STUDY REPORT SYNOPSIS

REVEAL

REtrospective, obserVational study to describe the treatment patterns and outcomes of Epidermal Growth Factor Receptor mutant (EGFRm) locally Advanced or metastatic Non-Small-Cell Lung Cancer (NSCLC) patients in Belgium

Milestones:	First patient enrolled:	21 December 2018
	Last patient enrolled:	18 June 2019
	Date of database closure for report:	17 July 2019
	Date of database re-opening/closing for report:	21 August 2019
Phase of development:	Retrospective, observational trial	
Sponsor:	AstraZeneca NV/SA (Belgium & Luxembourg)	
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This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
1/2/3L	First/second/third-line treatment
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
ECOG	Eastern Cooperative Oncology Group
EGFR(m)	Epidermal Growth Factor Receptor (mutated)
ESMO	European Society for Medical Oncology
eCRF	electronic Case Report Form
mOS	Median Overall Survival
mPFS	Median Progression-Free Survival
mTDT	Median Time-to-Discontinuation of Treatment
mTST	Median Time-to-start of Subsequent Treatment
NR	Not Reported
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
RECIST	Response Evaluation Criteria In Solid Tumours
RWE	Real-World Evidence
SD	Standard Deviation
SoC	Standard of Care
SRS	Stereotactic Radiation Surgery
TDT	Time-to-Discontinuation of Treatment
TKI	Tyrosine Kinase Inhibitor
TST	Time-to-start of Subsequent Treatment
WBRT	Whole Brain Radiation Therapy

RESPONSIBLE PARTIES

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	Scientific Writer	Report writing	Modis Life Sciences	
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Background/rationale:

Background

In the past 10 years, treatment algorithms for non-small-cell lung cancer (NSCLC) have dramatically evolved and are increasingly branching out as a result of better clinical and biological patient selection and availability of new agents, such as tyrosine kinase inhibitors (TKIs) for tumours bearing activating epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase gene rearrangements [Dong, 2019].

First and second generation ($1^{st}/2^{nd}$ generation) EGFR-TKIs (gefitinib, erlotinib and afatinib) have been considered as the standard of care (SoC) at the time of study initiation as first-line (1L) treatment of advanced EGFR mutant (EGFRm) NSCLC based on the superior progression-free survival (PFS) (9-13 vs 5-7 months) compared to platinum-based chemotherapy [Novello, 2016; Dong J, Li B, Lin D, et al. Advances in Targeted Therapy and Immunotherapy for Non-small Cell Lung Cancer Based on Accurate Molecular Typing. Front Pharmacol. 2019 Mar 12; 10: 230.

Douillard, 2014; Mok, 2009; Fukuoka, 2011; Zhou, 2011; Rosell, 2012; Wu, 2014; Sequist, 2013]. Median overall survival (mOS) rates for 1L treatment with erlotinib, gefitinib and afatinib range between ~19 and ~28 months [Zhou, 2015; Zhao, 2015; Yang, 2015]. Based on these results, clinical guidelines recommend determining the patient's EGFR mutation status prior to treatment [Novello, 2016; Planchard, 2018]. Despite increased median PFS (mPFS) when using $1^{st}/2^{nd}$ generation EGFR-TKIs, most patients will still progress after 9-13 months of treatment. Various mechanisms of resistance to first-generation TKIs have been described, among which the T790M acquired mutation is the most common (50%-60%) [Sequist, 2011; Yu, 2013; Nagano, 2018].

Osimertinib, an oral, selective, third-generation, irreversible EGFR-TKI inhibitor with activity against the T790M mutation as well as the EGFR-TKI sensitizing mutations, is currently the only drug registered and reimbursed in Belgium for treatment in patients who have developed the EGFR T790M resistance mutation based on the phase III AURA3 trial, which showed an improved progression-free survival (PFS) (10.1 vs 4.4 months, $p < 0.001$) and response rate (71% vs 31%, $p < 0.001$) [Mok, 2017] compared to osimertinib with platinum-pemetrexed chemotherapy in T790M-positive patients after 1^{st} or 2^{nd} generation EGFR-TKI resistance. The drug has also shown promising activity against central nervous system metastases, including leptomeningeal disease [Yang, 2017; Mok, 2017]. The mOS for second-line (2L) treatment with osimertinib in the AURA3 trial was 26.8 months [Wu, 2019]. More recently, a phase III study (FLAURA), comparing osimertinib with standard EGFR-TKI treatment (gefitinib or erlotinib) as 1L treatment, demonstrated a significantly increased mPFS for osimertinib (18.9 vs. 10.2 months; $p < 0.001$) with the benefit confirmed in patients across all subgroups, including patients with brain metastases at baseline [Soria, 2018]. A significant increase in mOS was also demonstrated for osimertinib in FLAURA (38.6 vs. 31.8 months; $p = 0.0462$) [Ramalingam, 2020]. This led to the approval of osimertinib in June 2018 by the European Medicines Agency for use as 1L in EGFRm patients and reimbursement in Belgium for this

indication as of May 2019. Osimertinib has recently become the preferred SoC choice for 1L treatment of EGFRm NSCLC patients according to the ESMO guidelines [Planchard, 2018].

At the time of study initiation however, clinical guidelines recommended the use of 1st/2nd generation EGFR-TKIs as the SoC for the 1L treatment of patients with advanced EGFRm NSCLC and osimertinib as 2L treatment for patients who developed the T790M mutation after EGFR-TKI treatment [Novello, 2016].

Rationale

To our knowledge, there are no data available in the Belgian population describing the patient care in the 1L setting for advanced EGFRm NSCLC. Therefore, this study aimed to describe the treatment patterns and patient outcomes in this patient population throughout their disease in Belgium to evaluate the need and impact of (future) novel therapies for treating EGFRm NSCLC.

Furthermore, we aimed to investigate the proportion of patients receiving or not a definitive, systemic therapy for NSCLC after progression on a first EGFR-TKI, patient and disease characteristics associated herewith as well as EGFR testing at diagnosis and after progression on an EGFR-TKI.

Objectives:

Primary:

- To evaluate demographic characteristics for patients diagnosed with locally advanced or metastatic EGFRm NSCLC between 01 September 2015 and 31 December 2017.
- To evaluate NSCLC disease characteristics for 1L, 2L and third-line (3L) treatment during the observation window.
- To evaluate treatment patterns for 1L, 2L and 3L treatment during the observation window.
- To evaluate patient outcomes for 1L, 2L and 3L treatment during the observation window in terms of reason for treatment discontinuation, loss to follow-up and death of the patient.
- To evaluate the proportion of patients receiving a subsequent definitive, systemic treatment for NSCLC or no definitive, systemic treatment for NSCLC/best supportive care after progression on their previous therapy.
- To describe the EGFR mutation testing in NSCLC at diagnosis and relapse on 1L EGFR-TKI.

Secondary:

- To evaluate secondary patient outcomes for 1L, 2L and 3L treatment, in terms of PFS, time-to-discontinuation of treatment (TDT) and time-to-start of subsequent treatment (TST).
- To evaluate the OS, overall for all EGFRm NSCLC patients and depending on receipt of osimertinib treatment and line of osimertinib treatment.

Study design: This was a retrospective, observational, multi-centre study to evaluate treatment patterns and outcomes of patients diagnosed with locally advanced and metastatic EGFRm NSCLC in Belgium.

Data source: Patients were enrolled in 17 Belgian centres. Principal investigators were (pneumo-)oncologists, who were adequately qualified by experience and ability to perform the study. Patient data were collected through medical chart review and encoded into an electronic Case Report Form (eCRF). eCRFs were designed to gather data that had been collected as part of usual care of the patient. There were no protocol-mandated visits, procedures or diagnostic tests required.

Study population: The population consisted of 141 eligible adult patients diagnosed with advanced or metastatic EGFRm NSCLC between 01 September 2015 and 31 December 2017.

Inclusion criteria: Patients meeting the following criteria were selected:

- Male or female, aged at least 18 years.
- Pathologically confirmed NSCLC.
- Tumour harboured a mutation of EGFR.
- Diagnosis (radiologically or pathologically confirmed) of locally advanced or metastatic NSCLC, not amenable to curative surgery or chemoradiotherapy between 01 September 2015 and 31 December 2017.

Exclusion criteria: The following exclusion criteria were applied:

- No follow-up data available after diagnosis of locally advanced or metastatic EGFRm NSCLC.
- Patients who objected participation in the study.

Statistical methods: The analysis of the collected information only consisted of descriptive data. No formal statistical hypotheses have been formulated. The final report of this observational, retrospective study consists of a descriptive presentation of the collected data.

<u>Primary objectives analyses</u>

Demographic, baseline and NSCLC characteristics:

The analyses of demographic and baseline characteristics as well as NSCLC disease characteristics at diagnosis were provided overall. NSCLC disease characteristics after progression on 1L, 2L or 3L were calculated by treatment line.

Treatment patterns:

The proportion of patients receiving a subsequent definitive, systemic treatment for NSCLC or no definitive, systemic treatment for NSCLC/best supportive care after progression in 1L, 2L or 3L was calculated by line as well as overall for patients who progressed on 1L, 2L or 3L EGFR-TKI. A subgroup analysis was performed for patients with/without/unknown T790M mutation.

Duration of treatment beyond progression was also analysed according to the type of treatment received (1st or 2nd generation EGFR-TKI, osimertinib, chemotherapy, immunotherapy or other).

Patient outcomes:

Patient outcomes were calculated overall, by treatment line and grouped by type of treatment received in each line (1st or 2nd generation EGFR-TKI, osimertinib, chemotherapy, immunotherapy or other).

Secondary objectives analyses:

PFS:

PFS was evaluated as continuous PFS, mPFS, PFS rate at 6, 12, 18 and 24 months using Kaplan-Meier estimator separated by treatment line (1L, 2L, 3L) and grouped by type of treatment received in each line (1st or 2nd generation EGFR-TKI, osimertinib, chemotherapy, immunotherapy or other).

TDT/TST:

TDT/TST was calculated as overall TDT/TST, median TDT/TST (mTDT/mTST), TDT/TST rate at 6, 12, 18 and 24 months overall and separated by treatment line (1L, 2L, 3L) and grouped by type of treatment received in each line (1st or 2nd generation EGFR-TKI, osimertinib, chemotherapy, immunotherapy or other).

TST:*

TST* (without considering death) was analysed according to TST (see above).

OS:

OS was evaluated as continuous OS, mOS, OS rate at 6, 12, 18 and 24 months using Kaplan-Meier estimator overall and grouped by the receipt of osimertinib treatment (Y/N).

This retrospective, observational, multi-treatment, multi-centre study (REVEAL) was conducted to investigate treatment patterns and patient outcomes in a Belgian population of advanced EGFRm NSCLC patients throughout their disease in order to evaluate the impact of (future) novel therapies. Moreover, the study was performed to describe the proportion of patients receiving or not a definitive, systemic treatment for NSCLC/best supportive care after progression on a first EGFR-TKI, as well as patient and disease characteristics associated herewith and to give an idea about EGFR testing patterns at diagnosis and after progression on a first EGFR-TKI.

Results:

Demographics and baseline NSCLC disease characteristics

Overall, the 141 patients investigated represented a typical EGFRm NSCLC population with European origin: 63.1% female, 95.0% Caucasian, 94.3% non-squamous cell carcinomas/adenocarcinomas, median age of 69 years, 51.1% never-smokers. The majority of patients (88.7%) was diagnosed with metastatic NSCLC of which 23.4% with

brain/leptomeningeal metastases. Most patients had an ECOG performance status of 1 or 0 (44.7% and 31.9%, respectively).

NSCLC disease characteristics after progression

The majority of progressions on any line (after 1L/2L/3L) were located in the lung, followed by bone, pleura and brain. After progression on 1L, most patients still had an ECOG performance status of 1 or 0 (40.0% and 26.7%, respectively), although the frequency of patients with status 2 had increased (13.3%). After progression on 2L, the proportions of status 0 and 1 decreased (16.7% with status 0, 25.0% with status 1), and those for status 2 and 3 increased (20.8% with status 2 and 4.2% with status 3). However, for a relatively high percentage of patients (20% at start of 2L and 33.3% at start of 3L), the ECOG score was unknown at progression. After progression, the percentage of brain/leptomeningeal metastases increased (42.2% and 41.7% had brain/leptomeningeal metastases during or at start of 2L or 3L treatment, respectively).

Treatment patterns

Even though the majority of patients received 1st or 2nd generation EGFR-TKIs (73.8%) in 1L, a substantial proportion received chemotherapy (17.7%), immunotherapy (2.1%) or other therapies (2.1%). Of the 25 patients treated with chemotherapy in 1L, 44.0% had a common mutation. After treatment discontinuation in 1L, EGFR-TKIs were provided to 37.7% patients in 2L and 11.1% in 3L. A total of 11.3% of all patients received their first EGFR-TKI in 2L. Osimertinib was provided to 23.4% of patients in 2L and 11.1% in 3L. No patients received osimertinib in 1L. The proportion of patients receiving chemotherapy increased in further lines (20.8% in 2L and 50.0% in 3L). Similarly, immunotherapy treatment increased in 2L and 3L (7.8% and 11.1%, respectively). The relative frequency of patients with treatment beyond progression was 69.0%, 52.8% and 14.3% in 1L, 2L and 3L, respectively, but most of these patients were treated less than 3 months beyond progression.

Patients receiving subsequent therapy

Overall, 73.8% of patients who progressed on their first EGFR-TKI and discontinued treatment (on the line on which they progressed) received a subsequent definitive, systemic treatment for NSCLC. Hence, 26.2% of patients did not receive a subsequent systemic treatment after progression on a first EGFR-TKI. A total of 32.8% of patients who progressed on their first EGFR-TKI and discontinued their treatment, received osimertinib.

Patient outcomes

The relative frequency of treatment discontinuation only slightly differed between the treatment lines (77.3% of patients in 1L, 72.7% in 2L and 77.8% in 3L). The main reason for treatment discontinuation in all lines was progression (1L: 44.0%; 2L: 58.9%, 3L: 42.9%). Within the observation window, 27 patients (19.1%) died in 1L, 18 (23.4%) in 2L and 17 (47.2%) in 3L. None of these deaths were considered related to treatment.

EGFR testing at diagnosis

In total, 158 EGFR tests were performed in the 141 enrolled patients, of which the majority needed only one test to obtain a final positive result (88.7%). When considering the results from all tests (but duplicate/triplicate results counted only once), exon 19 deletions were detected in 41.1% and exon 21 L858R mutations in 29.8% of patients. A surprisingly high proportion of patients was identified with rare EGFR mutations only (29.1%). The most common biopsy type was tumour (80.1% of all final results considered). The median time between disease diagnosis and first positive EGFR test was 15.0 days, with an additional 9 days calculated between the first positive result and start of 1L treatment. About half of the tests were performed inhouse and half externally (52.5% versus 47.5%, respectively; all tests considered) and no important differences were observed in testing turn around times according to the testing location.

T790M testing after progression on first EGFR-TKI

Overall, 65 patients progressed on a first EGFR-TKI, of whom 47 (72.3%) had a T790M test performed and of these, 53.2% were tested positive for T790M. The most common biopsy types were tumour and liquid (44.0% each when considering only final positive results). The median time between disease progression in 1L (2L) and receipt of the T790M test result was 16.5 days (17.0 days) and an additional 12 days were calculated between the final T790M test result and start of 2L or 3L treatment.

Secondary outcomes

Secondary outcomes could only be obtained for a limited number of lines and treatment subgroups. Due to the (statistical) limitations related to the analysis of these endpoints in this study, they need to be interpreted with caution. Most interestingly, a mPFS of only 7.59 months (95% CI: 6.47, 11.76) was observed for patients treated with 1st or 2nd generation EGFR-TKIs in 1L. In all patients the mOS of 27.43 months was comparable to earlier observations seen in literature.

mTDT after 1L treatment with chemotherapy was relatively short (1.97 months). Since we assume that some patients in the study started 1L chemotherapy due to extended waiting times before EGFR test result or due to fast progression which required to start a therapy quickly, the short mTDT might partly be explained by elective and quick switches in some of the patients from chemotherapy to EGFR-TKI therapy when the EGFR result was obtained.

Due to the limitations described in the discussion section, the results of the REVEAL study should be considered as exploratory and be interpreted on a descriptive level.

General conclusion

The results from this real-world study in Belgium highlight that even though the majority of patients who were diagnosed with EGFRm advanced NSCLC (73.8%) received 1st/2nd generation EGFR-TKIs in 1L, a substantial proportion received other treatments. In addition, we observed that 26% of EGFRm patients did not receive a subsequent, systemic treatment for NSCLC after having progressed and discontinued on their first EGFR-TKI. Seventy-two percent of patients progressing on a 1st/2nd generation EGFR-TKI were tested for the T790M mutation and approximately half of these were tested positive (but leaving nearly 30% of patients untested). Finally, only about one third of patients having progressed on and discontinued a first EGFR-TKI were treated with osimertinib. These observations should be taken into account when deciding on 1L treatment, which should optimize benefits for patients in terms of PFS, OS and toxicity. The study showed that EGFR and T790M testing have been optimised in Belgium within a relatively short timeframe as seen in the frequent use of liquid biopsies for testing next to tissue biopsies, especially at progression and times to result for EGFR testing that are in line with European and Belgian guidelines.

MILESTONES

Milestone	Date
First patient enrolled:	21 December 2018
Last patient enrolled:	18 June 2019
Date of database closure for report:	17 July 2019
Date of database re-opening/closing for report:	21 August 2019

1. LIST OF REFERENCES

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