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Short Communication

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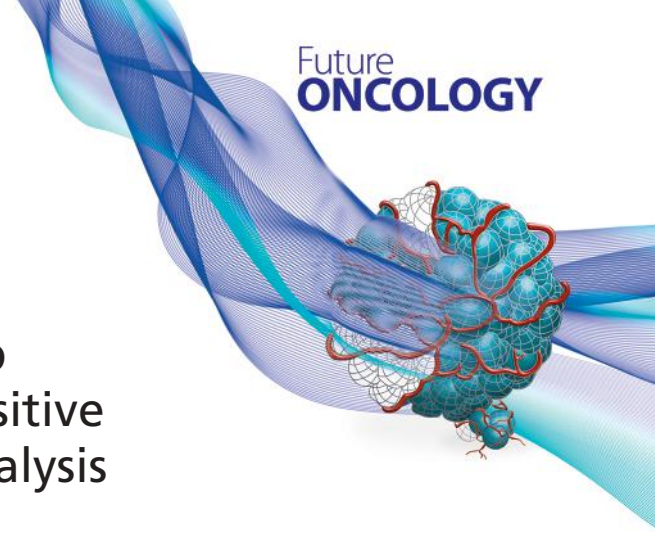

Sequential afatinib and osimertinib in patients with *EGFR* mutation-positive non-small-cell lung cancer: final analysis of the GioTag study

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Aim: Final overall survival (OS) and time on treatment analysis of patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC) who received sequential afatinib and osimertinib. **Patients & methods:** Patients (n = 203) had T790M-positive disease following first-line afatinib and started osimertinib treatment ≥10 months before data entry. Primary outcome was time on treatment; OS analysis was exploratory. **Results:** Median time on treatment with afatinib and osimertinib was 27.7 months (90% CI: 26.7–29.9). Median OS was 37.6 months (90% CI: 35.5–41.3); median OS was 41.6 and 44.8 months in Del19-positive patients and Asian patients, respectively. **Conclusion:** In real-world clinical practice, sequential afatinib and osimertinib was associated with encouraging outcomes in patients with *EGFR* mutation-positive NSCLC, especially in Del19-positive patients and Asian patients.

Clinical Trial Registration: NCT03370770 (ClinicalTrials.gov)

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Keywords: afatinib • EGFR • NSCLC • osimertinib

Three generations of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are now approved in the first-line setting for patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC): the first-generation reversible TKIs, erlotinib and gefitinib; the second-generation irreversible ErbB family blockers, afatinib and dacomitinib; and the third-generation EGFR TKI, osimertinib [1–5].

In randomized clinical trials, the second- and third-generation EGFR TKIs have significantly improved progression-free survival versus first-generation TKIs in first-line treatment of *EGFR* mutation-positive NSCLC [6–8]. Exploratory analysis of the ARCHER-1050 trial indicated that dacomitinib was associated with improved overall survival (OS) versus gefitinib, and LUX-Lung 7 showed a trend toward OS benefit with afatinib [9,10]. Recent data from the FLAURA Phase III trial demonstrated significantly prolonged OS with first-line osimertinib compared with the first-generation EGFR TKIs (gefitinib or erlotinib) in patients with *EGFR* mutation-positive NSCLC [11]. However, as acquired resistance to first-line EGFR TKI therapy is inevitable, the availability of subsequent treatment options following disease progression is a key consideration when assessing therapeutic choices.

Emergence of the T790M mutation in exon 20 of *EGFR* is the predominant molecular resistance mechanism to gefitinib, erlotinib and afatinib. This mutation presents in approximately 50–73% of tumors at the time of

acquired resistance, with the likelihood being highest in patients with Del19-positive disease [12–16]. Osimertinib has demonstrated impressive activity in T790M-positive patients [17]. In contrast, targeted therapy options following first-line osimertinib treatment remain limited due to the heterogeneity of osimertinib resistance mechanisms, which are still not fully understood [18,19]. Chemotherapy is often the only option for patients who progress on osimertinib treatment in everyday clinical practice.

It has therefore been suggested that, at least in some patients, reserving osimertinib as a second-line therapy option may maximize time on targeted treatment and defer the need for more toxic chemotherapy regimens. The GioTag study was a global, observational, multicenter study designed to assess outcomes in EGFR TKI-naive patients with *EGFR* mutation-positive (Del19/L858R) NSCLC who received sequential afatinib and osimertinib treatment in a real-world clinical practice setting [20,21]. Importantly, for real-world clinical practice, the study included elderly patients and those with poor prognostic characteristics (Eastern Cooperative Oncology Group performance status [ECOG PS] ≥2 or stable brain metastases) who are often under-represented in or excluded from randomized clinical trials.

At the initial and updated analyses (May 2018 and April 2019, respectively), results were encouraging, particularly for Del19-positive patients and Asian patients [20,21]. Here, we report findings from the final analysis, including updated time on treatment and OS data.

Materials & methods

Study design & patients

The design of the GioTag study has been described previously [20,21]. In brief, GioTag was a global, observational study conducted across ten countries (Austria, Canada, Israel, Italy, Japan, Singapore, Slovenia, Spain, Taiwan and the USA; NCT03370770). Data were collected between December 2017 and December 2019 for patients with *EGFR* mutation-positive (Del19 and L858R) NSCLC who had T790M-positive disease after first-line afatinib and subsequently received osimertinib. To limit selection bias, each participating center assessed the health records of a maximum of 15 consecutive patients. All patients must have initiated osimertinib ≥10 months prior to enrollment to avoid early censoring and ensure mature data. Data were collected directly from sites via manual medical chart review (n = 77; 38%) or from electronic health records (n = 126; 62%) supplied by Cardinal Health (OH, USA). Verification of source data were undertaken for 30% of patients. Informed consent was provided where required.

Outcomes & assessments

The primary outcome was time on treatment, defined as the time from the first dose of afatinib to that of the last dose of osimertinib or death. The OS analysis was exploratory and was defined as time from start of afatinib treatment to death.

Statistical analysis

Data cut-off for this final analysis was 28 November 2019 and data for all enrolled patients were included. Time on treatment and OS were estimated using the Kaplan–Meier method; for patients still on treatment, time on treatment was censored at the date of data collection.

Results

Baseline demographics and characteristics of the 204 patients included in the analysis have been described previously [20,21]. The GioTag population reflected real-world clinical practice and included patients with ECOG PS ≥2 (15.2%) and those with CNS metastases (10.3%), in addition to the usual patient population included in clinical trials. Patients were predominantly Caucasian (58.8%) but also included Asian (24.5%) and African–American (8.8%) patients. At the start of afatinib treatment, 73.5% of patients had a Del19 mutation and 26.0% had the L858R mutation. One patient had both Del19 and L858R.

Most patients received the approved starting doses of afatinib (40 mg/day; 83.7%) and osimertinib (80 mg/day; 98.0%). One patient was excluded from the analysis due to reports of conflicting data. At the time of this final analysis (December 2019), 120 (59.1%) patients had died, 31 (15.3%) were lost to follow-up and 52 (25.6%) were alive; of these 52, 29 remained on osimertinib treatment and 11 had discontinued osimertinib treatment.

After a median follow-up of 33.9 months, the median time on treatment for sequential afatinib and osimertinib was 27.7 months (90% CI: 26.7–29.9; Figure 1A). For Asian patients (n = 50), median time on treatment was 37.1 months (90% CI: 28.1–40.3) and in patients with Del19-positive tumors (n = 149), median time on treatment

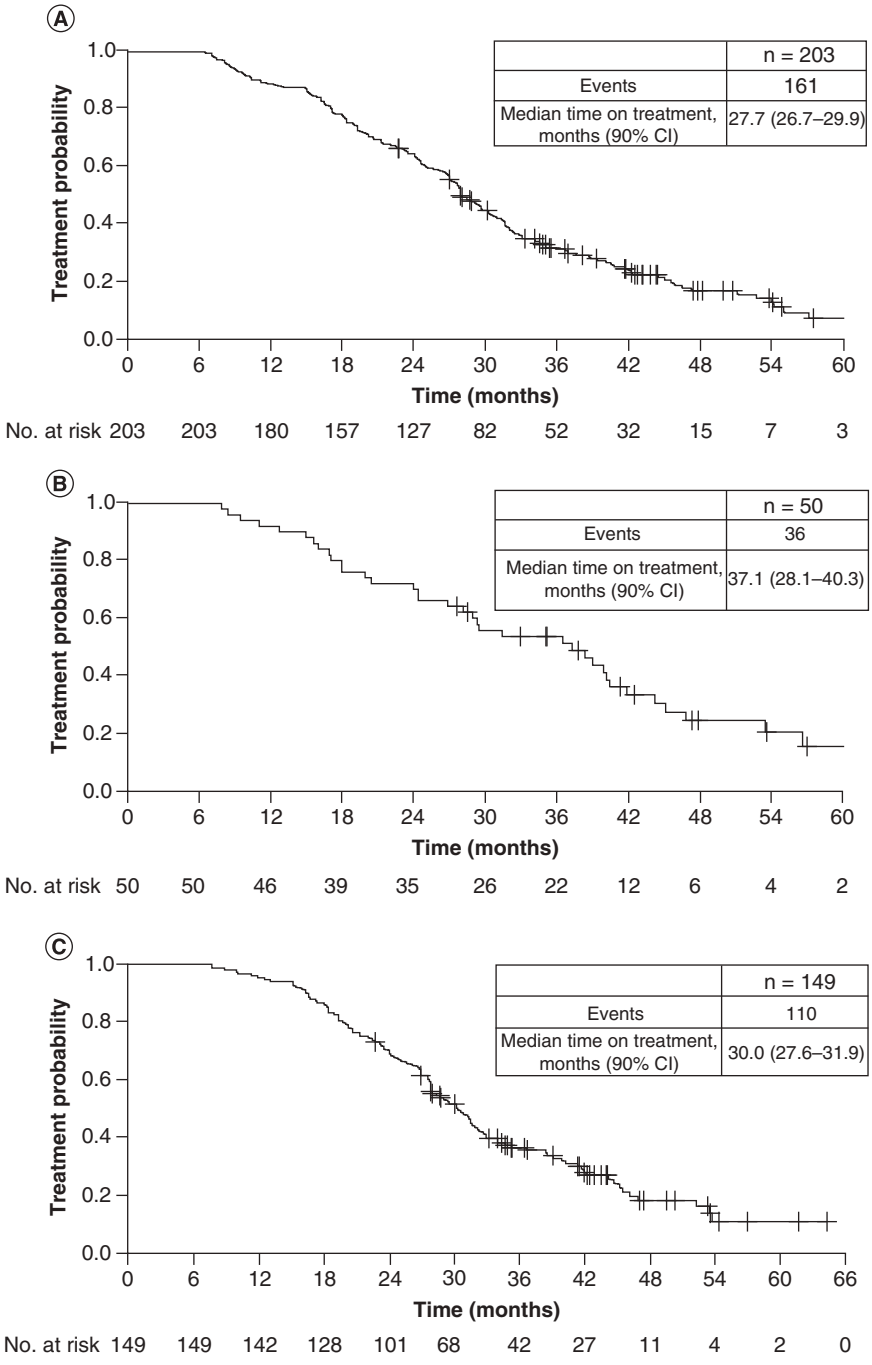

Figure 1. Time on treatment with sequential afatinib and osimertinib. (A) All patients; **(B)** Asian patients; and **(C)** patients with Del19-positive tumors.

was 30.0 months (90% CI: 27.6–31.9) (Table 1 & Figure 1). In the 31 Asian patients with Del19-positive disease, median time on treatment was 40.0 months (90% CI: 36.4–45.0). Clinical benefit was also consistent across patient subgroups often excluded from clinical trials: median time on treatment was 22.2 months in patients with brain metastases, 27.3 months in patients aged ≥65 years and 22.2 months in those with ECOG PS ≥2 (Table 1).

As reported previously, overall median time on afatinib was 11.9 months (90% CI: 10.9–12.2) [20]. Median time on osimertinib treatment was 15.6 months (90% CI: 13.6–17.1) overall, 18.9 months (90% CI: 13.6–23.3) in Asian patients and 16.5 months (90% CI: 14.9–17.9) in patients with Del19-positive tumors.

Overall median OS was 37.6 months (90% CI: 35.5–41.3) with a 2-year survival rate of 80% (Figure 2A).

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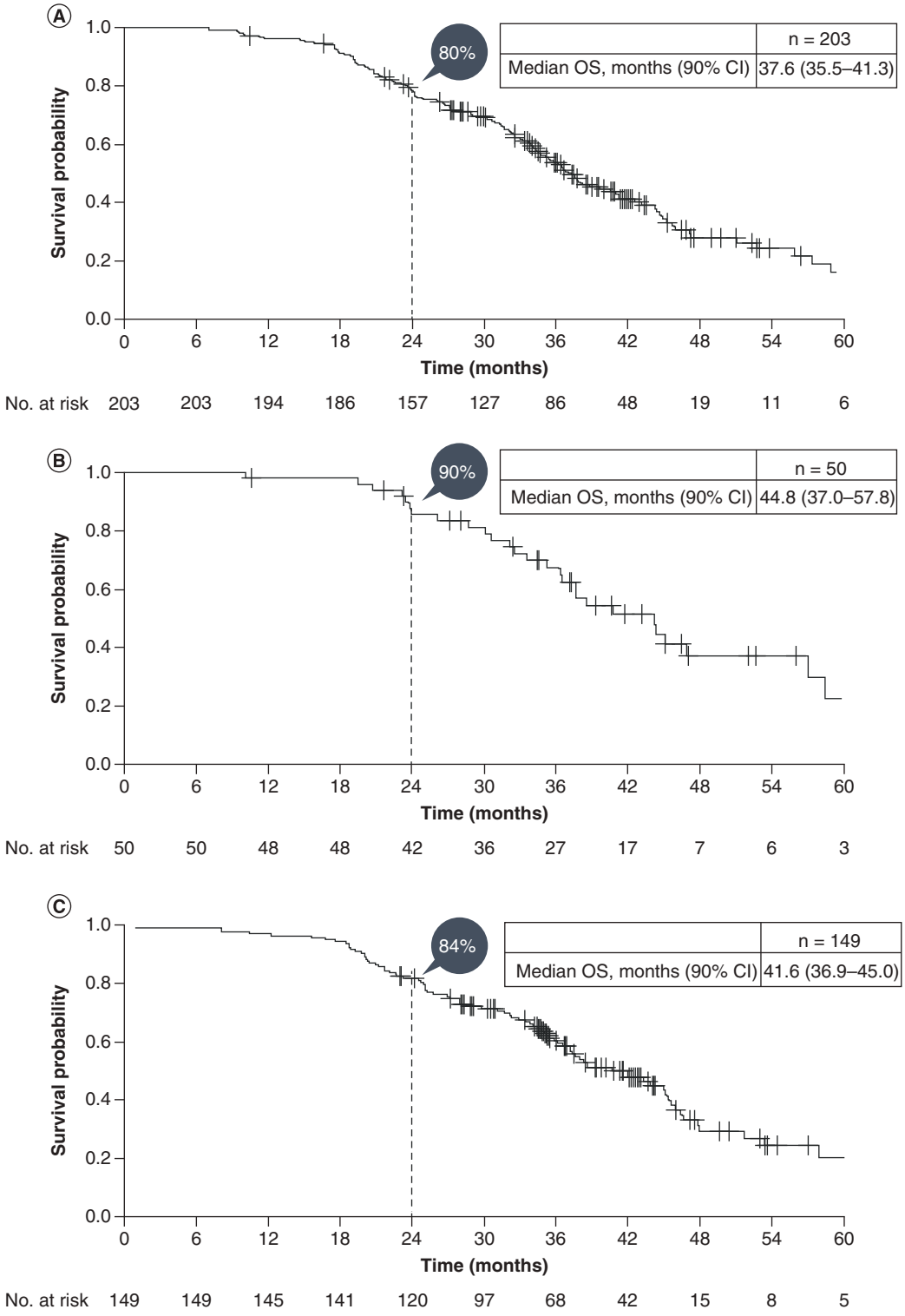

Figure 2. Overall survival in patients treated with sequential afatinib and osimertinib. (A) All patients; **(B)** Asian patients; and **(C)** patients with Del19-positive tumors.
OS: Overall survival.

Table 1. Time on treatment and overall survival across patient subgroups.

Baseline demographic/disease characteristic	Median time on treatment (90% CI), months	Median OS (90% CI), months
Overall population	27.7 (26.7–29.9)	37.6 (35.5–41.3)
Ethnicity		
Non-Asian (n = 137)	27.6 (26.3–29.3)	36.7 (34.4–41.6)
Asian (n = 50)	37.1 (28.1–40.3)	44.8 (37.0–57.8)
Age at start of afatinib (years)		
<65 years (n = 132)	28.7 (26.8–30.0)	37.6 (35.7–41.3)
≥65 years (n = 71)	27.3 (20.4–31.3)	36.9 (33.0–44.8)
EGFR mutation at start of afatinib		
Del19 (n = 149)	30.0 (27.6–31.9)	41.6 (36.9–45.0)
L858R (n = 53)	19.1 (16.8–26.3)	33.0 (29.8–37.0)
Presence of brain metastases		
Yes (n = 21)	22.2 (16.8–29.9)	31.0 (19.5–45.0)
No (n = 182)	28.1 (27.0–30.3)	38.0 (35.9–41.6)
ECOG PS		
0/1 (n = 152)	30.0 (28.1–31.7)	41.0 (37.6–45.0)
≥2 (n = 31)	22.2 (16.0–26.5)	32.0 (24.5–34.5)

ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR: Epidermal growth factor receptor; OS: Overall survival.

Median OS was 44.8 months (90% CI: 37.0–57.8) in Asian patients and 41.6 months (90% CI: 36.9–45.0) in patients with Del19-positive disease (Figure 2); in Asian patients with Del19-positive disease, OS was 45.7 months (90% CI: 38.2–57.8). Median OS was consistent in patients with poor prognostic characteristics: 31.0 months in patients with brain metastases, 36.9 months in patients aged ≥65 years and 32.0 months in those with ECOG PS ≥2 (Table 1). Median time from discontinuation of osimertinib treatment to death was 5.6 months (90% CI: 4.3–8.0).

For the 168 patients who received the recommended starting dose of afatinib (40 mg), median time on treatment and OS were 27.7 months (90% CI: 26.7–29.9) and 38.0 months (90% CI: 35.9–41.3), respectively. Median time on treatment and OS were 38.2 months (90% CI: 28.9–40.3) and 44.8 months (90% CI: 38.2–57.8) in Asian patients and 29.9 months (90% CI: 27.6–32.7) and 40.3 months (90% CI: 36.8–44.8) in those with Del19-positive disease, respectively. In the 29 Asian patients with Del19-positive disease who started on afatinib 40 mg, median time on treatment and OS were 40.0 months (90% CI: 36.4–46.7) and 45.0 months (90% CI: 38.2–57.8), respectively.

Discussion

These final results of the GioTag study further demonstrate that sequential afatinib and osimertinib treatment is a feasible and effective therapeutic strategy in a broad, real-world population of patients with *EGFR* mutation-positive NSCLC who acquired T790M, confirming results from the previous analyses [20,21]. Overall, median time on sequential afatinib and osimertinib treatment was 27.7 months for this patient population, consistent with the findings of the primary and interim analyses of the GioTag study (median times on treatment of 27.6 and 28.1 months, respectively) [20,21]. The OS data reported here represent the most mature analysis of OS with sequential afatinib and osimertinib to date. Particularly favorable outcomes were seen in patients with Del19-positive disease and Asian patients, with prolonged median time on treatment and a median OS of over 3.5 years reported for both subgroups. Across the overall population and patient subgroups, time on treatment and OS curves have not changed substantially from the previous analyses [20,21], although some median values have changed, likely due to the capturing of just a single point on the curve and small patient numbers in some of the subgroups.

Importantly, these clinical benefits were consistent across patient subgroups, including those with poor prognostic characteristics such as brain metastases, age ≥65 years or ECOG PS ≥2, who are often excluded from or under-represented in randomized clinical trials. Of note, the clinical benefit seen here in patients aged ≥65 years is consistent with that recently reported in a meta-analysis of clinical trial data, which suggested that EGFR TKIs have substantial benefit in elderly patients [22]. Further, it should be noted that prior afatinib treatment did not appear to diminish time on treatment with second-line osimertinib, with patients remaining on second-line

osimertinib treatment for a median of 15.6 months overall and slightly longer in Asian patients and those with Del19-positive tumors.

These data are in agreement with other studies assessing sequential afatinib and osimertinib. In 37 patients who received osimertinib therapy after first-line afatinib in the LUX-Lung 3, 6 and 7 studies, median time on osimertinib was 20.2 months (95% CI: 12.8–31.5) and median OS was not reached after a median follow-up of 4.7 years [23]. Recent observational data also support prolonged osimertinib treatment after first-line afatinib [24]. Retrospective analysis of the few patients treated with dacomitinib or afatinib in the Phase III ARCHER-1050 and Phase IIB Lux-Lung 7 trials who went on to receive osimertinib (n = 22 and n = 20, respectively), demonstrated that median OS was 36.7 months with sequential dacomitinib and osimertinib, and not reached (3-year OS rate of ~90%) with sequential afatinib and osimertinib, respectively [9,10].

The data presented here raise the question of the most appropriate therapeutic strategy: sequential afatinib and osimertinib or first-line osimertinib. OS is clearly a key consideration when selecting first-line treatment. Since the previous analyses of the GioTag study, OS data from the Phase III FLAURA study of first-line osimertinib have been reported; median OS of 38.6 months with osimertinib compared with 31.8 months with first-generation EGFR TKIs (gefitinib or erlotinib) (hazard ratio [HR]: 0.80; 95% CI: 0.64–1.00; p = 0.046) [11]. Consequently, osimertinib is increasingly used as a first-line treatment of choice. However, it should be noted that the OS benefit of first-line osimertinib in the 347 Asian patients included in the FLAURA study was less clear with a HR of 1.00 (95% CI: 0.75–1.32; median OS 37.1 months with osimertinib and 35.8 months with erlotinib/gefitinib) [11,25]. While direct comparisons are limited, not least because the FLAURA study enrolled patients with Del19 or L858R *EGFR* mutations at diagnosis, whereas the GioTag study only collected data from patients who acquired the T790M mutation after first-line afatinib treatment, the overall OS (37.6 months) reported for the broad, real-world patient population in the GioTag study is similar to that seen in the FLAURA trial. While further work may be needed to further identify patients likely to acquire the T790M mutation, and to identify therapeutic options for T790M-negative patients, it seems that some patient subgroups, such as those with Del19-positive disease and Asian patients, may benefit from a sequential therapy approach.

Further prospective validation is needed to address the question of the optimum therapeutic approach in patients with *EGFR* mutation-positive NSCLC. The final OS analysis of the Phase III AURA-3 trial, comparing second-line osimertinib with chemotherapy following first-line progression on EGFR TKIs in 419 patients with *EGFR* mutation-positive NSCLC demonstrated a numerical OS advantage for osimertinib, although this was not statistically significant (median OS: 26.8 vs 22.5 months; HR: 0.87; 95% CI: 0.67–1.12; p = 0.277) [26]. The Phase II APPLE trial (which compares sequential gefitinib/osimertinib vs first-line osimertinib) [27] should also be informative in terms of comparing the OS benefits of different sequential regimens.

As discussed previously [20], the main limitations of the GioTag study were its retrospective nature, lack of a comparator arm and potential for selection bias. The potential for selection bias was minimized as much as possible, for example by including only consecutive patients who fulfilled all of the inclusion criteria and limiting enrollment to a maximum of 15 patients per site. Nevertheless, this may have inadvertently introduced selection bias by either excluding those who died on first-line afatinib or under-representing those who derived long-term benefit from first-line afatinib; data from the LUX-Lung trials estimate these to be approximately 6 and 10–20% of patients, respectively.

Conclusion

These final data from the real-world GioTag study confirm those of the previous analyses and demonstrate that sequential afatinib followed by osimertinib is a feasible and effective therapeutic strategy in real-world patients with *EGFR* mutation-positive NSCLC who develop T790M.

Of note, median OS was over 3.5 years in Asian patients and those with Del19-positive disease, suggesting that sequential use of TKIs could potentially allow these *EGFR* mutation-positive NSCLC patients to receive long-term, chemotherapy-free treatment.

Summary points

- The international, observational GioTag study is the first to evaluate outcomes of patients who received first-line afatinib followed by osimertinib; initial and updated analyses showed encouraging results for this sequential approach, particularly for Del19-positive patients and Asian patients. Here, we report findings from the final analysis, including updated time on treatment and overall survival (OS) data.
- Patients had advanced, *EGFR* mutation-positive (Del19, L858R) non-small-cell lung cancer with T790M-positive disease following first-line afatinib and must have started osimertinib treatment ≥10 months prior to data entry. The primary outcome was time on treatment from initiation of afatinib until discontinuation of osimertinib; the OS analysis was exploratory.
- Overall, in 203 patients analyzed, the median time on EGFR-TKI treatment was 27.7 months (90% CI: 26.7–29.9). Median time on treatment was particularly encouraging in patients with Del19-positive disease (median 30.0 months [90% CI: 27.6–31.9]) and Asian patients (median 37.1 months [90% CI: 28.1–40.3]).
- Clinical benefit was also consistent across patients with poor prognosis; for example, those with Eastern Cooperative Oncology Group performance status ≥2 and stable brain metastases also appeared to derive clinical benefit (median time on treatment 22.2 months for both subgroups).
- Overall median OS was 37.6 months (90% CI: 35.5–41.3) with a 2-year survival rate of 80%. Particularly encouraging results were again seen for Del19-positive and Asian patients: median OS was 44.8 months (90% CI: 37.0–57.8) in Asian patients and 41.6 months (90% CI: 36.9–45.0) in patients with Del19-positive disease.
- In the 31 Asian patients with Del19-positive disease, median time on treatment was 40.0 months (90% CI: 36.4–45.0) and median OS was 45.7 months (90% CI: 38.2–57.8).
- These final data from the real-world GioTag study confirm those of the previous analyses and demonstrate that sequential afatinib followed by osimertinib is a feasible and effective therapeutic strategy in real-world patients with *EGFR* mutation-positive non-small-cell lung cancer who develop T790M, particularly those with Del19-positive disease and Asian patients.

Supplementary data

An infographic accompanies this paper and is included at the end of the references section in the PDF version. To view or download this infographic in your browser please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0740

Author contributions

The authors are fully responsible for all content and editorial decisions, they were also involved at all stages of manuscript development and have approved the final version.

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Ethical conduct of research

The study was carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline for Good Clinical Practice, Good Epidemiological Practice, Guidelines for Good Pharmacoepidemiology Practice and relevant sponsor Standard Operating Procedures.

The study was initiated only after all required legal documentation was reviewed and approved by the respective Institutional Review Board/Independent Ethics Committee and competent authority according to national and international regulations.

Data sharing statement

The datasets generated and analyzed during the study are available from MH on reasonable request.

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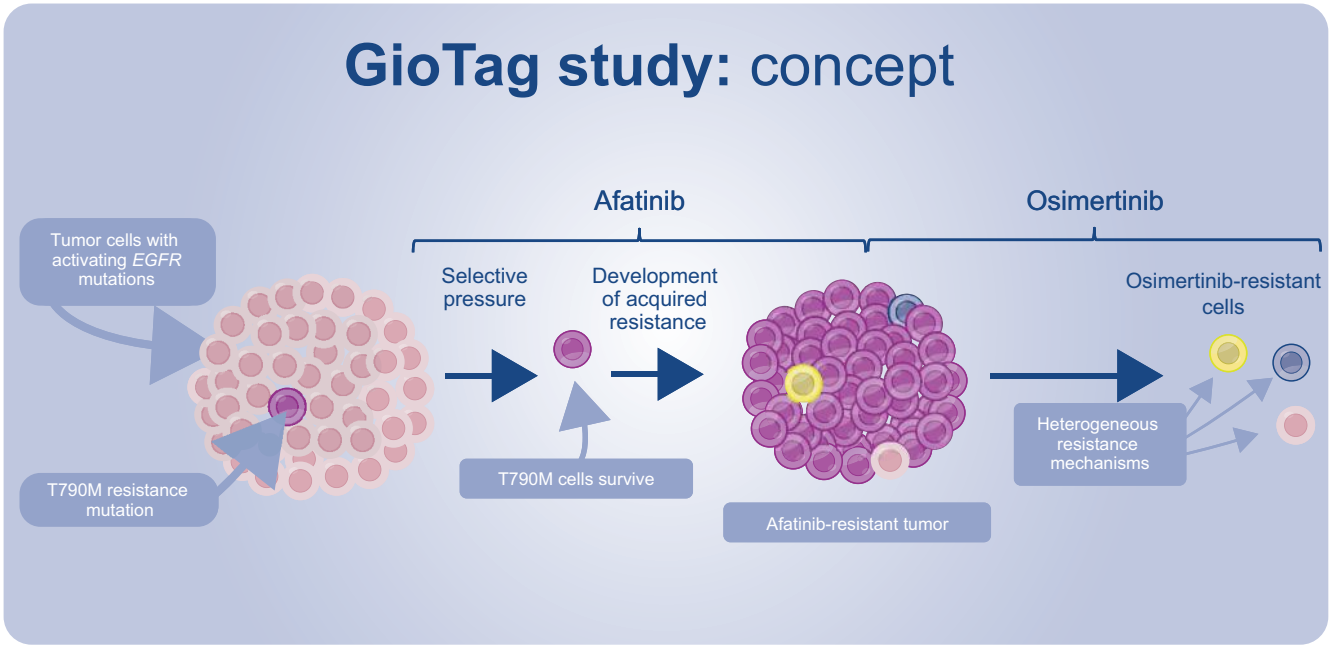
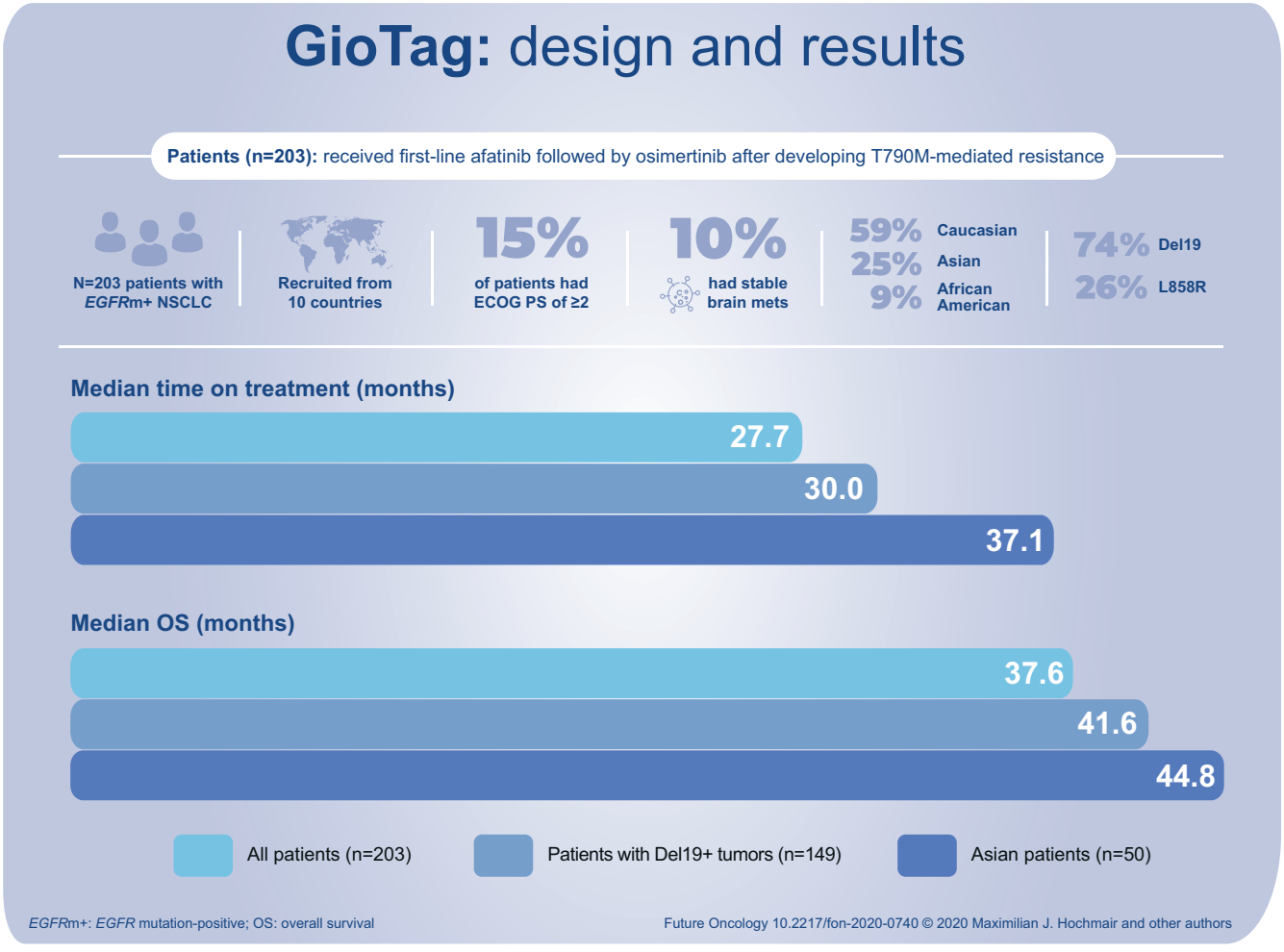

GioTag study: concept
Afatinib
Osimertinib
Tumor cells with activating *EGFR* mutations
Selective pressure
Development of acquired resistance
Osimertinib-resistant cells
Heterogeneous resistance mechanisms
T790M resistance mutation
T790M cells survive
Afatinib-resistant tumor


GioTag: design and results
Patients (n=203): received first-line afatinib followed by osimertinib after developing T790M-mediated resistance
N=203 patients with *EGFR*m+ NSCLC
Recruited from 10 countries
15% of patients had ECOG PS of ≥2
10% had stable brain mets
59% Caucasian
25% Asian
9% African American
74% Del19
26% L858R
Median time on treatment (months)
27.7
30.0
37.1
Median OS (months)
37.6
41.6
44.8
All patients (n=203)
Patients with Del19+ tumors (n=149)
Asian patients (n=50)
*EGFR*m+: *EGFR* mutation-positive; OS: overall survival
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Short Communication

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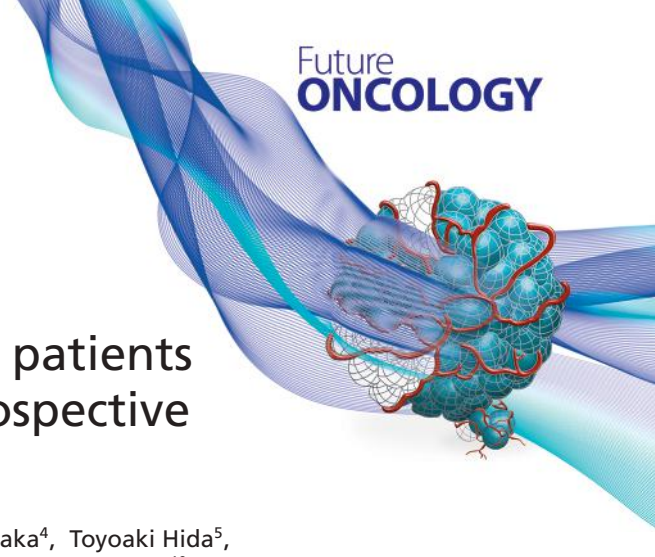

Therapies after first-line afatinib in patients with *EGFR*m$^+$ NSCLC in Japan: retrospective analysis of LUX-Lung 3

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Aim: Acquired resistance to EGFR tyrosine kinase inhibitors is inevitable in non-small-cell lung cancer. To inform subsequent treatment decisions, we retrospectively assessed therapies following afatinib in Japanese patients from LUX-Lung 3. **Patients & methods:** LUX-Lung 3 was a randomized, open-label, Phase III study of afatinib versus cisplatin/pemetrexed in treatment-naive patients with *EGFR* mutation-positive (*EGFR*m$^+$) advanced lung adenocarcinoma. **Results:** Among 47 Japanese patients who discontinued first-line afatinib, 91/81/62% received ≥one/two/three subsequent therapies. The most common second-line therapies were platinum-based chemotherapy (38%) and a first-generation EGFR tyrosine kinase inhibitor (17%). Median overall survival (afatinib vs cisplatin/pemetrexed) was 47.8 versus 35.0 months (not significant). **Conclusion:** First-line afatinib does not appear to diminish suitability for subsequent therapies in *EGFR*m$^+$ non-small-cell lung cancer.

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Keywords: afatinib • EGFR • non-small-cell lung cancer

EGFR tyrosine kinase inhibitors (TKIs) are the first-line treatment of choice for patients with *EGFR* mutation-positive (*EGFR*m$^+$) non-small-cell lung cancer (NSCLC) [1,2]. Five EGFR TKIs are available, having demonstrated robust clinical activity in this setting: the first-generation TKIs, erlotinib and gefitinib; the second-generation irreversible ErbB family blockers, afatinib and dacomitinib; and the third-generation EGFR wild-type sparing TKI, osimertinib [1,3–12].

Recent head-to-head trials have demonstrated that later-generation TKIs offer better efficacy outcomes than first-generation TKIs for first-line treatment of *EGFR*m$^+$ NSCLC [10,11,13–16]. In the Phase IIb LUX-Lung 7 trial, afatinib significantly improved progression-free survival (PFS), time-to-treatment failure and objective response rate versus gefitinib [14,15], with a numerical, but nonsignificant difference in overall survival (OS) [15]. Dacomitinib also demonstrated significantly improved PFS versus gefitinib in the Phase III ARCHER 1050 trial, and, in exploratory analysis, OS was prolonged with dacomitinib versus gefitinib [10,13]. Furthermore, in the Phase III FLAURA trial, first-line osimertinib conferred a considerable PFS [11] and OS [16] advantage over gefitinib/erlotinib.

While these trials are clearly important in guiding first-line treatment decisions, given the inevitable acquired resistance to EGFR TKIs of any generation [17], subsequent therapy options are an important consideration in order to maximize OS. Clinical studies have shown that the most common mechanism of acquired resistance to erlotinib, gefitinib and afatinib is the emergence of the gatekeeper T790M mutation in exon 20 of the *EGFR* gene

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(~50–70% of cases) [18–23]. In patients with T790M-mediated resistance, osimertinib represents a clear second-line treatment option, having demonstrated striking efficacy in this setting [23–25]. By comparison, mechanisms of resistance to osimertinib appear to be very heterogeneous [26,27], although MET-amplification and *EGFR* C797S mutation have been identified as being among the most frequent [28]. Therefore, at present, treatment options for patients who progress on first-line osimertinib are less clear and are likely to incorporate chemotherapy and potentially, immune checkpoint inhibitors [28–30]. Reflecting the uncertainty around second-line therapy for *EGFR*m$^+$ patients, the recent guidelines issued by the Japanese Lung Cancer Society do not provide specific recommendations for T790M-negative patients progressing after first-line EGFR TKI treatment. Rather, healthcare professionals, including Japanese physicians, are referred to generic treatment recommendations for all patients with driver oncogenes, which include cytotoxic chemotherapy during any line of treatment [30]. Furthermore, the Pan-Asian adapted Clinical Practice Guidelines recommend platinum-doublet chemotherapy as second-line therapy for T790M-negative *EGFR*m$^+$ patients [29]. Analysis of clinical outcomes in patients undergoing second-line treatment is therefore important to better inform therapeutic decision-making [28].

A retrospective analysis of the LUX-Lung 3 (afatinib vs cisplatin plus pemetrexed), LUX-Lung 6 (afatinib vs cisplatin plus gemcitabine) and LUX-Lung 7 datasets was undertaken to gain insight into postprogression therapy following first-line afatinib, and provide some insight into treatment practices and suitability for subsequent therapy [31]. This analysis demonstrated that 71% of patients with exon 19 deletion (Del19)/L858R *EGFR*m$^+$ NSCLC were sufficiently fit to receive at least one subsequent therapy following afatinib [31] and that uptake of subsequent therapies was particularly high in countries with optimized comprehensive cancer care (80%), including Japan (89%) [31]. Optimizing the treatment of NSCLC, which is primarily diagnosed during older age, is important particularly in Japan because the elderly population is predicted to increase at a higher rate than most Organisation for Economic Co-operation and Development (OECD) countries [31,32].

In a previous subanalysis of LUX-Lung 3 [33], PFS benefit with afatinib versus chemotherapy was similar in 77 Japanese patients with Del19/L858R *EGFR*m$^+$ NSCLC (13.8 vs 6.9 months; hazard ratio [HR]: 0.28; 95% CI: 0.15–0.52; $p < 0.0001$) as in all 308 patients with Del19/L858R *EGFR*m$^+$ NSCLC (13.6 vs 6.9 months; HR: 0.47; 95% CI: 0.34–0.65) [8]. Moreover, as with the overall dataset, afatinib conferred notable OS benefit versus chemotherapy in Japanese patients with *EGFR* Del19- or L858R-positive tumors (46.9 vs 35.0 months; HR: 0.57; 95% CI: 0.29–0.1.12; $p = 0.10$). Afatinib was similarly well tolerated in Japanese patients, with no unexpected safety signals [33]. In this prior Japanese subanalysis of LUX-Lung 3, 89.6% of patients received subsequent therapy after discontinuation of afatinib [33]; however, the number, duration, nature and impact of specific subsequent therapies has not yet been assessed. There is a relatively wide range of treatment options now available in Japan for patients with *EGFR*m$^+$ NSCLC, but a paucity of data relating to the sequencing of these agents. Evaluation of survival outcomes in patients who received different therapeutic modalities following first-line afatinib may therefore add to the overall clinical knowledge and assist healthcare professionals, including Japanese physicians and patients when making treatment choices.

In this retrospective analysis of LUX-Lung 3, we assessed the impact of first-line afatinib on uptake and duration of subsequent therapies, including other EGFR TKIs and chemotherapy, and OS, in Japanese patients with NSCLC harboring common (Del19 or L858R) *EGFR* mutations.

Methods

Study design & patients

Detailed study design, patient inclusion and exclusion criteria, and methods for the primary analysis of LUX-Lung 3 have been described previously [8]. In brief, LUX-Lung 3 was a randomized, open-label, Phase III study of afatinib versus cisplatin plus pemetrexed in patients with previously untreated stage IIIB/IV lung adenocarcinoma and centrally confirmed *EGFR* mutations. Randomization was stratified by *EGFR* mutation type (Del19, L858R or other) and race (Asian or non-Asian). Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients with clinically asymptomatic and controlled brain metastases (stable for ≥4 weeks, not requiring treatment with anticonvulsants or steroids, and no leptomeningeal disease) were permitted. The primary end point was PFS by independent blinded review.

LUX-Lung 3 was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines on Good Clinical Practice, and the protocol was approved by the institutional review boards at each participating center. All patients provided written informed consent.

Treatment

Eligible patients in LUX-Lung 3 were randomized 2:1 to receive oral afatinib 40 mg once daily, or up to six cycles of intravenous cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 once every 21 days. Treatment was continued until investigator-assessed disease progression or intolerable adverse events (AEs) necessitating discontinuation of therapy.

Tumor assessment

Tumors were assessed by computed tomography or MRI every 6 weeks for the first 48 weeks, and every 12 weeks thereafter until disease progression or start of new anticancer therapy, according to RECIST version 1.1. Molecular testing of tumor samples at progression/discontinuation was neither mandatory nor documented.

Analysis of subsequent therapies

Following discontinuation of first-line afatinib or platinum-based chemotherapy in LUX-Lung 3, any further treatment decisions were made by the treating physician. Patients were followed up every 21 ± 7 days from the end-of-treatment visit until disease progression or start of a subsequent anticancer treatment, at which point patients entered an observation period. During observation, details of subsequent therapy and progression were collected from patient notes or by telephone contact with the patient every 60 ± 15 days until death or 5 years after the last follow-up visit, whichever occurred first.

Statistical analysis

Post hoc analysis of subsequent therapies was conducted in Japanese patients with NSCLC harboring common (Del19/L858R) *EGFR* mutations. Incidence, type and duration of subsequent therapy (overall and by treatment line) are reported using descriptive statistics, including descriptive medians for time on treatment. Maximum percentage tumor shrinkage and percentage growth from nadir (smallest tumor diameter), by investigator assessment, at the time of stopping first-line afatinib were also analyzed.

Cox proportional hazards models and stratified log-rank tests were used to compare OS between patients randomized to afatinib or chemotherapy, and Kaplan–Meier estimates were used to construct survival curves and calculate median OS values.

Results

Patients

The disposition of the overall study population [8] and the Japanese population enrolled in LUX-Lung 3 [33] have been described previously. In LUX-Lung 3, 54 Japanese patients were randomized to first-line afatinib and all received study treatment; 29 patients were randomized to chemotherapy and 28 were treated. Baseline characteristics were generally similar across the treatment arms, and to those of the overall study population [8,33]. 50 Japanese patients assigned to afatinib and 27 Japanese patients assigned to chemotherapy had NSCLC tumors harboring the common Del19/L858R *EGFR* mutations [33]. Of these patients, 47 (94%) and 27 (100%), respectively, had discontinued first-line therapy at the time of data cutoff (March 2016). 43 (91%) patients received subsequent therapy following afatinib (Table 1), with 81% and 62% of patients receiving third- and fourth-line therapy, respectively. Uptake of subsequent therapy following first-line afatinib was higher in the Japanese subgroup compared with the wider LUX-Lung 3 population (Table 1).

Analysis of subsequent therapies

Afatinib followed by chemotherapy

Following discontinuation of first-line afatinib, 28 (60%) patients received single-agent chemotherapy (predominantly third-line) and 21 (45%) received platinum-based chemotherapy (predominantly second-line; Tables 1 & 2). Median time on single-agent chemotherapy across all treatment lines was 3.1 months (range: 0.03–17.2 months), and on platinum-based chemotherapy was 5.3 months (range: 0.7–28.7 months; Table 2). Median time on any chemotherapy treatment across all lines was 12.6 months (range: 0.03–28.7 months; Table 2); this included patients who received bevacizumab in combination with platinum-based chemotherapy (n = 16), bevacizumab plus single-agent chemotherapy (n = 1) or other chemotherapy combinations (n = 6), as well as those treated with single-agent (including platinum-based) chemotherapy. Treatment sequence for patients who received first-line afatinib followed by second-line chemotherapy is shown in Figure 1.

Table 1. Rates of subsequent systemic therapy in patients with non-small-cell lung cancer harboring common *EGFR* mutations who discontinued first-line afatinib in LUX-Lung 3.

Line	All patients[†]							Japanese patients[†]						
	Any[‡]	Platinum-based CT	Single-agent CT	Any CT regimen[§]	First-generation TKI monotherapy[¶]	Any EGFR TKI[#]	Other	Any[‡]	Platinum-based CT	Single-agent CT	Any CT regimen[§]	First-generation TKI monotherapy[¶]	Any EGFR TKI[#]	Other
Any	154 (78)	106 (54)	84 (43)	137 (70)	86 (44)	100 (51)	7 (4)	43 (91)	21 (45)	28 (60)	37 (79)	26 (55)	34 (72)	2 (4)
Second	154 (78)	94 (48)	9 (5)	125 (63)	24 (12)	28 (14)	1 (<1)	43 (91)	18 (38)	2 (4)	33 (70)	8 (17)	10 (21)	0
Third	120 (61)	13 (7)	55 (28)	79 (40)	33 (17)	40 (20)	1 (<1)	38 (81)	3 (6)	25 (53)	34 (72)	3 (6)	4 (9)	0
Fourth	72 (37)	7 (4)	24 (12)	36 (18)	27 (14)	33 (17)	3 (2)	29 (62)	4 (9)	6 (13)	13 (28)	13 (28)	15 (32)	1 (2)

Data represented as n (%).
[†]Percentages are of patients who discontinued afatinib (overall: n = 197; Japanese subset: n = 47; data cutoff: March 2016).
[‡]Any subsequent systemic treatment.
[§]CT or CT-based combination.
[¶]Erlotinib or gefitinib.
[#]EGFR TKI monotherapy or EGFR TKI-containing combination.
CT: Chemotherapy; TKI: Tyrosine kinase inhibitor.

Table 2. Median time on treatment of subsequent chemotherapy treatment in Japanese patients harboring common *EGFR* mutations who discontinued first-line afatinib.

Line	Platinum-based chemotherapy		Single-agent chemotherapy		Any chemotherapy regimen†	
	Median time on treatment, months (range)	n (%)‡	Median time on treatment, months (range)	n (%)‡	Median time on treatment, months (range)	n (%)‡
Any	5.3 (0.7–28.7)	21 (45)	3.1 (0.03–17.2)	28 (60)	12.6 (0–28.7)	37 (79)
Second	4.1 (0.7–15.7)	18 (38)	1.6 (0.8–2.3)	2 (4)	5.8 (0.7–24.9)	33 (70)
Third	7.5 (4.5–13.0)	3 (6)	2.3 (0.03–14.1)	25 (53)	2.4 (0–14.1)	34 (72)
Fourth	3.3 (1.0–8.0)	4 (9)	1.1 (0.03–3.4)	6 (13)	1.0 (0–8.0)	13 (28)

†Chemotherapy or chemotherapy-based combination.
‡Percentages are of patients who discontinued afatinib (N = 47; data cutoff: March 2016).

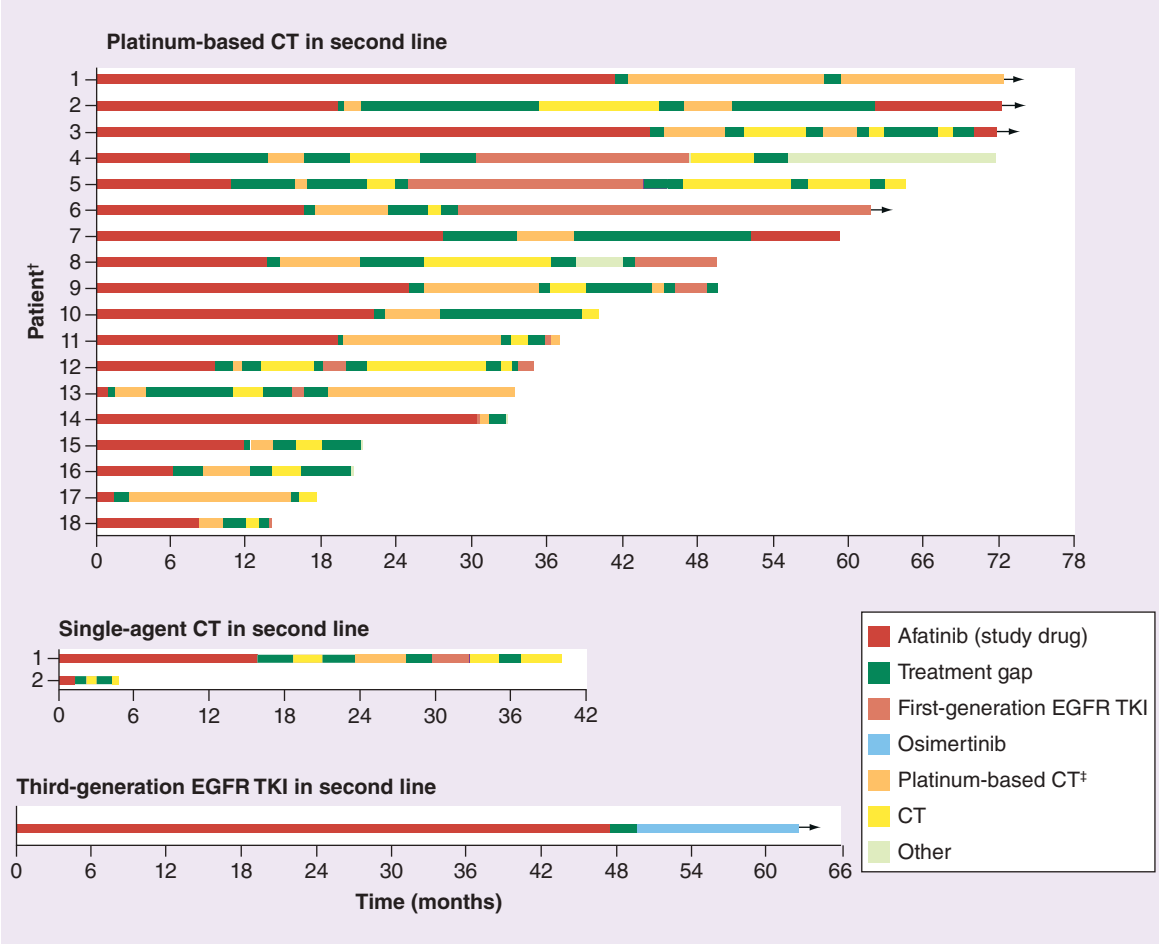


Figure 1. Treatment sequence and duration for patients who received second-line platinum-based chemotherapy, single-agent chemotherapy or a third-generation EGFR TKI.
Arrow denotes that treatment was still ongoing at data cutoff.
†Patients were ordered by total treatment duration, including any treatment gaps.
‡Includes platinum-based CT plus bevacizumab.
CT: Chemotherapy; TKI: Tyrosine kinase inhibitor.

Afatinib followed by first-generation EGFR TKIs

26 (55%) patients received a first-generation EGFR TKI (erlotinib or gefitinib) after discontinuing afatinib (Table 3), predominantly as fourth-line treatment (n = 13; 28%). Median time on treatment across all lines of subsequent first-generation EGFR TKI was 4.4 months (range: 0.2–41.0 months; Table 3).

Table 3. Median time on treatment of subsequent EGFR tyrosine kinase inhibitor treatment in Japanese patients harboring common *EGFR* mutations who discontinued first-line afatinib.

Line	First-generation EGFR TKI		Any EGFR TKI†	
	Median time on treatment, months (range)	n (%)‡	Median time on treatment, months (range)	n (%)‡
Any	4.4 (0.2–41.0)	26 (55)	5.8 (0.2–41.0)	34 (72)
Second	4.0 (0.4–41.0)	8 (17)	4.1 (0.4–41.0)	10 (21)
Third	4.0 (3.1–21.0)	3 (6)	5.5 (3.1–21.0)	4 (9)
Fourth	2.0 (0.2–32.9)	13 (28)	3.0 (0.2–32.9)	15 (32)
Fifth	2.6 (1.1–6.6)	5 (11)	2.1 (0.9–10.2)	10 (21)

†EGFR TKI monotherapy or EGFR TKI-containing combination.
‡Percentages are of patients who discontinued afatinib (N = 47; data cutoff: March 2016).
TKI: Tyrosine kinase inhibitor.

Eight (17%) patients who discontinued afatinib treatment continued 'seamless' EGFR TKI therapy with a first-generation EGFR TKI as second-line therapy (Figure 2A). Median time on first-generation TKI treatment in the second line was 4.0 months (range: 0.4–41.0 months) and was the same in the third line (median: 4.0 months; range: 3.1–21.0 months; Table 3). Median total time on subsequent EGFR TKI treatment across all lines was 5.8 months (range: 0.2–41.0 months; Table 3); this included afatinib (n = 8) or osimertinib (n = 1) monotherapy, and EGFR TKI-containing combination therapies (n = 3), in addition to first-generation EGFR TKI monotherapy.

All patients who received a first-generation TKI in the second-line experienced tumor shrinkage with afatinib prior to discontinuation (Figure 2B). Of these eight patients, six discontinued afatinib due to progressive disease; regrowth of target tumors was observed in four of the six tumors. Two patients discontinued afatinib due to AEs.

Afatinib followed by osimertinib

Only one patient received osimertinib following discontinuation of afatinib. Time on first-line afatinib treatment was 47.6 months, and time on second-line osimertinib treatment was 12.9 months (Figure 1); however, osimertinib treatment was still ongoing at data cutoff.

Impact of EGFR mutational subgroup on subsequent treatment

Type of subsequent therapy and median treatment duration by *EGFR* mutational status are shown in Figure 3. Some differences were observed in median treatment duration according to *EGFR* mutational status across the different lines and therapies. However, the very small-sample sizes preclude any firm conclusions.

Overall survival

At data cutoff (March 2016), median follow-up time for OS was 23.7 months. Median OS among Japanese patients with common *EGFR* mutations was 47.8 months for afatinib versus 35.0 months for cisplatin plus pemetrexed (HR: 0.75; 95% CI: 0.44–1.27; p = 0.284; Figure 4).

Discussion

In this retrospective analysis of Japanese patients from LUX-Lung 3 with NSCLC harboring common (Del19/L858R) *EGFR* mutations, patients who received first-line afatinib demonstrated a very high uptake of subsequent therapies (91%, compared with 78% in the overall study population [33]). Median OS was nearly 4 years, likely reflecting the high uptake, multiple lines (62% received ≥four lines) and long duration of subsequent therapies. It is probable that the high uptake of subsequent therapies among Japanese patients is, at least in part, due to Japan's public social health insurance system that provides universal health coverage for all citizens [32], and as a result, easy and timely access to approved therapies.

The most frequently received subsequent therapy was single-agent chemotherapy (received by 60% of patients in any line), although first-generation EGFR TKI monotherapy (55%) and platinum-based chemotherapy (45%) were also commonly received. Platinum-based chemotherapy was the most common second-line treatment, with a median duration of approximately 4 months. Although retrospective, these data suggest that first-line afatinib does not adversely affect suitability of subsequent therapy in Japanese patients with *EGFR*m$^+$ NSCLC, and most patients were fit enough to receive further treatment. This is reassuring given that platinum-based chemotherapy is still the preferred second-line therapy in patients with T790M-negative or unknown *EGFR*m$^+$ NSCLC [29,30].

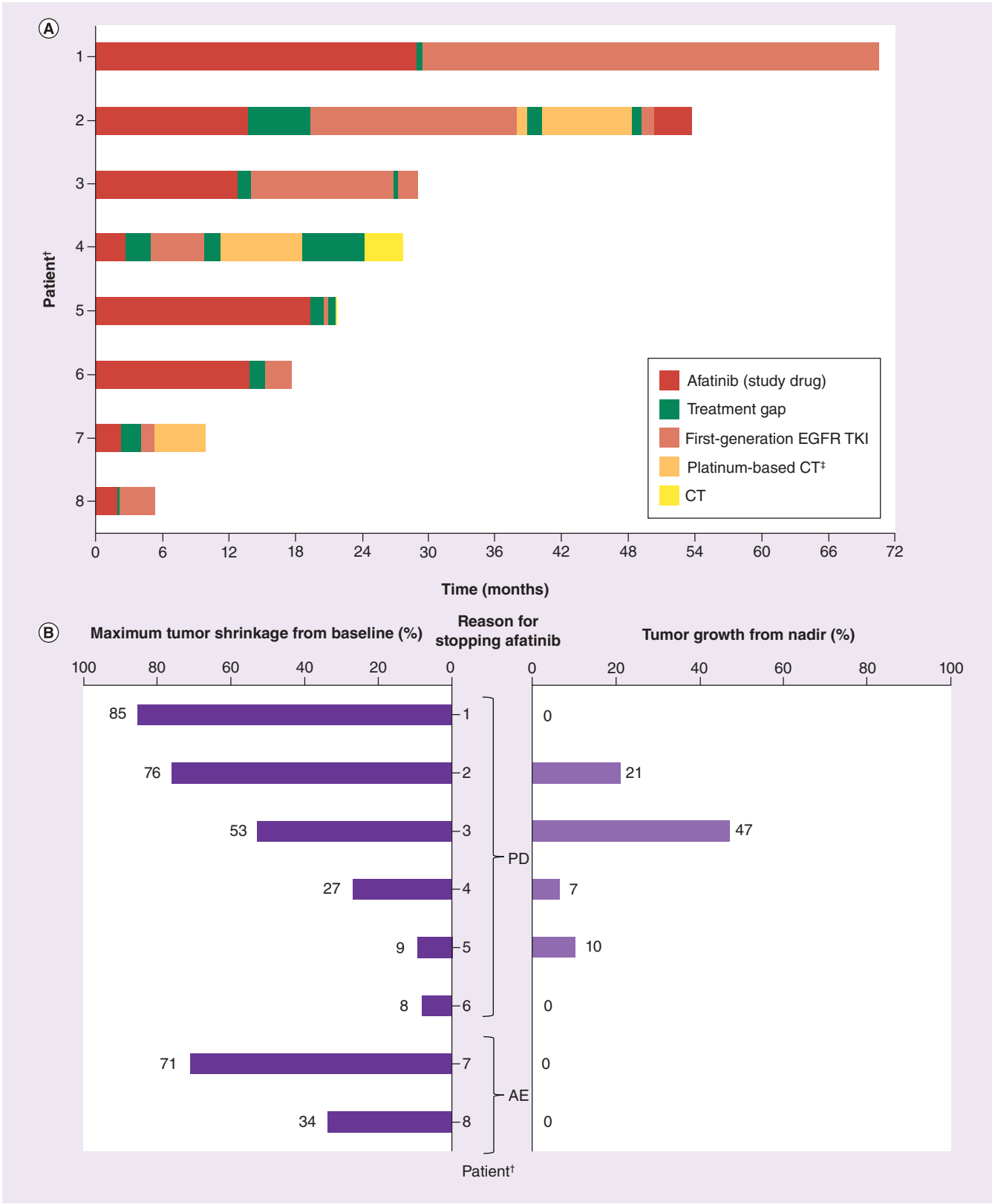
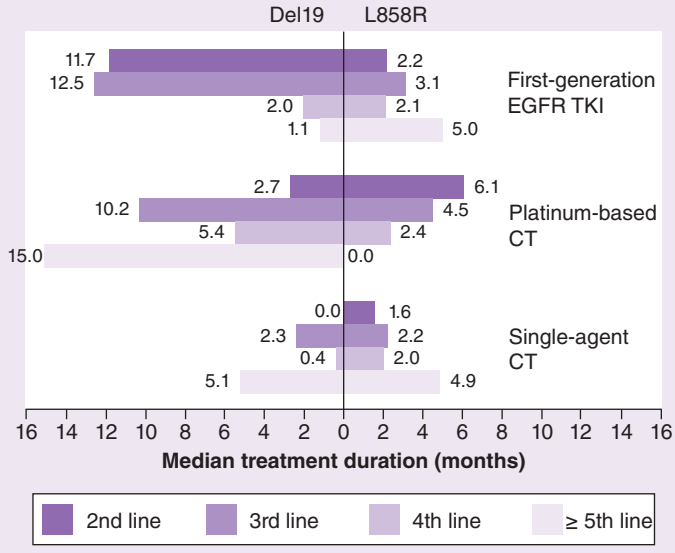


Figure 2. Treatment sequence and duration, reasons for discontinuation, maximum tumor shrinkage, and percentage tumor growth from nadir for the eight Japanese patients who received a second-line, first-generation EGFR TKI. **(A)** Treatment sequence and duration; **(B)** reasons for discontinuation, maximum tumor shrinkage and percentage tumor growth from nadir (both investigator assessed) at the time of stopping afatinib treatment.

†Patients were ordered by total treatment duration, including any treatment gaps **(A)**, or by maximum percentage tumor shrinkage from baseline **(B)**.

‡Includes platinum-based CT plus bevacizumab.

AE: Adverse event; CT: Chemotherapy; PD: Progressive disease; TKI: Tyrosine kinase inhibitor.



Subsequent therapy	Line	Patients, n (%) Del19 (n = 19)	L858R (n = 24)
First-generation EGFR TKI	2	4 (21)	4 (17)
	3	2 (11)	1 (4)
	4	5 (26)	8 (33)
	≥5	2 (11)	5 (21)
Platinum-based CT	2	10 (53)	8 (33)
	3	2 (11)	1 (4)
	4	2 (11)	2 (8)
	≥5	1 (5)	0 (0)
Single-agent CT	2	0 (0)	2 (8)
	3	9 (47)	16 (67)
	4	4 (21)	2 (8)
	≥5	5 (26)	4 (17)

Figure 3. Rates of subsequent systemic therapy and duration of subsequent treatment in Japanese patients who discontinued first-line afatinib, by *EGFR* mutational status. Frequencies relate to the overall number of patients with each mutation type who received one subsequent therapy.
Del19: Exon 19 deletion; TKI: Tyrosine kinase inhibitor.

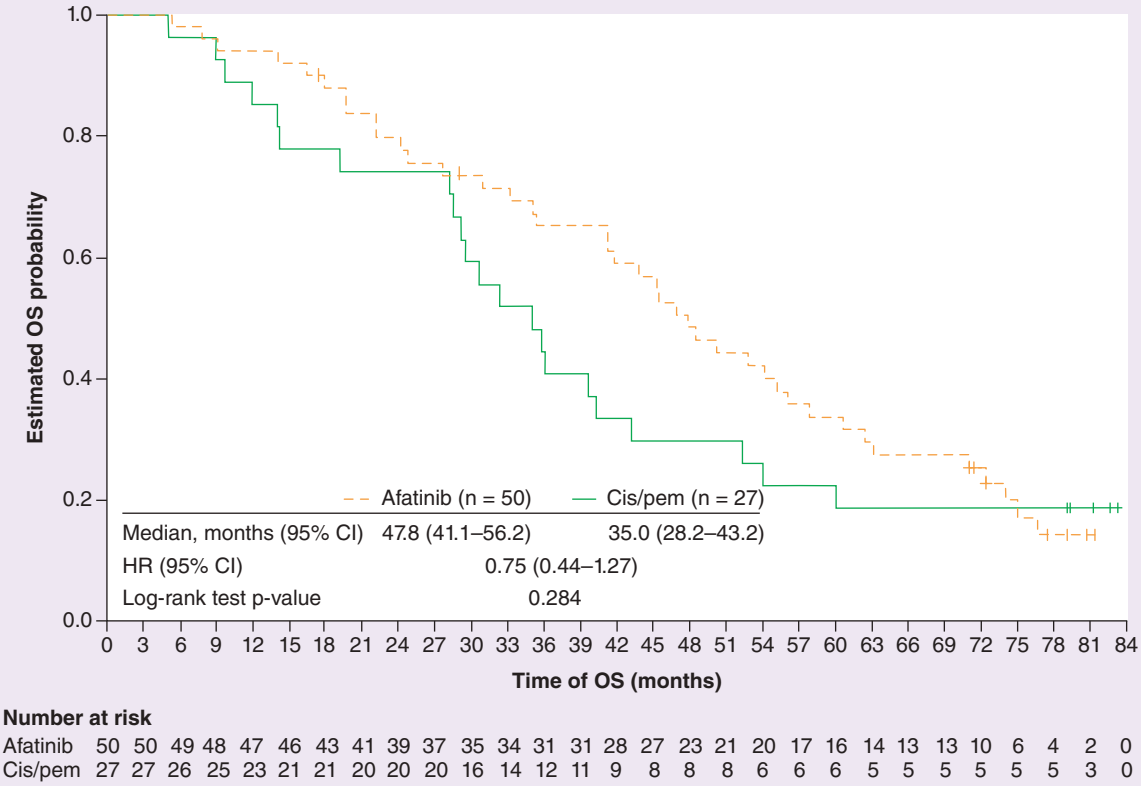


Figure 4. Kaplan–Meier curve of OS in Japanese patients in LUX-Lung 3 who had a common *EGFR* mutation.
Cis: Cisplatin; HR: Hazard ratio; OS: Overall survival; Pem: Pemetrexed.

In another retrospective analysis of Japanese patients with *EGFR*m$^+$ NSCLC (N = 1660), 97% of patients received an EGFR TKI as part of their treatment regimen in 'real-world' clinical practice [34]. Median OS among all patients in this 'real-world' population was 30.8 months. It was common for patients to receive multiple lines of EGFR TKI therapy, and to switch between different TKIs (39% of patients received ≥2 TKIs) [34]. Taken together with our findings of encouraging median time on EGFR TKI treatment after afatinib discontinuation (5.8 months in any line), these data suggest that EGFR TKI switching and rechallenge might further extend the survival of patients with *EGFR*m$^+$ NSCLC [34,35].

Of 47 patients who had discontinued afatinib in our analysis, only one patient went on to receive subsequent treatment with osimertinib, reflecting the limited availability of osimertinib at the time the LUX-Lung 3 study was undertaken, and the fact that, in line with the study protocol, mutation testing on progression was not mandatory. Nevertheless, the time that this patient spent on second-line osimertinib (12.9 months, with treatment still ongoing at data cutoff) was comparable to that in previous reports of sequential EGFR TKI-osimertinib treatment (8–13 months) [23,24]. The potential benefit of sequential afatinib-osimertinib treatment for patients with T790M-acquired resistance has been demonstrated in a pooled analysis of LUX-Lung 3, 6 and 7 (n = 37; median OS: not reached after 4.7 years' follow-up) and the global, observational real-world GioTag study (n = 203; median OS: 41.3 months after 30.3 months' follow-up) [28,31,36]. Based on published estimates of at least 70% uptake of subsequent therapy [31] and around 45–70% of patients developing T790M-mediated resistance following failure of afatinib [21,22,37], we can estimate that almost half of patients with *EGFR*m$^+$ NSCLC who receive first-line afatinib could be eligible to receive second-line osimertinib [23,24]. Although the availability, specificity and sensitivity of liquid biopsy-based PCR and next-generation sequencing analyses continue to improve worldwide, including in Japan, identification of acquired T790M mutations is still limited by tissue availability and the sensitivity of commonly used assays [38–41]. Thus, it is unclear whether the uptake of second-line osimertinib in the real-world clinical setting would be as high as estimated.

In our analysis, patient numbers were too low to make meaningful conclusions relating to subsequent treatment duration by tumor *EGFR* Del19/L858R mutational type. However, findings from the much larger pooled analysis of subsequent therapies in LUX-Lung 3, 6 and 7 [31] suggested that uptake rates of EGFR TKI therapy or chemotherapy after discontinuation of afatinib were similar regardless of whether a tumor harbors an *EGFR* Del19 or L858R mutation.

We acknowledge that the data presented herein are based on only a small number of Japanese patients, with no formal statistical analysis plan, and a relatively short follow-up duration, which precludes any conclusions on the long-term effects of the treatments received post-afatinib. There are also clear limitations relating to the retrospective nature of the analysis. For example, because of the absence of mandatory testing, few data are available regarding mechanisms of acquired resistance to afatinib in the LUX-Lung studies; therefore, the rate of T790M accrual has been assumed based on incidences reported in the literature. Furthermore, we acknowledge that the clinical management of patients with *EGFR*m$^+$ NSCLC in Japan has changed substantially since the study was conducted, with a better understanding of the molecular biology of NSCLC, more frequent follow-up and widespread access to liquid biopsy-based molecular analysis at disease progression, and a broader range of treatment options now available. Although no data are available, as yet, on the use of immune checkpoint inhibitors post-afatinib in *EGFR*m$^+$ patients, a subanalysis of the Phase III IMPower150 study suggests that incorporation of the PD-L1 inhibitor, atezolizumab, into second-line chemotherapy-based regimens, can improve outcomes following failure of first-line EGFR TKIs [42]. Such combination regimens represent further potential second- or third-line options following afatinib. Although this study is unable to provide any insights into the use of these and other newly approved agents post-afatinib, we believe our data on subsequent therapy duration and survival provide a benchmark against which to measure any additional benefit conferred by the newer therapeutic modalities.

Conclusion

Despite some study limitations, most notably the small size of our dataset, this analysis suggests that afatinib does not diminish the potential for subsequent therapies, including chemotherapy and other EGFR TKIs, in Japanese patients with advanced NSCLC harboring common *EGFR* mutations. The median OS of almost 4 years from the start of afatinib treatment suggests that Japanese patients with common *EGFR* mutations can derive prolonged benefit following first-line afatinib. These data on the use of subsequent chemotherapy and/or first-generation EGFR TKIs following afatinib treatment may assist healthcare professionals, including Japanese physicians, in determining the optimal role of afatinib within treatment sequencing for newly diagnosed Japanese patients.

Data disposition

The trial is registered on ClinicalTrials.gov, identifier: NCT00949650.

Summary points

- Patients with EGFR mutation-positive (*EGFR*m$^+$) non-small-cell lung cancer inevitably develop resistance to EGFR tyrosine kinase inhibitors (TKIs), yet few data are available to guide subsequent treatment decisions.
- This retrospective study used data from LUX-Lung 3 to evaluate treatment patterns and overall survival after first-line afatinib in Japanese patients with advanced lung adenocarcinoma harboring common *EGFR* mutations.
- Analysis included 47 Japanese patients who had progressed prior to data cutoff and showed that a high proportion received at least one (91%), two (81%) or three (62%) subsequent lines of systemic therapy after afatinib was discontinued.
- The uptake of subsequent treatments was higher in the Japanese subgroup than in the overall population of LUX-Lung 3, although the general trends in uptake of specific subsequent therapies were similar.
- The most frequently received second-line treatments in Japanese patients in LUX-Lung 3 were platinum-based chemotherapy (38%) and first-generation TKI (erlotinib or gefitinib) monotherapy (17%).
- Only one patient received second-line osimertinib (due to limited availability at the time and nonmandatory mutation testing on progression), but time on osimertinib was comparable to that of previous reports of sequential EGFR TKI-osimertinib treatment.
- Results of our study suggest that afatinib does not diminish the potential for subsequent therapies, including chemotherapy and other EGFR TKIs, in Japanese patients with *EGFR*m$^+$ non-small-cell lung cancer.

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Data sharing statement

The datasets generated and analyzed during the study are available from H Yoshioka on reasonable request.

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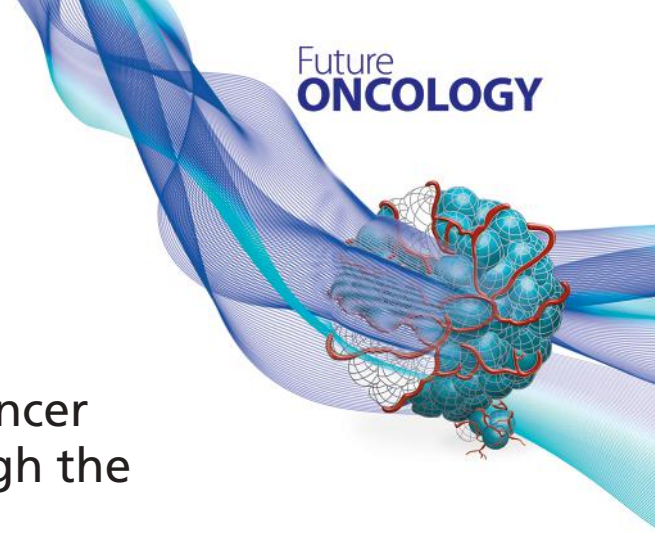

Real-world treatment duration in ALK-positive non-small-cell lung cancer patients receiving brigatinib through the early access program

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Aim: To assess time-to-treatment discontinuation (TTD) of brigatinib following treatment with ALK tyrosine kinase inhibitor(s) (TKIs) in patients with ALK-positive (ALK+) non-small-cell lung cancer (NSCLC) receiving brigatinib through the international early access program. **Patients & analysis:** Analysis was performed for patients with ALK+ NSCLC treated with prior ALK TKIs, including next-generation ALK TKIs. **Results:** Data for 604 patients (21 countries), including patients with prior next-generation ALK TKIs, were reported. The median TTD of brigatinib in patients with prior crizotinib, alectinib, ceritinib or lorlatinib was 10.0, 8.7, 10.3 and 7.5 months, respectively. **Conclusion:** Brigatinib appears to be effective and tolerable in real-world clinical practice regardless of prior treatment with first or NG ALK TKIs.

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Keywords: alectinib • anaplastic lymphoma kinase positive non-small-cell lung cancer • brigatinib • ceritinib • compassionate use • crizotinib • early access • lorlatinib • real-world evidence • treatment duration

Lung cancer is the fourth most common type of cancer worldwide, with an estimated 2.1 million new cases diagnosed and 1.8 million deaths each year [1]. Non-small-cell lung cancer (NSCLC) represents 85% of all lung cancer cases, and the majority of patients present with advanced disease [2]. Genomic analyses indicate that *ALK* gene rearrangements are responsible for 3–5% of NSCLC cases, mainly of the adenocarcinoma histotype [3–5]. While lung cancer often affects individuals of older age with a smoking history, ALK-positive (ALK+) NSCLC patients are usually younger (median age of 51 years) and light or nonsmokers [6].

Until recently, the first-line (1L) treatment option for patients with ALK+ NSCLC was the first-generation ALK tyrosine kinase inhibitor (TKI) crizotinib [7–9]. However, most patients develop resistance to crizotinib due to multiple resistance mechanisms, including secondary mutations, and experience progression within 12 months [10]. The brain is a sanctuary metastatic site in ALK+ NSCLC, and due to poor central nervous system (CNS) coverage of crizotinib, the majority of crizotinib-treated patients develop brain metastases [10,11]. Numerous next-generation (NG) ALK TKIs have been developed, including ceritinib, alectinib, brigatinib and lorlatinib, allowing the possibility of sequencing these agents to extend patient benefit and improve outcomes [12–18]. These NG ALK TKIs have a wide spectrum of activity against crizotinib-resistant *ALK* mutations, and are more potent and have better CNS penetration than crizotinib [19,20].

The current European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) treatment guidelines for ALK+ NSCLC recommend alectinib, crizotinib, ceritinib or brigatinib in the 1L setting, although brigatinib has not received European Medicines Agency (EMA) or US FDA approval as a 1L therapy [8,9]. For patients with oligometastatic progression, local treatment, such as surgery or radiotherapy,

and continued targeted treatment with ALK TKIs are recommended [8,9]. Patients with systemic progression on crizotinib, particularly with CNS involvement, should receive alectinib, ceritinib or brigatinib; however, the optimal targeted treatment has not been established [8,9,19,20]. NCCN also recommends systemic therapy options such as PD-1/PD-L1 inhibitor monotherapy for patients with multiple lesions [11]. ESMO guidelines recommend lorlatinib only to patients progressing on an NG ALK TKI [8]. In the USA, the FDA granted accelerated approval of lorlatinib, based on tumor response rate and duration of response, for patients with ALK+ metastatic NSCLC whose disease has progressed on crizotinib and ≥1 other ALK inhibitor for metastatic disease; or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease [21].

Platinum-based chemotherapy and the four-drug regimen (atezolizumab plus bevacizumab, paclitaxel and carboplatin; not EMA approved) are the only ESMO recommendations for patients with metastatic disease who fail targeted therapy with ALK TKIs [8]. The IMpower150 randomized, open-label Phase III study aimed to test the efficacy of the four-drug regimen against the standard-of-care bevacizumab plus carboplatin and paclitaxel in chemotherapy-naive patients with metastatic NSCLC (mNSCLC) [22]. This study included a limited number of patients with ALK+ NSCLC (n = 40), and the results were reported as part of the larger subgroup of patients with EGFR-mutation-positive NSCLC (EGFR+ status n = 124); thus, the benefits of the four-drug regimen in ALK+ NSCLC patients are unclear [22]. The NCCN recommends continued ALK TKI treatment and local therapy for patients progressing on targeted therapies, and advises lorlatinib or systemic therapy options for those progressing on NG ALK TKI with multiple systemic lesions [9].

The international brigatinib early access program (EAP) was initiated in July 2016 to enable early access to brigatinib in response to an unsolicited request for patients with ALK+ NSCLC who received prior *ALK* TKIs and were unable to participate in clinical studies. At the time of the analysis, more than 20 countries participated in the program. The primary objective of the brigatinib EAP was to enable access for eligible patients with an unmet need; any data generated are incidental. Nevertheless, accumulating evidence supports the benefit of brigatinib in patients with ALK+ NSCLC in the real-world setting from individual countries [23,24].

The objective of this retrospective observational study of data from the EAP was to assess real-world treatment duration of brigatinib following treatment with ALK TKIs in patients with ALK+ NSCLC who received treatment through the international brigatinib EAP.

Materials & methods

Participants

Adult (≥18 years) patients were eligible for treatment with brigatinib in the EAP if they: had histologically or cytologically confirmed locally advanced NSCLC (aNSCLC) or mNSCLC; had an *ALK* rearrangement detected according to local standard procedure; received prior ALK TKI (before June 2018) or were resistant to or intolerant of crizotinib (after June 2018); and could not be adequately treated with medications approved or available through clinical trials in their country of residence. At the time of the analysis, this international EAP included 604 patients in multiple countries from the Americas, Asia and Europe [25].

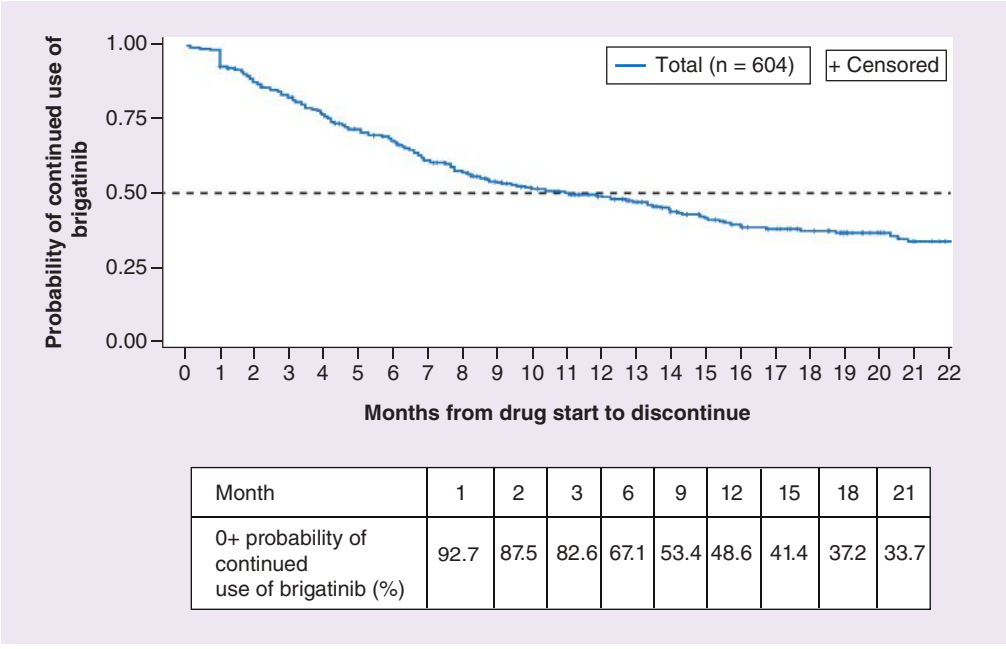
Outcomes

Patient baseline demographics & clinical characteristics

Patient data including age, gender, latest performance status (PS) and therapies received prior to treatment with brigatinib were collected as part of the initial eligibility screening to receive access to brigatinib through the EAP. The data were entered into a database with a cut-off date of November 2018.

Brigatinib time-to-treatment discontinuation

Time-to-treatment discontinuation (TTD) is an end point calculated using real-world data, and is defined as the time from the start of a therapy to the time when treatment is discontinued for any reason. Brigatinib TTD was selected as an efficacy end point, as it was consistently captured through voluntary, physician-reported data on discontinuation forms. Discontinuation was either confirmed for patients with a discontinuation form or assumed if there was a gap of >120 days between data cut-off date (November 2018) and last medication shipment date. Patients who did not meet these criteria were censored at the end of available follow-up. TTD was estimated from Kaplan-Meier curves. Reasons for brigatinib discontinuation were summarized as frequency counts and percentages.



Month	1	2	3	6	9	12	15	18	21
0+ probability of continued use of brigatinib (%)	92.7	87.5	82.6	67.1	53.4	48.6	41.4	37.2	33.7

Figure 1. Probability of continued use of brigatinib across all lines of therapy.

Statistical analyses

Data were analyzed using SAS software (version 9.4). Brigatinib TTD and probability of continued use of brigatinib were estimated from Kaplan–Meier curves. Subgroup analyses were conducted based on whether patients had received crizotinib, alectinib, ceritinib or lorlatinib prior to brigatinib and by number of ALK inhibitors received prior to brigatinib.

Results

Participants & baseline characteristics

At the time of analysis, a total of 604 patients had received brigatinib through the EAP in countries including Argentina, Austria, Brazil, Estonia, Finland, France, Germany, Hong Kong, Italy, Mexico, The Netherlands, Norway, Portugal, Russian Federation, Singapore, Spain, Sweden, Switzerland, Taiwan, Turkey and the UK. The number of participants in each country was not available. Median patient age was 58.0 years, 56.8% of patients were females and 52.0% of patients had a PS of one (Table 1). Among patients with ALK TKI history prior to brigatinib, 64.2% had received two or fewer (median of two) ALK TKIs prior to brigatinib. Most patients (29.5%) had received ceritinib as the most recent ALK TKI prior to brigatinib, 19.0% of patients had received crizotinib as the most recent ALK TKI prior to brigatinib and 13.1% had been treated with alectinib as the most recent ALK TKI (Table 1).

Brigatinib TTD

Across all lines of therapy

During the 27.5-month period over which the retrospective data analysis was conducted, median brigatinib TTD was 11.0 months (95% CI: 8.7–13.9), and the probability of continued use of brigatinib was 67.1% at 6 months and 48.6% at 12 months (Figure 1).

Subgroup analyses based on prior ALK TKIs

Duration of brigatinib treatment was analyzed for subgroups of patients treated with various ALK TKIs prior to brigatinib.

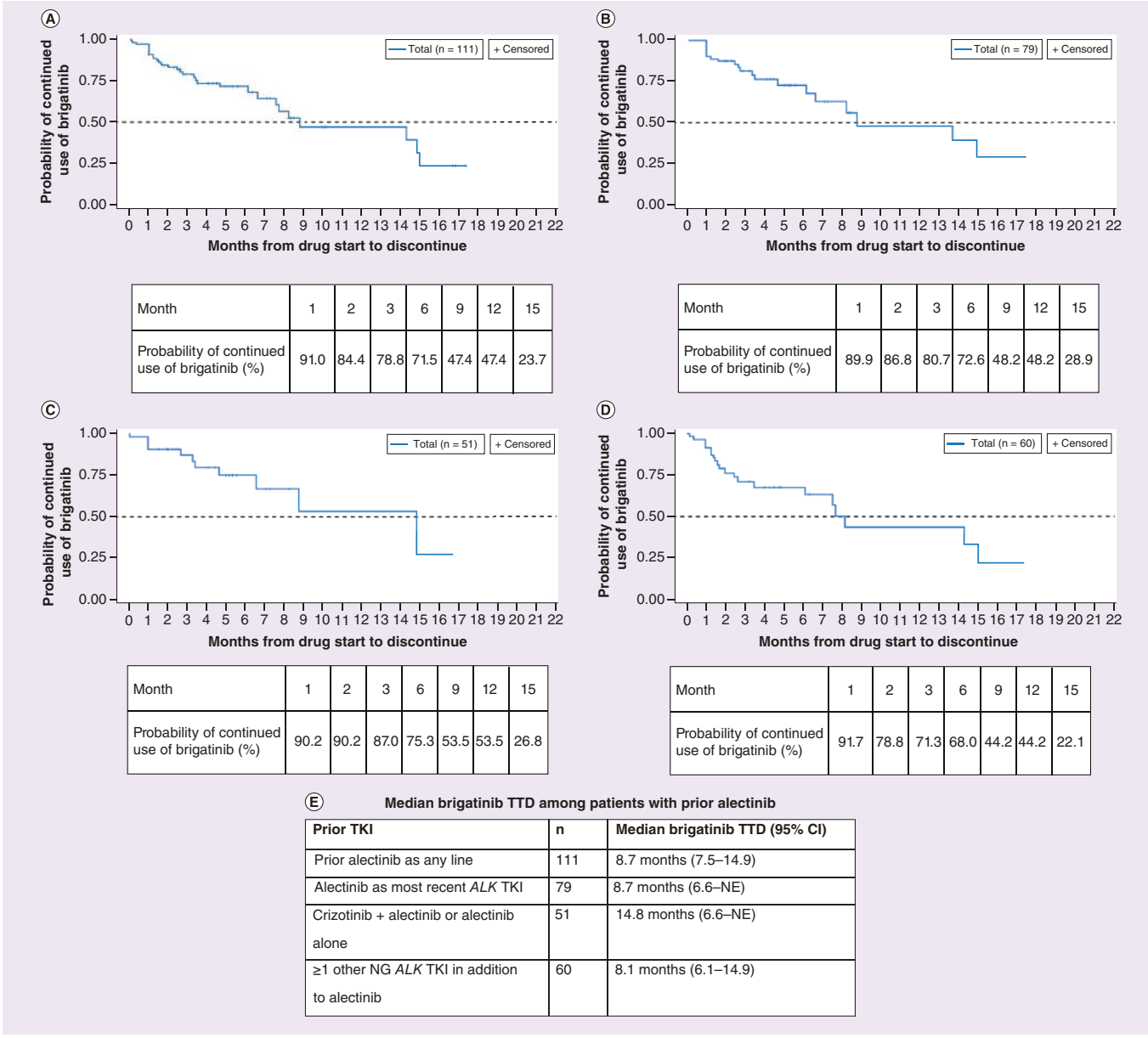
Table 1. Baseline characteristics of patients in the brigatinib early access program.

Characteristics	Patients (n = 604)
Age, median (range)	58.0 (19–94)
Gender	
Males	256 (42.4)
Females	343 (56.8)
Missing	5 (0.8)
Latest performance status	
0	205 (33.9)
1	314 (52.0)
2	49 (8.1)
Missing	36 (6.0)
Number of prior ALK TKIs	
1	155 (25.7)
2	209 (34.6)
3+	69 (11.5)
Missing	171 (28.3)
Prior ALK TKI	
Alectinib	8 (1.3)
Alectinib + Ceritinib	3 (0.5)
Alectinib + Ensartinib	1 (0.2)
Ceritinib	28 (4.6)
Ceritinib + Lorlatinib	2 (0.3)
Crizotinib	117 (19.4)
Crizotinib + Alectinib	43 (7.1)
Crizotinib + Alectinib + Ceritinib	38 (6.3)
Crizotinib + Alectinib + Ceritinib + Lorlatinib	10 (1.7)
Crizotinib + Alectinib + Lorlatinib	8 (1.3)
Crizotinib + Ceritinib	155 (25.7)
Crizotinib + Ceritinib + Lorlatinib	13 (2.2)
Crizotinib + Ensartinib	1 (0.2)
Crizotinib + Lorlatinib	4 (0.7)
Ensartinib	1 (0.2)
Entrectinib	1 (0.2)
Missing	171 (28.3)
Most recent ALK TKI	
Alectinib	79 (13.1)
Ceritinib	178 (29.5)
Crizotinib	115 (19.0)
Crizotinib + Ceritinib	1 (0.2)
Ensartinib	3 (0.5)
Entrectinib	1 (0.2)
Lorlatinib	31 (5.1)
Missing	196 (32.5)

Data represented as n (%), unless otherwise stated.
EAP: Early access program; TKI: Tyrosine kinase inhibitor.

Prior alectinib

Overall, 111 patients received alectinib as any line of therapy prior to brigatinib. These patients had a median TTD of brigatinib of 8.7 months (95% CI: 7.5–14.9), and a probability of continued use of brigatinib of 71.5 and 47.4% at 6 and 12 months, respectively (Figure 2A). Among the 111 patients receiving alectinib, 79 had received alectinib as the most recent ALK TKI prior to brigatinib. These patients had a median TTD of brigatinib



Month	1	2	3	6	9	12	15
Probability of continued use of brigatinib (%)	91.0	84.4	78.8	71.5	47.4	47.4	23.7

Month	1	2	3	6	9	12	15
Probability of continued use of brigatinib (%)	89.9	86.8	80.7	72.6	48.2	48.2	28.9

Month	1	2	3	6	9	12	15
Probability of continued use of brigatinib (%)	90.2	90.2	87.0	75.3	53.5	53.5	26.8

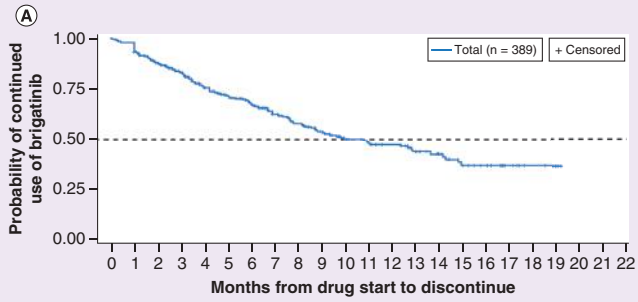
Month	1	2	3	6	9	12	15
Probability of continued use of brigatinib (%)	91.7	78.8	71.3	68.0	44.2	44.2	22.1

E **Median brigatinib TTD among patients with prior alectinib**

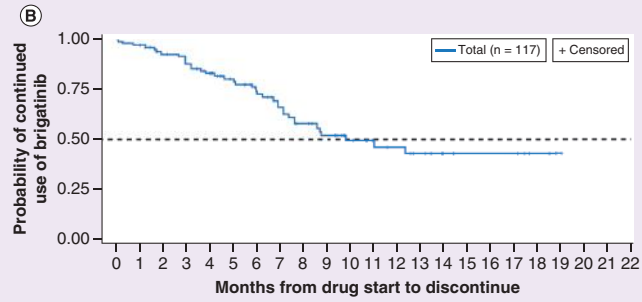
Prior TKI	n	Median brigatinib TTD (95% CI)
Prior alectinib as any line	111	8.7 months (7.5–14.9)
Alectinib as most recent *ALK* TKI	79	8.7 months (6.6–NE)
Crizotinib + alectinib or alectinib alone	51	14.8 months (6.6–NE)
≥1 other NG *ALK* TKI in addition to alectinib	60	8.1 months (6.1–14.9)

Figure 2. Brigatinib use among patients with prior alectinib. (A) Patients with prior alectinib as any line. **(B)** Patients with alectinib as most recent ALK TKI. **(C)** Patients with crizotinib + alectinib or alectinib alone. **(D)** Patients with ≥1 other NG ALK TKI in addition to alectinib. **(E)** Median brigatinib TTD among patients with prior alectinib.
NE: Not evaluable; NG: Next-generation; TKI: Tyrosine kinase inhibitor; TTD: Time-to-treatment discontinuation.

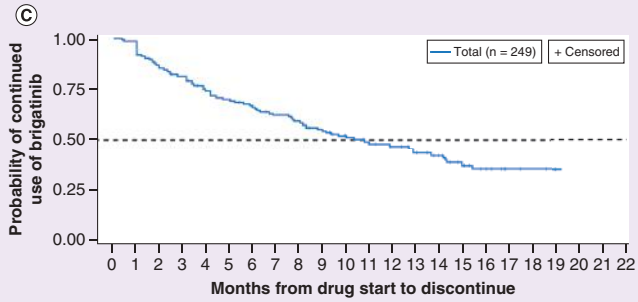
of 8.7 months (95% CI: 6.6–not evaluable [NE]), and a 72.6 and 48.2% probability of continued use of brigatinib at 6 and 12 months, respectively (Figure 2B). Patients who had received crizotinib plus alectinib or alectinib alone (n = 51) prior to brigatinib had a median TTD of brigatinib of 14.8 months (95% CI: 6.6–NE), and a 75.3 and 53.5% probability of continued use of brigatinib at 6 and 12 months, respectively (Figure 2C). Patients who had previously received ≥1 other NG ALK inhibitor (e.g., ceritinib or lorlatinib) in addition to alectinib (n = 60) had a median TTD of 8.1 months (95% CI: 6.1–14.9), and a 68.0 and 44.2% probability of continued use of brigatinib at 6 and 12 months, respectively (Figure 2D). The majority of these patients also received prior crizotinib. The median TTD of these subgroups is summarized in Figure 2E.



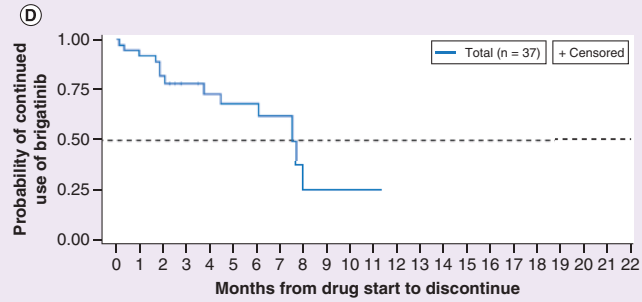
Month	1	2	3	6	9	12	15	18
Probability of continued use of brigatinib (%)	91.0	84.4	78.8	71.5	47.4	47.4	23.7	36.1



Month	1	2	3	6	9	12	15	18
Probability of continued use of brigatinib (%)	97.4	92.9	88.1	72.9	52.3	46.7	43.3	43.3



Month	1	2	3	6	9	12	15	18
Probability of continued use of brigatinib (%)	92.0	85.5	81.1	66.0	54.0	46.0	36.7	34.8



Month	1	2	3	6	9
Probability of continued use of brigatinib (%)	91.9	81.8	78.1	68.3	24.8

E **Median brigatinib TTD among patients with prior crizotinib or lorlatinib**

Prior TKI	n	Median brigatinib TTD (95% CI)
Prior crizotinib as any line	389	10.0 months (8.2–13.6)
Prior crizotinib alone	117	9.8 months (7.3–NE)
Prior ceritinib as any line	249	10.3 months (8.1–13.6)
Prior lorlatinib as any line	37	7.5 months (4.5–NE)

Figure 3. Brigatinib use among patients with prior ALK tyrosine kinase inhibitors. (A) Patients with prior crizotinib as any line. **(B)** Patients with prior crizotinib alone. **(C)** Patients with prior ceritinib as any line. **(D)** Patients with prior lorlatinib as any line. **(E)** Median brigatinib TTD among patients with prior crizotinib or lorlatinib.
NE: Not evaluable; TKI: Tyrosine kinase inhibitor; TTD: Time-to-treatment discontinuation.

Prior crizotinib, ceritinib or lorlatinib

Patients who had received crizotinib as any line of therapy prior to brigatinib (n = 389) had a median TTD of brigatinib of 10.0 months (95% CI: 8.2–13.6), and a 66.9 and 46.6% probability of continued use of brigatinib at 6 months and 12 months, respectively (Figure 3A). Those who received crizotinib with no other prior ALK TKI before initiating brigatinib (n = 117) had a median TTD of brigatinib of 9.8 months (95% CI: 7.3–NE), and a 72.9 and 46.7% probability of continued use of brigatinib at 6 and 12 months, respectively (Figure 3B). Patients receiving ceritinib treatment as any line of therapy prior to brigatinib (n = 249) had a median TTD of brigatinib of 10.3 months (95% CI: 8.1–13.6), and a 66.0 and 46.3% probability of continued use of brigatinib at 6 and 12 months, respectively (Figure 3C). Patients who had received lorlatinib treatment as any line of therapy prior to brigatinib (n = 37) had a median TTD of brigatinib of 7.5 months (95% CI: 4.5–NE), and a 68.3% probability

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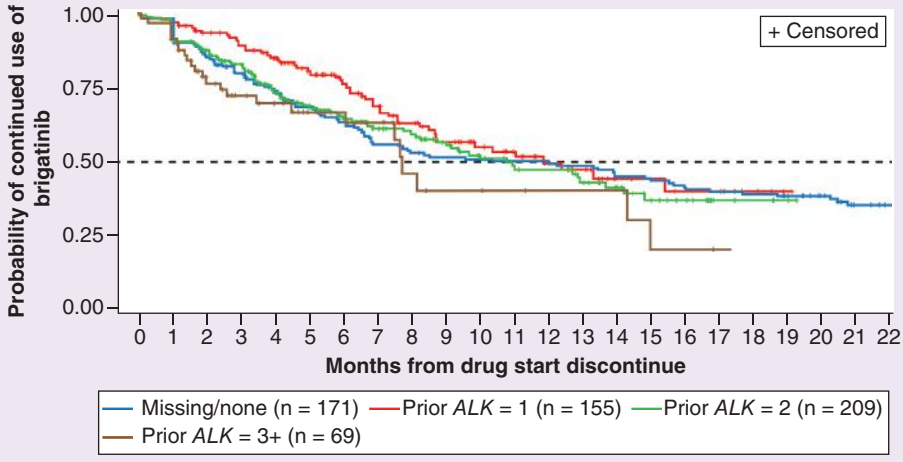

	Month	1	2	3	6	9	12	15	18	21
Probability of continued use of brigatinib (%)	1 *ALK* TKI	96.8	93.6	89.4	76.3	56.5	49.3	44.3	39.9	–
	2 *ALK* TKIs	91.4	87.3	82.9	64.4	55.4	47.3	36.9	36.9	–
	≥3 *ALK* TKIs	91.3	78.6	72.4	66.7	40.1	40.1	20.1	–	–
	Missing	91.2	85.7	80.1	63.7	51.4	49.2	44.0	38.7	35.0

Ⓑ **Median brigatinib TTD by number of prior *ALK* inhibitors**

Prior TKI	n	Median brigatinib TTD (95% CI)
1 *ALK* TKI	155	11.8 months (8.7–NE)
2 *ALK* TKIs	209	10.8 months (8.2–14.1)
≥3 *ALK* TKIs	69	7.7 months (6.1–14.9)
Missing	171	10.3 months (6.7–15.7)

Figure 4. Brigatinib use by number of prior ALK tyrosine kinase inhibitors. (A) Patients with one to three prior ALK TKIs. **(B)** Median brigatinib TTD by number of prior ALK inhibitors.
NE: Not evaluable; TKI: Tyrosine kinase inhibitor; TTD: Time-to-treatment discontinuation.

of continued use of brigatinib at 6 months (Figure 3D). The median TTD of these subgroups are summarized in Figure 3E.

Number of prior ALK TKIs

Patients were also grouped by number of ALK TKIs prior to brigatinib. Out of the 155 receiving one prior ALK TKI, 117 received crizotinib (Table 1). Patients with one ALK TKI prior to brigatinib had a median TTD of brigatinib of 11.8 months (95% CI: 8.7–NE), and a 76.3 and 49.3% probability of continued use of brigatinib at 6 and 12 months, respectively. Patients receiving two ALK TKIs prior to brigatinib (n = 209) had a median TTD of brigatinib of 10.8 months (95% CI: 8.2–14.1), and a 64.4 and 47.3% probability of continued use of brigatinib at 6 and 12 months, respectively. Patients receiving three or more ALK TKIs prior to brigatinib (n = 69) had a median TTD of brigatinib of 7.7 months (95% CI: 6.1–14.9), and a 66.7 and 40.1% probability of continued use of brigatinib at 6 and 12 months, respectively. Among patients with missing information on the number of ALK TKIs prior to brigatinib (n = 171), the median TTD of brigatinib was 10.3 months (95% CI: 6.7–15.7), and the probability of continued use of brigatinib was 63.7% at 6 months and 49.2% at 12 months (Figure 4).

Table 2. Reasons for brigatinib treatment discontinuation.

Reason for treatment discontinuation	n (%)
Total patients	604
Discontinued	260 (43.0)
Adverse event	4 (0.7)
Disease progression	64 (10.6)
Death	15 (2.5)
Lost to follow-up	1 (0.2)
Other	31 (5.1)
Assumed discontinued (discontinuation defined by gap)†	145 (24.0)

†Discontinuation was assumed for patients without confirmed discontinuation if there was a gap of >120 days between data cutoff date (7 November 2018) and last medication shipment date. Discontinuation date was last shipment date plus 30 days.

Reasons for discontinuation

Out of the 604 patients enrolled in the EAP, 260 (43.0%) had discontinued brigatinib at the time of the analysis. Few patients reported discontinuation due to adverse events (n = 4, 0.7%), 64 (10.6%) had disease progression, and 15 (2.5%) patients died (Table 2). 24% of patients were assumed discontinued but did not indicate a reason for ending treatment.

Discussion

Since its inception, the international brigatinib EAP has enabled patients with ALK+ NSCLC from more than 20 countries to access brigatinib, an NG ALK TKI, providing real-world evidence (RWE) of brigatinib safety and efficacy in clinical practice. Patients were granted access to brigatinib as long as there was a clinical benefit, and TTD was used as a proxy end point to assess the efficacy of brigatinib. A recent *post hoc* analysis of 18 randomized clinical trials involving 8947 patients supports the use of TTD as a potential end point to assess the efficacy of therapies for mNSCLC. The *post hoc* analysis assessed the relationship between TTD, progression-free survival (PFS), and overall survival (OS) in trials that were submitted to the FDA as part of New Drug Applications or Biologic License Applications [26]. Findings showed TTD was more closely associated with PFS (r = 0.87; 95% CI: 0.86–0.87) than with OS (r = 0.68; 95% CI: 0.67–0.69) across therapeutic classes [26]. The median TTD exceeded median PFS, particularly in the oncogene-directed targeted therapy subgroup, which included EGFR and ALK. This may reflect the common practice of continued treatment beyond objective disease progression as long as a measurable benefit can be extended to the patient, as defined by response evaluation criteria in solid tumors [26].

For patients included in the brigatinib EAP, the median TTD of brigatinib was 11.0 months, despite a heterogeneous patient population pretreated with multiple ALK inhibitors. Continuous use of brigatinib was seen post-alectinib with a median TTD of 8.7 months, and post-ceritinib with a median TTD of 10.3 months. Brigatinib was also used post-lorlatinib, with a median TTD of 7.5 months. Consistent with previous real-world data for patients treated with NG ALK TKIs, brigatinib was well tolerated, with few observed adverse events [15–17,27–29].

An ongoing Phase II trial to investigate the activity of brigatinib in patients whose disease has progressed on prior NG ALK TKIs (ClinicalTrials.gov identifier: NCT02706626) will further refine the feasibility of a sequencing strategy for brigatinib use in this patient population [30]. Preliminary results from this Phase II trial showed a median PFS (mPFS) of 6.4 months (95% CI: 4.6–NE) at a median follow-up of 6.7 months. The patients in this study were pretreated with a median of three prior ALK TKIs, which may account for the relatively shorter PFS as compared with the brigatinib TTD of 11.0 months (95% CI: 8.7–13.9) reported in the EAP across all lines of therapy [30]. The results from the Phase II trial suggest brigatinib has activity after progression on NG ALK TKI in patients with stage IIIB/IV ALK+ NSCLC [30]. An additional study is underway to further address the efficacy of brigatinib after progression on alectinib or ceritinib (ClincialTrials.gov identifier: NCT03535740).

Previous reports have demonstrated real-world effectiveness of brigatinib. The BRIGALK study was a retrospective analysis of 104 patients with ALK+ NSCLC admitted into the brigatinib EAP in France from 1 September 2016 to 1 January 2018 [23]. Among patients pretreated with ≥2 ALK TKIs, mPFS was 6.6 months (95% CI: 4.8–9.9) with a median OS of 17.2 months (95% CI: 11.0–not reached) [23]. At brigatinib initiation, these patients had a poorer PS (PS 0–1: 59.1%, PS ≥2: 40.9%) than those in the present study (PS 0–1: 85.9%, PS 2: 8.1%) [23]. In an independent report of patients with ALK+ NSCLC receiving brigatinib at a single institution

in Austria, the overall mPFS was 9.9 months, whereas the largest treatment cohort (patients receiving brigatinib after crizotinib failure) showed an mPFS of 8.4 months [24]. In another real-world data collection in the broader brigatinib EAP conducted in Europe (UVEA-Brig), which included data from Italy, Norway, Spain and the UK, mPFS was 5.7 months [31]. The observed differences in the effectiveness of brigatinib in the real-world setting could reflect dissimilar patient characteristics, varied treatment history, disparities in regional care paradigms and measured clinical outcomes. Taken together, these data suggest that brigatinib is effective in real-world clinical practice regardless of previous treatment with NG ALK TKIs.

Treatment of ALK+ NSCLC has rapidly evolved from crizotinib as the standard 1L therapy in 2015 to NG ALK TKIs as current initial therapy. As patients relapse on NG ALK TKIs, optimal sequencing of treatment is currently being investigated. The results of this study indicate that brigatinib may be associated with a clinical benefit in the real-world setting, as patients remained on therapy for a considerable duration after NG ALK TKIs, including alectinib.

Limitations

This study was associated with several limitations. First, data analyzed from the EAP were collected from access forms, shipment records and voluntary discontinuation forms, and may be subject to error. Second, quantification of therapeutic efficacy, particularly when it is dependent on line of treatment, should be interpreted with caution. TTD is not an established end point, and it is contingent upon a patient's clinical circumstance and their assessment by physicians. Patients and physicians may be inclined to discontinue treatment early to receive a newer agent, shortening the TTD, and if fewer alternate treatment options exist, patients and physicians may persist on treatment longer, lengthening the TTD. Current treatment guidelines for oligometastatic progression recommend continued targeted treatment with the addition of local therapy, which may also lengthen the TTD. Further research is needed to validate TTD as an end point for use in pragmatic real-world trials. Third, the limited population of terminally-ill, heavily pre-treated patients with aNSCLC and short follow-up may have influenced the observed TTD. Fourth, AEs were collected in a database but not linked to discontinuation, and detailed AE analysis is still ongoing. Fifth, data on chemotherapy regimens were not captured. Last, lack of randomization in RWE studies is a source of variability, introducing potential for bias from unknown confounding variables obscuring treatment effects.

Conclusion

This retrospective observational study of data from the EAP in over 600 patients with ALK+ NSCLC pretreated with ALK TKI provides RWE of the efficacy and safety of brigatinib. The median TTD of brigatinib observed among patient subpopulations treated with prior alectinib, ceritinib or lorlatinib are encouraging and suggest brigatinib can provide clinical benefit for patients with progressive disease regardless of prior line of therapy. The safety profile of brigatinib was largely consistent with previous reports.

Author contributions

All authors contributed to the study design, data analysis and manuscript development.

Financial & competing interests disclosure

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Summary points

- The brigatinib international early access program (EAP) commenced in 2016 to enable unsolicited expanded access to brigatinib for patients with ALK+ non-small-cell lung cancer (NSCLC) who had no other effective therapeutic options and were unable to participate in a clinical study.
- Real-world data on brigatinib in patients with ALK+ NSCLC previously treated with ALK tyrosine kinase inhibitors (TKIs), including next-generation ALK TKIs alectinib, ceritinib or lorlatinib, could be extracted from the EAP.
- As of November 2018, data for 604 patients in 21 countries enrolled in the EAP could be collected.
- Time-to-treatment discontinuation (TTD) was used as a proxy for tolerability and effectiveness of brigatinib in the absence of reported clinical outcomes in the EAP.
- Brigatinib TTD in patients with previous crizotinib, alectinib, lorlatinib or ceritinib was 10.0, 8.7, 7.5 and 10.3 months, respectively.
- Among patients who received one previous ALK TKI, brigatinib TTD was 11.8 months, while in those receiving two or three prior ALK TKIs, brigatinib TTD was 10.8 and 7.7 months, respectively.
- Based on voluntary physician-reported data on discontinuation forms, the majority of patients (57.0%) remained in the EAP and few had discontinued brigatinib treatment due to adverse events (0.7%) or disease progression (10.6%). 2.5% of patients died while participating in the EAP and 24% of patients were assumed discontinued but did not indicate a reason for discontinuation.
- The encouraging efficacy of brigatinib observed in the EAP suggests that brigatinib is effective and tolerable in the real-world setting regardless of previous ALK TKI treatment.

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Clinical Trial Protocol

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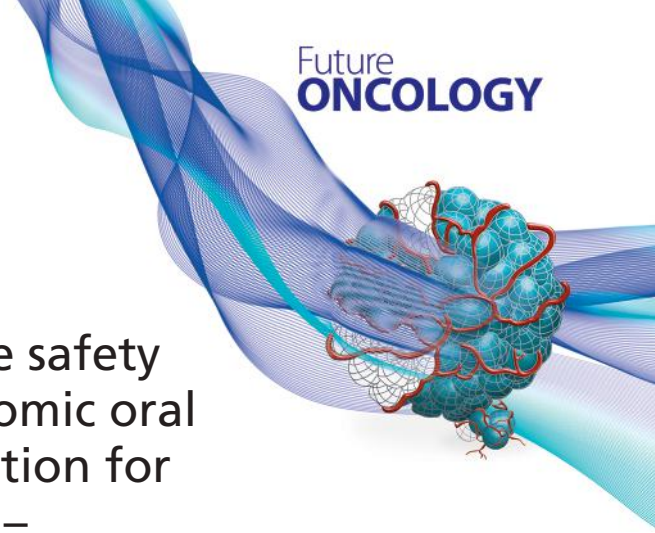

Open-label Phase II trial to evaluate safety and efficacy of second-line metronomic oral vinorelbine–atezolizumab combination for stage-IV non-small-cell lung cancer – VinMetAtezo trial, (GFPC‡ 04-2017)

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Metronomic chemotherapy is defined as frequent low-dose administration without prolonged drug-free breaks. Combining immune-checkpoint inhibitors and metronomic chemotherapy is a new approach to improve responses and delay onset of resistance to immune-checkpoint inhibitors. This multicenter, Phase II, open-label, single-arm study was designed to assess the safety and efficacy of metronomic oral vinorelbine in combination with immune-checkpoint inhibitors in advanced non-small-cell lung cancers progressing after first-line platinum-based chemotherapy. The recommended metronomic oral vinorelbine dose will be determined during a safety run-in period including 12 patients; the main study will include 59 additional patients. The primary outcome is progression-free survival at 4 months. Secondary outcomes are safety of the combination, median overall survival, objective response rate, disease-control rate at 4 months and quality of life (NCT03801304).

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Keywords: immunotherapy • metronomic chemotherapy • non-small-cell lung cancer • second line

Lung cancer is the leading cause of cancer deaths in USA, with 5-year survival at ~16%. Representing >85% of lung cancers, non-small-cell lung cancer (NSCLC) is the most common type. Unfortunately, most of these patients are diagnosed with locally advanced or metastatic disease [1–4].

Immunotherapy enhanced a paradigmatic shift in NSCLC treatment, especially through the anti-PD1 or its ligand's (PD-1/PD-L1) pathway. PD-1 [3] is an immune-checkpoint receptor expressed by activated T cells. Upon binding to its ligands, PD-L1 and PD-L2, PD-1 normally moderates ongoing immune responses and prevents autoimmunity [3]. Several compounds have been used as second-or-more-line agents [4]. For first-line, chemotherapy-treated patients, immunotherapy is a second-line option. In this setting, nivolumab and pembrolizumab (anti-PD-1) and atezolizumab (anti–PD-L1) monoclonal antibodies were approved and have gradually been introduced into clinical management of advanced NSCLCs [5,6].

Despite these notable advances, persistently low objective response rates (ORRs) to second-line immune-checkpoint inhibitors NSCLC treatment [7] have led to new second-line options, especially immunotherapy–chemotherapy combinations [2]. Second-line immune-checkpoint inhibitors therapy might be combined with chemotherapy to improve immunotherapy efficacy for regimens without major toxicity. Currently, many drugs

are combined with immunotherapy as first- or second-line regimens. Oral vinorelbine has been used for many years to treat NSCLCs [8,9]. Metronomic chemotherapy is defined as frequent low-dose administration without prolonged drug-free breaks to reduce toxic effects and prevent rapid revascularization that can promote tumor growth during therapy breaks [9]. The immunostimulatory effects of metronomic chemotherapy are: induced immunogenic cancer-cell death [10]; enhanced antigen presentation through dendritic cell modulation [11] and increased cancer-cell immunogenicity [12]; preferential regulatory T-cell depletion [13]; modulation of myeloid-derived suppressor cells [14]; and heightened immune-effector–cell cytotoxic activity, for example, of tumor-specific T cells [15]. Metronomic chemotherapy–immunotherapy synergism has been reported [16].

Using oral vinca alkaloid vinorelbine for metronomic therapy has been accorded considerable attention, especially because of its potent anti-angiogenic and pro-immune and microtubule-targeting properties at low dose [17,18]. Activity was reported in elderly patients against metastatic breast cancer, advanced refractory NSCLCs [19,20] and advanced NSCLCs [21]. Barlesi *et al.* [22] recently published the usefulness of a mathematical model to determine the optimal metronomic vinorelbine dose for NSCLC and mesothelioma patients. In most studies, the recommended metronomic oral vinorelbine (MOV) dose alone is 50 mg/day, thrice weekly [19,20,23]. The MOVE trial, prescribing first-line MOV alone for elderly patients, achieved 18.6% ORR [23]. Sutiman *et al* recently comparing two MOV doses combined with erlotinib for NSCLC patients obtained good disease control (~50%) [24]. Safety of MOV combined with sorafenib for advanced NSCLC patients was described previously [25]. More recently the safety of MOV was also confirmed by a retrospective multicentric analysis including 270 advanced NSCLC [26] and an individual patient-data meta-analysis including 9 studies and 418 patients [27].

We describe here the design of a multicenter, Phase II, open-label, single-arm study designed to assess the safety and efficacy of MOV in combination with atezolizumab and the result of a running safety phase. The study hypothesis is based on immunotherapy potentialization by metronomic chemotherapy, herein the atezolizumab–MOV combination, whose safety and efficacy have not been assessed previously.

Materials & Methods

This multicenter, Phase II, open-label, single-arm study was designed to assess atezolizumab–MOV safety and efficacy in patients with advanced NSCLCs.

Eligibility criteria for inclusion were: advanced NSCLC or relapsed locally advanced NSCLC, without activating *EGFR* mutation or *ALK* rearrangement, progressing after first-line platinum-doublet–based chemotherapy, according to RECIST v1.1; a measurable lesion (RECIST v1.1); age ≥18 years, with ECOG PS <3 and life expectancy >12 weeks; adequate laboratory-test-documented organ-function results during the 3 weeks preceding study enrollment; effective contraception for women of child-bearing potential; national healthcare insurance and written informed consent to participate.

The main noneligibility criteria were: small cell lung, bronchioalveolar or neuroendocrine cancer; known hypersensitivity to immunotherapy; radiotherapy (except for bone or brain) within the 3 months preceding baseline imaging; persistent clinical adverse events (AEs) attributed to prior treatment; active or untreated computed tomography or magnetic resonance imaging detected CNS metastases during screening and prior radiographic assessments; uncontrolled pleural effusion; pericardial effusion; ascites requiring recurrent drainage procedures; uncontrolled/symptomatic hypercalcemia requiring continued bisphosphonate or denosumab use; prior autoimmune disease; human immunodeficiency virus or active hepatitis B- or C-positivity; systemic corticosteroid up to 10 mg/day or other systemic immunosuppressant use during the 2 weeks preceding study enrollment; or anticipated need for systemic immunosuppressant(s) during the trial.

Study design

A run-in phase aimed to ensure the safety of the fixed-dose atezolizumab (1200 mg iv. on day 1, every 21 days)–MOV (40-mg dose, thrice weekly for 3 weeks) combination; the latter was chosen based on the literature [23,25,26]. To assess tolerance, the numbers (%) of AEs, according to National Cancer Institute CTCAE, will be recorded. Toxicity will be determined by the number (%) of grade-≥3 AEs in the first 12 patients during the first cycle, with >20% grade-≥3 specific immune-related or oral vinorelbine-related AEs defining dose toxicity. A ≤6-week trial interruption will allow Data Safety Monitoring Board (DMSB) case review.

In the case of toxicity, the dose will be decreased to 30 mg, thrice weekly. The same AE-assessment procedure will be applied to the following 12 patients.

Table 1. Adverse events during the run-in phase (n = 12).

	Grades ≤2		Grades >2	
Adverse event	**1**	**2**	**3**	**4**
Hematologic	1	1	–	–
Infectious	1			
Neurologic	–	1		
Vascular thrombus	–	2		
Fatigue		2		
Digestive	5	3		
General disorders	–	3	2†	–
Pain	–	1	1†	–
Cutaneous	1	1		

†Not drug related.

The main study

Once the safety run-in phase has been completed and the regimen validated, the study design will be as follows: MOV (40 or 30 mg, thrice weekly for 3 weeks) in combination with fixed atezolizumab infusions (1200 mg iv. on day 1, every 21 days). Patients will be treated until disease progression. When progression according to RECIST criteria occurs, MOV will be stopped. Atezolizumab will be continued until clinical progression. Overall, 71 patients will be enrolled in this Phase II study, including the 12 safety run-in-phase participants.

Cross-sectional analyses will attempt to identify relevant biomarkers and evaluate their relationship(s) to clinical outcomes. The specific analysis will be based on PD-L1 expression, but other biomarkers would be tested.

Outcomes

The primary outcome is PFS rate at 4 months. The secondary outcomes are median PFS, median OS, tolerance according CTAE, ORR, disease-control rate and quality of life during the study using the EORTC QLQ-C30 scale.

Statistical analyses

This open-label, multicenter, Phase II study used the exact single-stage Phase II design defined by A'hern [28]. The sample size is based on an exact binomial distribution.

Minimal efficacy hypothesis (p1) is set at 55% event-free rate of PFS at 4 months; (p0), indicating that the strategy is clearly ineffective, is set at 40% PFS at 4 months (based on the OAK study's 43% PFS at 4 months). With a 5% alpha-risk (unilateral perspective) and a 20% β-risk, the number of assessable subjects is set at 71. The Phase III trial threshold is 36 successes/71 subjects, with success defined as a subject without death or progression at 4 months. The percentage of patient successes at 4 months will be described with its 95% confidence interval, estimated by the exact method. $p < 0.05$ will define statistical significance. The intent-to-treat population (all patients included) will be analyzed. The per-protocol population will also be analyzed. The results will be presented according to the CONSORT Statement recommendations.

The statistical analysis plan will be validated by the trial's Scientific Committee.

Ethical considerations

The study will be conducted in compliance with the principles of the Declaration of Helsinki, and each participating institution's Institutional Review Board has approved the protocol. All patients must give written informed consent before any screening or inclusion procedures. The regulatory authority approved the protocol on 24 October 2018 and the Ethics Committee on 22 November 2018 (NCT03801304, EudraCT number: 2018-000164-28).

Results

The trial was opened in four centers for the run-in phase (25 January 2019 to 19 March 2019). 12 patients were included: the DMSB reviewed 25 AEs (Table 1). Three grade-3 AEs occurred: deteriorated general condition attributed to increased size of brain metastases, not treatment-related; metastasis-related bone pain, not treatment-

related, that was rapidly attenuated with specific treatment and without affecting the protocol; loss of appetite and weight loss, possibly treatment-related, leading to protocol interruption for 1 week.

The DMSB recommended transition to the main study at the 40-mg/day, thrice weekly, MOV dose on 16 April 2019, which was validated by the regulatory authority.

Discussion & conclusion

The safety and efficacy study of the atezolizumab–MOV combination will enable us to determine whether metronomic chemotherapy administration can enhance the efficacy of immunotherapy alone with an acceptable tolerance profile. Depending on market-access times, the majority of patients diagnosed with advanced NSCLC are or will be eligible for first-line combination immunotherapy–platinum-doublet chemotherapy regimens, but most of them will progress on them. No management recommendations for second-or-more lines exist for these patients but the possibility of immunotherapy–metronomic chemotherapy reintroduction, after a therapeutic pause or after second-line chemotherapy is an alternative option worth exploring. This Phase II trial will enable safety and efficacy evaluations of the atezolizumab–MOV combination.

Executive summary

Background

- Atezolizumab, a monoclonal antibody targeting PD1-L1, is approved for second-line treatment of non-small-cell lung cancers.
- The concept of metronomic chemotherapy is defined as frequent, low-dose administration without prolonged drug-free breaks.
- New options for second-line therapy of non-small-cell lung cancers are needed.
- Combining immune-checkpoint inhibitors and metronomic chemotherapy is such a new approach to improve responses and retard development of resistance to immune-checkpoint inhibitors.

Trial design

Open-label Phase II trial to evaluate safety and efficacy of second-line metronomic oral vinorelbine–atezolizumab combination for stage-IV non-small-cell lung cancer

Disclaimer

Sponsors were involved in the study design, but not in patient inclusion, collection and interpretation of data, writing the report and the decision to submit the article for publication. This multicenter Phase II, open-label, single-arm study was designed to assess the safety and efficacy of the metronomic oral vinorelbine and atezolizumab combination.

Financial & competing interests disclosure

The study was sponsored and funded by Laroche Company and Pierre-Fabre Oncology Company. A Vergnenegre reported travel, grant and honorariums from AZ, Roche, MSD, BMS, Pierre Fabre; Isabelle MONNET travel from Roche; H Lena reported travel, grant and honorariums from AZ, Roche, MSD, BMS; Christos CHOUAID grant, travel, honorariums from Roche Pierre Fabre Oncologie AstraZeneca, BMS, MSD Bayer; Gilles Robinet reported grant, travel, honorariums from Roche Pierre Fabre Oncologie AstraZeneca, BMS, MSD Bayer Acya Bizieux. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Short Communication

Future ONCOLOGY

Real-world disease burden and outcomes of brain metastases in *EGFR* mutation-positive non-small-cell lung cancer

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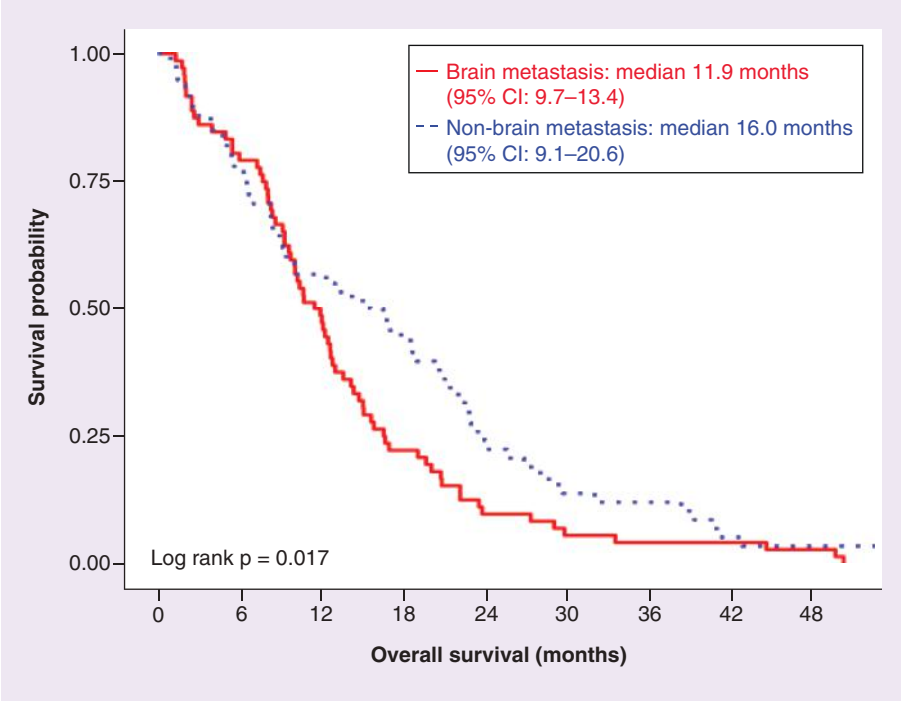
Aim: To evaluate the real-world impact of brain metastases (BM) among patients with *EGFR* mutation-positive (*EGFR*m) metastatic non-small-cell lung cancer (NSCLC). **Materials & methods:** This retrospective, observational matched cohort electronic health record study assessed adults with *EGFR*m metastatic NSCLC with/without BM. **Results:** Among 402 patients split equally between both cohorts (±BM) ,the majority were Caucasian (69%), female (65%) and with adenocarcinoma (92%). Overall symptom burden and ancillary support service use were higher and median overall survival from metastatic diagnosis was significantly shorter in BM patients (11.9 vs 16 months; p = 0.017). **Conclusion:** BM in *EGFR*m NSCLC patients can negatively impact clinical outcomes. New targeted therapies that can penetrate the blood–brain barrier should be considered for treating these patients.

Graphical abstract:



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Keywords: brain metastases • CNS • *EGFR* • EGFR-TKI • non-small-cell lung cancer • NSCLC • osimertinib • real-world

Future Medicine

Lung cancer is the most common cancer worldwide [1]. In the USA, over 200,000 new cases are diagnosed annually and it is the leading cause of cancer-related mortality for both men and women [2]. Most patients are diagnosed at a late stage, with approximately 70% of new diagnoses having locally advanced or metastatic disease, which can include specifically brain or central nervous system (CNS) metastases [3].

The incidence of brain metastasis is increasing, potentially due to better treatment and prolonged survival [4]. This condition can be associated with significant burden of illness [5–7]. In addition, the brain is a common site of metastasis, occurring in 17–65% of patients with primary lung cancer [8]. The brain can be a safe harbor for tumor growth even when there is good visceral control, due to the limited ability of systemic therapies to cross the blood–brain barrier [9,10].

Molecular understanding of non-small-cell lung cancer (NSCLC) in the past few years has revolutionized the treatment of this type of lung cancer, with the introduction of targeted therapies which are less toxic than conventional chemotherapies [11,12]. Biomarkers and associated targeted therapies have improved diagnoses and prognoses for many patients with NSCLC [13].

EGFR mutations are observed in approximately 14% of patients with NSCLC [14]. The *EGFR* mutation-positive (*EGFR*m) subtype is associated with specific pathologic features. The prevalence of brain metastases in *EGFR*m patients specifically is not well known and the incidence may increase as a consequence of improved survival with emerging therapies [15].

The objective of this study was to evaluate patient characteristics, symptom burden, support care services and outcomes, including time to treatment failure (TTF) and overall survival (OS), in patients with *EGFR*m metastatic NSCLC, with and without brain metastases, in a real-world community oncology setting.

Materials & methods

Study design & data sources

This was a retrospective, observational matched cohort electronic health record (EHR) study of patients who received care within a US Oncology Network clinic between January 1 2014 and July 31 2016, with follow-up through March 31 2017. Institutional Review Board approval was obtained for the study. Patients with *EGFR*m metastatic NSCLC with and without brain metastases were identified from the iKnowMed EHR and matched 1:1 by 10-year age bands and sex. The US Oncology Network is affiliated with approximately 60 community oncology practices across 25 states, with approximately 1400 physicians. Data were initially collected via programmatic queries of the iKnowMed EHR system and supplemented with chart review to confirm eligibility, assign into cohorts and to collect clinical symptoms and referrals for ancillary support services. Included patients were $\geq$18 years of age at diagnosis of NSCLC, with confirmed *EGFR*m metastatic disease and at least two visits during the study period (including the follow-up period). Patients could have developed brain metastases before or after receipt of therapy. Patients enrolled in clinical trials or with other concomitant cancer diagnoses during the study period were excluded. The Social Security Death Index was used to supplement vital status from the EHR data. The index date for the cohort of patients with evidence of brain metastases was the date of diagnosis of brain metastases. The index date for the cohort of patients without evidence of brain metastases was the start date of the first treatment for their closest matched line of therapy. Brain imaging at the time of diagnosis was not required for entry into the study; however, among patients with imaging performed, timing and type of imaging used was collected. CNS symptoms and use of ancillary support services were abstracted from chart review through progress notes and use of referrals. All symptoms were abstracted regardless of reason as causality may not be able to be attributed retrospectively.

Statistical analysis

Comparative analyses between the brain metastasis and non-brain metastasis cohorts were performed using χ^2/Fisher's exact test (for categorical variables) and t-test/Mann–Whitney U test/analysis of variance (ANOVA)/Kruskal–Wallis test (for the continuous variables), as applicable. TTF was calculated from the start of treatment to the end of treatment for any reason or censoring. In the brain metastasis cohort, treatment start was calculated from start of treatment following the diagnosis of brain metastasis, and in patients without brain metastasis, from the start of the equivalent line of therapy to understand treatment durations at similar points in the trajectory of care. OS for both cohorts was calculated from the date of metastatic diagnosis and patients alive at the end of the study or lost to follow-up were censored. Kaplan–Meier methods were used for TTF and OS estimates

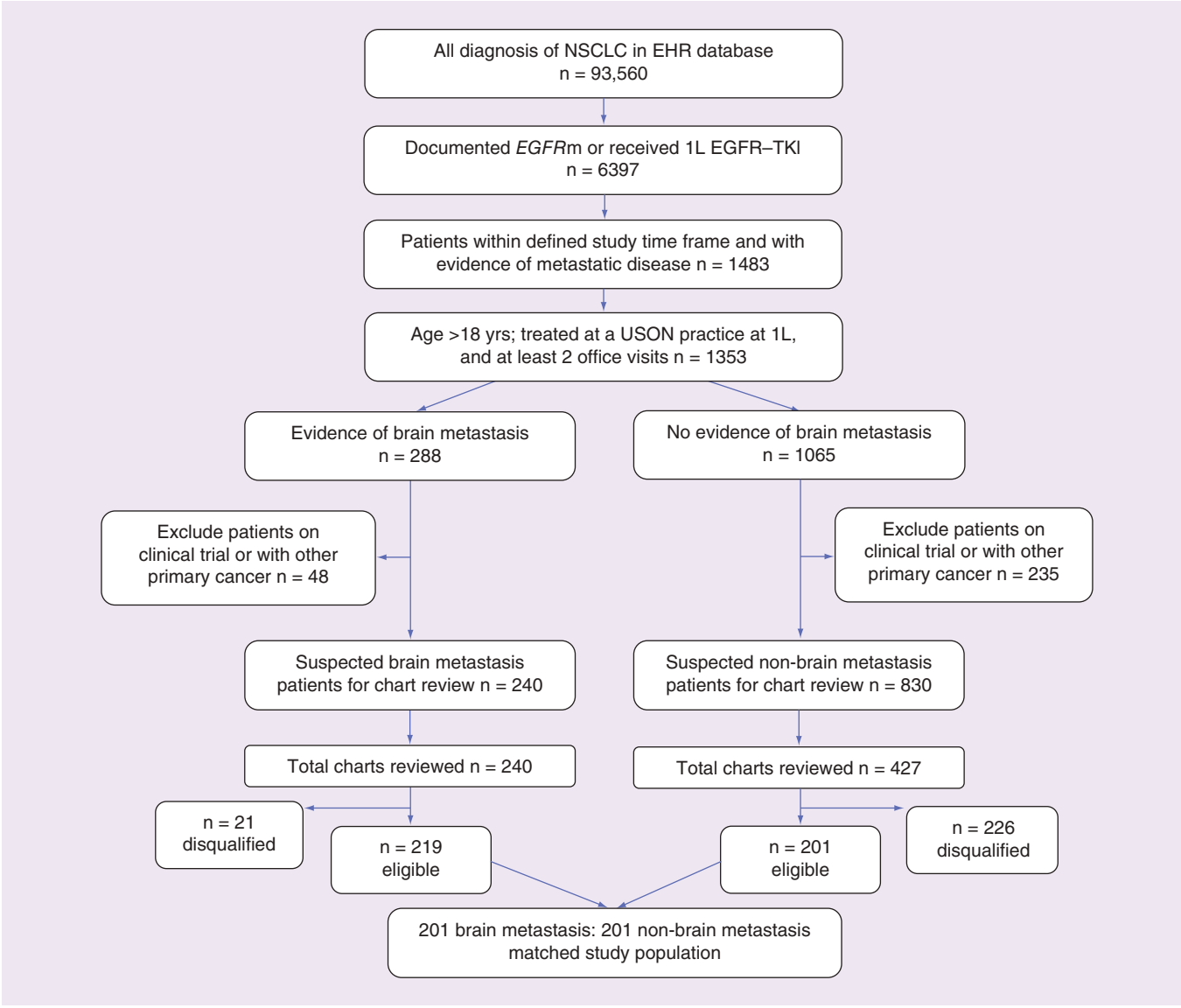

Figure 1. Patient selection.
1L: First line; *EGFR*m: *EGFR* mutation positive; EHR: Electronic health record; NSCLC: Non-small-cell lung cancer; TKI: Tyrosine kinase inhibitor; USON: US Oncology Network.

and log-rank tests were used to determine differences. Statistical significance was defined as p-values <0.05. The analyses were conducted using SAS® (version 9.4, SAS Institute Inc., NC, USA).

Results

Patient characteristics

Over 93,000 patients with NSCLC were identified from the EHR database (Figure 1). Approximately 7% were documented as *EGFR*m, as identified from structured EHR data collected, or as having received a first-line EGFR tyrosine kinase inhibitor (TKI) for which *EGFR* status would be confirmed from chart review. After application of other structured data eligibility criteria, 667 patient charts underwent chart review to confirm eligibility and obtain at least the 200 patients for each cohort. Among patients initially identified as having no brain metastases, a common reason for disqualification was the discovery of brain metastasis during chart review, in at least 15% of patients. After cohort matching, 402 final patients were included, 201 patients with brain metastases and 201 patients without brain metastases.

The patient characteristics were similar across both cohorts. Overall, the majority of patients were Caucasian (68.7%), female (65.2%), never smokers (41.5%) and with adenocarcinoma histology (92.0%). Patients ranged from stage I to IV disease at initial diagnosis; however, most patients were initially diagnosed with stage IV disease (75.1%) and those with earlier stages at diagnosis were later metastatic. However, patients with brain metastases were significantly younger than those without (median age: 70 vs 77 years; p = 0.0004) and a higher proportion of patients with brain metastasis were initially diagnosed with stage IV disease (81.6%) than those without (68.7%; p = 0.04; Table 1). Among the patients with brain metastases, baseline brain imaging within 30 days of metastatic diagnosis occurred in 86% of patients, demonstrating that most patients did have brain imaging around the time of metastatic diagnosis. The predominant imaging method used was MRI in 80.1% of patients, CT scan in 6.5% and unknown in 13.4%. Most patients with brain metastases (67%) had CNS symptoms present at the time of diagnosis of brain metastases, although approximately a third did not have CNS symptoms noted.

Clinical symptoms & support services

CNS symptoms were observed in both cohorts, though rates for most were observed to be significantly higher in patients with brain metastases. Symptoms occurring in at least 10% of patients with brain metastases but in <10% in patients without brain metastases included seizures, speech problems, focal neurologic deficits, drowsiness, problems with memory and altered mental status (Table 2). Symptoms occurring in >10% of patients in both the non-brain metastases and brain metastases cohorts included nausea, vomiting, vision disorder, headache and balance/mobility symptoms. Patients with brain metastases had significantly greater use of home healthcare, nutrition therapy, physical therapy, rehabilitation and social work services than patients without brain metastases (Table 3).

Clinical outcomes

Most patients were receiving first-line treatment at study entry, 93.0% (n = 187) in the brain metastasis cohort and 96.5% (n = 194) of patients without brain metastasis. Similar proportions of patients were treated with a first-generation EGFR-TKI in the two cohorts: 78.1% (n = 157) of patients with brain metastasis and 73.6% (n = 148) of patients without brain metastasis. Median TTF was similar between both cohorts; 10.9 months (95% CI: 9.5–12.0) for patients with brain metastasis and 10.4 months (95% CI: 8.9–12.2) for patients without; p = 0.5184 (Figure 2). However, median OS from metastatic diagnosis was significantly lower in patients with brain metastasis than patients without (11.9 months [95% CI: 9.7–13.4] vs 16.0 months [95% CI: 9.1–20.6], respectively; p = 0.017; Figure 3).

Discussion

Consistent with previous global studies of known characteristics of patients with *EGFR*m NSCLC, most patients in this study were female never smokers with adenocarcinoma histology [16]. However, unlike such global studies, where a higher proportion of Asian patients typically have *EGFR*m status, most patients in this study were Caucasian.

Ongoing research is being conducted to evaluate the association between *EGFR* mutation and CNS metastases and impact on outcomes. In one study by Stanic *et al.*, of 168 lung adenocarcinoma patients with CNS metastases, 28% (n = 47) of the patients had an *EGFR* mutation [4]. The time from brain metastases to death in *EGFR*m patients with brain metastases at diagnosis was 12.6 months compared with 6.8 months in patients without an *EGFR* mutation (p = 0.005).

In another study of 1522 patients with NSCLC, 30% of patients (n = 452) were *EGFR*m [17]. Among those with the *EGFR* mutation, 21% (n = 93) had brain metastases and 79% (n = 359) did not. Regardless of *EGFR* mutation status, median OS was significantly shorter in those patients with brain metastases than those without brain metastases (15 vs 20.6 months; p = 0.02). However, in the *EGFR*m patients specifically, there was no significant difference in median OS from the time of initial diagnosis in those patients with and without brain metastases (20.8 vs 25.1 months; p = 0.11).

In both of these previous studies, the number of patients with both an *EGFR* mutation and brain metastasis were small (n = 47 and n = 93 in either study). Given the limited information, our study helps establish some baseline understanding of symptoms and outcomes in patients prior to the availability of newer therapies and may allow us to understand how outcomes have changed over time in these patients, specifically with the use of new therapies. In our study, all patients were *EGFR*m and the sample size of patients with brain metastases was larger, with 201 patients. We observed the median TTF to be similar in patients with and without metastases and this

Table 1. Patient demographic and clinical characteristics.

Variable	Overall (n = 402)	Brain metastasis (n = 201)	Non-brain metastasis (n = 201)	p-value†
Age (years				
Median Range (min–max)	73.0 39–>90	70.0 39–>90	77.0 43.0–>90	0.0004
Gender				
Female	262 (65.2)	131 (65.2)	131 (65.2)	0.7549
Male	140 (34.8)	70 (34.8)	70 (34.8)	
Race				
African–American	31 (7.7)	15 (7.5)	16 (8.0)	0.4139
Caucasian	276 (68.7)	132 (65.7)	144 (71.6)	
Other	50 (12.4)	29 (14.4)	21 (10.4)	
Unknown	45 (11.2)	25 (12.4)	20 (10.0)	
Smoking status				
Current	19 (4.7)	9 (4.5)	10 (5.0)	0.7076
Former	121 (30.1)	49 (24.4)	72 (35.8)	
Never	167 (41.5)	75 (37.3)	92 (45.8)	
Unknown	95 (23.6)	68 (33.8)	27 (13.4)	
***EGFR* T790M mutation status**				
Negative	51 (12.7)	29 (14.4)	22 (10.9)	0.9834
Positive	60 (14.9)	34 (16.9)	26 (12.9)	
Unknown	291 (72.4)	138 (68.7)	153 (76.1)	
Stage at initial NSCLC diagnosis				
IA	12 (3.0)	2 (1.0)	10 (5.0)	0.04
IB	14 (3.5)	9 (4.5)	5 (2.5)	
IIA	12 (3.0)	4 (2.0)	8 (4.0)	
IIB	5 (1.2)	3 (1.5)	2 (1.0)	
IIIA	26 (6.5)	11 (5.5)	15 (7.5)	
IIIB	9 (2.2)	3 (1.5)	6 (3.0)	
IV	302 (75.1)	164 (81.6)	138 (68.7)	
Not documented	6 (1.5)	1 (0.5)	5 (2.5)	
Unknown	16 (4.0)	4 (2.0)	12 (6.0)	
Histology				
Adenocarcinoma	370 (92.0)	191 (95.0)	179 (89.1)	0.3459
Adenosquamous carcinoma	7 (1.7)	3 (1.5)	4 (2.0)	
Bronchiolo-alveolar carcinoma	4 (1.0)	1 (0.5)	3 (1.5)	
Unknown	16 (4.0)	5 (2.5)	11 (5.5)	
Unspecified NSCLC	5 (1.2)	1 (0.5)	4 (2.0)	
ECOG performance status at index				
ECOG 0	41 (10.2)	20 (10.0)	21 (10.4)	0.3098
ECOG 1	206 (51.2)	85 (42.3)	121 (60.2)	
ECOG 2	36 (9.0)	12 (6.0)	24 (11.9)	
ECOG 3	3 (0.7)	0 (0.00)	3 (1.5)	
Unknown	116 (28.9)	84 (41.8)	32 (15.9)	

†For comparison of brain metastasis and non-brain metastasis cohorts.
Data are presented as n (%) unless otherwise specified.
ECOG: Eastern Cooperative Oncology Group; NSCLC: Non-small-cell lung cancer.

may have been influenced by the observation that most patients were receiving first-line of therapy at study entry; however, median OS from time of metastatic disease was significantly shorter for patients with brain metastases at 11.9 months compared with those without (16.0 months).

Table 2. Clinical symptoms in patients with and without brain metastasis.

Symptoms	Overall (n = 402)	Brain metastasis (n = 201)	Non-brain metastasis (n = 201)	p-value†
Fatigue	288 (71.6)	164 (81.6)	124 (61.7)	<0.0001
Depression	104 (25.9)	65 (32.3)	39 (19.4)	0.0031
Seizure	35 (8.7)	34 (16.9)	1 (0.5)	<0.0001
Speech problems	38 (9.5)	34 (16.9)	4 (2.0)	<0.0001
Stroke	14 (3.5)	7 (3.5)	7 (3.5)	1
Vision disorder	77 (19.2)	53 (26.4)	24 (11.9)	0.0002
Vomiting	101 (25.1)	70 (34.8)	31 (15.4)	<0.0001
Cognitive impairment	27 (6.7)	19 (9.5)	8 (4.0)	0.0284
Pain or numbness	282 (70.1)	148 (73.6)	134 (66.7)	0.127
Balance/mobility	111 (27.6)	73 (36.3)	38 (18.9)	<0.0001
Changes in mood/personality	17 (4.2)	8 (4.0)	9 (4.5)	0.8043
Nausea	198 (49.3)	123 (61.2)	75 (37.3)	<0.0001
Focal neurologic deficits	78 (19.4)	66 (32.8)	12 (6.0)	<0.0001
Drowsiness	65 (16.2)	46 (22.9)	19 (9.5)	0.0003
Headache	159 (39.6)	117 (58.2)	42 (20.9)	<0.0001
Problems with memory	75 (18.7)	61 (30.3)	14 (7.0)	<0.0001
Altered mental status	51 (12.7)	33 (16.4)	18 (9.0)	0.0246
Anxiety	144 (35.8)	83 (41.3)	61 (30.3)	0.0221

†For comparison of brain metastasis and non-brain metastasis cohorts.
Data are presented as n (%).

Table 3. Ancillary support service utilization in patients with and without brain metastasis.

Variables	Overall (n = 402)	Brain metastasis (n = 201)	Non-brain metastasis (n = 201)	p-value†
Home healthcare	95 (23.6)	63 (31.3)	32 (15.9)	0.0003
Nutrition therapy	54 (13.4)	35 (17.4)	19 (9.5)	0.0193
Mental health/psych evaluation/treatment	19 (4.7)	8 (4.0)	11 (5.5)	0.4807
Physical therapy	71 (17.7)	54 (26.9)	17 (8.5)	<0.0001
Rehabilitation	53 (13.2)	34 (16.9)	19 (9.5)	0.027
Social work/services	60 (14.9)	38 (18.9)	22 (10.9)	0.0251
Emergency room visit and hospitalizations post index	155 (38.6)	87 (43.3)	68 (33.8)	0.0515

†For comparison of brain metastasis and non-brain metastasis cohorts.
Data are presented as n (%).

Not surprisingly, symptom burden and use of ancillary support services were observed to be higher for patients with brain metastases. Notably, however, many of the same symptoms were present in both cohorts, potentially suggesting the presence of micrometastases not visible by scan. Additionally, some symptoms may have been associated with the extra-cranial disease and treatment and not the brain metastases. This reflects the ongoing need to be able to identify and provide effective treatments among patients with advanced *EGFR*m NSCLC. As new therapies prolong survival for *EGFR*m patients, a greater understanding of treatment-related burden of illness and longer-term complications is needed. New therapies to treat brain metastases or better management strategies for monitoring and treating at-risk patients, would address an important unmet medical need.

Treatment of brain metastasis can be multidisciplinary, including combinations of surgery, radiation and/or systemic therapies that may cross the blood–brain barrier. There is increasing evidence supporting the intracranial activity of EGFR-TKIs in patients with NSCLC and brain metastasis. One published review examined the use of the first-generation EGFR-TKIs gefitinib and erlotinib [9]. In the eight Phase II clinical trials included in the review, the intracranial response rates were 27–32% in unselected patients, 43–74% in patients with demographics associated with the *EGFR* mutation genotype such as Asian, never smoker and adenocarcinoma and 56–89% in patients with the *EGFR* mutation.

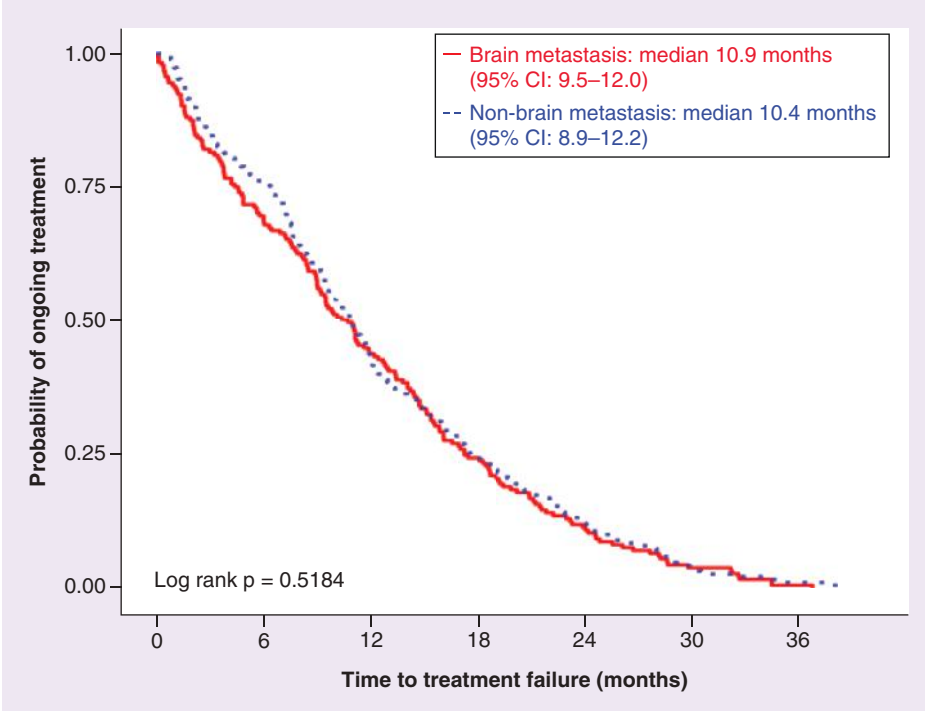

Figure 2. Median time to treatment failure in patients with and without brain metastasis.

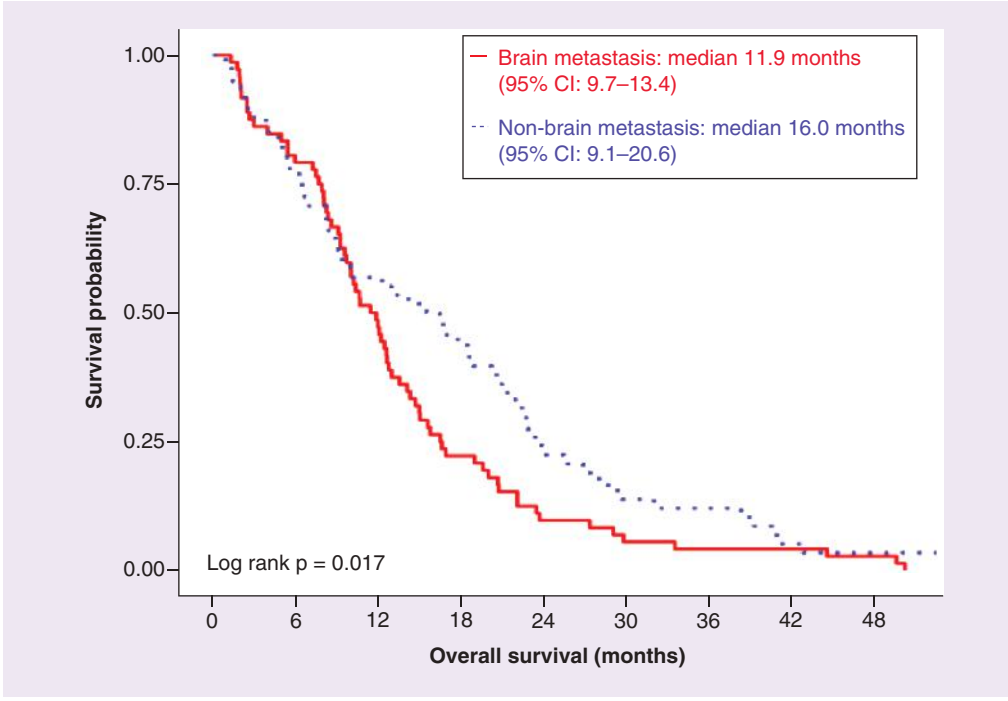

Figure 3. Median overall survival from metastatic diagnosis in patients with and without brain metastasis.

The CNS activity of newer generation EGFR-TKIs have been shown in preclinical studies [18–21]. Osimertinib, a third-generation, irreversible, oral, EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitizing mutations and the *EGFR* T790M resistance mutation, has been shown to achieve significant exposure in the brain compared with other EGFR-TKIs [18,19].

In our study, the majority of patients had received first-line treatment with the first-generation EGFR-TKI erlotinib at time of study entry, with no patients receiving a third-generation EGFR-TKI, as this treatment was not approved during the course of this study. Recently, the Phase III FLAURA trial compared the third-generation EGFR-TKI osimertinib with either erlotinib or gefitinib as first-line treatment of *EGFR*m advanced NSCLC [21]. Approximately 20% of patients in the trial had CNS metastases and fewer CNS progression events were observed in patients treated with osimertinib (6%) versus those receiving erlotinib or gefitinib (15%) [22]. Final OS results from FLAURA demonstrated significantly longer OS in those who received osimertinib versus comparator EGFR-TKI, with a 20% lower risk of death (median OS of 38.6 months, 95% CI: 34.5–41.8; vs 31.8 months, 95% CI: 26.6–36.0, respectively; p = 0.046) [23].

A recent meta-analysis of 4373 patients who had NSCLC with brain metastases suggests that *EGFR* mutations are associated with significantly improved OS compared with *EGFR* wild-type (hazard ratio: 0.73; 95% CI: 0.54–0.99; p = 0.045) [24]. This may be due to better CNS efficacy of early-generation EGFR-TKIs than chemotherapy; nonetheless, the occurrence of CNS metastases in patients with *EGFR*m NSCLC remains high [25,26]. Further research to understand the impact of specific treatments used in the *EGFR*m landscape on symptom burden and survival outcomes in patients with brain metastases is warranted.

Strengths/limitations

The strengths of this study lie in the clinically rich real-world data used to assess patient symptoms and outcomes for patients with *EGFR*m NSCLC with and without brain metastases in the community-based setting. Limitations include the retrospective, observational nature of the study, including the potential for missing data and documentation errors in the EHR. The iKnowMed EHR contains information on patients when they are seen by their physicians or as reported to their physician and recorded in the EHR. Therefore, patient treatment history outside the US Oncology Network may not be well captured. Referrals for ancillary services were captured; however, volume and frequency of use were not. Additionally, this may have been under-captured if patients received these services outside of the network.

Conclusion

These data demonstrate an unmet treatment need for patients with *EGFR*m metastatic NSCLC with brain metastasis. Given recent developments in the treatment landscape, future research should explore how new targeted therapies, such as third-generation EGFR-TKIs, impact clinical outcomes among these patients and how CNS burden changes in the real world once third-generation EGFR-TKIs are used more extensively.

Summary points

- Approximately 70% of lung cancer cases are diagnosed at late-stage, either locally advanced or metastatic disease; the brain is a common site of metastasis in non-small-cell lung cancer (NSCLC) and is often a safe harbor for tumor growth, as most therapies do not cross the blood–brain barrier.
- Approximately 14% of patients with NSCLC are *EGFR* mutation-positive; however, the prevalence of brain metastases in these patients specifically is not well known.
- This retrospective, observational matched cohort study compared patient characteristics, disease burden (including symptoms and support care services) and outcomes in a real-world community-based setting in patients with advanced *EGFR* mutation-positive NSCLC with and without brain metastases.
- After cohort matching, 402 final patients were included in this study, 201 patients with brain metastases and 201 patients without brain metastases.
- Patients with brain metastases were significantly younger and had a higher proportion of initial diagnosis at stage IV disease than those without brain metastases.
- Central nervous system (CNS) symptoms were present in patients with and without brain metastasis, although occurrence was higher in patients with brain metastasis.
- Rates of most ancillary support service use were higher in patients with brain metastases compared with those without brain metastasis.
- Furthermore, median overall survival from metastatic diagnosis was shorter in patients with brain metastasis than patients without; therefore, treating brain metastases remains an important unmet medical need for these patients.

Author contributions

The authors were fully responsible for all content and editorial decisions, involved at all stages of manuscript development and have approved the final version.

Financial & competing interests disclosure

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Ethical conduct of research

Institutional Review Board approval was obtained for the study.

Data sharing statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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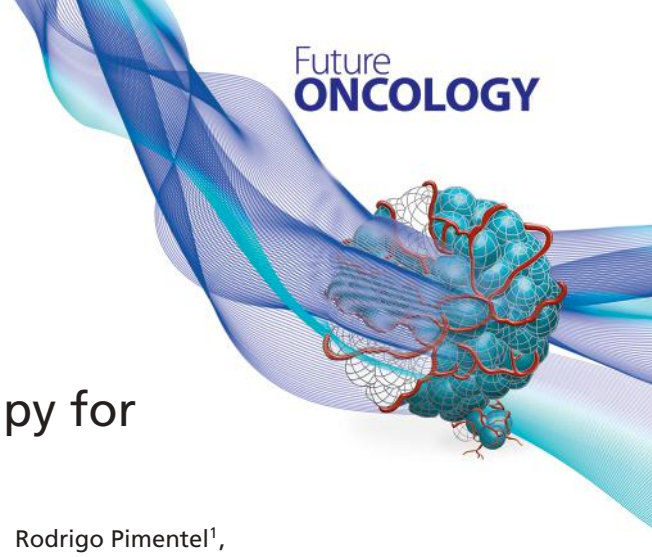

Real-world incidence and cost of pneumonitis post-chemoradiotherapy for Stage III non-small-cell lung cancer

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Aim: To estimate the real-world incidence and timing of radiation pneumonitis following chemoradiotherapy for Stage III non-small-cell lung cancer and compare costs between patients with and without radiation pneumonitis. **Methods:** Retrospective analysis using the Symphony Health Integrated Dataverse. **Results:** Pneumonitis incidence was 12.4% with a 177-day mean time to onset. Patients with versus without pneumonitis were more frequently admitted to the hospital (33.8 vs 19.2%, $p < 0.0001$) and seen in the emergency room (51.9 vs 35.8%, $p < 0.0001$) and had higher mean total healthcare costs (US$4251 vs US$3969 per-patient per-month; $p = 0.0163$). **Conclusion:** Although pneumonitis significantly increased healthcare resource utilization and costs in chemoradiotherapy-treated stage III non-small-cell lung cancer, the per-patient per-month differential was <10%. Such financial assessments are critical for cost–benefit analysis.

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Keywords: burden of disease • chemoradiotherapy • cost • non-small-cell lung cancer • pneumonitis

Chemoradiotherapy (CRT) is the standard of care for patients with unresectable stage III non-small-cell lung cancer (Stage III NSCLC) [1]. The annual incidence rate of NSCLC was reported as 38.61 per 100,000 patients in 2016 [2]. CRT has been shown to significantly improve overall survival in unresectable, Stage III NSCLC patients across a number of randomized clinical trials [3–5]. While CRT provides a substantial clinical and survival benefit, it is also associated with toxicity. Radiation induced lung injury (RILI) is an adverse event associated with CRT. RILI can manifest as radiation pneumonitis for up to a year after completion of CRT or as radiation fibrosis beyond that period and at high severity grades is associated with significant morbidity and mortality [6,7]. Radiation-related pneumonitis can occur as early as 4 weeks but in some cases 12 months post treatment [8–10].

Durvalumab, a PD-L1 inhibitor, has become the new standard of care as consolidation therapy after CRT for unresectable Stage III NSCLC patients, having conferred improvements in the 12 and 18 month progression-free survival rates (55.9/44.2% with durvalumab vs 35.5/27.0% with placebo respectively) in the Phase III PACIFIC trial. In the PACIFIC trial, the incidence of all-grade pneumonitis in patients with an adverse event was 12.6% in the durvalumab arm versus 7.7% in the placebo arm and grade 3/4 at 1.9 versus 1.7% respectively [11].

Based on our review of the literature no published studies have described the real-world incidence of pneumonitis in Stage III NSCLC patients receiving CRT [12]. Here, we describe the results of a claims-based analysis, for which the primary objectives were to estimate the real-world incidence and timing of pneumonitis post-CRT initiation for Stage III NSCLC and to compare treatment costs between patients with and without pneumonitis.

Materials & methods

Data source

This was a retrospective analysis using the linked longitudinal claims database Symphony Health Integrated Dataverse (IDV), conducted in accordance with International Society for Pharmacoeconomics and Outcomes

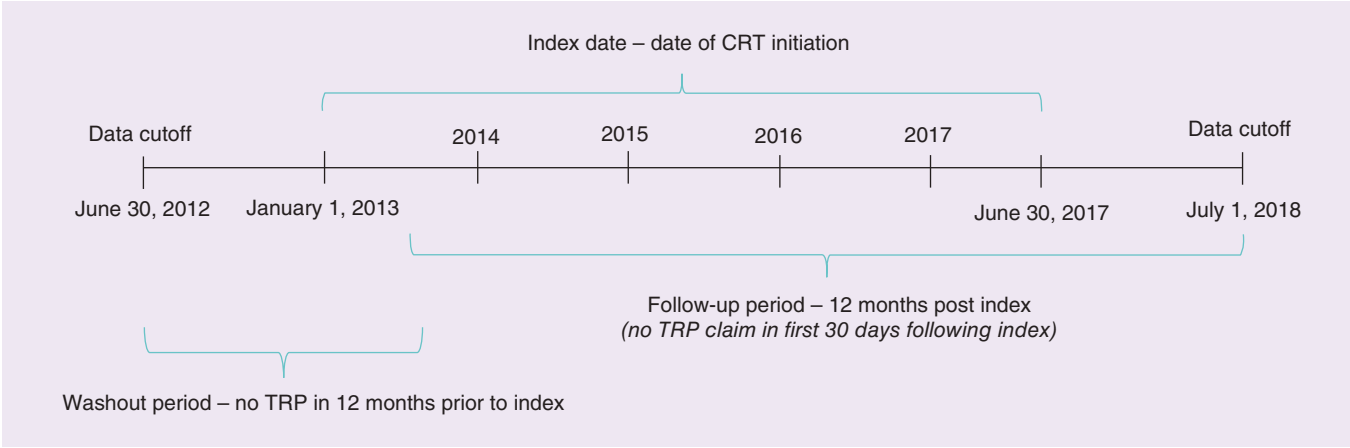

Figure 1. Study design: definition of incident population.
CRT: Chemoradiation; TRP: Treatment-related pneumonitis.

Research guidelines for retrospective studies [13]. The Symphony Health IDV integrates data from physician practices, pharmacies and hospitals, providing a broad longitudinal view of healthcare delivery and patient usage patterns that are representative of the US population across age, sex, geography and payment type (including commercial, Medicare and Medicaid plans). Medical, pharmacy and hospital claims data are linked through a common de-identified patient field with a unique code for each patient. The data source contains claims for 280 million active unique patients, representing over 73% of specialty prescriptions, 58% of medical claims and 30% of hospital claims volume in the US. Currently, these data are collected from approximately 903,500 sources, covering 13.1 million employer groups and 1.8 million prescribers.

Patient identification

Patients with Stage III NSCLC who received CRT between 01/01/2013–06/30/2017 (study period) were selected for this analysis (Figure 1). Patients were followed from the initiation of CRT therapy with the index date defined as the date of the initiation of the chemotherapy regimen or radiation therapy (whichever came first) used for CRT. The inclusion criteria included a diagnosis of lung cancer (ICD-9 codes 162.2–162.5, 162.8, 162.9; ICD-10 codes C34.00–C34.02, C34.10–C34.12, C34.2, C34.30–C34.32, C34.80–C34.82, C34.90–C34.92) during the study period, no claims for surgical resection related to lung cancer, and receipt of treatment with CRT per NCCN guidelines for NSCLC [1]. Patients who had $\geq$ 5 radiation claims within 45 days of chemotherapy start were defined as receiving concurrent CRT; those who had $\geq$ 5 radiation claims 45 days after chemotherapy start were defined as receiving sequential CRT. Patients were also required to be age $\geq$18 years at their earliest claim for CRT, to have at least 12 months of claims activity prior to CRT treatment (baseline period), and to have at least 12 months of claims activity post index date. Claims activity during a quarter was used in lieu of enrollment data that are not available in the IDV. The exclusion criteria included participation in a clinical trial at any time after lung cancer diagnosis (ICD-10 code Z00.6; ICD-9 code V70.7; HCPCS codes G0276, G0293, G0294, S9988, S9990, S9991, G9057, S9992, S9994, S9996; or Modifier Codes Q0, Q1), diagnosis of small cell lung cancer (defined as patients who received irinotecan, temozolomide or topotecan following CRT and patients who received prophylactic cranial irradiation (CPT code 77470) any time during the study period), any history of pneumonitis prior to CRT and diagnosis or treatment of a second primary malignancy prior to CRT. To limit the patient population to Stage III NSCLC patients, patients with secondary malignancy codes (ICD-9 codes 196.XX, 197.XX, 198.XX or ICD-10 codes C77.XX, C78.XX, C79.XX) during their initial CRT were also excluded. Baseline demographic and clinical characteristics, including comorbidities, were assessed during the baseline period.

Incident pneumonitis was defined using a set of ICD-9/ICD-10 codes indicating a diagnosis of pneumonitis (ICD-9 codes 495.9, 516.30, 516.32, 516.33, 516.35, 516.36, 516.39; ICD-10 codes J67.9, J84.11X); pulmonary manifestations due to radiation or other sources (ICD-9 codes: 508.0, 508.1, 508.8, 508.9, ICD-10 codes J70.0, J70.1, J70.2, J70.3, J70.4, J70) or pulmonary conditions (ICD-9 code 518.89). While pneumonitis diagnosis codes are present within the ICD code list, in a clinical setting pneumonitis can be a diagnosis based on exclusion of other

pulmonary conditions that appear in Stage III NSCLC patients and, therefore, challenging to define this diagnosis in administrative claims data. Given this, other codes such as those for pulmonary disorders or manifestations due to radiation treatment are used in addition to pneumonitis specific codes to capture potential pneumonitis in claims data [14,15]. Patients were identified as having an incident case if they had no history of pneumonia/pneumonitis prior to CRT treatment and excluding pneumonia/pneumonitis diagnosis within 30 days after CRT treatment to control for post-obstructive pneumonia. The cumulative incidence of pneumonitis was reported as the proportion of CRT patients with incident pneumonitis within 12 months of CRT treatment while the incidence rate was reported as the number of pneumonitis cases per 1000-person months of follow-up post CRT.

Assessment of pneumonitis management & healthcare resource utilization

Medical management of pneumonitis was assessed for patients with a diagnosis of pneumonitis based on the above criteria. Medical management included patients receiving therapy for treatment of pneumonitis (e.g., treatment with intravenous [IV] steroids such as methylprednisolone and dexamethasone) or patients being admitted to a setting where their pneumonitis would be monitored (e.g., an ER or inpatient admission). The frequency of medical management approach for patients with Stage III NSCLC was reported during the follow-up period.

Healthcare resource utilization was evaluated using admission codes for hospitalization, ER and office visits and other outpatient visits. Setting of care were defined using the Centers for Medicare & Medicaid Services (CMS) place of service (POS) codes or claim type codes in the IDV. Settings of care included inpatient, office visits, emergency room (ER) and other outpatient visits (outpatient). Direct medical costs were calculated based on standardized costs. All standardized drug costs were based on CMS 2017 average sales price (ASP) [16] for infused and injectable drugs and average wholesale price (AWP) from First Data Bank for oral drugs [17]; standardized procedure costs were based on Medicare Physician Fee Schedule (MPFS) [18], Hospital Outpatient Payment System (OPPS) and Clinical Laboratory Fee Schedule (CLAB) from CMS [19].

For inpatient costs, the HCUP [20] cost per hospitalization day were used to account for room and board, procedures and medications that are not itemized on the claim. For drugs and procedures that were itemized on the claim, we used MPFS facility standardized costs for procedures and CMS ASP and WAC costs for drugs. Costs and utilization were reported per-patient per-month (PPPM). All costs were adjusted to 2018 dollars.

Analysis

Descriptive analyses assessing patient baseline and clinical characteristics, and economic outcomes (resource utilization and costs) were conducted using means, standard deviations (SDs), and medians for continuous variables and frequencies and proportions for categorical variables. Comparisons between patients with and without incident pneumonitis were performed using t-tests for continuous variables and chi square tests for categorical variables. Nonparametric equivalents to these tests (including the Mann–Whitney U test and Fisher Exact Test respectively) were used in cases were normality of results could not be assumed. All analysis was performed using SAS 9.4.

Results

Study population

We identified 7559 Stage III NSCLC patients treated with CRT in the Symphony Health IDV, of which 5979 patients did not have pneumonitis in the baseline period. Of those, 742 patients had incident pneumonitis identified during the 12 months post CRT initiation. The majority of the population of patients with incident pneumonitis (739 patients) had concurrent CRT while only three patients had sequential CRT. The cumulative incidence of treatment-related pneumonitis was 12.4% (742/5,979) with an annual incidence rate ranging from 5.5 to 18.1%. The average incidence rate (cases/1000-person months) across the study period was 126.4 (95% CI: 117.4–135.8). Mean time to incident pneumonitis was 177 days (median, 169 days).

Demographic and clinical characteristics are presented in Table 1. Of the 5979 NSCLC patients treated with CRT that were identified, the mean age at the time of treatment was approximately 66.9, the population was evenly distributed based on gender (50.7% female vs 49.3% male) and the mean Quan-adapted Charlson comorbidity index (CCI) score was 5.2. Overall, no significant differences were observed in the demographic characteristics between patients with and without pneumonitis. Regarding clinical characteristics, patients with pneumonitis had a longer median follow-up from the index date (22.5 vs 20.45 months) and a higher baseline CCI at CRT initiation (5.85 vs 5.13, $p < 0.0001$). A significantly higher proportion of patients with pneumonitis had chest pain, dyspnea, fatigue and interstitial lung disease at baseline ($p < 0.001$, see Table 2 for details). While the mean length

Table 1. Demographic and clinical characteristics.

	Pneumonitis n = 742		No pneumonitis n = 5237		p-value
Gender (n, %)					
Male	374	50.4%	2572	49.1%	0.5099
Female	368	49.6%	2665	50.9%	
Age at earliest claim for NSCLC (years)					
Mean (SD)	66.85	(8.1)	66.72	(8.2)	0.6882
Median (min, max)	68	(33.0, 79.0)	68	(36.0, 79.0)	
Age at earliest claim for CRT (years)					
Mean (SD)	67.01	(8.1)	66.89	(8.2)	0.7020
Median (min, max)	68	(33.0, 79.0)	68	(36.0, 79.0)	
US region (n, %)					
Northeast	149	20.1%	896	17.1%	0.0507
South	193	26.0%	1413	27.0%	
Midwest	162	21.8%	1037	19.8%	
West	232	31.3%	1845	35.2%	
Unknown	6	0.8%	46	0.9%	
Primary payer (n, %)					
Assistance programs	16	2.2%	106	2.0%	0.2012
Cash	11	1.5%	68	1.3%	
Commercial	300	40.4%	1989	38.0%	
Managed Medicaid	38	5.1%	362	6.9%	
Medicaid	25	3.4%	125	2.4%	
Medicare	352	47.4%	2578	49.2%	
Unknown	0	0.0%	9	0.2%	
Year of diagnosis of lung cancer (n, %)					
2013	154	20.8%	528	10.1%	<0.001
2014	230	31.0%	1034	19.7%	
2015	135	18.2%	1149	21.9%	
2016	156	21.0%	1769	33.8%	
2017	67	9.0%	757	14.5%	
Quan-adapted Charlson comorbidity index (CCI)					
Mean (SD)	5.85	(3.38)	5.13	(3.51)	<0.0001
Median (min, max)	6.0	(0, 16.0)	4.0	(0, 16.0)	
Baseline comorbidities, (n, %)					
Arrhythmia	12	1.6%	37	0.7%	0.0100
Arthralgia	32	4.3%	105	2.0%	0.0001
Bradycardia	15	2.0%	50	1.0%	0.0087
Chest pain	97	13.1%	428	8.2%	<0.0001
Colitis	12	1.6%	38	0.7%	0.0126
Diarrhea	41	5.5%	186	3.6%	0.0085
Dyspnea	43	5.8%	113	2.2%	<0.0001
Edema	33	4.4%	157	3.0%	0.0351
Fatigue, asthenia	153	20.6%	746	14.2%	<0.0001
Hepatitis	2	0.3%	2	0.0%	0.0225
Interstitial lung disease	62	8.4%	87	1.7%	<0.0001
Leukopenia	20	2.7%	75	1.4%	0.0100
Neutropenia	153	20.6%	837	16.0%	0.0015
Osteoarthritis	20	2.7%	55	1.1%	0.0002
Pain	55	7.4%	227	4.3%	0.0002
Rash and Acne	18	2.4%	72	1.4%	0.0278

CRT: Chemoradiotherapy; NSCLC: Non-small-cell lung cancer.

Table 1. Demographic and clinical characteristics (cont.).

	Pneumonitis n = 742		No pneumonitis n = 5237		p-value
Thrombocytopenia	64	8.6%	280	5.3%	0.0003
Vomiting	56	7.5%	579	11.1%	0.0037
Months from lung cancer diagnosis to CRT initiation					
Mean (SD)	1.8	(3.8)	2.0	(4.1)	0.2134
Median (min, max)	1.1	(0, 46.6)	1.1	(0, 48.4)	
Months of follow-up from diagnosis of lung cancer					
mean (SD)	28.2	(13.7)	25.7	(12.1)	<0.0001
median (min, max)	24.3	(9.5, 63.2)	22.4	(6.9, 64.9)	
Months of follow-up from initiation of CRT					
Mean (SD)	26.4	(13.3)	23.7	(11.5)	<0.0001
Median (min, max)	22.5	(8.8, 58.7)	20.4	(4.7, 58.9)	
Type of CRT received (n, %)					
Sequential CRT	3	0.4%	41	0.8%	0.2588
Concurrent CRT	739	99.6%	5196	99.2%	0.2588
Patients who have more than one CRT regimen (n, %)	19	2.6	366	7.0	<0.0001
Patients who restarted CRT after pneumonitis (n, %)	18	2.4	–	–	N/A
Type of chemotherapy used in CRT (n, %)					0.0021
Carboplatin + etoposide	74	10.0%	478	9.1%	
Carboplatin + paclitaxel	455	61.3%	3172	60.6%	
Carboplatin + pemetrexed disodium	25	3.4%	388	7.4%	
Cisplatin + etoposide	171	23.0%	1070	20.4%	
Cisplatin + pemetrexed disodium	16	2.2%	126	2.4%	
Cisplatin + vinblastine sulfate	1	0.1%	3	0.1%	

CRT: Chemoradiotherapy; NSCLC: Non-small-cell lung cancer.

of follow-up was significantly different between the two groups, the mean follow-up was approximately 2 years post CRT-initiation for both groups indicating sufficient time in both cohorts to have observed a pneumonitis event.

Chemotherapy regimen

No difference in the duration of chemotherapy prescribed with CRT was observed between patients with or without pneumonitis (median of 42.0 days for both cohorts) nor was there a difference in the number of chemotherapy cycles (median of 7.0 for both cohorts) or the duration of radiation therapy (median of 57.0 vs 56.0 days). Among all patients, median duration of CRT therapy ranged from 28 to 65 days across different first-line regimens, with carboplatin + etoposide having the longest duration.

A multivariate logistic regression analysis showed that the use of carboplatin + pemetrexed, comorbidity index score and the specific baseline comorbidities dyspnea and interstitial lung disease were strong predictors of pneumonitis after CRT treatment ($p < 0.0001$). The odds of incident pneumonitis with sequential vs concurrent chemotherapy was 0.574 based on a multivariate logistic regression model; however, this finding was not statistically significant ($p = 0.366$). A summary of these results is shown in Table 2.

Pneumonitis medical management

The mean number of medical management interventions during the follow up period was similar among patients regardless of the type of pneumonitis management approach that was employed (ER admission, inpatient stay or IV steroids). There was, however, a higher frequency of inpatient stays as a medical management approach

Table 2. Multivariate logistic regression results.

Predictors of time to incident pneumonitis	Total n = 5979			
	Odds of pneumonitis vs no pneumonitis	Lower CL	Upper CL	p-Value
Age at initiation of CRT (years, continuous)	1.004	0.994	1.015	0.415
Gender (ref: Male)	0.930	0.794	1.091	0.373
Comorbidity index score at initiation of CRT	1.061	1.037	1.085	<0.0001
CRT chemotherapy type (ref: carboplatin + paclitaxel)				
Carboplatin + etoposide	0.913	0.691	1.206	0.522
Carboplatin + pemetrexed disodium	0.389	0.255	0.595	<0.0001
Cisplatin + etoposide	1.087	0.888	1.331	0.420
Cisplatin + pemetrexed disodium	0.863	0.502	1.483	0.593
Comorbidities (ref: no symptoms)				
Colitis	2.052	1.039	4.055	0.039
Dyspnea	2.183	1.493	3.192	<0.0001
Bradycardia	1.452	0.785	2.688	0.235
Edema	1.210	0.808	1.812	0.356
Endocrinopathy	1.536	0.492	4.793	0.460
Fatigue, asthenia	1.338	1.090	1.643	0.005
Interstitial lung disease	4.652	3.286	6.586	<0.0001
Respiratory infections	1.791	0.580	5.534	0.311
Thrombocytopenia	1.382	1.021	1.869	0.036
Region (ref: Northeast)				
Midwest	0.881	0.688	1.128	0.315
South	0.816	0.644	1.032	0.090
West	0.806	0.642	1.011	0.062
Type of chemotherapy used in CRT treatment (ref: Concurrent)				
Sequential CRT vs Concurrent CRT	0.574	0.172	1.913	0.366

CL: Confidence limit; CRT: Chemoradiotherapy.

Table 3. Patients with medical management of pneumonitis.

		Total n = 5979
Number of patients with pneumonitis (n, %)	742	12.4%
Medical Management Approaches (n, %)		
Emergency room (ER)	166	22.4%
Inpatient	129	17.4%
Intravenous steroids (IV steroids)	134	18.1%

(ER: 1.62, inpatient: 2.12, IV steroids: 1.58). Admission to the ER and inpatient stay was only counted as medical management if an administrative claim for these admissions had codes for pneumonitis on the claim. The proportion of Stage III NSCLC patients with pneumonitis medical management were as follows: ER visits (22.4%), inpatient hospitalization (17.4%) and IV steroids (18.1%). Oral steroids were prescribed to 82.7% of patients with pneumonitis; however, these drugs are widely used for various aspects of cancer management, with 81.2% of patients without pneumonitis also having a script for oral steroids. A summary of the patients who received medical management of their pneumonitis is shown in Table 3.

All-cause HRU

Patients with pneumonitis were more frequently admitted to the hospital (33.8 vs 19.2%, $p < 0.0001$) and seen in the ER (51.9 vs 35.8%, $p < 0.0001$) for any reason (Table 4). Outpatient visits followed the same trend with significant increases among the patients with pneumonitis versus those without pneumonitis (outpatient visits: 100.0 vs 99.1%, $p = 0.0088$). Office visits were also higher among pneumonitis patients, although the difference was not statistically significant (92.7 vs 90.9%). The number of patients with at least 1 pharmacy claim were

Table 4. All-cause healthcare resource utilization during the full follow-up period.

	Pneumonitis n = 742		No pneumonitis n = 5237		p-value
Inpatient PPPM					
Patients with ≥1 inpatient hospitalization	n = 251	33.8%	n = 1005	19.2%	<0.0001
Mean number of inpatient hospitalizations for patients with ≥1 inpatient hospitalization (SD, median)	0.170	(0.152, 0.083)	0.138	(0.108, 0.083)	0.0023
Mean LOS per hospitalization (SD, median)	0.416	(1.236, 0.250)	0.565	(2.147, 0.167)	0.1493
ER visits PPPM					
Patients with ≥1 ER visit	n = 385	51.9%	n = 1876	35.8%	<0.0001
Mean number of ER visits (SD, median)	0.207	(0.183, 0.167)	0.170	(0.207, 0.083)	0.0005
Office visits PPPM					
Patients with ≥1 clinic/office visit	n = 688	92.7%	n = 4762	90.9%	0.1076
Mean number of clinic/office visits (SD, median)	1.182	(0.722, 1.083)	0.974	(0.645, 0.833)	<0.0001
Outpatients PPPM					
Patients with ≥1 outpatients	n = 742	100.0%	n = 5189	99.1%	0.0088
Mean number of outpatient visits (SD, median)	3.033	(1.649, 2.667)	2.507	(1.750, 2.167)	<0.0001
Pharmacy claims PPPM					
Patients with ≥1 Rx claim	n = 742	100.0%	n = 5213	99.5%	1.000
Mean Rx claims among patients with ≥1 Rx claim (SD, median)	6.533	(3.322, 6.083)	5.879	(3.388, 5.250)	<0.0001
Patients with ≥1 steroid claim	n = 614	82.7%	n = 4254	81.2%	0.3193
Patients with ≥1 dexamethasone or Solu-Medrol claim	n = 611	82.3%	n = 4247	81.1%	0.4146
Patients with ≥1 steroid claim 6 months after the start of CRT treatment	n = 161	21.7%	n = 875	16.7%	0.0008

CRT: Chemoradiotherapy; ER: Emergency room; LOS: Length of stay; PPPM: per-patient per-month.

similar between patients with and without pneumonitis; however, those with pneumonitis had significantly more pharmacy claims (mean of 6.53 vs 5.88 PPPM; $p < 0.0001$). While the use of steroids over the full study period was similar, use of steroids at least 6 months post CRT treatment was significantly greater among patients with pneumonitis (21.7 vs 16.7%; $p = 0.0008$).

A sensitivity analysis was performed, comparing all cause HRU for incident pneumonitis patients with one claim for pneumonitis (453 patients) versus patients with two or more claims (289 patients). Patients with two or more claims for pneumonitis had a higher mean number of inpatient visits PPPM (0.18 vs 0.16) but fewer outpatient visits (mean of 1.68 vs 1.61 PPPM, respectively) although these differences were not statistically significant. Only the number of office visits was significantly higher for patients with two or more claims versus patients with one claim (1.31 vs 1.10 PPPM, $p = 0.0002$). The proportion of patients using steroids was also higher in for patients with two or more claims for pneumonitis (87.2 vs 79.9%; $p = 0.0104$).

All-cause costs

Mean all-cause total healthcare costs during the full follow-up period were significantly higher for patients with pneumonitis versus those without pneumonitis ($4251 vs $3969 PPPM; $p = 0.0163$), as were medical-specific costs ($1153 vs $1037 PPPM; $p = 0.0014$) (Table 5). When assessing the component costs, the increase in costs were driven by significantly higher outpatient costs and oral pharmacy costs in pneumonitis patients.

Sensitivity analysis comparing all-cause costs for patients with one claim for pneumonitis versus patients two or more claims found no significant differences between these groups for any setting of care (data not shown).

Discussion/conclusion

In this retrospective observational study, we found that pneumonitis was observed in 12.4% of Stage III NSCLC patients receiving CRT. The median time to incident pneumonitis was approximately 6 months after initiating CRT. Medical management for pneumonitis was primarily administered through inpatient stay although there was only a slightly higher frequency of this approach compared with ER visits and administration of IV steroids. Further, these approaches are not mutually exclusive with some patients transitioning from an ER to an inpatient stay or receiving IV steroids in either an ER or inpatient setting. HRU was higher among patients developing pneumonitis and translated into a 7.1% PPPM total cost increase compared with patients without pneumonitis.

Table 5. All-cause costs during the full follow-up period.

	Pneumonitis n = 742			No pneumonitis n = 5237			p-value
Total healthcare costs (mean, SD, median)	$4251.30	$2974.60	$3476.50	$3969.70	$3044.40	$3220.70	0.0163
Medical costs only	$1153.20	$899.70	$903.10	$1037.00	$1092.70	$780.00	0.0014
Component costs (mean, SD, median)							
Inpatient	$298.40	$594.90	$76.00	$291.00	$1348.60	$54.70	0.8970
Emergency room (ER)	$92.60	$119.80	$54.00	$67.40	$76.40	$44.20	0.0001
Office visit	$290.80	$273.90	$231.40	$275.30	$303.60	$193.90	0.1716
Outpatient services	$734.90	$604.10	$565.30	$707.80	$747.10	$487.20	0.2680
Pharmacy	$3098.20	$2683.30	$2341.50	$2938.40	$2621.80	$2269.30	0.1283
Oral pharmacy costs	$2840.80	$2637.30	$2061.30	$2594.80	$2553.60	$1873.20	0.0173

The real-world incidence of treatment-related pneumonitis is in line with previously reported observations [21–25]. The incidence of pneumonitis in lung cancer patients is reportedly as high as 43% detected by radiographic means [21], while symptomatic pneumonitis has been found in the range of 5–15% of patients [21,22,24,25] and approached 30% in a patient-level meta-analysis [12]. In Radiation Therapy Oncology Group (RTOG) 0617, which found no benefit for high-dose versus standard-dose radiotherapy as a component of concurrent CRT in Stage III NSCLC, incidence of acute and late pneumonitis in the standard-dose CRT (no cetuximab) arm were 9.9 and 13.7%, respectively, for all grades and 4.6 and 1.5%, respectively for grade 3 or higher events [23]. Our study identified four predictors pneumonitis after CRT, namely use of carboplatin + pemetrexed, comorbidity index score and presence of dyspnea and interstitial lung disease. Pemetrexed use has been previously established as more toxic [25]. Prior studies have provided insight into other risk factors and predictors for treatment-related pneumonitis in the NSCLC population (e.g., age, dose-volume factors, chemotherapy schedule, use of concurrent vs sequential CRT) [23,26] as well as its possible influence on poor overall survival for NSCLC patients [27].

To our knowledge, this is the first published analysis on pneumonitis in a real-world CRT-treated Stage III NSCLC population. In addition to clinical measures (e.g. incidence of pneumonitis, duration of medical management), we examined HRU and costs within the population. For inpatient, ER and outpatient visits, we observed a significant increase in HRU during the follow-up period. This was reflected in an increase in total healthcare costs as well as total medical costs. Overall, our HRU and cost analyses support that patients who develop pneumonitis incur higher healthcare costs, warranting close monitoring to allow for early identification in the Stage III NSCLC population. Given the median time to pneumonitis of almost 6 months, physicians need to monitor patients both during and months following CRT treatment.

Given the nature of retrospective data, known limitations of selection bias and information bias exist. Analyses based on claims data are limited by the lack of clinical details and the use of data that were primarily collected for billing purposes. Enrollment data are not available within the IDV dataset; therefore, continuous enrollment was determined based on claims activity by quarter based on the assumption that patients who had a claim in a given quarter were likely had active enrollment during that quarter. The limitation of this method is that some events may have been missed if there was a change in the patients point of care location or in their benefits enrollment during a quarter where they had claims activity. There are no specific diagnosis codes for NSCLC or lung cancer staging. Stage III NSCLC patients were defined as patients with a lung cancer diagnosis who were treated with drug regimens common for NSCLC and no history of surgical resection or secondary malignancies. Pneumonitis is often a diagnosis of exclusion and may overlap with other pulmonary conditions. To account for that, we used diagnostic codes for pneumonitis as well as pneumonia and other related pulmonary adverse event. Also, we excluded patients who had an event within the first 30 days after index to avoid capturing postobstructive pneumonia which may have led to an underestimation of pneumonitis. Finally, there are significant differences between the design of prospective clinical trials and this retrospective study that may have enriched the population for having these events and therefore make comparison a challenge. Further while this methodology is robust, it also does not account for a full patient history or provider notes that may be more conclusive for pneumonitis but are not available in administrative claims.

Our study documented real-world rates of incident pneumonitis that were in line with rates observed in clinical trials. Patients with pneumonitis had significant increase in HRU and total healthcare costs. While the cost differences observed in this study are statistically significant, the mean cost difference ($282 PPPM) was <10%

and may not be clinically or economically meaningful. The median time to incident pneumonitis was 6 months although pneumonitis could occur within one month or 12 months or more after CRT. The clinical benefit of CRT, a component of the standard of care for Stage III NSCLC that confers improved overall survival in this population, comes with the potential for complications such as pneumonitis, which should be monitored well after the end of the CRT treatment regimen.

Future perspective

CRT is currently the standard of care for Stage III NSCLC and is likely to continue to be utilized for treatment for the foreseeable future. Using data from real world evidence studies (such as the current study) the potential for complications can be better controlled for through monitoring and early intervention after a patient is treated.

Summary points

- Patients with Stage III non-small-cell lung cancer (Stage III NSCLC) who receive chemoradiotherapy (CRT) are known to be at risk of radiation-induced pneumonitis, for which the real-world incidence, timing and costs remain unclear.
- In our retrospective claims-based analysis of Stage III NSCLC patients treated with CRT, treatment-related pneumonitis developed in 12.4% of patients after a mean of 177 days (6 months).
- Duration of chemotherapy, number of chemotherapy cycles and duration of radiation therapy did not differ between patients with versus without pneumonitis.
- Conversely, use of carboplatin + pemetrexed, comorbidity index score and baseline dyspnea and interstitial lung disease were strong predictors of pneumonitis after CRT ($p < 0.0001$).
- Patients with versus without pneumonitis were more frequently admitted to the hospital (33.8 vs 19.2%, $p < 0.0001$) and seen in the emergency room (51.9 vs 35.8%, $p < 0.0001$).
- Additionally, patients with pneumonitis had significantly more pharmacy claims (mean of 6.53 vs 5.88 PPPM; $p < 0.0001$) and use of steroids at least 6 months post CRT treatment (21.7 vs 16.7%; $p = 0.0008$).
- From a cost standpoint, pneumonitis was associated with significant increases in mean all-cause total healthcare costs during the full follow-up period ($4251 vs $3969 PPPM; $p = 0.0163$) and medical-specific costs ($1153 vs $1037 PPPM; $p = 0.0014$).
- These real-world results are consistent with incidence rates derived from clinical trials and support monitoring for pneumonitis beyond completion of CRT.

Author contributions

KJ Ryan and B Seal were responsible for study conception, design, data interpretation and drafting, and revision of the manuscript. D Nero, CH Lee and JK Kish were responsible for the study design, data manipulation, analytic reporting and drafting of the manuscript. BA Feinberg, R Pimentel and A Gajra provided clinical guidance and provided support in the revision of the manuscript.

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KJ Ryan and B Seal are employed by AstraZeneca and owns stock in AstraZeneca. AstraZeneca sponsored the study and provided financial support for the conduct of the research and for preparation of the article. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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