Clinical Study Report Synopsis	
Study Code	D4191R00036
Edition Number	V0.1
Date	23 September 2023
NCT Number	NCT04836975

A Multicenter Retrospective Observational Study to Reveal the Patterns of Presentation Management and Outcome of Patients with Small Cell Lung Cancer (SCLC) and Stage III Non-Small Cell Lung Cancer (NSCLC) in Saudi Arabia: REVEAL Study

2. SYNOPSIS

Background/rationale

Lung cancer is the leading cause of cancer-related mortality around the world, and it continues to have an enormous impact on the health systems of all countries. There are two major histological subtypes of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for almost 85% of all lung cancer cases; the commonest subtypes are squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma (5).

The management of SCLC did not change significantly for more than two decades before the introduction of immunotherapy. It is usually divided into two broad stages for management purposes; although TNM stages are used officially, these two categories are the limited and extensive stages (15,16). Limited-stage SCLC is usually treated with concurrent chemoradiotherapy followed by chemotherapy, then prophylactic brain irradiation (17,18). Extensive-stage SCLC is usually treated with systemic therapy that is chemotherapy-based with platinum and VP16 with the recent approval of checkpoint inhibitors for this disease (19,20).

There is limited information available in Saudi Arabia that includes information on diagnosis, treatment patterns, and their effectiveness and survival duration of patients with small-cell lung cancer and stage III NSCLC. In this context, this multicenter non-interventional study (NIS) aimed to retrospectively identify the treatment patterns in Saudi patients. The collected data is expected to contribute to helping identify the unmet treatment needs, besides providing baseline data for evaluating the impact of therapies for treating SCLC and stage III NSCLC. This study aimed also to identify any unmet needs in the diagnosis, work-up, and management of these diseases.

Objectives

Primary objective(s)

1. To characterize the treatment patterns of patients diagnosed with primary Small Cell Lung Cancer "SCLC" (Extensive stage & Limited Stage) / stage III Non-Small Cell Lung Cancer "NSCLC".

Secondary objective(s)

1. To describe the demographic and clinical characteristics of patients diagnosed with primary SCLC (Extensive stage & Limited Stage) / stage III NSCLC in a real-world setting.

2. To estimate clinical outcomes (Best Response, Progression-Free Survival "PFS"* and Overall Survival "OS"**) and to describe metastases from the date of treatment initiation to the end of follow-up.

   ***PFS is defined as the time from the date of treatment initiation to the date of disease progression on or after first-line therapy or death, whichever occurs first.**

   ****The Overall Survival (OS) following the date of initial diagnosis and date of initiation of each line of therapy (LOT) received from the index date to the end of follow-up.**

Exploratory Objective(s)

1. To assess treatment effectiveness (Objective Response Rate "ORR" and Disease Control Rate "DCR").
2. To describe healthcare resource utilization (HCRU) associated with primary SCLC (Extensive stage & Limited Stage) / stage III NSCLC treatment.

Study design

This was a multicenter, retrospective cohort of patients diagnosed with primary SCLC (limited or extensive stage) or stage III NSCLC. The main objective of this non-interventional study (NIS) was to characterize the treatment patterns from the index date (defined as the date of initial diagnosis of primary SCLC (Extensive stage & Limited Stage) or stage III NSCLC) to the end of follow-up (defined as the earliest of death, last available medical record or end of the observation period "defined as the date of data abstraction"), including the type of treatment received, duration of each treatment regimen, and reasons for stopping treatment regimen.

Data source

Eligible patients (both alive and deceased) had their data anonymously abstracted from their medical records into a centrally designed electronic case report form (eCRF). Patient screening and inclusion were estimated to start in Q4 2021-Q1 2022, and last until the end of Q3-Q4 2022, or the target sample is achieved, whichever is earlier.

Study population

The study population was identified by participating physicians involved in these patients' diagnosis, treatment, and management through the review of established patient medical records. Patients diagnosed with primary SCLC (Extensive stage & Limited Stage) or stage III NSCLC between 01 January 2015 and 31 December 2019 were targeted for study inclusion. This allows for at least nine months of follow-up for living patients recruited on the last day of

the enrolment window, which was deemed sufficient to assess the secondary outcomes of this study. It was estimated that a total of 95 patients diagnosed from 01 January 2015 onwards will be included in this NIS.

Inclusion criteria:

1. Adult male or female (≥18 years old or according to the age of majority as defined by local regulations).
2. First-ever diagnosis of lung cancer (absence of previous diagnosis of lung cancer, including SCLC and NSCLC) in the patient's medical records.
3. Patients either diagnosed with a primary diagnosis of SCLC (extensive or limited) or stage III NSCLC, confirmed by pathology, between 01 January 2015 and 31 December 2019.
4. Medical records available at the participating site reflect at least nine months of follow-up from the index date (unless the patient died within the first nine months of diagnosis).

Exclusion criteria:

1. Patients with concomitant cancer at the time of diagnosis other than SCLC or stage III NSCLC, except for non-metastatic non-melanoma skin cancers or in situ or benign neoplasms. Cancer was considered concomitant if it occurred within five years of NSCLC or SCLC diagnosis.
2. Patients initially diagnosed with stage I to II NSCLC who have progressed to stage III.
3. Current or prior use of "Durvalumab" treatment.

Statistical methods:

This was a descriptive and non-interventional study. Statistical Package for Social Sciences (SPSS) version 24 was used in the analysis. Data was quality checked for any erroneous entry.

Categorical variables were summarized by count and percentages. Continuous variables were summarized by mean and standard deviation, median, and IQR. All percentages, means, medians, and percentiles were formatted to one decimal place.

Time-to-event data, including rates of affected patients, were evaluated descriptively using Kaplan-Meier survival curves. The survivor function was summarized using the range, the 25th

and 75th percentiles, and the median survival. A two-sided 95% confidence interval for the median was explored. The plot of Kaplan-Meier estimates was presented.

Results

A total of 40 patients were included in the REVEAL study. In our study, the majority of patients were males and Arab in ethnicity, with a mean age of 61.8± 11.8 years and a mean BMI of 26.3±5.0 Kg/m^2.

Twenty-six patients were current smokers, with a mean pack-year of 21.8±16.6. ECOG status at the time of diagnosis showed that most of the patients had performance status (PS): 1 (50%), 3 (17.5%), and 2 (12.5%). At the end of follow-up, which was at least nine months for living patients recruited on the last day of the enrolment window, the mean BMI was 25 kg/m2, and 37.5% were current smokers, and the performance status was 3 among 22.5%, 2 in 12.5%, and 1 in 17.5% of the included patients.

Over half of the patients (57.5%) were diagnosed with Primary Small Cell Lung Cancer SCLC; six were diagnosed as limited stage SCLC, and 17 were diagnosed with extensive-stage SCLC. Seventeen (42.5%) patients were diagnosed with Stage III Non-Small Cell Lung Cancer (NSCLC). As for the pathological assessment of the tumor tissue, 52.5% were diagnosed as small cell carcinoma, followed by adenocarcinoma in 22.5% and squamous cell carcinoma in 15%. Only two patients were EGFR-positive.

Patients diagnosed before Feb 2016 were staged using the 7th edition AJCC of NSCLC. Seven patients were staged as IIIA, four patients with stage IIIB, and six didn't have available records for staging. Regarding patients diagnosed starting from Feb 2016, three were staged as IIIA, one as stage IIIB, and 13 had no available staging data.

Metastases was reported in 16 (94%) patients. Visceral and non-visceral Mets were reported to be equally affected; bone is the most affected non-visceral organ, while the liver is the most affected visceral site.

Comorbidity score, Charlson comorbidity index (CCI), showed that 45% had Low, 30% had Medium (1–2), and 25% had High burden of comorbidities. Only one patient had HBV positive, while none had autoimmune diseases or HCV infection. None of the eligible patients had

autoimmune diseases or hepatitis C virus, while only one patient gave a history of HBV infections. CCI was low in 32.5%, moderate in 22.5%, and high burden in 45%.

Patients received 87 treatment regimens; the largest proportion were lines of treatment (57.5%), followed by chemoradiation 32.2%. Most treatment regimens were the initial treatment (69%) and received via the intravenous route (87.4%) and every three weeks in frequency (60.9%). Carboplatin (35.7%) and etoposide (31.4%) were the most received chemotherapeutic agents. The mean number of received cycles was 4.7± 2.0 cycles. Sixty (69%) regimens were received as a first line, while 17 (19.5%) regimens as a second line. The median duration of treatment lines was 5 (IQR 2.5) months. The main reason for stopping chemotherapy was progression, accounting for 36.8%. At the end of follow-up, the best response to chemotherapy post-treatment regimen showed that 21 (24.1%) patients achieved partial response, nine (10.3%) patients achieved stable disease, and 35 (40.2%) patients progressed on treatment.

Regarding radiation therapy, the majority (55%) received palliative therapy, followed by chemoradiation (35%). Sites of radiation were lung (57.5%), followed by bone (30%). The median duration of radiation therapy was 32 (IQR 30) days. Only seven patients underwent surgical procedures.

The median progression-free survival (PFS) of all the received treatment regimens was 5 (95% CI 3.9-6.1) months, and the commonest metastatic progression site was the liver (10 patients), followed by CNS affection and lymph node metastases in eight patients. At the same time, the lung was the most common non-metastatic site of progression, affecting 14 (16.1%) patients. Distant metastasis was present in 18 (45%) patients at the end of follow-up, mainly affecting visceral sites, followed by non-visceral and CNS equally.

Twenty-four (60%) patients died at the end of the follow-up period, with a median overall survival of 17 (95% CI 6.5-27.4) months. Most of the patients died of cancer-related causes.

Outcomes of therapy showed 25.3% as the rate of objective response rate and 35.6% as the disease response rate.

Thirty-two (80%) patients were hospitalized during the study period, with a mean number of hospitalizations of 2.3±1.9 times. Most of the visits were at the hospital care level, and the reasons for admission were mainly respiratory symptoms.

Eleven patients were admitted to the ICU, while 35 patients visited outpatient clinics with a mean of 31.1±22.7 visits, and 30 (75%) patients conducted an emergency department visit with a mean of 4.1±3.1 visits. Most of the patients underwent one or more imaging modalities during their hospital visits.

Conclusion

REVEAL study was conducted to increase the knowledge regarding the available information on treatment patterns, clinical characteristics, clinical outcomes, treatment effectiveness outcomes, and healthcare resource utilization associated with primary SCLC (Extensive stage & Limited Stage) or stage III NSCLC treatment in the real-world setting. Although the study was terminated because it did not reach the planned sample size, the available data may describe the current treatment pattern and patient characteristics in the KSA.

Most of the treatment regimens were lines of treatment followed by chemoradiation. Carboplatin and etoposide were the most received chemotherapeutic agents. The main reason for stopping chemotherapy was progression. The majority of patients received palliative therapy followed by chemoradiation. The commonest metastatic progression site was the liver. At the same time, the lung was the most common non-metastatic site of progression. Most of the hospitalization visits were at the hospital care level, and the reasons for admission were mainly respiratory symptoms.

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