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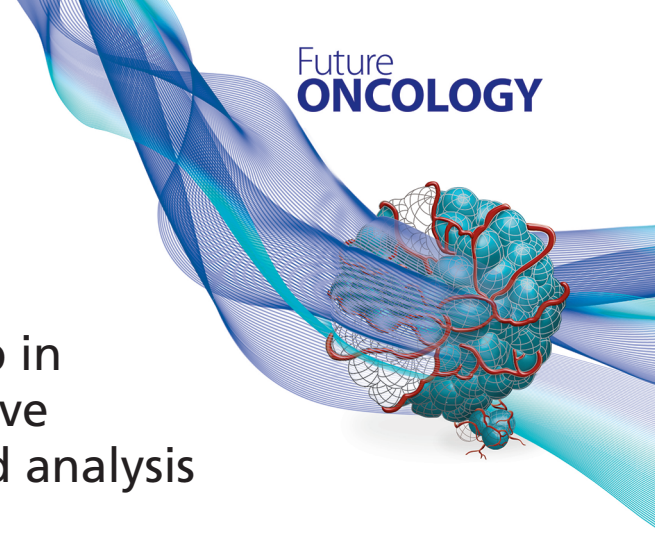

Short Communication

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

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Aims: Overall survival (OS) and updated time to treatment failure (TTF) analysis of patients with *EGFR* mutation-positive (Del19, L858R) non-small-cell lung cancer who received sequential afatinib/osimertinib in the real-world GioTag study. **Patients & methods:** Patients had T790M-positive disease following first-line afatinib and received osimertinib treatment (n = 203). Primary outcome was TTF. The OS analysis was exploratory. **Results:** Median OS was 41.3 months (90% CI: 36.8–46.3) overall and 45.7 months (90% CI: 45.3–51.5) in patients with Del19-positive tumors (n = 149); 2-year survival was 80 and 82%, respectively. Updated median TTF with afatinib and osimertinib was 28.1 months (90% CI: 26.8–30.3). **Conclusion:** Sequential afatinib/osimertinib was associated with encouraging OS/TTF in patients with *EGFR* T790M-positive non-small-cell lung cancer, especially in patients with Del19-positive tumors.

Trial registration number: NCT03370770

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Keywords: afatinib • NSCLC • osimertinib • sequential • T790M

Several EGFR tyrosine kinase inhibitors (TKIs) are now available for the treatment of *EGFR* mutation-positive non-small-cell lung cancer (NSCLC): the first-generation, reversible EGFR TKIs, erlotinib and gefitinib; the second-generation irreversible ErbB family blockers, afatinib and dacomitinib and the third-generation irreversible EGFR TKI, osimertinib. Recent randomized trials have demonstrated that afatinib [1], dacomitinib [2] and osimertinib [3] all confer significantly improved progression-free survival versus first-generation TKIs. However, in the absence of any head-to-head data, it is unclear whether it is best to use second- or third-generation TKIs as upfront treatment of choice. Furthermore, it is currently unclear which agent, or sequence of agents, maximize overall survival (OS), the most important measure of treatment efficacy.

Osimertinib in a first-line treatment setting has demonstrated strong clinical activity and tolerability in patients with *EGFR* mutation-positive NSCLC [3]. However, it is also approved for, and demonstrated impressive activity as, second-line treatment in patients with T790M-positive tumors [4], the predominant mechanism of acquired resistance to first- and second-generation EGFR TKIs (~50–70% of cases [5–8]). Given that, as yet, no estab-

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lished targeted treatment options are available following failure of osimertinib, there is an argument for reserving osimertinib for second-line use following failure of a second-generation EGFR TKI.

No prospective OS data are currently available to compare different sequential regimens of EGFR TKIs. However, retrospective analysis of clinical trial data [9], and real-world cohort studies [5,10,11], indicate that sequential use of afatinib and osimertinib is feasible and confers prolonged periods of chemotherapy-free treatment in patients with T790M-positive tumors. Given the paucity of data, we undertook the observational, retrospective, global, multicenter GioTag study. This study assessed 204 EGFR TKI-naive patients, treated in a 'real-world' clinical setting, who received first-line afatinib, went on to develop T790M-positive acquired resistance and subsequently received second-line osimertinib [12]. Median time to treatment failure (TTF), the primary outcome, was 27.6 months (90% CI: 25.9–31.3 months) and was particularly encouraging in patients with an *EGFR* Del19 activating mutation (30.3 months) and Asian patients (46.7 months).

At the initial database lock (May 2018), patients enrolled onto GioTag had been followed up for a median of 28.2 months (range: 14.0–96.8 months). At this time, 63 patients had died (30.9%) and OS analysis was immature. Here, we describe an interim analysis (database lock: April 2019) at which point 42% of patients had experienced an OS event. We have also reanalyzed TTF.

Patients & methods

Study design

The design of the GioTag study was described previously [12]. In brief, it is a global, observational study conducted across ten countries (Austria, Canada, Israel, Italy, Japan, Singapore, Slovenia, Spain, Taiwan and USA; NCT03370770). The analysis was restricted to patients aged ≥18 years with common *EGFR* activating mutations (Del19/L858R), who received first-line afatinib and had a documented T790M mutation (as per local methodology and practice) following its failure. In order to limit selection bias, each participating center assessed the health records of a maximum of 15 consecutive patients between 28 December 2017 and 31 May 2018. All patients must have initiated osimertinib ≥10 months prior to enrollment to avoid early censoring and ensure mature data. Data were collected from two different sources: 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 was undertaken for 30% of patients. All patients provided informed consent.

Outcomes & assessments

The primary outcome was TTF, defined as the time from the first dose of afatinib to that of the last dose of osimertinib or death. Analysis of OS was exploratory.

Statistical analysis

For this interim analysis, updated data were collected from 94 patients for whom electronic health records were available (all from the USA). The use of electronic data, which facilitated rapid analysis, represented the first step of a two-step process. This two-step approach was necessary because database lock was different for the two different data sources. Final analysis, incorporating data from manual chart reviews of a further 29 patients is anticipated in early 2020. The TTF and OS were estimated using the Kaplan–Meier method; for patients still on treatment, TTF was censored at the date of data collection.

Results

Patients

Baseline characteristics of the 204 patients included in the analysis have been described previously [12]. The GioTag population reflected real-world clinical practice and included patients with ECOG PS of ≥2 (15.2%) and those with CNS metastases (10.3%). Patients were predominantly Caucasian (58.8%) but also included Asians (24.5%) and African–Americans (8.8%). 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%). At the time of database lock (April 2019), 85 (41.9%) patients had died, 26 (12.8%) were lost to follow-up, and 92 (45.3%) were alive including 63 (31.0%) who remained on osimertinib. One patient was excluded from the analysis due to reports of conflicting data.

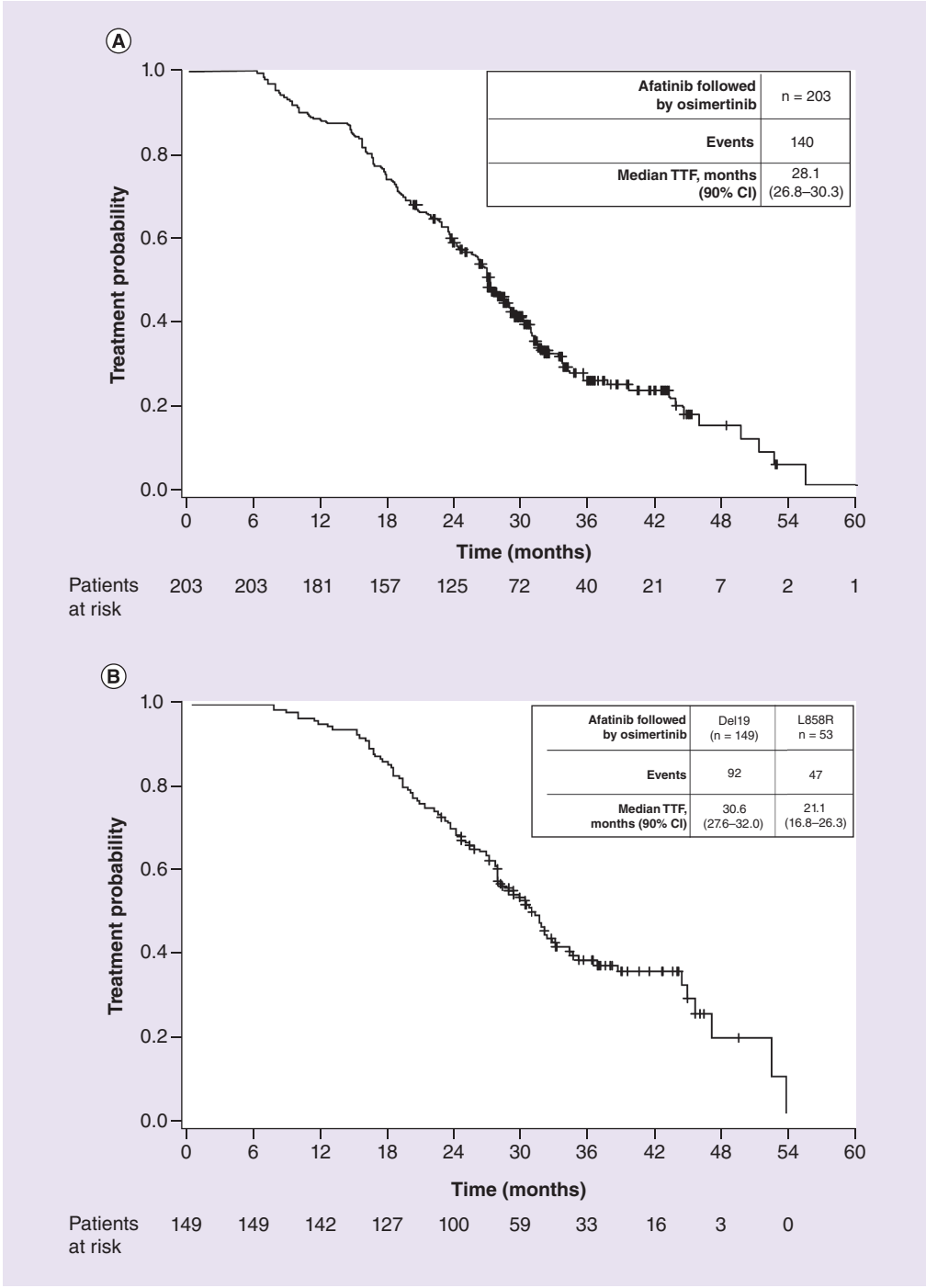

Figure 1. Overall time to treatment failure with sequential afatinib and osimertinib. (A) All patients; **(B)** patients with Del19-positive tumors.
TTF: Time to treatment failure.

Time to treatment failure

Updated median TTF for sequential afatinib and osimertinib was 28.1 months (90% CI: 26.8–30.3; Figure 1A). Median TTF was 30.6 months (90% CI: 27.6–32.0; Figure 1B) in patients with Del19-positive tumors. Median TTF on osimertinib was 15.6 months (90% CI: 13.8–17.1) overall and 16.4 months (90% CI: 14.9–17.9) in patients with Del19-positive tumors.

Overall survival

After a median follow-up of 30.3 months (interquartile range: 24.0–36.8), median OS was 41.3 months (90% CI: 36.8–46.3; Figure 2A). The 2-year OS rate was 80%. Median OS was 45.7 months (90% CI: 45.3–51.5; Figure 2B) in patients with Del19-positive tumors (2-year OS rate of 82%).

Outcomes in patients who started on afatinib 40 mg/day

In patients who started on the approved afatinib dose (40 mg/day; n = 168), the 2-year OS rate was 82% and median OS was 45.3 months (90% CI: 37.6–47.6; Supplementary Figure 1). In patients with Del19-positive tumors (n = 122), median OS was 45.7 months (90% CI: 45.3–47.6). Median TTF was 28.1 months (90% CI: 26.8–30.6) overall (Supplementary Figure 2) and 30.6 months (90% CI: 27.6–33.8) in patients with Del19-positive tumors.

Discussion

In this updated analysis of the GioTag study, sequential afatinib and osimertinib conferred OS of almost 3.5 years, and TTF of over 2 years, in a broad population of patients with *EGFR* mutation-positive NSCLC treated in a real-world clinical setting. We acknowledge that these data are retrospective, subject to selection bias and do not substitute for prospective trials of sequential EGFR TKI regimens. Nevertheless, given the paucity of prospective OS data at the moment, these findings suggest that sequential treatment with afatinib followed by osimertinib is worthy of further clinical evaluation. Furthermore, of note, prior treatment with afatinib did not appear to preclude prolonged TTF with second-line osimertinib (15.6 months), suggesting that the activity of osimertinib may not be substantially diminished if used in a second-line setting.

In patients with Del19-positive tumors, OS was almost 4 years, overall TTF was 2.5 years and TTF with osimertinib was 16.4 months. Previous studies have consistently demonstrated that Del19 is a marker of favorable prognosis and predicts better outcomes with EGFR TKIs than L858R [13]. Indeed, afatinib previously demonstrated OS benefit versus chemotherapy in patients with Del19-positive tumors in the Phase III LUX-Lung 3 (median: 33.3 vs 21.1 months; HR: 0.54; 95% CI: 0.36–0.79; p = 0.0015) and LUX-Lung 6 (median: 31.4 vs 18.4 months; HR: 0.64; 95% CI: 0.44–0.94; p = 0.023) trials [14]. Accordingly, Del19- and L858R-positive tumors should possibly be regarded as two different disease entities. The reasons underlying differences in sensitivity of these tumors to EGFR TKIs are not completely understood but probably reflect differences in the impact of the mutations on the tertiary structure of the receptor and downstream signaling cascades [13]. Our data suggest that sequential afatinib and osimertinib may be a promising treatment option in patients with Del19-positive tumors, especially when one considers that these tumors have a higher likelihood of acquiring T790M (~75%) than L858R-positive tumors (up to 58%) [5,15,16]. As all the updated data in this analysis were derived from patients treated in the USA, few additional data are yet available for Asian patients included in GioTag (who, in the initial analysis, showed very encouraging TTF of 46.7 months). For this reason, we were unable to assess OS in the Asian subgroup at this time (OS maturity in Asian patients is currently 28%). Given the encouraging TTF in Asians, we envisage that OS will be increased when these patients are incorporated into the final analysis.

While the selection of first-line EGFR TKI therapy in patients with *EGFR* mutation-positive NSCLC is a complex question, the likelihood of maximizing OS is clearly an important consideration. Several prospective trials indicate that second-generation EGFR TKIs provide encouraging OS versus first-generation EGFR TKIs in this setting. Exploratory analysis of the Phase III ARCHER 1050 trial demonstrated that dacomitinib significantly improved OS versus gefitinib (median: 34.1 vs 26.8 months; HR: 0.76; 95% CI: 0.58–0.99; p = 0.044 [17]). In the Phase IIB LUX-Lung 7 trial (which, unlike ARCHER 1050, included patients with brain metastases, an indicator of poor prognosis) median OS with afatinib was 27.9 months versus 24.5 months with gefitinib (HR: 0.86; 95% CI: 0.66–1.12; p = 0.258 [18]). Very few patients treated with dacomitinib or afatinib in these studies went on to receive osimertinib (n = 22 and n = 20, respectively), reflecting its limited availability at the time. Nevertheless, retrospective analysis of these patients demonstrated that median OS was 36.7 months with sequential dacomitinib and a third-generation TKI, and not reached (3-year OS rate of ~90%) with sequential afatinib and a third-generation TKI, respectively [17,18]. In the AURA and AURA2 trials, which assessed osimertinib following failure of first-line EGFR TKI treatment (n = 411), median OS with second- or later-line osimertinib was 26.8 months [19]. Overall, therefore, the results of GioTag add to a growing body of evidence supporting further clinical evaluation of sequential EGFR TKIs.

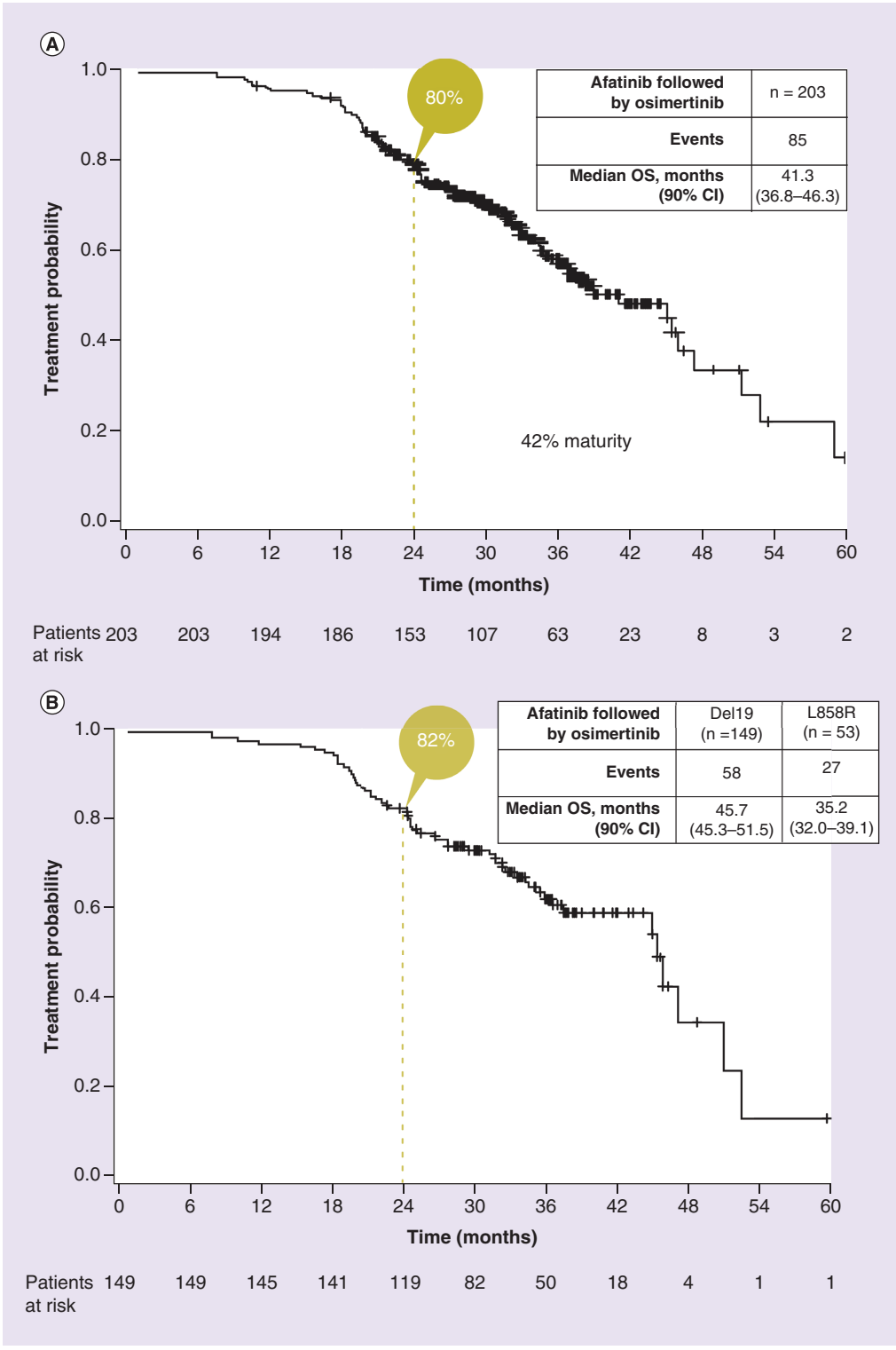

Figure 2. Overall survival in patients treated with sequential afatinib and osimertinib therapy. (A) All patients; **(B)** patients with Del19-positive tumors.
OS: Overall survival.

The results of the current study, and other studies, pose the question of whether it is preferable to utilize osimertinib as first-line therapy, or whether it is better to hold it back for second-line use. On one hand, first-line osimertinib is highly active, with progression-free survival according to independent central review of 17.7 months in the Phase III FLAURA trial [3]. Also, as it is EGFR wild-type sparing, osimertinib has a favorable tolerability profile, with very low rates (≤2%) of class-related grade ≥3 AEs such as diarrhea and rash/acne [3]. These factors support the use of osimertinib in a first-line setting. On the other hand, no targeted treatment options have been clinically validated following the failure of osimertinib, reflecting the heterogeneity of its resistance mechanisms [20,21]. Although clinical trials assessing agents that target putative resistance mechanisms (e.g., MET amplification) [20] are ongoing, currently the most common postprogression therapy following osimertinib is platinum-based chemotherapy [22]. Therefore, sequential use of second-generation EGFR TKIs, followed by osimertinib, could potentially confer a net increase in the duration of chemotherapy-free treatment, and perhaps OS, compared with first-line osimertinib. This hypothesis requires prospective validation. Several ongoing studies should be informative in terms of comparing the OS benefits of different sequential regimens, including final OS analysis of the Phase III FLAURA and AURA-3 trials and the Phase II APPLE trial (which is comparing sequential gefitinib/osimertinib vs first-line osimertinib [23]). However, no ongoing prospective trials are directly comparing outcomes in patients receiving sequential second- and third-generation EGFR TKIs versus patients who receive third-generation EGFR TKIs in the first line.

There are a number of practical and clinical challenges to implementing a sequencing strategy of afatinib followed by osimertinib. First, improvements in the access to, and sensitivity of, T790M mutation detection assays are probably required. The further development of sensitive liquid biopsy techniques may help address this issue. Of note, in a recent study that utilized a sensitive droplet-digital PCR technique, the T790M detection rate in 67 patients who progressed on afatinib was 73%, suggesting that liquid biopsy tests could increase the identification of patients who may benefit from second-line osimertinib [5]. Second, approximately 30–40% of patients treated with first-line afatinib will progress due to T790M-independent mechanisms and will therefore be ineligible for subsequent osimertinib. Potential treatment options for these patients, such as atezolizumab, bevacizumab and chemotherapy [24], require further evaluation in this setting. Third, not all patients who receive first-line afatinib will be deemed fit enough to receive subsequent therapy, although recent data indicate a very high rate of subsequent therapy after afatinib (~80%), especially in countries with optimized supportive cancer care [9]. Finally, second-generation TKIs, such as afatinib, are probably associated with higher rates of grade ≥3 AEs than osimertinib (though no head-to-head data exist). However, clinical trial and real-world data indicate that afatinib-related AEs are predictable and manageable with tolerability-guided dose adjustment [25–27], such that discontinuation rates due to AEs with afatinib and osimertinib are comparable.

Conclusion

In conclusion, these retrospective results from the GioTag study indicate that sequential afatinib and osimertinib may confer encouraging OS in patients with *EGFR* mutation-positive NSCLC and T790M in a real-world clinical setting, especially in Del19-positive patients. Therefore, sequential EGFR TKI therapy warrants further consideration as a potential means of providing prolonged, chemotherapy-free, clinical benefit.

Summary points

- Previously, the real-world observational GioTag study indicated that sequential use of afatinib and osimertinib warranted further assessment as a treatment strategy in patients with *EGFR* mutation-positive non-small-cell lung cancer; however, overall survival (OS) data were immature.
- In this updated analysis, median OS was 41.3 months (90% CI: 36.8–46.3) and 2-year OS rate was 80%.
- In patients with an *EGFR* Del19 mutation at the onset of treatment with afatinib, median OS was 45.7 months (90% CI: 45.3–51.5) and 2-year OS rate was 82%.
- Overall, the median time on EGFR-TKI treatment was 28.1 months (90% CI: 26.8–30.3).
- Median time on osimertinib treatment was 15.6 months (90% CI: 13.8–17.1) indicating that substantial clinical benefit with osimertinib can be achieved in a second-line setting following afatinib.
- These data, along with high rate of accrual of T790M in patients treated with afatinib, especially in patients with Del19-positive disease, indicate that sequential afatinib followed by osimertinib is potentially a feasible therapeutic strategy.
- Prospective data are required to evaluate the OS of patients treated with different EGFR-TKIs, and sequential regimens, in patients with *EGFR* mutation-positive non-small-cell lung cancer.

Supplementary data

An infographic accompanies this paper at the end of the references section. To download the infographic that accompanies this paper, please visit the journal website at:

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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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Data sharing statement

The datasets generated and analyzed during the study are available from MJ Hochmair on reasonable request. Clinical trial registration number: NCT03370770.

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 Harmonization 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.

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. Park K, Tan EH, O'Byrne K *et al.* Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a Phase 2B, open-label, randomised controlled trial. *Lancet Oncol.* 17(5), 577–589 (2016).
2. Wu YL, Cheng Y, Zhou X *et al.* Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, Phase III trial. *Lancet Oncol.* 18(11), 1454–1466 (2017).
3. Soria JC, Ohe Y, Vansteenkiste J *et al.* Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N. Engl. J. Med.* 378(2), 113–125 (2018).
4. Mok TS, Wu YL, Ahn MJ *et al.* Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N. Engl. J. Med.* 376(7), 629–640 (2017).

▶5. Hochmair MJ, Buder A, Schwab S *et al.* Liquid-biopsy-based identification of EGFR T790M mutation-mediated resistance to afatinib treatment in patients with advanced EGFR mutation-positive NSCLC, and subsequent response to osimertinib. *Target Oncol.* 14(1), 75–83 (2019).

- **A real-world cohort study which demonstrated that 73% of patients treated with afatinib developed T790M-mediated resistance, based on a sensitive blood biopsy assay.**

▶6. Arcila ME, Oxnard GR, Nafa K *et al.* Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. *Clin. Cancer Res.* 17(5), 1169–1180 (2011).

▶7. Sequist LV, Waltman BA, Dias-Santagata D *et al.* Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci. Transl. Med.* 3(75), 75ra26 (2011).

▶8. Yang JC, Ahn MJ, Kim DW *et al.* Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study Phase II extension component. *J. Clin. Oncol.* 35(12), 1288–1296 (2017).

▶9. Park K, Bennouna J, Boyer M *et al.* Sequencing of therapy following first-line afatinib in patients with EGFR mutation-positive non-small cell lung cancer. *Lung Cancer* 132, 126–131 (2019).

- ●● **A retrospective analysis of LUX-Lung 3, 6 and 7 demonstrating that, even in the preosimertinib era, 71% of patients treated with afatinib were fit enough to receive at least one further line of treatment.**

10. Roeper J, Lueers A, Netchaeva M *et al.* 1359P Impact on OS and PFS of 2nd and 3rd generation TKI in EGFR mt+ and ALK+ pts: results of the NOWEL network. *Ann. Oncol.* 28(Suppl. 5), 486 (2017).

11. Tamiya M, Tamiya A, Suzuki H *et al.* 1459P Which of afatinib and gefitinib/erlotinib is the better EGFR-TKI to be followed by osimertinib? *Ann.Oncol.* 29(Suppl. 8), viii527–viii528 (2018).

▶12. Hochmair MJ, Morabito A, Hao D *et al.* Sequential treatment with afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: an observational study. *Future Oncol.* 14(27), 2861–2874 (2018).

- ●● **The first reported data from the GioTag study, demonstrating median TTF of 27.6 months in 204 patients treated with sequential afatinib and osimertinib.**

▶13. Reguart N, Remon J. Common EGFR-mutated subgroups (Del19/L858R) in advanced non-small-cell lung cancer: chasing better outcomes with tyrosine kinase inhibitors. *Future Oncol.* 11(8), 1245–1257 (2015).

▶14. Yang JC, Wu YL, Schuler M *et al.* Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, Phase III trials. *Lancet Oncol.* 16(2), 141–151 (2015).

▶15. Jenkins S, Chih-Hsin Yang J, Janne PA *et al.* EGFR mutation analysis for prospective patient selection in two Phase II registration studies of osimertinib. *J. Thorac Oncol.* 12(8), 1247–1256 (2017).

▶16. Ke EE, Zhou Q, Zhang QY *et al.* A higher proportion of the EGFR T790M mutation may contribute to the better survival of patients with exon 19 deletions compared with those with L858R. *J. Thorac Oncol.* 12(9), 1368–1375 (2017).

▶17. Mok TS, Cheng Y, Zhou X *et al.* Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. *J. Clin. Oncol.* 36(22), 2244–2250 (2018).

- **Exploratory analysis of ARCHER 1050 demonstrating that the second-generation EGFR TKI, dacomitinib, was associated with prolonged overall survival (OS)versus gefitinib.**

▶18. Paz-Ares L, Tan EH, O'Byrne K *et al.* Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the Phase IIb LUX-Lung 7 trial. *Ann. Oncol.* 28(2), 270–277 (2017).

- **Prespecified OS analysis of LUX-Lung 7 demonstrating a trend toward improved OS with afatinib versus gefitinib.**

▶19. Ahn MJ, Tsai CM, Shepherd FA *et al.* Osimertinib in patients with T790M mutation-positive, advanced non-small cell lung cancer: long-term follow-up from a pooled analysis of 2 Phase II studies. *Cancer* 125(6), 892–901 (2019).

20. Ramalingam SS, Cheng Y, Zhou C *et al.* LBA50 Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the Phase III FLAURA study. *Ann. Oncol.* 29(Suppl. 8), viii740 (2018).

▶21. Oxnard GR, Hu Y, Mileham KF *et al.* Assessment of resistance mechanisms and clinical implications in patients with EGFR T790M-positive lung cancer and acquired resistance to osimertinib. *JAMA Oncol.* 4(11), 1527–1534 (2018).

▶22. Planchard D, Boyer MJ, Lee JS *et al.* Postprogression outcomes for osimertinib versus standard-of-care EGFR-TKI in patients with previously untreated EGFR-mutated advanced non-small cell lung cancer. *Clin. Cancer Res.* 25(7), 2058–2063 (2019).

- **Analysis of postprogression therapies in patients treated with first-line osimertinib in FLAURA.**

▶23. Remon J, Menis J, Hasan B *et al.* The APPLE trial: feasibility and activity of AZD9291 (osimertinib) treatment on positive plasma T790M in EGFR-mutant NSCLC patients. EORTC 1613. *Clin. Lung Cancer* 18(5), 583–588 (2017).

▶24. Reck M, Mok TSK, Nishio M *et al.* Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label Phase 3 trial. *Lancet Respir. Med.* 7(5), 387–401 (2019).

▶25. Yang JC, Sequist LV, Zhou C *et al.* Effect of dose adjustment on the safety and efficacy of afatinib for EGFR mutation-positive lung adenocarcinoma: *post hoc* analyses of the randomized LUX-Lung 3 and 6 trials. *Ann. Oncol.* 27(11), 2103–2110 (2016).

▶26. Schuler M, Tan EH, O'Byrne K *et al.* First-line afatinib vs gefitinib for patients with EGFR mutation-positive NSCLC (LUX-Lung 7): impact of afatinib dose adjustment and analysis of mode of initial progression for patients who continued treatment beyond progression. *J. Cancer Res. Clin. Oncol.* 145(6), 1569–1579 (2019).

▶27. Halmos B, Tan EH, Soo RA *et al.* Impact of afatinib dose modification on safety and effectiveness in patients with EGFR mutation-positive advanced NSCLC: results from a global real-world study (RealGiDo). *Lung Cancer* 127, 103–111 (2019).