ORIGINAL ARTICLE

Molecular Epidemiology and Treatment Patterns of Patients With EGFR Exon 20-Mutant NSCLC in the Precision Oncology Era: The European EXOTIC Registry

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Dr. Xenidis is deceased.

Disclosure: Petros Christopoulos has received research funding from AstraZeneca, Novartis, Roche, and Takeda, speaker's honoraria from AstraZeneca, Novartis, Roche, Takeda, support for attending meetings from AstraZeneca, Eli Lilly, Gilead, Novartis, Takeda, and personal fees for participating to advisory boards from Boehringer Ingelheim, Chugai. Ilias Athanasiadis reports honorary lectures, consulting fees, expert testimony and travel/congress fees from Roche, MSD, BMS, Amgen, AstraZeneca, Sanofi, Novartis. Giannis Mountzios reports honorary lectures, consulting fees, expert testimony and travel/congress fees from Roche, MSD, BMS, Amgen, AstraZeneca, Sanofi, Novartis, Takeda, Pfizer, Amgen, Janssen. Davide Mauri reports consulting fees from Roche Hellas, Novartis Greece, BMS Greece, MSD Greece, AstraZeneca Greece, Takeda Hellas, Janssen Greece, GSK Greece, Amgen Hellas, Sanofi Greece, Boehringer Greece; Honoraria payment or expert testimony from Roche Hellas, Novartis Greece, BMS Greece, MSD Greece, AstraZeneca Greece, Takeda Hellas, Janssen Greece, GSK Greece, Amgen Hellas, Sanofi Greece, Boehringer Greece; Travel support from Roche Hellas, Novartis Greece, BMS Greece MSD Greece, AstraZeneca Greece, Takeda Hellas, Janssen Greece, GSK Greece, Amgen Hellas, Sanofi Greece, Boehringer Greece. Efthymiadis Konstantinos reports Travel Grants and Honoraria payment from Amgen Hellas, MSD Greece, Pfizer Hellas, Roche Hellas. Kokkalis Alexandros reports no conflict of interest. Ippokratis Korantzis reports honorary lectures, consulting fees, expert testimony and travel/congress fees from Roche, MSD, BMS, Amgen, AstraZeneca, Sanofi, Novartis. Dimitrios Mavroudis reports honorary lectures, consulting fees, expert testimony and travel/congress fees from Roche Hellas, BMS Greece, MSD Greece, AstraZeneca Greece, GSK Greece, Sanofi Greece, Gilead Greece Georgios Oikonomopoulos reports honorary lectures, consulting fees, expert testimony and travel/congress fees from Roche Hellas, BMS Greece, MSD Greece, AstraZeneca Greece, GSK Greece, Sanofi Greece, Gilead Greece. Martin Reck reports honorary lectures, consulting fees, expert testimony and travel/congress fees from Amgen, AstraZeneca,Boehringer-Ingelheim,BMS,Beigene,Lilly Mirati, MSD, Merck, Novartis, Pfizer, Sanofi, Regeneron, Roche, Takeda, Samsung, Bioepis. Emmanouil Saloustros reports honorary lectures, consulting fees, expert testimony and travel/congress fees from MSD Greece, AstraZeneca Greece, Gilead Sciences Hellas, Pfizer Hellas, Genesis Pharma. He is also member of European Society for Medical Oncology working groups (Adolescents and Young Adults working group, Breast cancer faculty) UNPAID, Hellenic Society of Medical Oncology UNPAID, Hellenic Oncology Research Group UNPAID. Walid Shalata reports honorary lectures, consulting fees, expert testimony and travel/congress fees from Roche Israel, Merck Israel, BMS Israel, MSD Israel. Giuseppe L. Banna reports honoraria payment from AstraZeneca and Astellas. Arselaj Prelaj reports honorary lectures, consulting fees, expert testimony from Roche, BMS, AstraZeneca, Italfarmaco. Anna Koumarianou reports honorary lectures, consulting fees, expert testimony and travel/congress fees from Roche Hellas, BMS Greece, MSD Greece, AstraZeneca GSK, Merck. David Planchard reports honorary lectures, consulting fees, expert testimony from AstraZeneca, Bristol-Myers Squibb, Celgene, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche, Janssen, Abbvie. Giulio Metro reports honorary lectures, consulting fees, expert testimony from Amgen, AstraZeneca, Pfizer, Takeda. Grigorios Rallis reports honorary lectures, consulting fees, expert testimony from

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Received 7 August 2022; revised 1 November 2022; accepted 5 November 2022
Available online - 20 November 2022

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Cite this article as: Mountzios G, Planchard D, Metro G, et al. Molecular epidemiology and treatment patterns of patients with EGFR exon 20-mutant NSCLC in the precision oncology era: the European EXOTIC registry. *JTO Clin Res Rep*. 2023;4:100433.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2022.100433

ABSTRACT

Introduction: Real-world evidence regarding molecular epidemiology and management patterns of patients with EGFR exon-20 mutated, advanced NSCLC outside the context of clinical trials is lacking.

Methods: We created a European registry for patients with advanced EGFR exon 20-mutant NSCLC diagnosed from January 2019 to December 2021. Patients enrolled in clinical trials were excluded. Clinicopathologic and molecular epidemiology data were collected, and treatment patterns were recorded. Clinical end points according to treatment assignment were assessed using Kaplan-Meier curves and Cox regression models.

Results: Data on 175 patients from 33 centers across nine countries were included in the final analysis. Median age was 64.0 (range: 29.7–87.8) years. Main features included female sex (56.3%), never or past smokers (76.0%), adenocarcinoma (95.4%), and tropism for bone (47.4%) and brain (32.0%) metastases. Mean programmed death-ligand 1 tumor proportional score was 15.8% (range: 0%–95%) and mean tumor mutational burden was 7.06 (range: 0–18.8) mutations per megabase. Exon 20 was detected in the tissue (90.7%), plasma (8.7%), or both (0.6%), using mostly targeted next-generation sequencing (64.0%) or polymerase chain reaction (26.0%). Mutations were mainly insertions (59.3%), followed by duplications (28.1%), deletions-insertions (7.7%), and the T790M (4.5%). Insertions and duplications were located mainly in the near loop (codons 767–771, 83.1%) and the far loop (codons 771–775, 13%) and only in 3.9% within the C helix (codons 761–766). Main co-alterations included mutations in TP53 (61.8%) and MET amplifications (9.4%). Treatment on mutation identification included chemotherapy (CT) (33.8%), CT-immunotherapy (IO) (18.2%), osimertinib (22.1%), poziotinib (9.1%), mobocertinib (6.5%), mono-IO (3.9%), and amivantamab (1.3%). Disease control rates were 66.2% with CT plus or minus IO, 55.8% with osimertinib, 64.8% with poziotinib, and 76.9% with mobocertinib. Corresponding median overall survival was 19.7, 15.9, 9.2, and 22.4 months, respectively. In multivariate analysis, type of treatment (new targeted agents versus CT ± IO) affected progression-free survival ($p = 0.051$) and overall survival ($p = 0.03$).

Conclusions: EXOTIC represents the largest academic real-world evidence data set on EGFR exon 20-mutant NSCLC in Europe. Indirectly compared, treatment with new exon 20-targeting agents is likely to confer survival benefit than CT plus or minus IO.

Keywords: Non–small-cell lung cancer; Epidermal growth factor receptor; Exon 20; Real-world data; Exotic

Introduction

Although usually described as "rare," insertions in exon 20 of the *EGFR* gene actually represent the third most common *EGFR* mutation type (10% of all *EGFR* mutations), after deletions in exon 19 and the L858R point mutation in exon 21, but bear worse prognosis compared with them.[1] In a recently reported indirect comparison from real-world evidence (RWE), the median overall survival (OS) was 16.2 (95% confidence interval [CI]: 11.04–19.38) months in the *EGFR* exon 20 insertion cohort versus 25.5 (95% CI: 24.48–27.04) months in the cohort with sensitizing mutations (adjusted hazard ratio = 1.75 [1.45–2.13], $p < 0.0001$), with corresponding 5-year survival rates of 8% and 19%, respectively.[2] Similar to "classical" activation mutations, exon 20 insertion (exon20ins) mutations also tend to be more common among women, never or light smokers, and patients with adenocarcinoma histology, and they are characterized by an increased prevalence for bone and brain metastases.[1,3]

The notorious resistance of exon 20-mutated NSCLC to conventional EGFR tyrosine kinase inhibitors (TKIs) is attributed to their particular structural and biochemical properties: More than 90% of the insertion mutations are located in the adjacent loop after the alpha-C helix of the intracellular domain of the receptor, specifically between amino acids 766 and 775, and usually involve insertions or duplications of one to four amino acids.[4] The presence of the exon20ins pushes the alpha-C helix in an "αC-in" conformation, resulting in constitutive activation and signaling.[4] Their unique location outside and far from the alpha-C helix, which harbors the adenosine triphosphatase binding pocket, renders these mutations resistant to conventional TKIs, because they typically act by covalent binding the adenosine triphosphatase binding pocket and competitive inhibition of downstream signaling.[3] In clinical practice, efficacy of chemotherapy (CT) and conventional first-to-third–generation TKIs such as gefitinib, afatinib, and osimertinib is modest, with median objective response rates (ORRs) below 25%, median progression-free survival (PFS) rarely exceeding 6 months, and median OS rarely exceeding 1 year.[5–7] More recently, biotechnology advances have allowed the development of novel agents exploiting new therapeutic strategies, such as TKIs, with high affinity for the loop adjacent to the alpha-C helix (poziotinib, mobocertinib) and the bispecific antibody amivantamab which targets both the extracellular domain of EGFR and the MET proto-oncogene, whose amplification is a well-characterized mechanism of

resistance to conventional EGFR TKIs.[4] These novel agents have been associated with improved clinical outcomes, including ORR of up to 40%, median PFS up to 8 months, and median OS reaching 2 years in heavily pretreated patients.[8–10]

Despite the aforementioned improvements, access to these novel compounds in most European countries outside of the context of clinical trials was possible only through early access programs (EAPs), as amivantamab received a conditional marketing authorization by European Medicines Agency on December 9, 2021,[11] and poziotinib and mobocertinib are not yet authorized in the European Union, as of July 2022. Because of the rarity of *EGFR* exon20ins mutations, randomized trials are difficult, and RWE acquire major importance. There is an immense need for international collaboration to gather an adequate number of patients which would allow firm conclusions to be drawn on this specific population. To address this topic, we created an international registry database for patients with exon 20-mutant NSCLC (all mutation types), treated in routine clinical practice or through EAP, outside of clinical trials. We aimed to record their molecular landscape, management strategies, and treatment patterns using RWE.

Materials and Methods

Patient Description and Main Objectives

EXOTIC was a noninterventional, international multicenter study with retrospective/prospective analysis of patient data. In January 2021, we created a retrospective-prospective European registry for patients with advanced *EGFR* exon 20-mutant NSCLC diagnosed from January 2019 to December 2021 for the retrospective cohort and from January 2022 for the prospective cohort. Treating physicians were able to report cases diagnosed as early as January 1, 2019, retrospectively and at the same time to prospectively enroll newly diagnosed cases until December 31, 2021, to allow adequate follow-up. All types of exon 20 mutations (insertions, duplications, indels, point mutations such as the T790M and C797S, and less frequent ones) were accepted for inclusion. Patients enrolled in clinical trials were excluded per protocol, but those who were included in EAP for new agents were allowed to participate. To be eligible for the study, patients had to have received at least one prior treatment for advanced disease, because all exon 20 targeting agents at the time of study design and initiation were available only as second- and beyond-line treatments. There was no restriction on the number of lines of treatment that each patient had received at the time of study entry. *EGFR* exon 20 mutations may have developed and detected at any time during the disease course, without affecting patient eligibility, provided that the mutation was known at the time of study entry. Each participating center signed a data transfer agreement policy (available as Supplementary Material 1), and the protocol was approved by the institution's institutional review board. Clinicopathologic and molecular epidemiology data were collected, and treatment patterns were recorded.

The study had the following three main objectives/primary end points: (1) to collect clinicopathologic and molecular epidemiology data on exon20in resistance mutations in patients with advanced NSCLC; (2) to study treatment patterns of patients with exon20in mutations across European countries outside the context of clinical trials; and (3) to report on efficacy data of new therapeutic agents (mainly poziotinib, mobocertinib, amivantamab) in daily clinical practice. A protocol synopsis is available at the Supplementary Material 2.

Statistical Considerations

The statistical plan included the following: (1) description of population characteristics; (2) association of clinicopathologic characteristics using Fisher's exact and Mann-Whitney *U* tests; (3) univariate analyses of population characteristics in relation to the type of mutation and type of treatment received using Wald test for differences between groups; and (4) estimation of Kaplan-Meier curves according to the type of mutation and type of treatment.

ORRs and disease control rates were reported according to the Response Evaluation Criteria in Solid Tumors criteria, version 1.1, as estimated by the treating physician. Disease control rate was defined as the sum of patients with complete response, partial response, or stable disease, on the basis of the same criteria. Because many patients had received various lines of treatments and to homogenize the data, PFS was defined as the time from starting of the second-line treatment to clinical or radiological progression of the disease, as evaluated by the Response Evaluation Criteria in Solid Tumors criteria version 1.1 and assessed by the treating physician, or death by any cause. OS was defined as the time from starting the second-line treatment to death regardless of cause. Patients still alive at the last visit were censored at the date of last follow-up. Patients without documented evidence of an event were censored at the date of last follow-up. Clinical end points according to treatment assignment were assessed using Kaplan-Meier curves and Cox regression models. Variables used in the univariate analysis included all the clinicopathologic and molecular features described in the results session (Table 1) assessed for their effect to the main outcomes, ORR, PFS, and OS. Multivariate analysis included variables that have been found to have statistical significance in univariate analysis and well established

Table 1. Main Clinicopathologic Characteristics of the EXOTIC Cohort

Variable	N = 175	%
Age (median, y, range)	64.04 (29.66-87.79)	
Sex (%)		
Male	76	43.7
Female	99	56.3
Performance status at entry		
0	75	42.8
1	79	45.1
2	14	8.0
3	4	2.3
Missing data	3	1.8
Smoking (%)		
Active	42	24.0
Former	81	46.3
Never	52	29.7
Histology		
Adenocarcinoma	167	95.4
Squamous	5	2.9
Large cell	1	0.6
Adenosquamous	2	1.1
Site of metastasis at diagnosis		
Brain	56	32.0
Bone	83	47.4
Contralateral lung	77	44.0
Extrathoracic lymph nodes	51	29.1
Pleural	59	33.7
Adrenal	39	22.2
Liver	30	17.1
Spleen	4	2.2
Pericardial	8	4.6
Peritoneal	5	2.8
PD-L1 expression % (mean, range)	15.8 (0-95)	
TMB mut/MB DNA (mean, range)	7.06 (0-18.8)	

mut/MB, mutation per megabase; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden.

prognostic factors in advanced NSCLC, including age at study entry, performance status at study entry, presence of comorbidities, line of treatment, and presence of central nervous system disease.

Results

Patient Characteristics

Data on 175 patients from 33 centers across eight countries (Greece, Spain, France, Italy, United Kingdom, Germany, Cyprus, and Israel) were included in the final analysis. Basic clinicopathologic characteristics of the study cohort are found in Table 1. Typical for *EGFR*-mutant NSCLC, median age was slightly younger than the average of patients with NSCLC (64.0 y), and there was a higher prevalence among women (56.3%), never or past smokers (76.0%), and those with adenocarcinoma histology (95.4%). As expected, almost half of the patients had skeletal metastasis at diagnosis (47.4%) and almost one-third had brain metastases (32%). Tumors were modestly immunogenic: Mean programmed death-ligand 1 tumor proportional score was 15.8% (range: 0–95, N = 110 patients) and mean tumor mutational burden was 7.06 mutations per megabase (range: 0–18.8, N = 51 patients). Of note, there were five cases of exon20in mutations in patients with squamous histology and two cases in patients with adenosquamous histotype (Table 1). Median follow-up for the patients followed retrospectively-prospectively was 19.1 months (retrospective cohort) and for the patients followed prospectively was 6.7 months, resulting in an overall median follow-up of 14.2 months for the whole study population.

Molecular Epidemiology

Exon 20 mutations were detected in the tissue (90.7%), in the plasma (8.7%), or both (0.6%), using mostly targeted next-generation sequencing (64.0%), or polymerase chain reaction (26.0%), and to a lesser extent whole exome sequencing/RNA sequencing (4%) (Fig. 1*A*). Mutations were mainly insertions (59.1%) followed by duplications (29.1%), deletions-insertions (7.3%), and the T790M point mutation (4.6%) (Fig. 1*B*). Insertions and duplications were located mainly in the near loop (codons 767–771, 83.1%) and the far loop (codons 771–775, 13%) and only in 3.9% within the C helix (codons 761–766) (Fig. 1*C*). Median allele frequency for the exon 20 alteration was 16.18% (range: 0.05%–78.1%). Main co-alterations included mutations in *TP53* (61.8%) and *MET* amplifications (9.4%).

Treatment Patterns and Clinical Outcomes

Treatment on detection of *EGFR* exon 20 mutation included chemotherapy (CT) (33.8%), CT-immunotherapy (IO) (18.2%), osimertinib (22.1%), poziotinib (9.1%), mobocertinib (6.5%), mono-IO (3.9%), and amivantamab (1.3%) (Fig. 2*A*). It should be again clarified that because detection of the mutation was done in different time points for each patient (at diagnosis or at a later stage in the course of the disease), the subsequent data refer to different lines of treatment, depending on the timing of detection of the mutation. With respect to the mode of drug acquisition, most of the therapies administered were already approved for the patients (77%), and for some of them, treatment became available through EAP (10%), off-label use of the drug after permission from local regulatory authorities (7%), or after approval by the private insurance of the patient and subsequent regulatory approval (4%) (Fig. 2*B*). After progression, the most frequently used next-line treatment was CT or CT-IO (56.5%), followed by

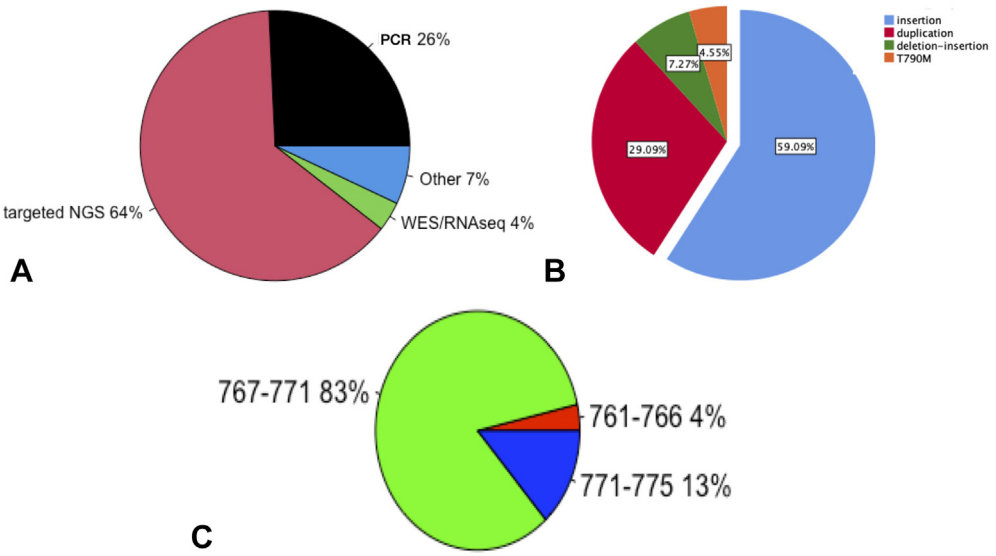

Figure 1. (*A*) Distribution of techniques used for *EGFR* exon 20 molecular analysis. (*B*) Distribution of the main types of *EGFR* exon 20 mutations. (*C*) Distribution of *EGFR* exon 20 mutations according to the location. NGS, next-generation sequencing; PCR, polymerase chain reaction; RNAseq, RNA sequencing; WES, whole exome sequencing.

mobocertinib (10.1%), mono-IO (7.2%), osimertinib (4.4%), or amivantamab plus lazertinib (2.9%).

ORRs according to the investigators were 39.3% with CT, 45.5% with chemo-IO, 16.7% with IO alone, 21.3% with osimertinib, 33.3% with poziotinib, and 50.0% with mobocertinib. Disease control rates, defined as the sum of complete/partial responses and stable disease at first re-evaluation, were 66.2% with CT with or without IO, 55.8% with osimertinib, 64.8% with poziotinib, and 76.9% with mobocertinib. Median PFS for the whole study cohort was 5.5 months (95% CI: 2.4–13.7 mo) among 144 patients with available data. Median OS for the whole study cohort was 19.7 months (95% CI: 15.2–26.3 mo) among 151 patients with assessable survival data. Survival did not differ according to sex, smoking history, and history of prior CT. Notably, median OS was not affected by the type of the exon 20 mutation (N = 132, Wald test for difference between groups on three *df* equals to 3.12, $p = 0.4$) (Fig. 3*A*).

With respect to the type of treatment received, median PFS among the 144 patients with available data was 7.8 months for CT with or without IO, 8.1 months for poziotinib, 3.9 months for osimertinib, and 11.8 months for mobocertinib. Similarly, median survival was 19.7 months for CT with or without IO, 15.9 months for poziotinib, 9.2 months for osimertinib, and 22.4 months for mobocertinib (Fig. 3*B*). The corresponding values for other treatment modalities were not assessable due to the small number of patients in each group and were categorized as "other" (Fig. 3*B*). In multivariate analysis, taking into consideration variables such as performance status, sex, year of diagnosis, line of treatment, and presence of central nervous system disease, type of treatment significantly affected OS, with a Wald test for

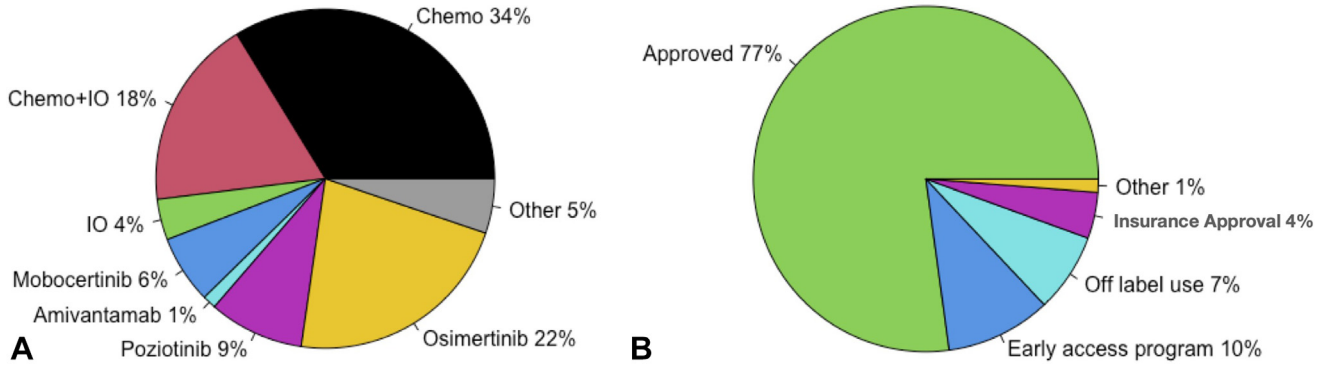

Figure 2. (*A*) Distribution of treatment modalities in the patient cohort. (*B*) Distribution of the main processes for drug acquisition. Chemo, chemotherapy, IO, immunotherapy.

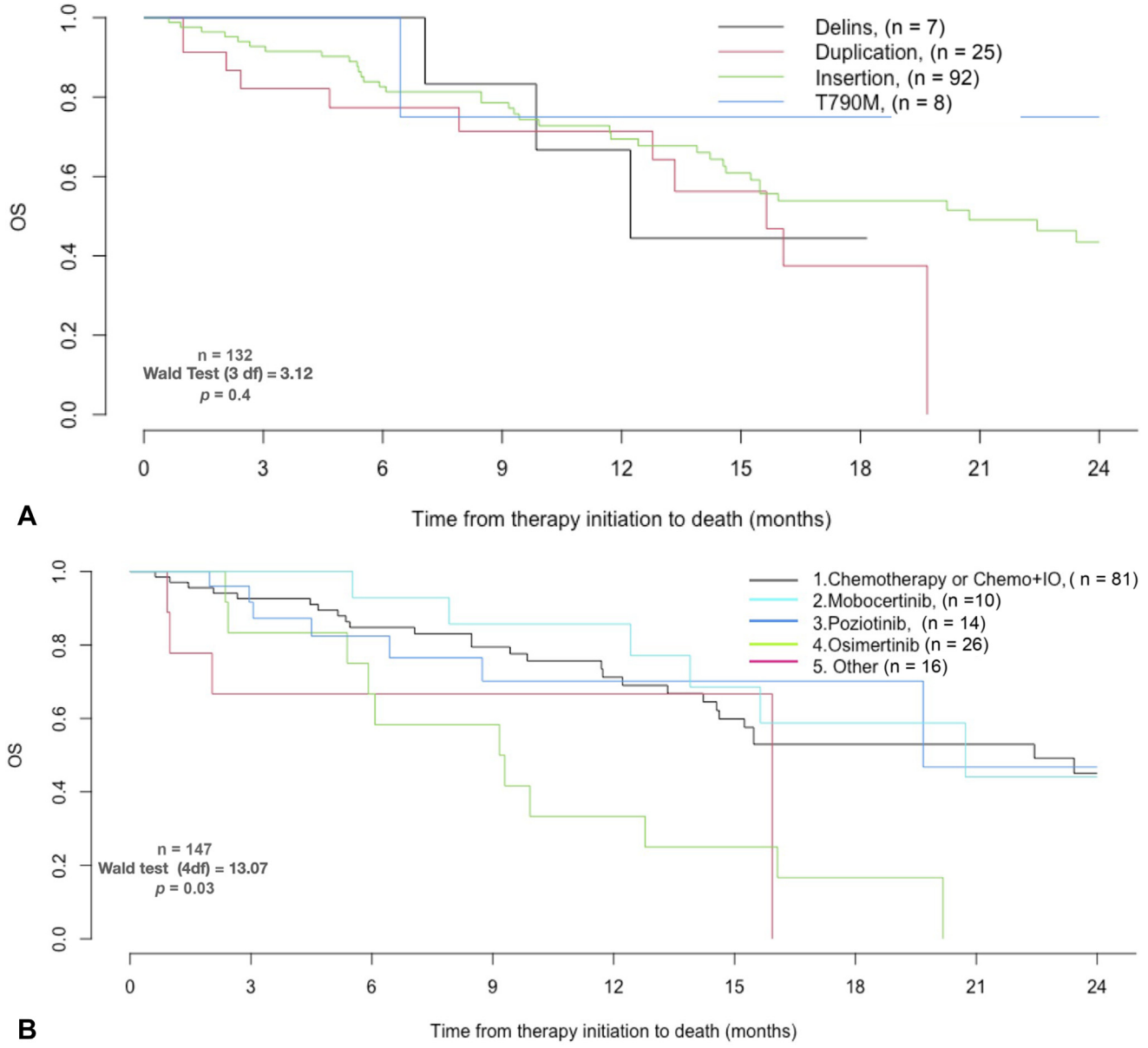

Figure 3. (*A*) Kaplan-Meier curves for median survival (starting from the beginning of second-line treatment) according to the type of *EGFR* exon 20 mutation. (*B*) Kaplan-Meier curves for overall survival (starting from the beginning of second-line treatment) according to the treatment modality received as second-line treatment (other includes the following: gefitinib N = 2, erlotinib N = 1, afatinib N = 4, immunotherapy N = 7, and amivantamab = 2).

difference between groups of 13.07 on four *df* ($p = 0.03$). Of note, treatment with CT with or without IO was associated with an increased risk of death, as compared with treatment with newer agents (mobocertinib, poziotinib, amivantamab) (hazard ratio = 3.0223, 95% CI: 1.49–6.12, $p = 0.006$).

Discussion

To the best of our knowledge, EXOTIC represents the largest academic effort to report RWE regarding molecular epidemiology and treatment patterns in patients with advanced, exon 20-mutated NSCLC reported to date. This pragmatic registry is representative of daily clinical practice in Europe, because it involved only patients treated outside the context of clinical trials. Given that all the novel exon 20-targeting agents were not authorized in Europe at the time of the study accrual (January 2019–December 2021), this database clearly illustrates the strategy used by treating physicians in Europe during the last three years. In the EXOTIC cohort, CT, alone or combined with IO, accounted for

more than half of the cases in first-line treatment, indicating oncologists tend to manage patients with exon20in NSCLC as their EGFR wild-type counterparts. Of note, the third-generation EGFR TKI osimertinib, found to have activity against the T790M point mutation, was also used extensively (22.1% of the cases) in an effort to tackle EGFR dependence. Nevertheless, osimertinib has been associated with modest outcomes in early clinical trials.[12–14] More diverse regimens were used after progression on first-line treatment, including chemo-IO combinations, mono-IO, and various combinations of TKIs. Notably, IO alone is associated with poor clinical outcomes in patients with exon 20-mutant advanced NSCLC.[15]

Exciting new molecules with pivotal mechanisms of action, including the TKIs poziotinib[16,17] and mobocertinib[10] and the bispecific antibody amivantamab[18] have recently entered the clinical arena of exon20in advanced NSCLC with encouraging early clinical data. In a recent phase 2 trial,[9] poziotinib was associated with an ORR of 32% and a median PFS of 5.5 months. These data add to existing evidence on poziotinib efficacy[19] and were further enhanced by data from the expanded access program of the drug.[20] Mobocertinib is also associated with favorable clinical outcomes, with objective responses of up to 30%, median PFS of 7.3 months in both chemo-naive (EXCLAIM cohort) and platinum-pretreated patients, and an impressive duration of response of 17.5 months for platinum-pretreated patients, whereas it was not reached in chemo-naive patients.[10] Finally, in the phase 1B to 2 CHRYSALIS trial,[8] amivantamab produced responses in 40% of the patients, with a median PFS of 8.3 months, median duration of response of 11.1 months, and a median OS of 22.8 months. In our cohort, these novel agents were available only through EAP, although a substantial number of patients also acquired them as off-label use, after case-by-case approval by regulatory authorities. Despite these limitations, a considerable proportion of patients (16% in our cohort) gained access to these pivotal agents through these procedures, underlying the importance of expanded access programs in routine clinical practice, especially when relevant clinical trials are not available. The clinical outcomes of patients in our registry are comparable with those of the aforementioned clinical trials, although our analysis was limited by the small number of patients who had access to novel agents, including amivantamab.

Importantly, the exact location of the exon 20 mutation matters: as found in both CHRYSALIS[8] and a recent trial of poziotinib,[9] mutations located in the near loop immediately after the alpha-C helix (codons 767–771) are associated with higher response rates compared with those located at the far loop (codons 771–775). In the latter study,[9] corresponding ORRs were 46% and 0% in the near loop versus the far loop, respectively ($p = 0.0015$). In EXOTIC, 83% of the mutations were located in the near loop and 4% within the helix, suggesting that in almost 90% of the cases, novel agents are expected to have high activity.

Although EXOTIC was not designed to compare treatment modalities, indirect comparison from subgroup difference analysis suggests that, collectively, use of newer agents in the first line is associated with a survival benefit compared with CT or CT-IO. This is in line with recent data suggesting amivantamab, indirectly compared with real-world therapies, is anticipated to confer an additional 10-month OS.[21] Another recent matching-adjusted indirect comparison between mobocertinib and amivantamab using mathematical projection analysis estimated that both agents are expected to have similar outcomes in terms of PFS and OS.[22] Confirmatory trials, such as the EXCLAIM-2 trial (NCT04129502) comparing directly mobocertinib with platinum-based CT as first-line treatment and trials combining CT with newer agents, including the PAPILLON trial comparing CT plus amivantamab with CT alone (NCT04538664), are currently ongoing.

Similar to all RWE studies, our registry harbors some inherent limitations: Data were collected in a retrospective/prospective manner and selection of cases was arbitrary, completely depending on the treating physician. Representation of treatment modalities was subjective and not balanced, largely dependent on the availability of EAP in each one of the participating countries. The latter, together with the exclusion of patients treated within clinical trials, resulted in underrepresentation of some novel agents, such as amivantamab (1.1% in EXOTIC). These numbers, however, reflect the actual pragmatic situation in each country on the basis of the availability of EAP during the last three years. Amivantamab was authorized by the European Medicines Agency in December 2021 and is now expected to be widely available in most European countries. Finally, similar to all RWE studies, analysis of clinical outcomes is restricted by missing data for some patients, and thus results in terms of disease control rate and OS should be interpreted with caution, until definitive results from ongoing prospective clinical trials become available.

In conclusion, EXOTIC is an important multinational RWE study in reflecting clinical practice patterns of treating physicians in patients with rare *EGFR* mutations in the precision oncology era. Our data suggest that in patients with *EGFR* exon 20-mutated NSCLC, first-line CT with or without IO will be gradually replaced by the use of novel, exon 20-targeting agents that are expected to herald a new standard in the management of this challenging disease entity. EXOTIC also underlines the value

of EAP that allow patients to benefit from novel agents before their approvals from regulatory authorities, especially in those countries where clinical trials are not available.

CRediT Authorship Contribution Statement

Giannis Mountzios: Conception and design, Statistical analysis, Data curation, Manuscript writing, Final approval of the manuscript.

David Planchard, Giulio Metro, Martin Reck, Giuseppe Lo Russo: Conception and design, Data curation, Final approval of the manuscript.

Dora Tsiouda, Arsela Prelaj, Sofia Lampaki, Walid Shalata, Mariona Riudavets, Petros Christopoulos, Nicolas Girard, Víctor Albarrán-Artahona, Rosario Garcia Campelo, Konstantinos Samitas, Giuseppe Luigi Banna, Ioannis Boukovinas, Abed Agbarya, Anna Koumarianou, Eleni-Isidora Perdikouri, Paris Kosmidis, Helena Linardou, David Mauri, Dimitrios Mavroudis, Ilias Athanasiadis, Haralambos Kalofonos, Nikolaos Xenidis, Ippokratis Korantzis, Alexandros Ardavanis, Grigorios Rallis, Achille Bottiglieri, Konstantinos Efthymiadis, Georgios Oikonomopoulos, Alexandros Kokkalis, Emmanouil Saloustros, Nikolaos Tsoukalas, Dimitra Bartzi, Panagiota Economopoulou, Amanda Psyrri: Data curation, Final approval of the manuscript.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at 10.1016/j.jtocrr.2022.100433.

References

1. Remon J, Hendriks LEL, Cardona AF, Besse B. EGFR exon 20 insertions in advanced non-small cell lung cancer: a new history begins. *Cancer Treat Rev*. 2020;90:102105.
2. Bazhenova L, Minchom A, Viteri S, et al. Comparative clinical outcomes for patients with advanced NSCLC harboring EGFR exon 20 insertion mutations and common EGFR mutations. *Lung Cancer*. 2021;162:154–161.
3. Meador CB, Sequist LV, Piotrowska Z. Targeting EGFR exon 20 insertions in non-small cell lung cancer: recent advances and clinical updates. *Cancer Discov*. 2021;11:2145–2157.
4. Friedlaender A, Subbiah V, Russo A, et al. EGFR and HER2 exon 20 insertions in solid tumours: from biology to treatment. *Nat Rev Clin Oncol*. 2022;19:51–69.
5. Wu JY, Yu CJ, Shih JY. Effectiveness of treatments for advanced non-small-cell lung cancer with exon 20 insertion epidermal growth factor receptor mutations. *Clin Lung Cancer*. 2019;20:e620–e630.
6. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015;16:830–838.
7. Piotrowska Z, Fintelmann FJ, Sequist LV, Jahagirdar B. Response to osimertinib in an EGFR exon 20 insertion-positive lung adenocarcinoma. *J Thorac Oncol*. 2018;13:e204–e206.
8. Park K, Haura EB, Leighl NB, et al. Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS phase I study. *J Clin Oncol*. 2021;39:3391–3402.
9. Elamin YY, Robichaux JP, Carter BW, et al. Poziotinib for EGFR exon 20-mutant NSCLC: clinical efficacy, resistance mechanisms, and impact of insertion location on drug sensitivity. *Cancer Cell*. 2022;40:754–767.e6.
10. Zhou C, Ramalingam SS, Kim TM, et al. Treatment outcomes and safety of mobocertinib in platinum-pretreated patients with EGFR exon 20 insertion-positive metastatic non-small cell lung cancer: a phase 1/2 open-label nonrandomized clinical trial. *JAMA Oncol*. 2021;7:e214761.
11. European Medicines Agency. Rybrevant (amivantamab). https://www.ema.europa.eu/en/documents/overview/rybrevant-epar-medicine-overview_en.pdf. Accessed August 1, 2022.
12. van Veggel B, Madeira R, Santos JFV, et al. Osimertinib treatment for patients with EGFR exon 20 mutation positive non-small cell lung cancer. *Lung Cancer*. 2020;141:9–13.
13. Yang GJ, Li J, Xu HX, et al. Osimertinib for Chinese advanced non-small cell lung cancer patients harboring diverse EGFR exon 20 insertion mutations. *Lung Cancer*. 2021;152:39–48.
14. Piotrowska Z, Wang Y, Sequist LV, Ramalingam SS. ECOG-ACRIN 5162: a phase II study of osimertinib 160 mg in NSCLC with EGFR exon 20 insertions. *J Clin Oncol*. 2020;38(suppl 15):9513–9513.
15. Metro G, Baglivo S, Bellezza G, et al. Sensitivity to immune checkpoint blockade in advanced non-small cell lung cancer patients with EGFR exon 20 insertion mutations. *Genes*. 2021;12:679.
16. Le X, Goldman J, Clarke J, et al. Poziotinib shows activity and durability of responses in subgroups of previously treated EGFR exon 20 NSCLC patients. *J Clin Oncol*. 2020;38(suppl 15):9514–9514.
17. Sacher A, Le X, Cornelissen R, et al. Safety, tolerability and preliminary efficacy of poziotinib with twice daily strategy in EGFR/HER2 Exon 20 mutant non-small cell lung cancer. *Ann Oncol*. 2021;32(suppl 1):S14–S19.
18. Yun J, Lee SH, Kim SY, et al. Antitumor activity of amivantamab (JNJ-61186372), an EGFR–MET bispecific antibody, in diverse models of EGFR exon 20 insertion-driven NSCLC. *Cancer Discov*. 2020;10:1194–1209.
19. Elamin YY, Robichaux JP, Carter BW, et al. Poziotinib for patients with HER2 exon 20 mutant non-small-cell lung cancer: results from a phase II trial. *J Clin Oncol*. 2022;40:702–709.

20. Prelaj A, Bottiglieri A, Proto C, et al. Poziotinib for EGFR and HER2 exon 20 insertion mutation in advanced NSCLC: results from the expanded access program. *Eur J Cancer*. 2021;202:235–248.
21. Minchom A, Viteri S, Bazhenova L, et al. Amivantamab compared with real-world therapies in patients with advanced non-small cell lung cancer harboring EGFR exon 20 insertion mutations who progressed after platinum-based chemotherapy. *Lung Cancer*. 2022;168:74–82.
22. Ou S-HI, Prawitz T, Lin HuamaoM, et al. Matching-adjusted indirect comparison (MAIC) of mobocertinib versus amivantamab in patients with non–small cell lung cancer (NSCLC) with EGFR exon 20 insertions (ex20ins). *J Clin Oncol*. 2022;40(suppl 16):9115–9115.