I.

Regarding treatment duration, in the neo-adjuvant setting, the mean duration of systemic cancer therapy was 109.7 days, representing an average of around 3 months. The mean duration of radiation therapy was 52.9 days, indicating a treatment period of around 2 months. For adjuvant therapy, the mean duration of systemic cancer therapy was 123.9 days, again averaging around 4 months, while the mean duration of radiation therapy was 71.2 days, suggesting a somewhat similar treatment period as in the neo-adjuvant setting.

The 3-year survival rate for all patients was 75.5%. This means that out of the total 755 patients, 75.5% were confirmed to be alive at the 3-year mark from the index date. Conversely, the failure rate, representing patients who did not survive for 3 years, was 24.5%.

Secondary objective:

Demographic and clinical-pathological characteristics:

Age: Overall, the mean age of the patients was 61.8 years varying at each stage and ranging from 60.9 to 63.1 years. The median age across all stages was 62 years. The mean age for patients undergoing neo-adjuvant chemotherapy or radiotherapy only was 60.1 years and surgery was 64.9 years. Patients receiving adjuvant therapy had a slightly lower mean age of 59.7 years, and those receiving both neo-adjuvant and adjuvant therapy had a mean age of 59.4 years.

Gender: Overall, males constituted 69.3% and female accounted for 30.7% of the total patients. Patients who underwent surgery, 148 (19.6%) were males and 96 (12.7%) were females. Similarly, the majority of patients receiving neo-adjuvant therapy, adjuvant therapy, and both therapies were males.

Ethnicity: The majority of patients were classified as Caucasian, but there was representation from various ethnicities like Arabic, Chinese, East Asian, Indian, and other ethnicities.

Smoking status: The prevalence of lung cancer was highest in ex-smokers (32.8%), followed by current smokers (32.3%) and never smokers (21.7%).

ECOG Performance Status: The majority of patients had a Performance Status of 1 (35.4%), indicating restricted physical activity but still able to perform light work. The distribution of ECOG Performance Status varied across different stages, with higher statuses observed in advanced stages.

TNM staging: Mosts patients had tumors in the right upper lobe, and the most common primary tumor stages were T2a (28.7%) and T3 (26.6%). Adenocarcinoma (57.5%) was the most common histological type, followed by Squamous cell carcinoma accounting for 25.6% of patients. The other histology types were much less common, with bronchiole-alveolar, large cell carcinoma, mixed, and undifferentiated NSCLC each accounting for less than 3% of patients..

Survival outcomes:

The survival rates specific to each treatment modality were analyzed, but no statistical significance was observed.

Overall survival: The median survival time from the index date to the end of follow-up or death due to any cause was 7.5 years (95% CI - 6.7 to NE years).

Prevalence of EGFR mutations and PD-L1 expression:

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EGFR mutations testing was done on 183 patients (i.e. 24.2 % of total polulation) and an EGFR mutation was present in a total of 52 patients (6.9% of the total population and 28.4% of the tested population).

PD L1 testing was done on 44 (5.8% of total population) patients and 23 (3.0 % of total population and 52.3% of tested population) patients were positive and 21 (2.8 % of total population and 47.7% of tested population) patients were negative. These results suggest that EGFR mutations are present in a relatively small portion of the population, whereas PD-L1 expression is more common among the subset of patients who were tested for it.

Biomarker testing strategies:

Immunohistochemistry antibodies such as 22C3, 28-8, and SP263 were used for PD-L1 expression testing

Compliance to neo-adjuvant and/or adjuvant treatments:

Completion rates varied across different treatment modalities, with higher rates observed in post-surgical systemic therapy and radiotherapy compared to pre-surgical therapy.

The main reasons for discontinuation included toxicity, disease progression, physician decision, and patient refusal.

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