Real World Outcomes Among Patients with Epidermal Growth Factor Receptor (EGFR) Mutated Metastatic Non-Small Cell Lung Cancer Treated with EGFR Tyrosine Kinase Inhibitors versus Immunotherapy or Chemotherapy in First-line Setting

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INTRODUCTION

- Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommended 1L therapy for stage IV EGFR mutated (EGFRm) metastatic non-small cell lung cancer (mNSCLC) patients with mutations such as exon 19 deletions or L858R mutations.[1]
- Factors such as long turnaround time for biomarker testing[2] and the relatively poor prognosis of stage IV mNSCLC[3] may lead to patients initiating non-targeted therapies before testing results are received.
- While starting treatment earlier may seem like the best approach for these patients, initiating inappropriate therapies such as immuno-oncology agents (IO), could result in suboptimal outcomes.[4]
- Real-world studies comparing effectiveness associated with the initiation of EGFR TKI vs. IO ± chemotherapy in 1L in patients with stage IV EGFRm mNSCLC are limited.

METHODS

- **Study Design:** Retrospective, observational, study of adult patients with stage IV EGFRm mNSCLC treated with EGFR TKI, IO with or without chemotherapy (IO ± chemotherapy), or chemotherapy alone identified between 5/2017 and 12/2019. Data was available until 6/2020 allowing for at least 6 months of follow up.
- **Data Source:** Flatiron Health Electronic Health Record Database.
  - This database contains longitudinal, de-identified patient-level data from a demographically and geographically diverse, nationally representative population in the US.
- **Index Date:** Date of 1L therapy initiation.
- **Outcomes**
  - **Timing of 1L Initiation:** Whether 1L therapy was initiated before or after the EGFR test result date. Adjusted logistic regression was used to calculate odds of 1L treatment initiation before testing result was received.
  - **Time to Next Treatment or Death (TTNTD):** Time from 1L initiation to earliest of 2L initiation or death. Cox proportional-hazards models and Kaplan-Meier technique were used to examine the effect of each treatment class on TTNTD.

Figure 1. Patient attrition

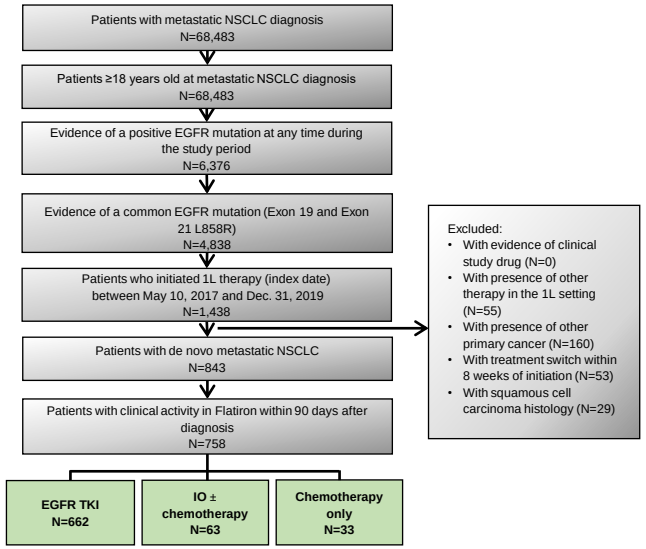
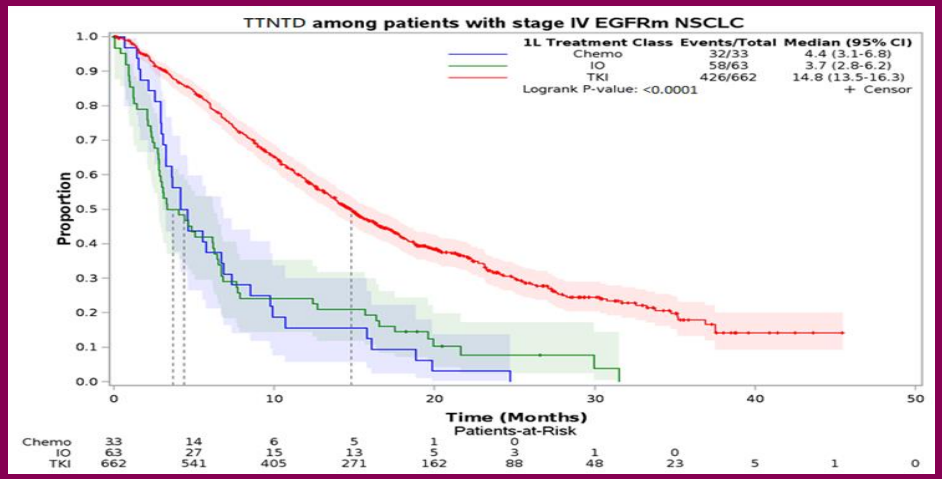


Figure 2. Time to next treatment or death among patients with stage IV EGFRm NSCLC



TTNTD for 1L EGFR TKI, IO ± chemotherapy, and chemotherapy was 14.8 months, 3.7 months, and 4.4 months, respectively

Table 1. Patient baseline characteristics

Characteristics		1L EGFR TKI N=662	1L IO ± chemotherapy N=63	1L chemotherapy only N=33
Age, mean ± SD		67.8 ± 11.0	66.4 ± 9.3	66.8 ± 11.0
Female, n (%)		444 (67.1)	37 (58.7)	16 (48.5)*
Race, n (%)	White	344 (52.0)	34 (54.0)	15 (45.5)
	Asian	103 (15.6)	7 (11.1)	2 (6.1)
	Black	42 (6.3)	6 (9.5)	2 (6.1)
	Hispanic	2 (0.3)	0 (0.0)	0 (0.0)
	Other	87 (13.1)	7 (11.1)	6 (18.2)
	Unknown	84 (12.7)	9 (14.3)	8 (24.2)
Region, n (%)	Northeast	119 (18.0)	14 (22.2)	5 (15.2)
	West	157 (23.7)	17 (27.0)	7 (21.2)
	Midwest	73 (11.0)	7 (11.1)	2 (6.1)
	South	219 (33.1)	19 (30.2)	18 (54.5)*
	Unknown	94 (14.2)	6 (9.5)	1 (3.0)
History of smoking, n (%)		283 (42.7)	30 (47.6)	23 (69.7)*
Time from diagnosis to 1L initiation, days, mean ± SD [median]		42.7 ± 46.3 [35.0]	38.8 ± 29.3 [30.0]	32.6 ± 19.5 [27.0]*
Histology, n (%)	Non-squamous cell carcinoma	651 (98.3)	62 (98.4)	33 (100)
	Not Otherwise Specified	11 (1.7)	1 (1.6)	0 (0)
ECOG grade, n (%)	0	179 (27.0)	22 (34.9)	12 (36.4)
	1	197 (29.8)	22 (34.9)	9 (27.3)
	2	79 (11.9)	4 (6.3)	3 (9.1)
	3	23 (3.5)	0 (0.0)	1 (3.0)
	4	1 (0.2)	1 (1.6)*	0 (0.0)
	Unknown	183 (27.6)	14 (22.2)	8 (24.2)
EGFR mutation type, n (%)	Exon 19 del.	374 (56.5)	34 (54.0)	15 (45.5)
	L858R	288 (43.5)	29 (46.0)	18 (54.5)

*Indicates p-value < 0.05 in comparison to EGFR TKI Cohort

Table 2. 1L therapy initiation based on timing of EGFR testing result*

Therapy type	1L Therapy (N=756)	1L initiation *before* EGFR testing results available (N=121)	1L Initiation *after* EGFR testing results available (N=635)
EGFR TKI	660 (87.3%)	62 (9.4%)	598 (90.6%)
IO ± chemotherapy	63 (8.3%)	39 (61.9%)	24 (38.1%)
Chemotherapy only	33 (4.4%)	20 (60.6%)	13 (39.4%)

*The date of the first positive EGFR test result was used. Patients were excluded if they received their EGFRm test result after 2L therapy initiation (2 patients in EGFR TKI group).

RESULTS

- Of 758 patients, 662 (87.3%) received 1L treatment with EGFR TKI, 63 (8.3%) received IO (monotherapy or in combination with chemotherapy), and 33 (4.4%) received chemotherapy alone (Table 1).
- A larger proportion of patients receiving 1L IO ± chemotherapy (61.9%) or 1L chemotherapy (60.6%) initiated therapy before receiving EGFR testing results compared to patients starting 1L EGFR TKIs (9.4%) (Table 2).
- Logistic regression showed that compared to EGFR TKIs, the odds of initiating 1L treatment before receiving EGFR test results were higher for IO ± chemotherapy (OR: 19.6, 95% CI: 10.4 – 37.1, p<0.001) and chemotherapy (OR: 14.1, 95% CI: 6.3 – 31.9, p<0.001), respectively.
- Median TTNTD was longer for patients treated with EGFR TKI (14.8 months, 95% CI: 13.5-16.3) compared to patients treated with IO ± chemotherapy (3.7 months, 95% CI: 2.8-6.2, p<0.001) and chemotherapy (4.4 months, 95% CI: 3.1-6.8, p<0.001) (Figure 1).
- After adjustment with Cox regression, patients treated with EGFR TKI had significantly lower likelihood of initiating 2L therapy or death compared to patients on IO ± chemotherapy (HR: 0.33, 95% CI: 0.24-0.43, p<0.001) or chemotherapy (HR: 0.34, 95% CI: 0.23-0.50, p<0.001).

DISCUSSION

Limitations

- As with most observational EHR based research studies, misclassification due to miscoding may be present, though this is expected to be non-differential with respect to treatment groups and outcomes.
- There may be some instances where the test result is known by the treating physician before it is recorded in the EHR. This may help to explain why approximately 9% of patients on EGFR TKIs initiated before test results were available in the EHR record.
- Given the limitations in measuring progression free survival in the Flatiron database, TTNTD was used as a proxy for PFS.

CONCLUSION

This study highlights the importance of adhering to NCCN Guidelines® and initiating EGFR TKIs as a first-line treatment among this patient population. Waiting to initiate 1L therapy until after testing results are received, if clinically feasible, may help ensure that providers are prescribing the appropriate treatment while minimizing impact of suboptimal regimens and associated side effects.

REFERENCES
1.Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed February 28, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org.
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DISCLOSURES
Jon Apple, Rahul Shenolikar, Kevin De Silva, and Ping Sun are currently employed by AstraZeneca at the time of the study. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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