Real-World Response and Outcomes in Non-Small Cell Lung Cancer Patients With Epidermal Growth Factor Receptor Exon 20 Insertion Mutations

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Background

- Epidermal growth factor receptor (EGFR) exon 20 insertion mutations (exon20ins) are present in 4%–12% of patients with EGFR-mutated non–small-cell lung cancer (NSCLC).[1-5]
- There is no targeted therapy approved for patients with EGFR exon20ins-mutant NSCLC. Most NSCLC patients with these rare mutations receive front-line platinum-based chemotherapy (chemo). Novel therapies, such as mobocertinib, are in development for treatment in this rare population.
- Information describing real-world treatment pattern and outcomes for patients with EGFR exon20ins-mutant NSCLC is limited.[6-8]
- Immuno-oncology (IO) therapy may be considered as available therapy, but the effectiveness of IO is not established in these patients.

Objective

- To describe treatment patterns and clinical outcomes in patients with advanced NSCLC (aNSCLC) harboring EGFR exon20ins.

Methods

Study Design

- This retrospective observational study used the nationwide Flatiron Health database (data cutoff: 29 February 2020), a longitudinal, de-identified database derived from electronic health record (EHR) data, containing patient-level structured and unstructured data curated via technology-enabled abstraction.[9-10]
- During the study period, the de-identified data originated from approximately 280 US cancer clinics (~800 sites of care).

Study Population (**Figure 1**)

- Four separate cohorts of patients with aNSCLC harboring EGFR exon20ins were selected from the de-identified Flatiron Health Database:
  - **First line (1L)**: Patients receiving 1L therapy after documented EGFR exon20ins (1L start date as index date).
  - **Second or later line (≥2L)**: Patients receiving ≥2L therapy after documented EGFR exon20ins (≥2L start date as index date).
  - **≥2L trial-aligned**: ≥2L patients with baseline characteristics aligned with the key eligibility criteria of the mobocertinib Trial NCT02716116 Part 3.
  - **≥2L post-platinum**: ≥2L trial-aligned patients (as defined above) previously treated with platinum-based chemo.

Methods

Outcomes

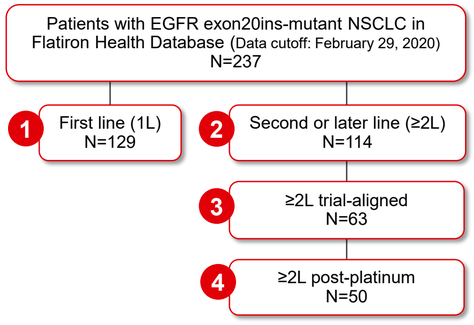
- Treatment pattern was assessed for the index line of therapy (LoT).
- The anti-tumor effectiveness of currently used standard of care was assessed, including:
  - Confirmed real-world overall response rate (rwORR) was defined as the proportion of patients on a given treatment who had a partial response (PR) or complete response (CR) assessment determination based on clinical documentation followed by a subsequent assessment of PR, CR, or stable disease throughout the course of a single LoT, among all patients in that cohort.
  - Real-world progression-free survival (rwPFS) was defined as the time from the index date to real-world progression or death from any cause. Patients were censored at the end of LoT or last clinic note date.
  - Overall survival (OS) was defined as the time from the index date to death. Patients for whom a date of death had not been identified were censored at the date of last confirmed activity.

Statistical Analysis

- Baseline characteristics were assessed within 3 months prior to the index date and reported with means, medians, and standard deviations for continuous variables, and frequencies and percentages for categorical variables.
- Treatment types were reported with frequencies and percentages.
- Kaplan-Meier method was used to estimate median OS and median rwPFS, and the corresponding 95% confidence intervals.

Results

Figure 1. Study cohorts



Results

Selected Baseline Characteristics

- Patient characteristics were similar among three ≥2L cohorts.

Table 1. Select baseline characteristics

Variables	1L (N=129)	≥2L Post-Platinum (N=50)
Median age, years (range)	66 (38-84)	64 (40-83)
Female, n (%)	84 (65.1)	34 (68.0)
Asian, n (%)	9 (7.0)	4 (8.0)
Smoking history, n (%)	66 (51.2)	21 (42.0)
Adenocarcinoma, n (%)	123 (95.3)	49 (98.0)
Brain metastasis, n (%)	38 (29.5)	17 (34.0)
ECOG PS, n (%)		
0-1	66 (51.2)	29 (58.0)
2-3	7 (5.4)	0 (0.0)
Missing	56 (43.4)	21 (42.0)
Median time from initial diagnosis, months	1.48	11.14
No. of prior systemic anticancer regimens, n (%)		
1	N/A	48 (96.0)
2		1 (2.0)
≥3		1 (2.0)

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Treatment Pattern of the Index LoT

- Treatment pattern was similar among three ≥2L cohorts, with IO being the most common index LoT.

Table 2. Treatment patterns of the index LoT

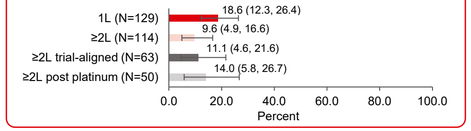
Index LoT n (%)	1L (N=129)	≥2L post-platinum (N=50)
EGFR TKI	37 (28.7)	10 (20.0)
EGFR TKI + mAb	1 (0.8)	0 (0.0)
IO	11 (8.5)	20 (40.0)
Other Chemo	3 (2.3)	7 (14.0)
Other Chemo + mAb	1 (0.8)	4 (8.0)
Platinum	1 (0.8)	0 (0.0)
Platinum + Other Chemo	40 (31.0)	5 (10.0)
Platinum + Other Chemo + IO	16 (12.4)	3 (6.0)
Platinum + Other Chemo + mAb	16 (12.4)	1 (2.0)
Other Therapy	3 (2.3)	0 (0.0)

mAb, monoclonal antibody; Platinum, platinum-based chemotherapy.

Confirmed rwORR

- Confirmed rwORR was poor in all cohorts, particularly in three ≥2L cohorts (**Figure 2**).

Figure 2. Confirmed rwORR, % (95% CI)



1L, first line; ≥2L, second or later line; CI, confidence interval; rwORR, real-world overall response rate.

Median OS and rwPFS

- In the 1L cohort, median rwPFS and median OS were 5.2 months and 17.0 months, respectively (**Figures 3 and 4**).
- In the ≥2L cohorts, median rwPFS ranged from 3.3 to 3.7 months and median OS ranged from 11.5 to 13.6 months (**Figures 3 and 4**).

Figure 3a. rwPFS, median (95% CI)

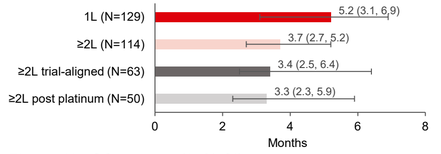
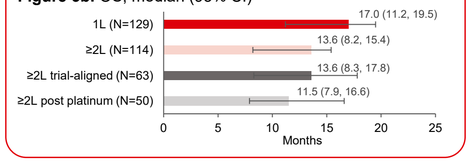


Figure 3b. OS, median (95% CI)



1L, first line; ≥2L, second or later line; CI, confidence interval; OS, overall survival; rwPFS, real-world progression-free survival.

Figure 4a. Kaplan-Meier plot for rwPFS in 1L cohort

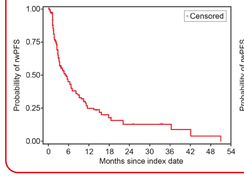
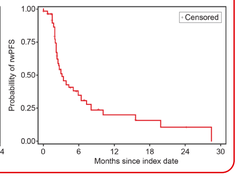


Figure 4b. Kaplan-Meier plot for rwPFS in ≥2L post-platinum cohort



1L, first line; ≥2L, second or later line; CI, confidence interval; rwPFS, real-world progression-free survival.

Therapy-Specific Response and Outcomes

- In patients treated with 1L platinum-based chemo, confirmed rwORR was 19.5% with median rwPFS of 5.7 months (**Table 3**).
- IO therapy was associated with poor confirmed rwORR and survival, consistently in the 1L and ≥2L setting (**Table 3**). Among patients treated with IO monotherapy, poor outcomes were consistently observed in patients with positive PD-L1 and patients with negative or unknown PD-L1 (confirmed rwORR: 5.0% and 4.3%, respectively).
- EGFR TKIs had limited clinical benefits with a poor confirmed rwORR of 2.7% in 1L, 5.0% in ≥2L, and 10.0% in ≥2L post-platinum cohort. Of 13 patients treated with 1L or ≥2L osimertinib, no patient had confirmed response (0%).

Table 3. Confirmed rwORR and survival outcomes by therapy

Cohort	N	Confirmed rwORR (95% CI)	Median OS (95% CI), months	Median rwPFS (95% CI), months
1L: Platinum	41	19.5% (8.8%, 34.9%)	17.0 (10.5, 33.2)	5.7 (3.0, 10.9)
1L: IO + Platinum	16	18.8% (4.0%, 45.6%)	11.3 (5.6, NR)	4.5 (1.2, 10.3)
1L: IO monotherapy	11	9.1% (0.2%, 41.3%)	11.0 (1.2, NR)	3.1 (1.1, 5.2)
1L: EGFR TKI	37	2.7% (0.1%, 14.2%)	10.7 (3.4, 22.3)	3.3 (2.2, 6.6)
≥2L post-platinum: IO monotherapy	20	5.0% (0.1%, 24.9%)	7.1 (2.5, 10.1)	2.2 (1.7, 3.0)
≥2L post-platinum: EGFR TKI	10	10.0% (0.3%, 44.5%)	12.2 (1.3, 17.8)	3.4 (0.0, 5.9)

1L, first line; CI, confidence interval; IO, immuno-oncology; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; rwORR, real-world overall response rate.

Limitations

- Data collection in the real-world setting may not be uniform. Specifically, in real-world practice, assessments of response were based on clinician's documentation and not on standard criteria such as RECIST; therefore, there is potential for variability and subjectivity.
- Given the small sample size, the outcome estimates tended to have large variances.
- Patients in the study were largely from the community setting, and outcomes like treatment patterns may not be generalizable to patients treated in an academic setting where prescribing practices may vary.

Conclusions

- In real-world settings, treatment patterns are diverse in patients with aNSCLC harboring EGFR exon20ins.
- Platinum-based chemo alone or in combination with other therapy was the most common 1L therapy.
- IO therapy, either as monotherapy or in combination with chemotherapy, appeared less effective for treatment of NSCLC with EGFR exon20ins.
- The real-world study provides a benchmark on the treatment outcomes in patients with aNSCLC harboring EGFR exon20ins and demonstrates an unmet need for improved therapeutic options for this population.

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