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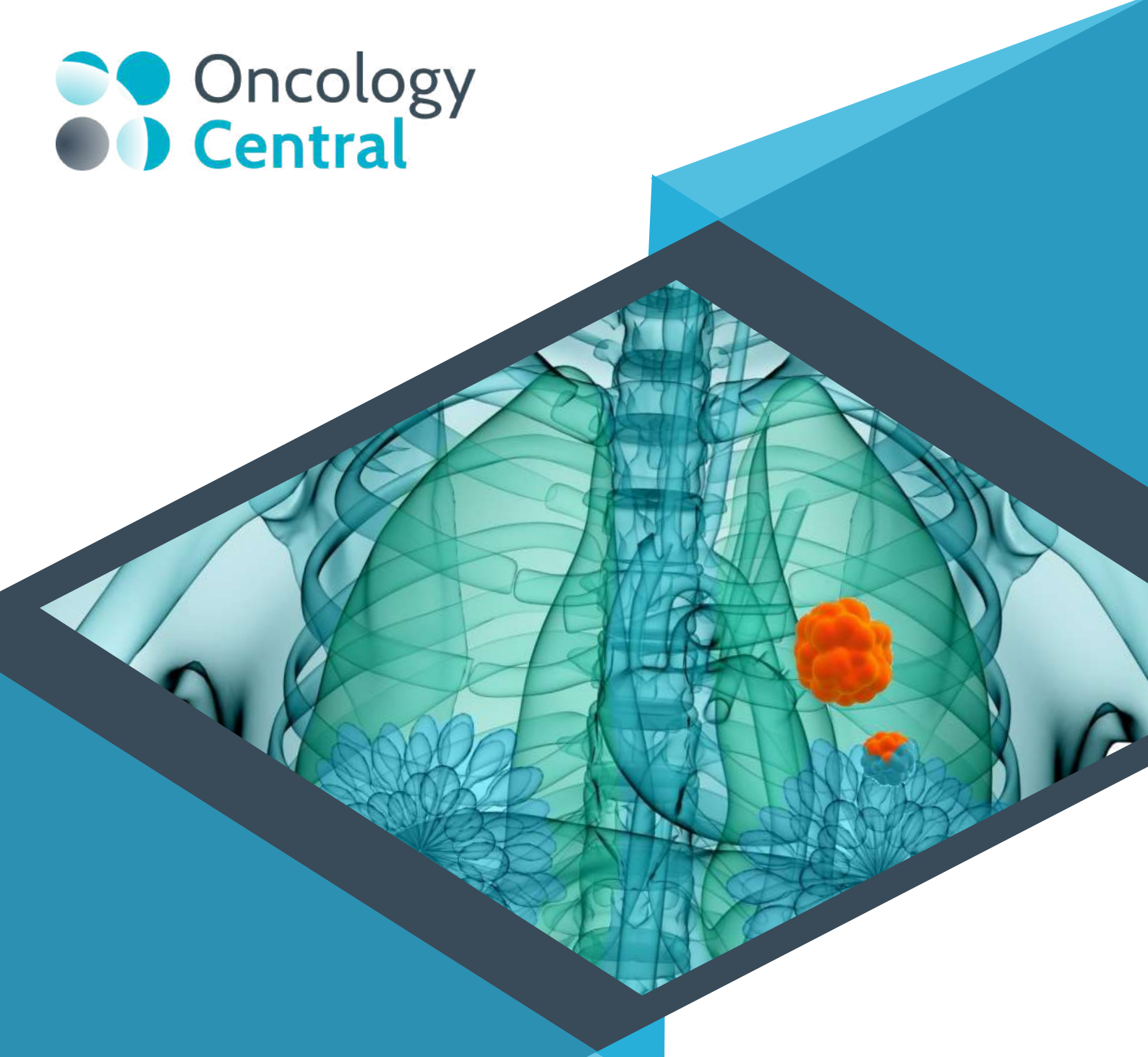

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Lung cancer: key clinical advancements

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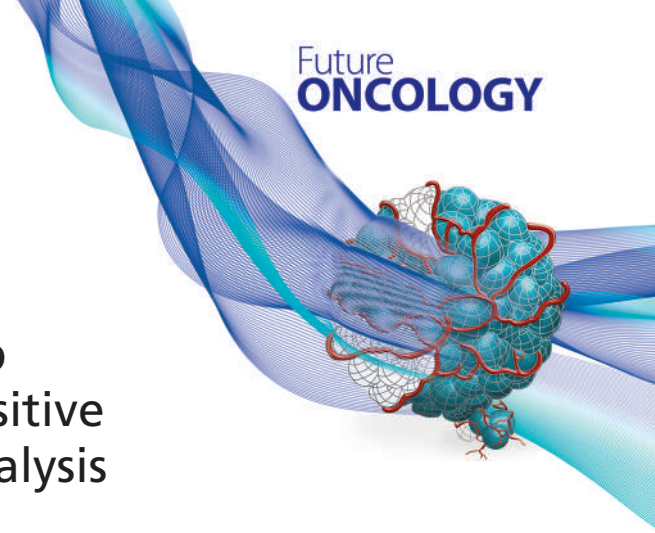

Sequential afatinib and osimertinib in patients with *EGFR* mutation-positive non-small-cell lung cancer: final analysis of the GioTag study

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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

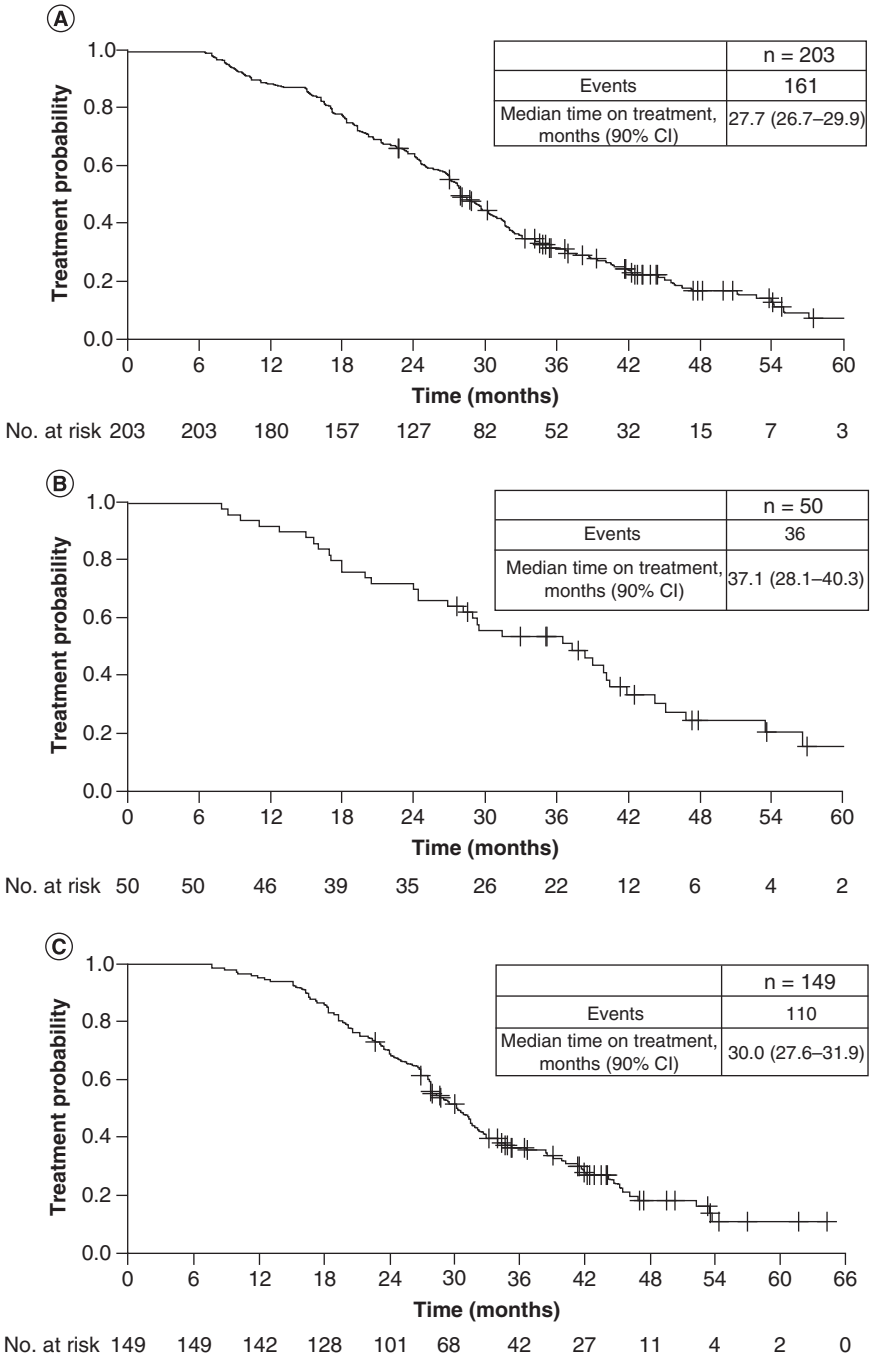

Figure 1. Time on treatment with sequential afatinib and osimertinib. (A) All patients; **(B)** Asian patients; and **(C)** patients with Del19-positive tumors.

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).

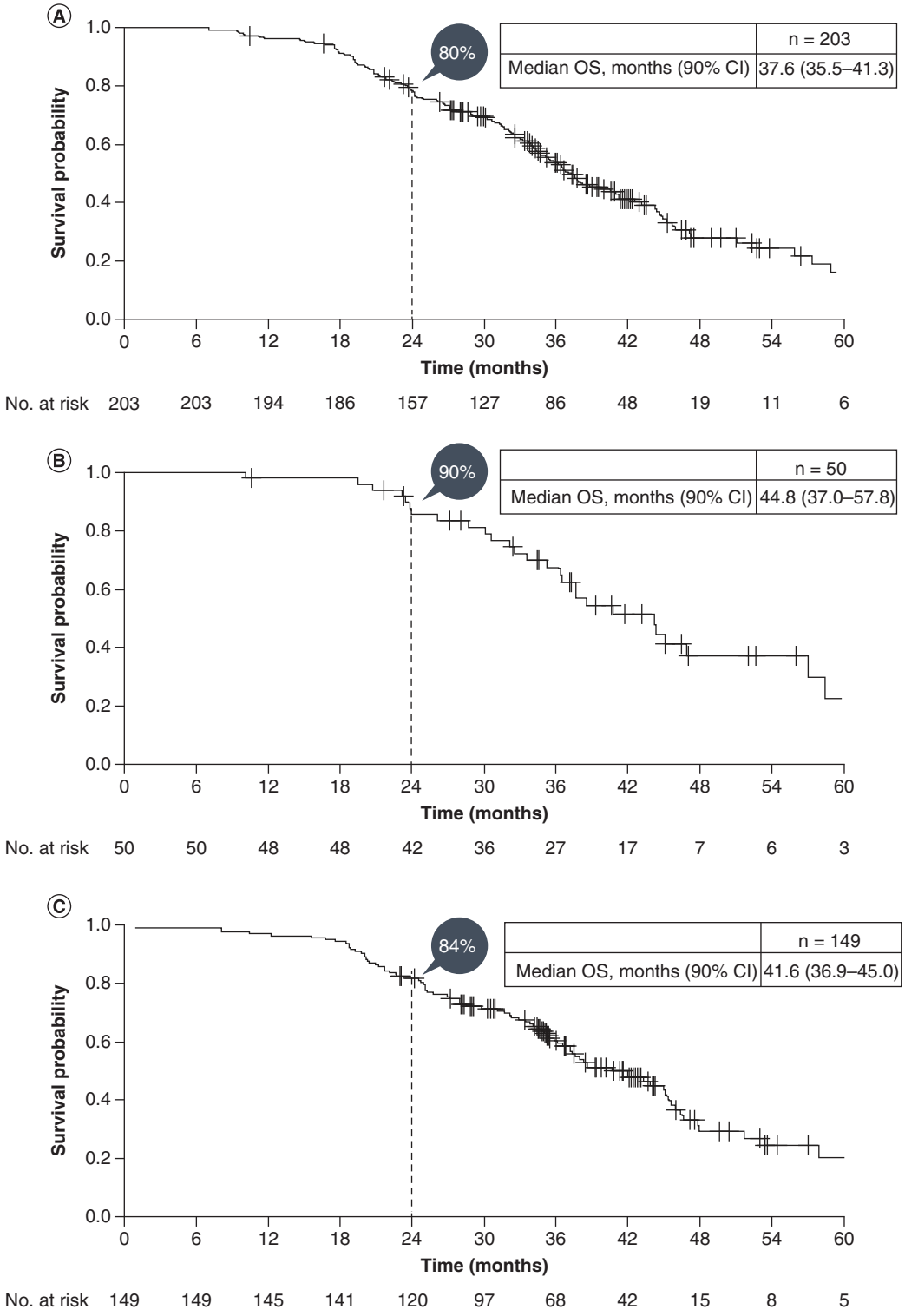

Figure 2. Overall survival in patients treated with sequential afatinib and osimertinib. (A) All patients; **(B)** Asian patients; and **(C)** patients with Del19-positive tumors.
OS: Overall survival.

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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- **Initial results from the GioTag study demonstrating prolonged time on treatment with sequential afatinib and osimertinib in patients with *EGFR* mutation-positive NSCLC.**

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- **Updated, interim results from the GioTag study which demonstrates prolonged OS with sequential afatinib and osimertinib in patients with *EGFR* mutation-positive NSCLC.**

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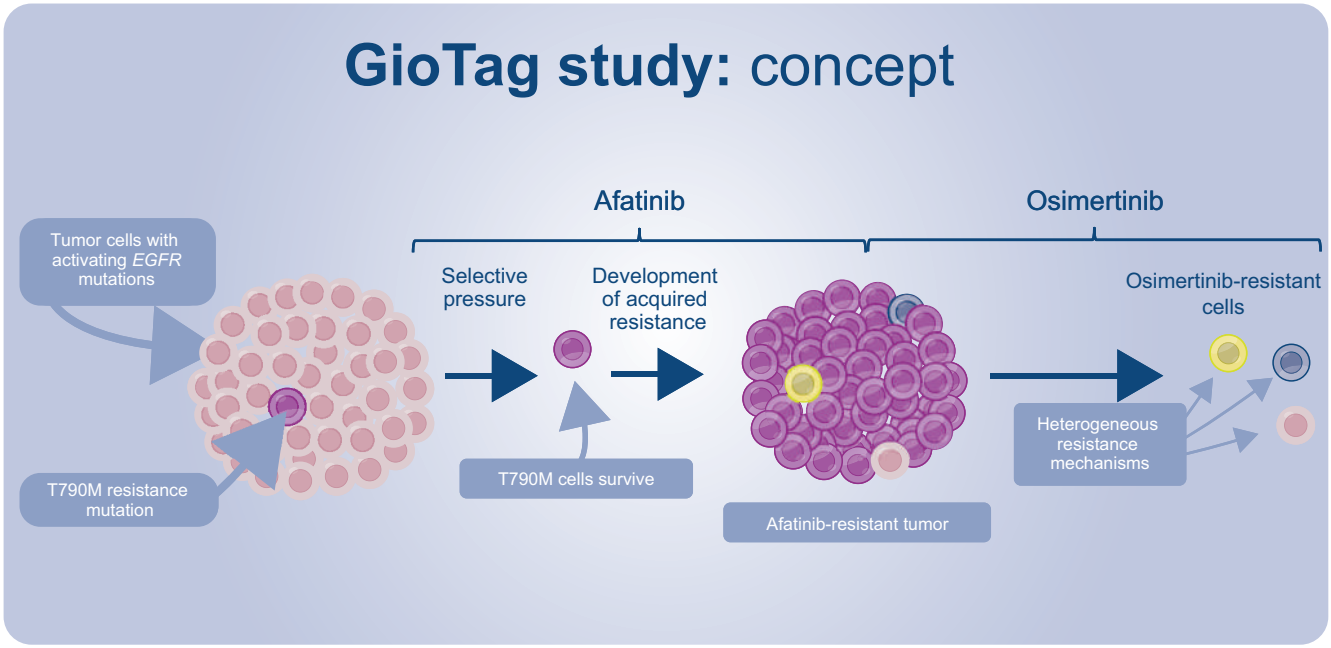
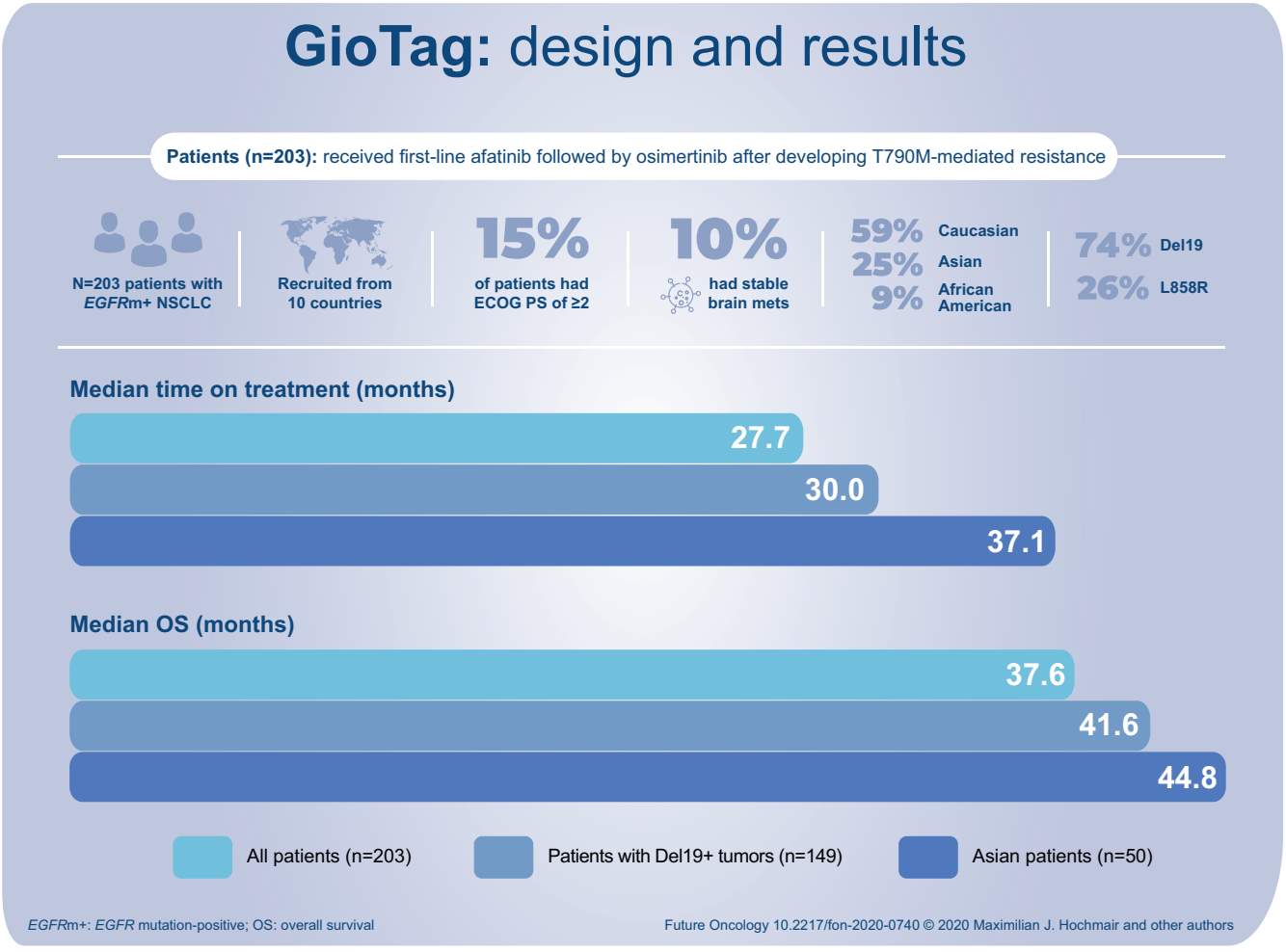
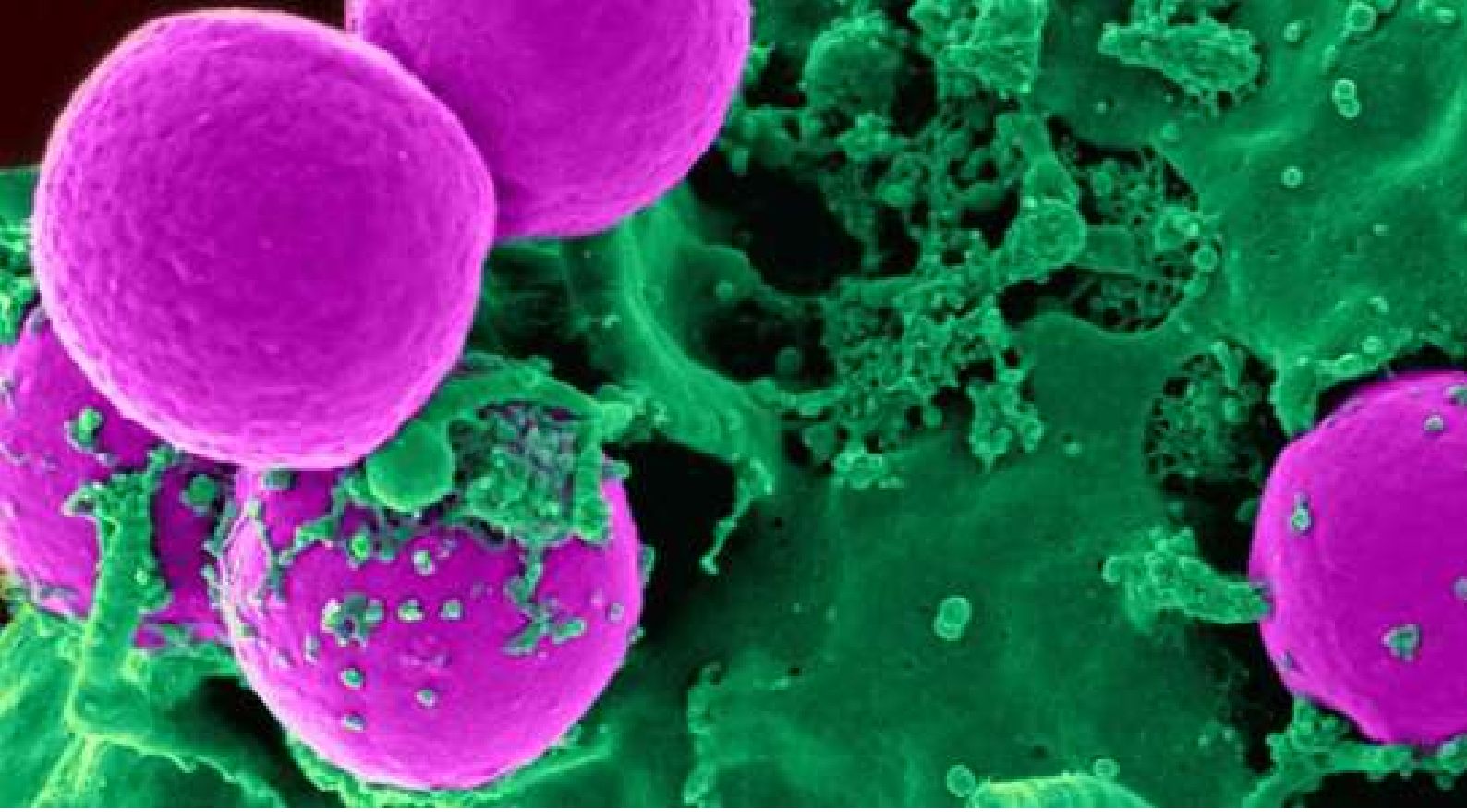

GioTag study: concept
Afatinib
Osimertinib
Tumor cells with activating *EGFR* mutations
Selective pressure
Development of acquired resistance
Osimertinib-resistant cells
Heterogeneous resistance mechanisms
T790M resistance mutation
T790M cells survive
Afatinib-resistant tumor


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
Future Oncology 10.2217/fon-2020-0740 © 2020 Maximilian J. Hochmair and other authors



What does the US FDA approval of trilaciclib mean for oncologists and their patients?

In this interview we speak with Jared Weiss from UNC's Lineberger Comprehensive Cancer Center (NC, USA) about challenges associated with treating small cell lung cancer (SCLC) and his thoughts on what the recent US FDA approval of trilaciclib, for the treatment of extensive SCLC patients to reduce chemotherapy-induced bone marrow suppression, could mean for SCLC patients.

Please introduce yourself and tell us about your career to date?

My name is Jared Weiss. I'm a medical oncologist and cancer researcher at UNC's Lineberger Comprehensive Cancer Center where I focus on lung cancer and head and neck cancer. Clinically, I am most interested in squamous cancers, SCLC and KRAS. From a research perspective, I largely focus on personalized immunotherapy, meaning cancer vaccines and cellular therapeutics.

Could you please provide us a brief overview of the current treatment options for SCLC?

SCLC presents in two stages. Limited stage disease has potential for cure and is treated with a combination of chemotherapy and radiation. Unfortunately, most cancer presents as extensive disease, which cannot be cured. Instead, it is treated with chemotherapy and immunotherapy with a goal of extending duration of life and preserving quality of life. The standard first line drug regimen is a combination of carboplatin, etoposide and a PDL1 inhibitor (atezolizumab or durvalumab). When cancer grows, standard second-line therapy is topotecan or lurbinectidin.

What are some of the limitations of the current treatments?

Efficacy and toxicity. With regards to efficacy, even with immunotherapy, median survival from diagnosis is only about a year. With regards to toxicity, all of the severe adverse events occurring in at least 10% of patients are related to myelosuppression—neutropenia (23%), anemia (14%), and thrombocytopenia (10%). Other common side effects include nausea, fatigue, anorexia and alopecia.

Trilaciclib was recently approved by the US FDA for the treatment of extensive SCLC patients to reduce chemotherapy-induced bone marrow suppression. In your opinion, how could this approval improve patient outcomes?

Clinicians have become complacent about myelosuppression and its harm to quality of life because it has been a cost of treatment for as long as we have used chemotherapy. However, while we may be used to problems such as neutropenia and fatigue, that does not change that our patients are still suffering. Trilaciclib has been shown to improve quality of life as measured by patient reported outcomes.

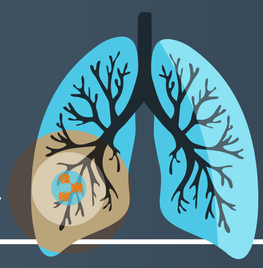
What key areas need to be focused on in the next 5 years to advance the quality of life of SCLC patients?

Trilaciclib is a major advance in myeloprotection. Interesting, although not surprisingly given its mechanism of action, it also protects against alopecia. It meaningfully reduces the toxicity of chemotherapy. When I reflect on the remaining suffering of my patients treated with trilaciclib, the major unmet need that I see is disease-related suffering. SCLC tends to grow aggressively in the central chest, clipping off airways, causing shortness of breath and pain. In my opinion, our next big advances in improving quality of life in SCLC will likely come from treatments that control the disease more effectively.

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Oncology Central or Future Science Group.

View online at Oncology Central:
https://www.oncology-central.com/what-does-the-us-fda-approval-of-trilaciclib-mean-for-oncologists-and-their-patients/

RECENT THERAPIES IN NON-SMALL-CELL LUNG CANCER (NSCLC)



with **Nicolas Girard**
Paris Saclay University
and Institute Curie

Current treatment options

Early-stage NSCLC

- Surgery is the key treatment
- Neoadjuvant and adjuvant chemotherapy may be delivered with limited benefit
- Adjuvant Tecentriq® (atezolizumab) following other treatment

EGFR-mutant NSCLC tumors

- Adjuvant *EGFR* tyrosine kinase inhibitor – Tagrisso® (osimertinib)

Non-mutant NSCLC tumors

- Neoadjuvant chemotherapy plus Opdivo® (nivolumab)

Locally advanced NSCLC tumors

- Chemoradiotherapy followed by Imfinzi® (durvalumab)

Metastatic tumors

- Tyrosine kinase inhibitors for *EGFR*/*ALK*/*ROS*/*BRAF*-positive tumors
- In other cases, immunotherapy as a single agent or combined with chemotherapy is used

Limitations & challenges of current treatments

- Acquired resistance to osimertinib in *EGFR*-mutant NSCLC patients
- Access to effective therapies
- Risk and cost of re-biopsy procedure
- Need for more predictive factors to better select patients for first-line immunotherapy-based treatment

Future predictions for NSCLC treatment options

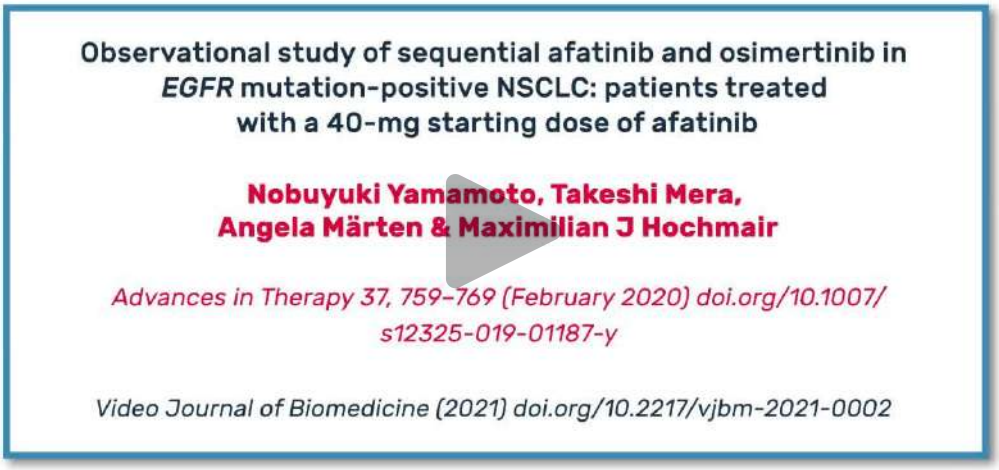
- More subtypes will be defined by rare molecular alterations
- Combination therapies with immune checkpoint inhibitors

Interviewee profile

Name:
Nicolas Girard

Affiliation:
Professor of Respiratory Medicine and Thoracic Oncology at the Paris Saclay University, Institute Curie and Head of the Thorax Institute Curie Montsouris (all Paris, France)

Video Journal of Biomedicine summarizes an article originally published in Advances in Therapy



Video Journal of Biomedicine

A recent publication from the Video Journal of Biomedicine summarizes an article originally published in Advances in Therapy entitled 'Observational Study of Sequential Afatinib and Osimertinib in EGFR Mutation-Positive NSCLC: Patients Treated with a 40-mg Starting Dose of Afatinib'.

The study was a post-hoc non-interventional, global, multicenter GioTag study, assessing sequential afatinib and osimertinib in patients with EGFR mutation-positive non-small cell lung cancer (NSCLC) who had recieved the approved 40-mg starting dose of afatinib. The findings support the clinical benefit for sequential afatinib and osimertinib.

View the video:
https://www.oncology-central.com/videos/sequential-afatinib-and-osimertinib-in-nsclc-patients/

Read the original publication:
https://link.springer.com/article/10.1007%2Fs12325-019-01187-y

Review

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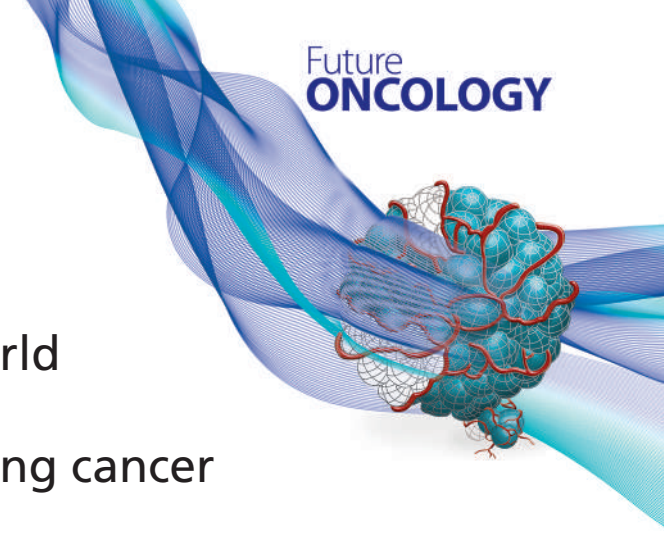

Benefits and limitations of real-world evidence: lessons from *EGFR* mutation-positive non-small-cell lung cancer

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While randomized controlled trials (RCTs) are the gold standard for evidence-based medicine, they do not always reflect real-world patient populations, limiting their generalizability and external validity. Real-world evidence (RWE), generated during routine clinical practice, is increasingly important in determining effectiveness outside of the tightly controlled conditions of RCTs, and is now recognized by regulatory bodies as a valuable complement to RCTs. Consequently, it is increasingly important for physicians to understand how RWE data can be used alongside clinical trial data. Here, we discuss the different types of real-world observational studies, outline the benefits and limitations of RWE, and, using examples from *EGFR* mutation-positive non-small-cell lung cancer, outline how RWE can be used to help inform treatment decisions.

Lay abstract: It is important to determine how well a drug works and how safe it is. This is often tested using randomized controlled trials – where a similar number of patients are randomly assigned to two groups, one of whom receives the drug and one who does not. To compare the results, the two groups of patients must be similar. So, these drug trials only include a narrow group of patients, who are often of similar age and with few additional illnesses. Unfortunately, not all patients who need the drug fit these criteria and it is important to know how well the drug works in these patients too. This is where 'real-world studies' come in. These studies include a much broader range of patients and can be very useful when used alongside randomized controlled trials. This article looks at the advantages and disadvantages of real-world studies, and how oncologists can use the results to help treat their patients. The article looks specifically at real-world studies in patients with *EGFR* mutation-positive non-small-cell lung cancer.

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Keywords: *EGFR* mutation-positive • EGFR TKIs • NSCLC • real-world

Randomized controlled trials (RCTs) have long been considered the gold standard when it comes to evidence-based medicine [1]. RCTs are conducted to assess the efficacy and safety of study drugs under well-defined, controlled clinical conditions and in selected patient populations. The strict inclusion and exclusion criteria used in RCTs create relatively homogeneous populations of participants with limited comorbidities and concomitant medications, who are likely to be compliant with the study requirements [2]. Further, the design of RCTs, including features such as randomization, blinding and intention-to-treat approaches, minimizes confounding factors and sources of bias, enabling differences in efficacy to be determined between two interventions [1,2]. Consequently, RCTs are considered to be highly reliable [3] and to have strong internal validity [1].

RCTs also have some limitations. For example, the conditions under which patients receive the study drug are tightly controlled, and the narrow patient populations included in RCTs are often not representative of the general population in real-world clinical practice; such 'real-world' patients may have poorer performance status and compliance, and may include higher proportions of elderly patients [2–5]. Consequently, many RCTs have limited generalizability [1,6], and the conclusions of tightly controlled RCTs may apply only to the selected patient population [7]. In addition, the treatment and follow-up periods are often short, potentially underestimating both

Table 1. Key features of randomized controlled trials and real-world studies.

Parameters	RCTs	Real-world studies
Purpose of study	Efficacy: does it work?	Effectiveness: does it work in the real world?
Type of study	Interventional	Observational
Design	Prospective	Prospective/retrospective
Patient population	Narrow, restricted, homogeneous	Diverse, large, unrestricted, heterogeneous
Eligibility criteria	Strict	May be highly flexible
Treatment	Fixed	Variable
Comparator	Standard of care/placebo	None/standard clinical practice/many alternative interventions
Randomization	Yes	No
Blinding	In some cases	No
Follow-up	As specified in protocol	Per routine practice
Attending physician	Investigator	Many practitioners
Patient monitoring	Continuous, per protocol, ICH-GCP-compliant	Variable

ICH-GCP: International Conference on Harmonisation-Good Clinical Practice; RCT: Randomized controlled trial.

long-term benefits and delayed hazards associated with treatment [8]. Further, RCTs can be slow and costly to conduct and analyze [6]; consequently, the comparator standard-of-care arm chosen when the trial is designed may not reflect the standard-of-care used when the trial is completed [9]. For example, an analysis of 14 RCTs across five cancer types reported that most standard-of-care control arms did not reflect the way trial-eligible real-world patients were treated in the USA [9].

Another, increasingly utilized, source of information regarding the efficacy and safety of therapeutic agents is real-world evidence (RWE) obtained from observational data generated during routine clinical practice. While RCTs measure efficacy (does it work?), RWE assesses effectiveness (does it work in routine clinical practice?) [10] (Table 1). Recent technological advances and the widespread use of electronic health records (EHRs) have created new opportunities for generating RWE [6], which is becoming increasingly recognized by clinicians, regulatory agencies and professional societies in the United States and Europe [11]. For example, in 2008 the US FDA implemented the Sentinel system, which accesses data from several electronic healthcare sources and has been used to examine potential safety issues associated with medicinal products, thereby avoiding the need for post-marketing studies [12]. In 2016, the US congress passed the 21st Century Cures Act allowing the use of RWE to support drug approval and meet post-approval study requirements [13–15]. To meet the requirements of this act, the FDA has since announced plans for a RWE Program, which will allow data gathered in routine clinical practice settings to inform FDA regulatory decisions [12]. Meanwhile, the NICE in the UK recently proposed expanding the use of RWE [16]. The American Society of Clinical Oncology (ASCO) has also recognized the 'untapped potential' of observational research to inform clinical decision making [17] and has launched CancerLinQ, a health technology system that can aggregate data from EHRs, to help source and analyze data from real-world sources [18].

The aim of this review is to provide an overview of the different types of real-world, observational studies, discuss the benefits and limitations of RWE as a complement to clinical trial data, and explain how such evidence can be used to help inform treatment decisions, using examples from recent observational studies in patients with epidermal growth factor receptor (*EGFR*) mutation-positive non-small-cell lung cancer (NSCLC). We performed a literature review of real-world studies that have been conducted in patients with advanced *EGFR* mutation-positive NSCLC. We searched PubMed and ASCO annual congress abstracts (up to 1 February 2020) with the following search terms: ('real-world' or 'observational') and ('EGFR' or 'epidermal growth factor') and ('NSCLC'). Articles identified from the database searches were selected based on their potential relevance to the topic of this narrative review. References cited in the selected articles were also checked for additional potentially contributory references.

What is RWE & how is it used?

Real-world data are defined as data collected from routine clinical care outside a RCT and can be gathered retrospectively or prospectively [4,6]; these data are then combined and analyzed to generate RWE [4]. Sources of real-world data include EHRs, insurance claims databases, patient registries (collections of population-based data such as the Surveillance, Epidemiology and End Results [SEER] database), patient charts, digital health solutions

Table 2. Key features of different types of real-world study.

Type of real-world study	Key features
Prospective observational studies	• Designed to assess predefined primary outcomes • Participants are not randomized; treatment is at the physician's discretion • Provide some of the strongest and most valid RWE
Retrospective observational studies	• Analyze historic data to assess specific outcomes • Are more likely to be subject to bias and confounding factors than prospective studies
Patient registries	• Organized systems that use observational methods to collect uniform clinical data on a population defined by a particular disease, condition, or exposure • Are typically prospective • Can collect clinical data for a large patient population and track how patients respond to particular therapies
Post-marketing studies	• Clinical studies that pharmaceutical companies agree to conduct at the time of regulatory approval • Can generate additional clinical evidence such as long-term safety/effectiveness data
Cohort studies	• Reports of the clinical experience/treatment of a group of patients, for example, at a single center
Case studies	• Reports on the clinical experience/treatment of a single patient

RWE: Real-world evidence.

and medical devices [4,11]. Novel real-world data can also be generated prospectively in observational studies. Such prospective observational studies are designed to assess pre-defined primary outcomes [19] and provide some of the most robust and valid RWE (Table 2). As with all real-world studies, participants are not randomized or otherwise pre-assigned to a treatment arm, the choice of treatment is up to patients and their physicians [20], and study participation does not affect the patients' diagnosis and treatment.

Other real-world studies include retrospective observational studies, patient registries and post-marketing commitment studies (Table 2). Retrospective observational studies analyze historical data to assess specific outcomes such as response, time on treatment and occurrence of adverse events (AEs); however, they are more likely to be subject to bias and confounding factors than prospective observational studies. Patient registries prospectively collect broad clinical data for a population defined by a particular disease, condition or exposure. They often include large numbers of patients without stringent eligibility criteria and, while not designed to assess prospectively defined outcomes, can be used to collect broad surveillance data for subsequent analysis [21]. Post-marketing commitment studies are those that a pharmaceutical company agrees to conduct when a new drug receives regulatory approval, but are not mandated by statute or regulation [22]. These post-marketing studies may generate additional clinical evidence including long-term drug effectiveness, duration of response and subgroup efficacy data, and are becoming increasingly utilized; a survey of the pharmaceutical and medical devices industry in the EU and the USA determined that 27% of real-world studies conducted by industry have been requested by regulatory authorities such as the US FDA and the European Medicines Agency [23]. In addition, although of more limited value, single-case reports, published literature and social media may also be mined for real-world data [12].

Owing to the limitations of generalizing result of RCTs to real-world populations, there is increased interest in 'pragmatic' clinical trials. These are prospective, randomized trials that aim to better reflect real-world clinical practice (both in terms of patient enrolment and trial conduct) and thereby increase applicability and generalizability of the results, while preserving as much internal validity as possible [11,24–27]. However, such interventional randomized trials are outside the focus of this review.

Advantages & limitations of real-world studies

Real-world studies reflect clinical experience across a broader and more diverse distribution of patients than prospective RCTs and, unlike RCTs, can provide insight into real-world treatment patterns, including dosing, compliance, adherence, off-label use and the balance between efficacy and safety in patient groups not included in RCTs [3,11,28]. They often include larger sample sizes and longer follow-up periods than RCTs, which can allow assessment of rare/long-term outcomes and provide additional safety information after drug approval. Data collection in patient registries (such as that involved in the US FDA Sentinel System [12]) can also aid post-marketing pharmacovigilance by providing an active surveillance system for the detection of any new safety signals [6]. Finally, as retrospective real-world studies use existing data sources, they can be more economical and time efficient than RCTs [3,11].

There are many well-recognized limitations that need to be addressed when assessing RWE versus evidence from a RCT [3,11,29,30]. For example, electronic data may be inconsistently collected or data on key variables may be

missed, both of which can reduce clinical validity [11]. For studies involving multiple study arms, in the absence of stratification, it is important to be aware of the potential for differences in patient characteristics between arms (selection bias) [11]. Propensity score matching (matching the characteristics of patients entering different arms of studies) can be used to reduce selection bias; however, this is only applicable to the small proportion of real-world studies that include multiple study arms. Other potential types of bias include recall (selective recall of events by patients and caregivers) and detection bias (where an event may be more likely to be captured in one particular patient group than another) [11].

Due to inherent differences in their design, patient populations and/or methods of analysis, RCTs and real-world studies may generate discrepant results. This makes direct comparisons between the two types of studies challenging and, ideally, best avoided. For example, a recent analysis for the ASCO Value Framework concluded that real-world survival estimates for cancer therapies were 16% lower than RCT efficacy [31], suggesting that RCTs may over-estimate the survival benefit of anti-cancer agents. For lung cancer specifically, the analysis estimated the difference to be 18%. These differences could be due to bias in RCTs, bias in observational studies or genuine differences in patient populations.

To maximize validity and applicability, real-world data should be accurate, consistently collected and verifiable to a similar level as prospective clinical trials [29]. Although the inherently diverse nature of real-world data makes it difficult to set consistent frameworks for acquisition, analysis and reporting, clearly labeling the data sources and recognizing the limitations of each study are important. Similarly, as the accuracy, reliability and applicability of real-world studies varies, the design of the study, the data captured and its analysis and reporting need to be considered before drawing any conclusions.

Learnings from real-world studies: examples from *EGFR* mutation-positive NSCLC

EGFR tyrosine kinase inhibitors (EGFR TKIs) are established standard-of-care agents for patients with *EGFR* mutation-positive NSCLC. Several EGFR TKIs, including the first-generation reversible agents, erlotinib and gefitinib, the second-generation irreversible ErbB family blockers, afatinib and dacomitinib, and the third-generation EGFR TKI osimertinib have become standard first-line treatments, based on data from seminal RCTs. Complementary to RCTs, real-world studies have provided numerous insights into the effectiveness and safety of EGFR TKIs in routine clinical use, and recent examples are shown in Table 3 and discussed below. The majority of these real-world studies have focused on the second-generation TKI afatinib, with less RWE available for the other EGFR TKIs. For dacomitinib and osimertinib, this is likely to be at least partly due to their more recent regulatory approvals. It should also be noted that, as conducting robust, high-quality real-world studies requires budget and effort, pharmaceutical company support may also affect the volume of real-world data available.

Here, we discuss how RWE:

- Expands upon RCT data to corroborate the effectiveness and safety of EGFR TKIs in real-world clinical practice, including long-term follow-up data and comparisons of the effectiveness of different EGFR TKIs;
- Facilitates analysis of the activity and tolerability of EGFR TKIs in patient subgroups generally underrepresented or excluded from RCTs, such as elderly patients, patients with brain metastases and patients with uncommon *EGFR* mutations;
- Provides information on real-world management of class-related toxicities; and provides interesting hypotheses and valuable information on the sequential use of EGFR TKIs following acquired resistance to first-line therapy.

Effectiveness in real-world clinical practice

Several observational studies have sought to determine whether the efficacy and safety of EGFR TKIs observed in RCTs is applicable to broader real-world patient populations. In the case of afatinib, front-line afatinib demonstrated superior PFS over platinum-doublet chemotherapy in the Phase III LUX-Lung 3/6 trials [56,57] and over gefitinib in the randomized Phase IIb LUX-Lung 7 trial [58]. In all three trials, median PFS with afatinib was approximately 11.0 months. These findings have been corroborated in a number of real-world studies (Table 3). For example, a large retrospective single-center study of 422 patients in Taiwan reported superior PFS with afatinib versus gefitinib (median PFS 12.2 vs 9.8 months; hazard ratio [HR]: 0.72; 95% CI: 0.54–0.97; p = 0.035) and a trend to longer PFS versus erlotinib (median PFS 12.2 vs 11.4 months; HR: 0.87; 95% CI: 0.62–1.20; p = 0.38) [32]. An analysis of health records for 1354 Japanese patients who received EGFR TKIs (215 afatinib, 726 gefitinib, 413 erlotinib) reported a median OS of 38.6 months with afatinib versus 30.9 months with erlotinib/gefitinib

Table 3. Recent examples of recent real-world studies of patients with advanced non-small-cell lung cancer.

Study description	Type of study	Patient population (n)	Key study findings	Ref.
Effectiveness in real-world clinical practice				
Taiwan comparative study	Retrospective, single-center study	Patients with *EGFR*m+ NSCLC who received first-line erlotinib, gefitinib or afatinib (n = 422)	Median PFS 12.2 months afatinib, 9.8 months gefitinib (p = 0.035), 11.4 months erlotinib (p = 0.38)	[32]
Japan comparative study	Retrospective, multicenter study	Patients with *EGFR*m+ NSCLC who received first-line EGFR TKIs (n = 1354)	Median OS 38.6 months afatinib, 30.9 months erlotinib/gefitinib (p = 0.0031 unadjusted)	[33]
Management of *EGFR*m+ NSCLC patients in the USA	Retrospective; utilized a large EHR-derived database	Unselected, previously untreated patients with *EGFR*m+ NSCLC (n = 961)	Median time to next therapy 13.1 months erlotinib, 12.1 months afatinib, 5.3 months non-EGFR targeted treatment, 4.2 months chemotherapy	[34]
First- vs second-generation EGFR TKIs in Canada	Single-center, retrospective review of population-based cohort	*EGFR*m+ NSCLC patients who had received ≥1 cycle of erlotinib/gefitinib (n = 414) or afatinib (n = 70)	Median OS 39 months afatinib versus 25 months erlotinib/gefitinib (HR: 0.69; p = 0.05)	[35]
First-line afatinib in Malaysian patients	Multicenter, retrospective observational study	Previously untreated *EGFR*m+ NSCLC patients (n = 85)	ORR: 76.5%; DCR: 95.3% Median PFS 14.2 months	[36]
Osimertinib in T790M-positive patients in France (EXPLORE T790M)	Early access program; retrospective, observational, multicenter study	T790M-positive *EGFR*m+ NSCLC patients who had received at least one prior EGFR TKI (n = 205)	Median PFS 12.4 months Median OS 20.5 months	[37]
Osimertinib as second-line therapy in T790M-positive patients (ASTRIS study)	Prospective, observational, international study	T790M-positive *EGFR*m+ NSCLC patients who had received at least one prior EGFR TKI (n = 3015)	Median PFS 11.1 months (95% CI: 11.0–12.0)	[38]
Patient subgroups not routinely included in clinical trials				
EGFR TKI use in French octogenarians with *EGFR*m+ NSCLC (OCTOMUT)	Observational, multicenter, retrospective study	*EGFR*m+ NSCLC patients aged ≥80 years (n = 114)	ORR: 63.3%; DCR: 78.9% Median PFS 11.9 months; median OS 20.9 months	[39]
Osimertinib after previous EGFR TKIs and/or chemotherapy in patients with CNS metastases in China	Retrospective, single-center study	T790M-positive *EGFR*m+ NSCLC patients who had received at least one prior EGFR TKI and who had CNS metastases (n = 22)	ORR: 40.9%; DCR: 86.4%; median PFS 8.5 months; CNS ORR: 53.3%	[40]
Osimertinib in T790M-positive pre-treated patients in Macau	Observational, single-center study; patients taken from named-patient program	T790M-positive *EGFR*m+ NSCLC patients who had received at least one prior EGFR TKI (n = 74); 26% had brain metastases	Median PFS 9.0 months Median OS 12.0 months in all patients; 8.0 months in patients with brain metastases, 13.0 months patients without brain metastases	[41]
Taiwan observational study	Retrospective, single-center study	*EGFR*m+ NSCLC patients who received first-line afatinib (n = 259); 82 had brain metastases	Median OS 36.7 months overall; 33.8 months vs not reached in patients without vs with brain metastases 63.4 and 72.3% response rates, respectively	[42]
Singapore observational study	Retrospective, single-center study	*EGFR*m+ NSCLC patients who received first-line afatinib (n = 125); 42 (34%) had brain metastases	Median PFS with afatinib 40 mg 13.3 vs 15.0 months in patients with vs without brain metastases	[43]
Afatinib, gefitinib and erlotinib in patients with uncommon *EGFR* mutations in Taiwan	Retrospective, single center study	*EGFR*m+ patients with uncommon mutations (n = 56) who received afatinib (n = 24) or erlotinib/gefitinib (n = 32)	Median PFS 11.0 months with afatinib, 3.6 months with erlotinib/gefitinib (excluding five patients with exon 20 insertions) Median PFS in patients with G719X/L861Q/S768I mutations 18.3 months with afatinib, 2.6 months with erlotinib/gefitinib	[44]
Real-world safety and management of AEs				
Evaluation of impact of dose adjustment on effectiveness of first-line afatinib (RealGiDo)	Global, noninterventional, retrospective observational study	*EGFR*m+ NSCLC patients initiating treatment with afatinib at least 6 months prior to enrollment (n = 228)	Median time to treatment failure 18.7 months overall, 19.5 months in patients remaining on ≥40 mg/day, 17.7 months in patients with dose reduction to <40 mg/day within the first 6 months and 19.4 months in patients with starting dose ≤30 mg/day (p = 0.54)	[45]

†Did not select for patients with EGFR mutations.

ADR: Adverse drug reaction; CNS: Central nervous system; DCR: Disease control rate; *EGFR*m+: Epidermal growth factor receptor mutation-positive; EGFR TKIs: Epidermal growth factor receptor tyrosine kinase inhibitors; EHR: Electronic health record; HR: Hazard ratio; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

Table 3. Recent examples of recent real-world studies of patients with advanced non-small-cell lung cancer (cont.).

Study description	Type of study	Patient population (n)	Key study findings	Ref.
Afatinib as first- and subsequent-line treatment	Prospective, post-marketing observational study	Unselected *EGFR*m+ NSCLC patients followed for 52 weeks after treatment initiation or until discontinuation (n = 1602)	40.1% ORR overall; 68.4% ORR in patients receiving first-line treatment; predictable ADR profile that was consistent with clinical trials; lower starting dose did not affect response rate; advanced age (≥75 years) did not adversely affect clinical benefits	[46]
Afatinib as first-line therapy	Multicenter, retrospective review of medical records	*EGFR*m+ NSCLC patients who received afatinib as first-line therapy (n = 76); 76.3% had a dose reduction	Median PFS 17.8 months overall; 18.5 vs 7.9 months in patients with vs without dose reduction (p = 0.018)	[47]
Afatinib as first-line treatment in Japanese patients	Multicenter, retrospective review of electronic medical records	*EGFR*m+ NSCLC patients who received first-line afatinib (n = 62)	Afatinib starting dose: 40, 11 and 11 received 40, 30 and 20 mg, respectively Median PFS 15.7 months overall; 15.7 vs 14.2 months in patients who started on 40 mg vs 30/20 mg afatinib (p = 0.978)	[48]
Real-world sequencing of therapy				
Sequential treatment with first-line afatinib followed by osimertinib in T790M-positive patients (GioTag)	Global retrospective, observational study	Consecutive patients with *EGFR*m+ NSCLC	Median time on treatment (afatinib followed by osimertinib) was 27.6 months; Asian patients (n = 50) 46.7 months	[49,50]
Osimertinib as second-line therapy following afatinib or gefitinib/erlotinib	Multicenter, retrospective study in Japan	T790M-positive *EGFR*m+ patients who received osimertinib after first-line afatinib or gefitinib/erlotinib (n = 111)	For patients who received osimertinib after first-line afatinib (n = 35) vs gefitinib/erlotinib (n = 76): ORR: 82.9 vs 53.9% (p = 0.0065) DCR: 91.4 vs 71.1% (p = 0.032) Median PFS 17.0 vs 9.7 months (p = 0.164)	[51]
Real-world analysis of adherence to guideline recommendations				
First-line targeted therapy use in China	Prospective, multicenter, observational study	Patients with *EGFR*m+ NSCLC (n = 461)	73.8% of *EGFR*m+ patients received first-line EGFR TKIs	[52]
Molecular testing and treatment patterns for patients with advanced NSCLC (PIvOTAL)†	Multinational, retrospective, observational study	Patients initiating first-line therapy for advanced NSCLC (n = 1440)	Patients with ≥1 molecular test varied from 42.9% (Brazil) to 85.3% (Taiwan) *EGFR*m+ frequency ranged from 17–28% in primarily Caucasian populations and 42–67% in Asian populations	[53,54]
Treatment decisions, clinical outcomes and pharmacoeconomics in NSCLC in Germany (REASON)	Multicenter, prospective, observational study	Patients with *EGFR*m+ NSCLC (n = 334)	56.6% of *EGFR*m+ NSCLC patients received first-line EGFR TKIs Median PFS 10.1 vs 7.1 months in patients receiving vs not receiving first-line TKI (p = 0.012)	[55]

†Did not select for patients with EGFR mutations.
ADR: Adverse drug reaction; CNS: Central nervous system; DCR: Disease control rate; *EGFR*m+: Epidermal growth factor receptor mutation-positive; EGFR TKIs: Epidermal growth factor receptor tyrosine kinase inhibitors; EHR: Electronic health record; HR: Hazard ratio; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

(HR: 0.68; p = 0.0031); this trend to longer OS remained after propensity score matching (adjusted by inverse probability treatment weighting [IPTW] HR: 0.78; p < 0.0001; adjusted by matching HR: 0.747; p = 0.0629) [33]. This superior real-world survival with afatinib over the first-generation EGFR TKIs was also demonstrated in a large retrospective study in Canada, in which median OS was 39 months with afatinib versus 25 months with gefitinib/erlotinib; this difference remained significant after propensity score matching (HR: 0.694; 95% CI: 0.47–1.00; p = 0.05) [35].

Little RWE is available on first-line treatment with the third-generation EGFR TKI, osimertinib, reflecting its recent approval in this setting. It is expected that robust data will become available in the near future given that osimertinib is now a preferred agent for first-line treatment of *EGFR* mutation-positive lung cancer in North America and Europe [59]. However, more RWE is available for osimertinib in the second-line setting. Such RWE demonstrates that the second-line efficacy seen in clinical trials is applicable to a broader, real-world population. For example, in the large prospective observational ASTRIS study median PFS was 11.1 months and median time to treatment discontinuation was 13.5 months in 3015 patients with the *EGFR* T790M mutation (the most common resistance mechanism to the first- and second-generation EGFR TKIs) who received osimertinib following prior treatment with a first- or second-generation EGFR TKI [38]. These results are consistent with the median PFS of 10.1 months reported in the AURA3 clinical trial of second-line osimertinib in T790M-positive patients [60].

Similarly, the retrospective EXPLORE T790M study reported a median PFS of 12.6 months in patients who received osimertinib as second-line therapy in the French early access program [37].

Effectiveness in patient subgroups often excluded from RCTs

Several real-world studies have also assessed EGFR TKIs in specific patient subgroups not routinely included in RCTs, such as patients of advanced age, patients with brain metastases, non-Caucasian and non-Asian patients, and patients with limited physical functioning with Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2. For example, while the median age of *EGFR* mutation-positive NSCLC patients enrolled in clinical trials is often 58–64 years [56–58,60,61], an analysis of the SEER database showed that 47% of lung cancer patients were aged ≥70 years [62]. The retrospective OCTOMUT study in France specifically assessed the effectiveness and tolerability of EGFR TKIs in elderly patients aged ≥80 years (mean age 83.9 years); of 114 patients, 54.4, 39.5 and 1.8% received gefitinib, erlotinib and afatinib, respectively. With a median PFS of 11.9 months (95% CI: 8.6–14.7) and overall response and disease control rates of 63 and 79%, respectively, clinical outcomes appeared similar to those seen for younger patients in other studies [39] (Table 3); importantly, tolerability profiles were also consistent with those seen for younger patients. In addition, a global retrospective study reported similar outcomes with front-line afatinib in patients aged ≥65 years and those aged <65 years (median time on treatment was 12.2 months [90% CI: 10.5–13.4] vs 11.8 months [90% CI: 10.5–12.1]; p = 0.241), respectively [49]. These studies reported that tolerability profiles in elderly patients were consistent with those reported for younger patients [39]. Finally, a retrospective observational study reported the proportions of patients who had tolerability-guided afatinib dose reductions were similar in patients aged <65 and those aged ≥65 years [45]. Together, such studies suggest that advanced age should not preclude the use of EGFR TKIs.

Brain metastases affect more than 25% of patients with lung cancer over the course of their disease [63]; however, a substantial proportion of these patients are often excluded from clinical trials due to overly restrictive eligibility criteria, resulting in limited prospective data available for this population. It is encouraging that contemporary trials, such as the FLAURA trial, are now allowing for the inclusion of patients with stable asymptomatic brain metastases with or without prior local radiation treatment. Recently, several retrospective studies have shown that, while outcomes are often inferior to those in patients without brain metastases, the second- and third-generation EGFR TKIs do provide clinical benefit in patients with brain metastases (Table 3). For example, in the French osimertinib early access program (EXPLORE T790M study) median PFS was 9.7 (95% CI: 7.7–13.5) and 15.1 (95% CI: 12.0–17.1) months (p = 0.21) in *EGFR* mutation-positive NSCLC patients with and without brain metastases, respectively [37]. Consistent results were seen in a smaller study in Macau in which median OS with osimertinib was 8.0 (95% CI: 4.2–11.8) and 13.0 (95% CI: 10.4–15.6) months, in patients with and without brain metastases, respectively [41]. Similarly, in a study in Singapore, median PFS with afatinib was 7.9 (95% CI: 5.1–13.3) and 15.0 (95% CI: 10.9–20.6) months (p = 0.140) in patients with and without brain metastases, respectively [43]; however, when restricted to patients who received afatinib 40 mg, median PFS was 13.3 months and 15.0 months in those with and without brain metastases, respectively (HR: 0.79; 95% CI: 0.34–1.80) [43]. Similarly, in a study in Taiwan, while OS was shorter in patients with brain metastases, response rates with afatinib were 63.4 and 72.3% in patients with and without brain metastases, respectively [42]. Further, a retrospective study in Taiwan reported that in real-world patients with *EGFR* mutation-positive NSCLC, median PFS was with afatinib was 9.9 and 13.1 months in patients with and without brain metastases, respectively [32]. Taken together, this RWE suggests that patients with brain metastases derive clinical benefit with afatinib and osimertinib.

The most common *EGFR* mutations in NSCLC are exon 19 deletions (Del19) and the L858R translocation on exon 21, found in approximately 45 and approximately 40% of *EGFR* mutation-positive NSCLC patients, respectively [64,65], and many clinical trials have restricted enrollment to patients with these mutations. However, many other *EGFR* mutations have been reported. These include T790M, the most common resistance mechanism to the first- and second-generation EGFR TKIs, and many uncommon mutations, including the major uncommon mutations, G719X, S768I, or L861Q, among others. Osimertinib has demonstrated particular effectiveness against tumors harboring T790M; indeed it was developed to overcome resistance to the first- and second-generation EGFR TKIs mediated by this acquired genetic alteration. However, less is known about the real-world activity of osimertinib against the uncommon mutations. There are also limited data on the activity of the first-generation EGFR TKIs erlotinib and gefitinib against uncommon mutations. In contrast, the results of several small retrospective real-world studies indicate that afatinib has activity against a number of uncommon mutations, particularly the major uncommon mutations G719X, S768I or L861Q (Table 3). For example, a single-center analysis of medical

records in Taiwan identified 56 patients with uncommon mutations who received EGFR TKIs (32 treated with gefitinib/erlotinib, and 24 treated with afatinib) [44]. In patients with uncommon mutations, median PFS was 11.0 months with afatinib versus 3.6 months for those receiving gefitinib/erlotinib (p = 0.03); in the subset of 24 patients with G791X, S768I or L861Q, median PFS was 18.3 and 2.6 months, respectively (p = 0.12) [44]. Further evidence for the activity of afatinib in patients with uncommon mutations was provided by a combined analysis of 54 patients from two observational studies (median PFS with afatinib was 10.7 months in patients with G791X, S768I or L861Q, and 7.3 months in patients with compound mutations) [66]. In addition, a large retrospective analysis of 315 EGFR TKI-naïve patients with uncommon mutations who received afatinib across 16 studies (including three clinical trials that included small numbers of patients with uncommon mutations) and 20 case reports, recently demonstrated that afatinib had activity against major uncommon mutations (median time-to-treatment failure 10.8 months; 95% CI: 8.1–16.6; ORR: 60.0%), compound mutations (14.7 months; 95% CI: 6.8–18.5; 77.1%), other uncommon mutations (4.5 months; 95% CI: 2.9–9.7; 65.2%) and some exon 20 insertions (4.2 months; 95% CI: 2.8–5.3; 24.3%) [67]. Together, this RWE indicates that afatinib is an effective therapeutic option for patients with uncommon *EGFR* mutations.

Real-world safety & management of AEs

Real-world studies can also provide long-term safety monitoring, confirming the results from RCTs or, potentially, identifying rare or late-occurring AEs or differences in AE rates between different patient populations (Table 3). Clinical trial data have demonstrated that EGFR TKIs are typically associated with gastrointestinal and cutaneous AEs. For example, in the Phase III LUX-Lung trials, diarrhea, rash/acne and stomatitis/mucositis were the most common treatment-related grade 3/4 AEs with first-line afatinib [56–58], and diarrhea, rash/acne and dry skin were most common in the Phase III FLAURA trial of first-line osimertinib [61]. The frequencies of these AEs have been broadly confirmed in several of the large, real-world studies described above, with no unexpected safety signals reported [21,38,45–47].

In addition to confirming the safety profiles reported in clinical trials, real-world studies in *EGFR* mutation-positive NSCLC have been used to assess the real-world use of AE-management strategies. For example, data from the LUX-Lung 3, 6 and 7 clinical trials demonstrated that protocol-specified afatinib dose-modification guidelines effectively reduced the incidence of AEs with afatinib without adversely impacting efficacy [45,68,69]; however, it was unknown whether such approaches were equally similarly effective outside of the tightly controlled clinical trial setting. In the global, retrospective observational RealGiDo study, of the 155 patients who started with the approved 40 mg dose of afatinib, 104 (67%) had a dose reduction. In these 104 patients, the incidence and severity of AEs were reduced, but outcomes were not affected (median time to progression was 20.0 months in patients who had a dose reduction and 20.8 months in the overall population) [45,68,69]. Similarly, two Japanese retrospective studies demonstrated that, in unselected real-world patient populations, first-line afatinib dose reduction could be used to manage treatment-related toxicity [48] without adversely impacting PFS [47,48].

Real-world sequencing of therapy

Recent clinical trial data provide compelling evidence for the use of osimertinib as a front-line therapy, with the Phase III FLAURA trial reporting a median OS of 38.6 months (95% CI: 34.5–41.8) with osimertinib and 31.8 months (95% CI: 26.6–36.0) with gefitinib/erlotinib (HR: 0.80; 95.05% CI: 0.64–1.00; p = 0.046) [70]. This agent is now the recommended first-line treatment in countries where it is commercially available in line with expert guidelines. However, resistance to EGFR TKIs is inevitable and resistance mechanisms following osimertinib appear to be heterogeneous [71], limiting the options for subsequent targeted therapy. In contrast, the T790M mutation is the most common resistance mechanism to the first- and second-generation EGFR TKIs, reported in up to 75% of patients after afatinib therapy [72]. As osimertinib is particularly effective in T790M-positive patients, some clinicians have postulated that a sequential treatment approach involving afatinib followed by osimertinib may be worth considering [71]. In the absence of clinical trial data, real-world studies have been used to assess this proposed approach. For example, the prospective observational GioTag study assessed first-line afatinib followed by osimertinib in *EGFR* mutation-positive NSCLC patients who acquired T790M [49,50]. In the overall population, median OS was 41.3 months (90% CI: 36.8–46.3), with a median OS of 45.7 months (90% CI: 45.3–51.5) in patients with Del19-positive tumors (Table 3) [50]. These data suggest that sequential treatment with afatinib followed by osimertinib is a feasible option in those patients who start afatinib as first-line therapy. However, questions remain about this approach. For example, one concern with this approach is the well-known attrition

of patients following progression on initial treatment, where approximately 30% of patients fail to proceed to salvage therapy after progression on front-line therapy. Moreover, the clinical benefit of osimertinib over earlier-generation EGFR TKIs may be driven in a major way by its efficacy against intracranial spread of the disease. The real-world data on sequential therapy might therefore be used to guide the development of a clinical trial rather than immediately changing current clinical practice recommendations.

Real-world analysis of adherence to guideline recommendations

Data from real-world studies can also identify whether routine clinical practice differs from current guideline recommendations and whether there are any regional differences in patient management strategies. In the USA, a large, retrospective study of EHRs of patients with NSCLC found that *EGFR* mutation-testing rates increased from 30.5% in 2011 to 78.4% in 2016, reflecting the increased utilization of molecular analysis to guide therapeutic decisions [34]. A large, international retrospective survey (conducted in Canada, France, Germany, Italy, Japan, South Korea, Spain, Taiwan, the UK and the USA) reported similar findings, with mutation testing requested in 77.0–84.0% of patients prior to selection of first-line treatment in 2016 [73]. However, substantial regional variation has also been reported, with the multinational retrospective PIvOTAL study demonstrating that rates of *EGFR* testing ranged from 42.9–85.3% of patients with advanced NSCLC across Australia, Brazil, Germany, Italy, Japan, Korea, Spain and Taiwan [53,54] (Table 3). Regional differences have also been identified in the proportion of real-world patients with *EGFR* mutation-positive NSCLC who receive an EGFR TKI as first-line therapy, with treatment rates ranging from 56.6 to 73.8% of patients across the USA, Germany and China [34,52,55], suggesting potential global variation in prescribing patterns despite similar treatment guidelines. A retrospective study conducted in Canada provided further insight into the prescribing patterns of EGFR TKIs in the real world, revealing that younger patients were more likely than older patients to receive afatinib over first-generation EGFR TKIs, despite the clinical benefits of afatinib being shown to be applicable to elderly patients in real-world clinical practice [39].

Conclusion

Although real-world studies are not able to achieve the high internal validity of RCTs, properly performed analyses of real-world data can provide valuable complementary data, which can be used to address the 'generalizability' limitations of RCTs and provide evidence on the external validity of their findings. In the case of *EGFR* mutation-positive NSCLC, real-world studies have confirmed that the efficacy and safety profiles of *EGFR* TKIs seen in RCTs are applicable to real-world populations, and provided valuable evidence on the activity of EGFR TKIs in patient populations not routinely included in RCTs, including elderly patients, patients with brain metastases and, for afatinib, patients with uncommon mutations. In conclusion, while real-world studies have widely acknowledged limitations and should not be directly compared with clinical trials, as demonstrated for *EGFR* mutation-positive NSCLC, quality evidence from large and reliable sources can provide valuable additional insights into the use of established therapies in routine clinical practice.

Future perspective

Over the next 5–10 years, there is likely to be a substantial increase in the number of published real-world studies. In turn, this expansion in RWE will increase the need for physicians to understand the benefits and limitations of such studies to fully appraise the results. Recognizing the importance of assessing therapies in patient populations truly reflective of the real-world patients who are ultimately to receive them, we also expect to see a further emphasis on conducting RCTs in more representative patient populations. Some of this effort is already underway and we expect further advances in conducting trials with equitable representation of patients defined by gender, race, geographic locations, advanced age and medical comorbidities.

For *EGFR* mutation-positive NSCLC specifically, it is likely that real-world data will continue to be used to clarify the optimal management of rare sensitizing *EGFR* mutations and we hope the future will advance treatment options for *EGFR* mutations currently considered non-sensitizing. Identifying options for subsequent therapy after progression on osimertinib is likely to be complex and highly dependent on the mechanisms of resistance. There are numerous ongoing trials addressing novel agents and combination therapies in this setting and real-world data are likely to contribute to this effort. Finally, real-world data are likely to inform the adherence rate of patients on oral EGFR TKI therapy, and whether occasional missed daily doses result in detectable differences in clinical outcomes.

The future treatment for *EGFR* mutation-positive disease is likely to build on the established efficacy of EGFR TKIs. Promising strategies such as combination with anti-angiogenic agents and cytotoxic chemotherapy will most

likely supplant single-agent therapy. In addition, the use of EGFR TKIs in the curative disease setting, either in addition to or in place of adjuvant cytotoxic chemotherapy, is likely to become widely accepted. RWE will be a useful approach to better understand patient and genomic subsets that benefit from this strategy. With the general acceptance of osimertinib as a preferred front-line-targeted agent, novel strategies to overcome resistance to this agent will be evaluated and hopefully result in new treatment options. Management of post-osimertinib progression is likely to be complex and highly dependent on the mechanisms of resistance. There are numerous ongoing trials addressing novel agents and combinations therapies in this setting. Repeat genomic testing at the time of progression is expected to guide subsequent line therapies.

Management of brain metastatic disease will remain a challenge in this disease and it is one area where RWE could inform novel management approaches for patients who have exhausted standard interventions such as radiation and EGFR TKIs.

Executive summary

Background

- Randomized controlled trials (RCTs) are the gold standard for clinical decision making, but the necessarily strict inclusion/exclusion criteria and tightly controlled conditions limit their generalizability to real-world clinical practice; consequently, real-world evidence (RWE) is increasingly valued as a complement to clinical trial data.

What is real-world data & how is it used?

- Real-world data are collected in routine clinical practice and can be gathered prospectively or retrospectively via a range of studies including prospective and retrospective observational studies, patient registries and post-marketing commitment studies.

The advantages & limitations of real-world studies

- RWE has broader generalizability than clinical trial data and can provide insights to the effectiveness and safety of a drug during routine care; however, limitations include the potential for bias and confounding factors that are controlled for in RCTs.

Learnings from real-world studies in *EGFR* mutation-positive NSCLC

- RWE can assess a range of clinical questions; real-world studies in *EGFR* mutation-positive NSCLC have been used to:
  - Demonstrate that the efficacy and safety profiles seen in clinical trials of EGFR TKIs are consistent in real-world populations;
  - Confirm that the EGFR TKIs afatinib and osimertinib are effective in patient subgroups not routinely included in RCTs, such as elderly patients, those with brain metastases and, in the case of afatinib, patients with uncommon mutations;
  - Propose the hypothesis, and demonstrating the feasibility, of sequential EGFR TKI therapy;
  - Identify differences in routine clinical practice compared with guideline recommendations.

Conclusion

- As demonstrated by studies in *EGFR* mutation-positive NSCLC, clinical evidence from real-world studies is a valuable and increasingly recognized, complement to data from RCTs.

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-2020-0951

Author contributions

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

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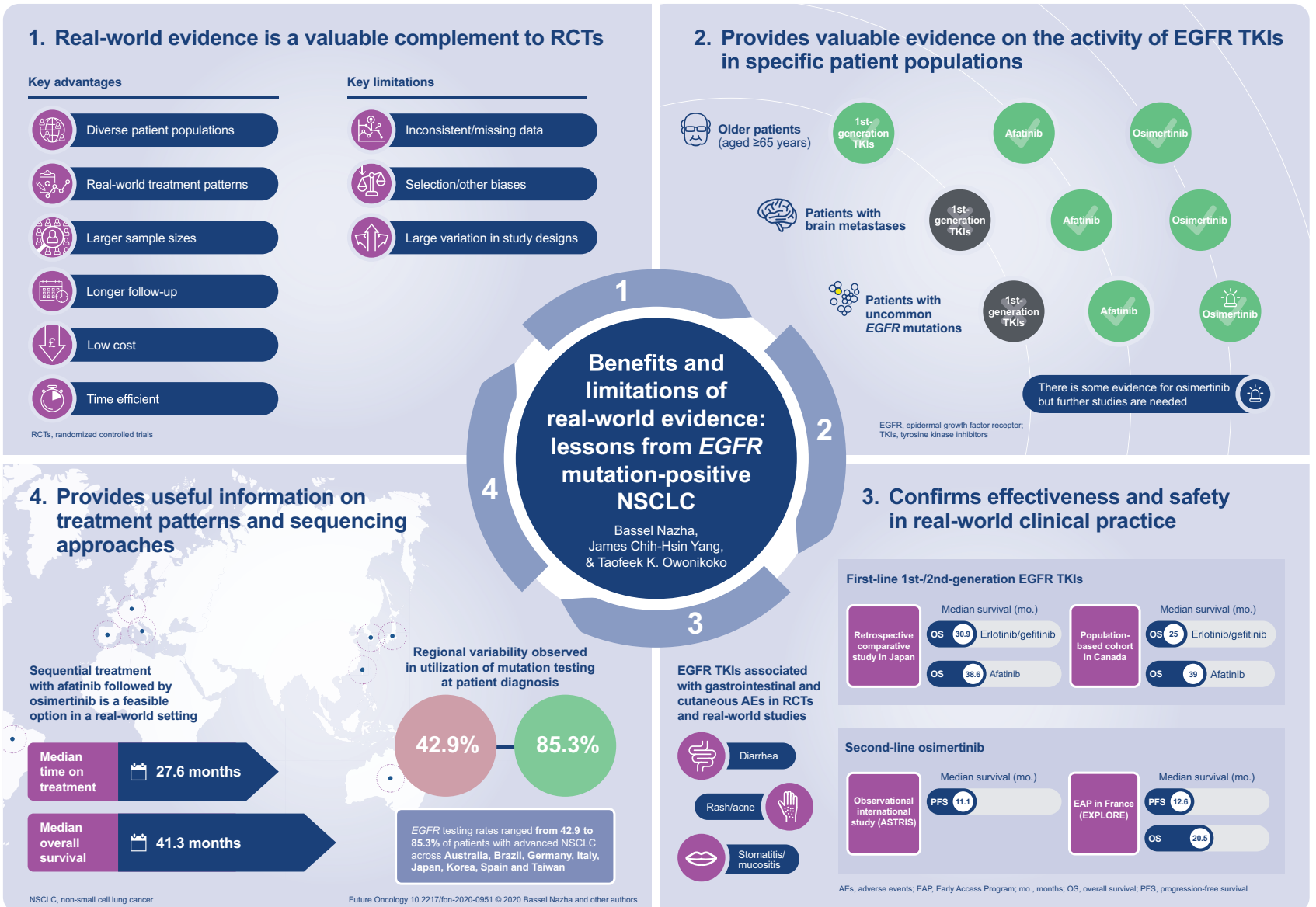

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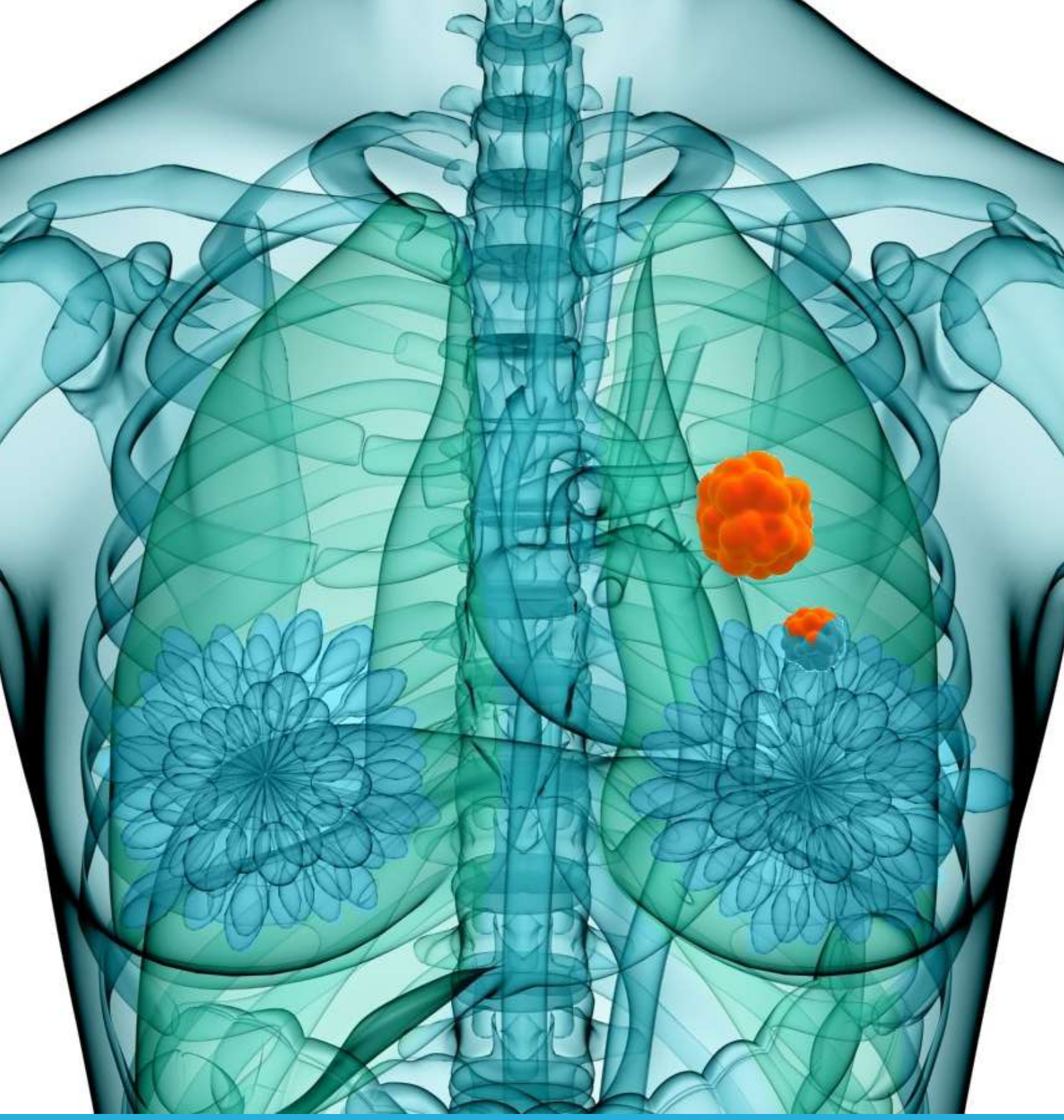

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