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Real-world evidence of first-line osimertinib effectiveness in Bulgarian patients: a retrospective analysis

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ABSTRACT

Background: Third-generation EGFR tyrosine kinase inhibitor (EGFR-TKI) osimertinib is approved as a first-line treatment against non-small-cell lung cancer (NSCLC) harboring sensitizing EGFR mutations. Herein, we perform a retrospective analysis of real-world data on first-line osimertinib treatment among Bulgarian patients with NSCLC, comparing treatment outcomes to FLAURA results.

Research design and methods: Patient data were obtained from electronic health records over a 4-year period. Baseline characteristics and endpoints (progression-free survival [PFS], objective response rate [ORR], and clinical benefit rate [CBR]) were compared. Iterative proportional fitting was performed to balance patient characteristics prior to survival analysis.

Results: A total of 365 patients on first-line osimertinib were included. Partial responses were more frequent in the RWE cohort (24% vs 13%), while the opposite was noted for stable disease (63% vs 80%). Complete response frequency was comparable (2% vs 1%). The ORR was higher in the real world compared to in FLAURA (26% vs 14%), whereas CBR was slightly higher in the trial (89% vs 94%). The real-world PFS was higher than reported in FLAURA (19.1 vs 18.9 months), with more favorable outcomes in the RWE cohort beyond 18 months.

Conclusion: RWE closely aligns with FLAURA results, suggesting even greater benefit of first-line osimertinib in the real-world setting.

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Real-world evidence; osimertinib; FLAURA; EGFR-TKI; tyrosine kinase inhibitor

1. Introduction

Lung cancer remains the most common cancer type and the major cause of cancer-related death in both males and women on a global scale [1]. Predictions point to substantial (>50%) increases in lung cancer incidence and mortality from 2020 to 2040 [2]. Approximately 85% of lung cancer cases are of the non-small-cell lung cancer (NSCLC) subtype. From a histological perspective, NSCLC is subclassified into adenocarcinoma (50%), squamous cell carcinoma (20–30%), and large cell carcinoma depending on its tissue of origin. Histological subtypes correlate with smoking history, and the two are associated with the presence of druggable genomic alterations, which are more frequent among adenocarcinomas and usually arise in never-smokers or light smokers [3–5]. NSCLC harbors a plethora of oncogenic alterations, of which activation mutations in driver kinases, including EGFR, HER2, and MET, hold the greatest relevance for NSCLC therapy [6]. The emergence of such activating mutations leads to oncogene addiction, which has fostered the development of small-molecule tyrosine kinase inhibitors (TKIs) targeting these aberrantly active kinases [7]. Patients whose tumors harbor EGFR-TKI-sensitizing mutations, most commonly a deletion in exon 19 and a point mutation (L858R) in exon 21 of the gene, benefit from treatment with first-generation (gefitinib, erlotinib, icotinib) and second-generation (afatinib, dacomitinib) TKIs [8–11]. Despite this initial benefit, patients on EGFR-TKIs develop resistance, with the EGFR T790M resistance mutation detected in over 50% of cases with disease progression [12–14]. Osimertinib, a third-generation EGFR-TKI, effectively targets tumors that harbor EGFR-sensitizing mutations and the T790M resistance variant. Based on clinical data from the AURA trial, it was initially approved for the treatment of metastatic NSCLC harboring T790M in patients who experience disease progression on EGFR-TKI therapy [15]. Subsequently, the FLAURA trial provided conclusive evidence for the superior safety and efficacy of osimertinib against treatment-naïve EGFR-mutated advanced NSCLC, when compared to gefitinib and erlotinib [16]. It is essential that clinical trial data are corroborated by the outcomes reported for the ever-growing patient population receiving osimertinib on a global scale. At present, there is a growing body of real-world evidence (RWE) on osimertinib use, which provides valuable insights on its safety and efficacy [17–21]. Herein, we retrospectively analyzed real-world data on first-line osimertinib

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efficacy in the Bulgarian patient population over a 4-year period and then compared treatment outcomes with the results of FLAURA in order to evaluate the translation of trial results into real clinical practice [16].

2. Methods

2.1. Patient data

The real-world data from patients treated with osimertinib and included in this analysis were retrospectively collected from the electronic health records of hospitals in Bulgaria. The data included patients with reimbursed therapy prescriptions and donated therapies. Information for the latter was extracted manually from free text or was imported from files provided by hospital doctors. Data were retrieved for a five-year period between 1 January 2019 and 31 December 2023. Following a manual check for consistency, errors, and missing values, data were analyzed using the Danny Analytics software tool (Sqiline, Sofia, Bulgaria), which allows for integrated analyses of health data to assess the influence of specific factors on patient outcome or the efficacy of a given regimen. This study was based on secondary usage of anonymized data using a hospital-integrated software. Ethics committee approval or patient informed consent were not required for this type of research as per local Bulgarian regulations.

2.2. Endpoints

The endpoints used for treatment outcomes included progression-free survival (PFS) rate, the objective response rate (ORR), and clinical benefit rate (CBR). The PFS rate was defined as the proportion of patients with the disease, who did not experience disease progression for a certain period. The ORR was defined as the proportion of patients with a complete or partial response to osimertinib for a certain period. CBR was defined as the proportion of patients with a complete response, partial response, or stable disease for a certain period after treatment with osimertinib. The 95% confidence intervals for ORR and CBR were calculated via the Wilson score method for binomial variables.

2.3. Survival analysis

Kaplan–Meier survival analysis was performed to assess PFS, with the confidence interval calculated via Greenwood's method. To account for differences in baseline characteristics between RWE and clinical trial patient data, which can bias the comparison and subsequent interpretation, iterative proportional fitting (IPF) was employed to balance selected characteristics prior to the survival analyses. IPF derives weights for a given characteristic in order to adjust the underlying distributions toward a target distribution. That is, if a trial cohort included 50% men and 50% women, while real-world data included 60% and 40%, respectively, IPF would derive weights so that the weighted sum in real-world data would also be 50:50. The characteristics considered collectively are:

- ECOG
- Age
- Gender
- Presence of stable asymptomatic CNS metastases

The ORR and CBR were calculated as defined in Endpoints. The 95% confidence interval was calculated using the Wilson score method for binomial variables.

2.4. Statistical methods of analysis

2.4.1. General principles

This study is descriptive in nature. No formal hypotheses are tested in this observational study. For categorical variables, absolute counts are reported in tables. The counts are accompanied by percentages. The total number of patients in each distribution is indicated at the top of each table. For continuous variables for RWE, the values are summarized in tables with the following statistics: mean, standard deviation, median, first and third quartiles, minimum and maximum values, and the number of patients on which the statistics were calculated. The same information was provided for RCT when published data was available.

For treatment outcome, the survival functions of PFS are estimated using Kaplan–Meier estimator. The confidence interval is calculated using Greenwood's method. Data is displayed in tables showing the number of patients at risk, the percentage who have experienced progression, and the 95% confidence interval at each cutoff point. The results are also illustrated using a Kaplan–Meier curve.

3. Results

3.1. Patient population

Across the participating Bulgarian hospitals, a total of 10,275 patients were diagnosed with NSCLC in the five-year period between 1 January 2019 and 31 December 2023. Of these, 6221 (60.6%) received the first line of treatment, while 4522 (44.3%) were tested for EGFR mutations, with an increasing number of patients tested each year (e.g. 654 in 2019 versus 1,296 in 2023). Furthermore, the proportion of patients tested among the diagnosed increased from 33.0% in 2019 to 57.5% in

Table 1. EGFR testing in patients diagnosed with NSCLC receiving their first line of treatment. Percentages relative to the total number of patients diagnosed in a given year are shown.

Year	Patients diagnosed (n)	First line of treatment (n, [%])	First line of treatment, EGFR-tested (n, [%])	First line of treatment, EGFR-positive (n, [%])
2019	1,981	1,211 (61.1%)	654 (33.0%)	120 (6.5%)
2020	1,921	1,213 (63.1%)	706 (36.8%)	117 (6.1%)
2021	2,015	1,228 (60.9%)	838 (41.5%)	110 (5.5%)
2022	2,106	1,400 (66.5%)	1,028 (48.8%)	125 (5.9%)
2023	2,252	1,569 (69.7%)	1,296 (57.5%)	147 (6.5%)

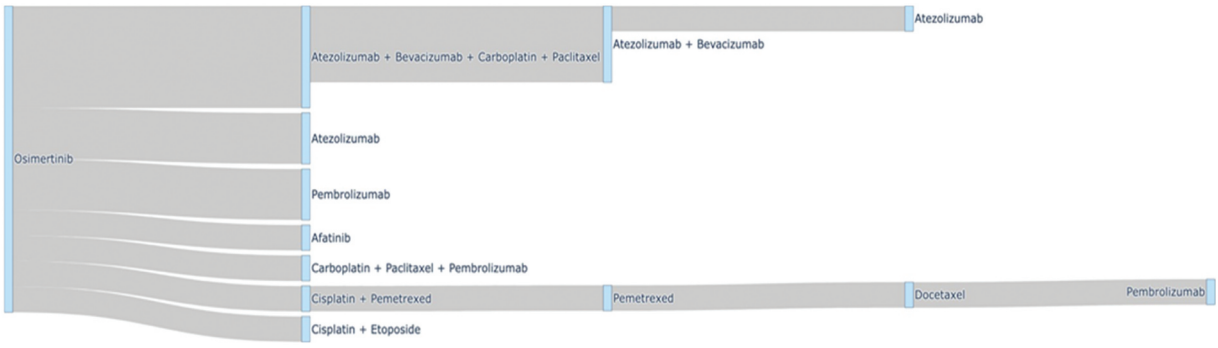

Figure 1. Therapies after progression in patients who received first-line osimertinib.

2023 (Table 1). Of those tested, 619 (13.7%) harbored EGFR mutations. An upward trend in newly diagnosed patients with EGFR mutations was also noted, with 147 in 2023 versus 110 in 2021, accounting for 6.5% and 5.5% of the total patients diagnosed in the respective year. All patients included in the study are selected to be tested and with confirmed EGFR mutation to ensure that they match those from the clinical trial.

Sixty-four percent were female, and the mean (SD) age at the start of treatment was 66.9 (10.1) years. ECOG status was 0, 1, 2, 3, 4 for 130 (26%), 328 (65%), 33 (7%), 11 (2%), and two (0.4%) patients from our real-world population. One-fifth of the patients (n = 101, 20%) had CNS metastases.

3.2. Treatment

Of the 504 patients treated with osimertinib, 365 (72.4%) received it as first-line treatment, while 139 (27.6%) received it as part of a latter line of treatment. Among the 365 patients with first-line osimertinib, 55 (15.1%) had received radiotherapy prior to osimertinib initiation. Further, 33 (9.0%) patients exhibited disease progression on first-line osimertinib, with 13 (3.6%) starting second-line treatment. Among the latter, more than half (n = 7, 53.8%) received atezolizumab, either as monotherapy (n = 2, 15.4%) or in combination with bevacizumab +carboplatin+paclitaxel (n = 5, 38.5%). Other second-line treatments included pembrolizumab (n = 2, 15.4%), afatinib (n = 1, 7.7%), cisplatin+etoposide (n = 1, 7.7%), cisplatin+pemetrexed (n = 1, 7.7%), and carboplatin+paclitaxel+pembrolizumab (n = 1, 7.7%) (Figure 1, Table 2).

The categories of therapy received after first-line osimertinib are summarized in Figure 2, with the chemotherapy +immunotherapy+targeted therapy regimen being most common.

Among the 139 patients receiving osimertinib in other treatment lines, 14 (10.1%) took osimertinib as adjuvant therapy. Further, 122 (87.8%) patients had received as previous therapy line 33 different regimens, summarized in Table 3. For one of these patients, the specific drugs administered were not specified. Most common among these previous regimens were afatinib (n = 38, 31.1%) and gefitinib (n = 34, 27.9%), followed by carboplatin+paclitaxel (n = 21, 17.2%) and erlotinib (n = 15, 12.3%). Forty-six (33.1%) of these 139 patients also received subsequent treatment regimens after osimertinib. Most common was the atezolizumab+bevacizumab +carboplatin+paclitaxel combination (n = 12, 26.1%), followed by docetaxel (n = 10, 21.7%), pemetrexed (n = 8, 17.4%), and nivolumab (n = 8, 17.4%). Atezolizumab+bevacizumab+carboplatin+paclitaxel (n = 11, 23.9%) and carboplatin+paclitaxel (n = 5, 23.9%) were also most common among the regimens taken directly after the osimertinib-containing regimen.

3.3. Baseline comparison between RWE and FLAURA trial data

The RWE for 365 patients who had received osimertinib allows for statistically meaningful comparisons to randomized clinical trial data from the FLAURA trial. The FLAURA trial evaluated the PFS of patients with previously untreated EGFR-mutant

Table 2. Second-line therapeutic regimens among patients progressing on first-line osimertinib.

Regimen	Patients (n)	Percentage (%)
Atezolizumab+bevacizumab+carboplatin +paclitaxel	5	38.5
Atezolizumab	2	15.4
Pembrolizumab	2	15.4
Afatinib	1	7.7
Carboplatin+paclitaxel+pembrolizumab	1	7.7
Cisplatin+etoposide	1	7.7
Cisplatin+pemetrexed	1	7.7
Total	13	100.0

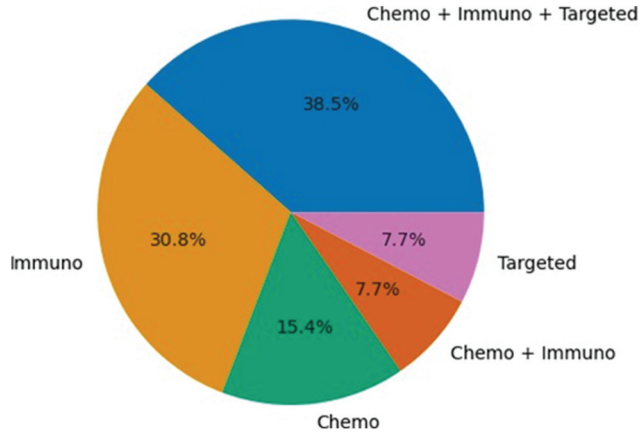

Figure 2. Categories of therapy received in the second line after first-line osimertinib.

Table 3. Previous therapeutic regimens among patients who received osimertinib after the first line of treatment.

Regimen	Patients (n)	Percentage (%)
Afatinib	38	31.1
Gefitinib	34	27.9
Carboplatin+paclitaxel	21	17.2
Erlotinib	15	12.3
Cisplatin+pemetrexed	6	4.9
Pemetrexed	5	4.1
Docetaxel	5	4.1
Pembrolizumab	4	3.3
Bevacizumab+erlotinib	4	3.3
Cisplatin+gemcitabine	4	3.3
Carboplatin+pemetrexed	3	2.5
Vinorelbine	3	2.5
Atezolizumab	3	2.5
Cisplatin+vinorelbine	2	1.6
Cisplatin+paclitaxel	2	1.6
Atezolizumab+bevacizumab+carboplatin +paclitaxel	2	1.6
Carboplatin+pembrolizumab+pemetrexed	2	1.6
Cisplatin+epirubicin (pharmorubicin) + ifosfamide	1	0.8
Bevacizumab+carboplatin+paclitaxel	1	0.8
Atezolizumab+carboplatin+paclitaxel	1	0.8
Bevacizumab	1	0.8
Nintedanib	1	0.8
Gemcitabine	1	0.8
Bevacizumab+carboplatin+gemcitabine	1	0.8
Erlotinib+bevacizumab	1	0.8
Docetaxel+nintedanib	1	0.8
Carboplatin	1	0.8
Crizotinib	1	0.8
Carboplatin+bevacizumab+paclitaxel	1	0.8
Cisplatin+vinblastine+vinorelbine	1	0.8
Carboplatin+gemcitabine	1	0.8
Cisplatin+pembrolizumab+pemetrexed	1	0.8
Carboplatin+paclitaxel+pembrolizumab	1	0.8
Chemotherapy	1	0.8

advanced NSCLC [16]. Closely matched gender groups were noted in the RWE and FLAURA cohorts, with female patients accounting for approximately 63% in both (Table 4). A similar age distribution was also noted, with medians of 65 and 64 in the RWE and FLAURA cohorts. The ECOG status of patients from the FLAURA trial was between 0 and 1. The majority of the patients from the RWE cohort had an ECOG status of 0 or 1. In addition, 14 and four patients had an ECOG status of 2 and 3, respectively, reflecting a worse overall performance status among the real-world cohort. A difference was observed in stable asymptomatic CNS metastases, which were present in 53 (19%) of the FLAURA patients and 59 (16.2%) patients from the RWE cohort.

Table 4. Baseline characteristics in the real-world and FLAURA cohorts.

Characteristic	RWE cohort (n = 365)	FLAURA (n = 279)
Sex (n, %)		
Female	229 (63%)	176 (63%)
Male	136 (37%)	103 (37%)
ECOG performance status (n, %)		
0	93 (25%)	112 (40%)
1	254 (70%)	167 (60%)
2	14 (4%)	–
3	4 (1%)	–
Age (at start)		
Median	65	64
Mean (SD)	64.2 (14.1)	–
Q1 – Q3	53–76	–
Min – Max	37–88	26–93
CNS metastases (n, %)	59 (16%)	53 (19%)

3.4. Survival analysis in the RWE and FLAURA

To compare survival between real-world and clinical trial data, we performed IPF for ECOG, age, gender, and CNS metastases. Tumor responses on osimertinib were not assessed in 62 (17%) of the 365 patients from the RWE cohort. A higher portion of patients experiencing progression was noted in the real world compared to FLAURA (11% versus 6%, respectively). The proportion of patients with a partial response was also greater in the RWE cohort (24% versus 13%), while the opposite trend was noted for patients with stable disease (63% versus 80%). The proportion of complete responses was comparable between the RWE (2%) and FLAURA (1%) groups. With regard to the overall benefit (complete and partial responses combined), a higher ORR was observed among the real-world cohort (26% versus 14%). In terms of combined partial, complete, and stable responses, a higher CBR was noted in the FLAURA cohort (94%) when compared to RWE (89%) (Table 5). A notable difference was observed for PFS at 24 months, at which point only four patients from the trial had not yet progressed compared to 56 patients in the RWE cohort. Following IPF, patients from the real-world cohort had a higher PFS compared to FLAURA patients, at 19.1 (95% CI 15.8–24.9) versus 18.9 months (95% CI 15.2–21.4), respectively (Figure 3). PFS was slightly lower in the RWE at 6 months (82% versus 88%), with comparable values at 12 (both 69%) and 18 months (52%). A higher PFS was noted in the RWE cohort at 24 months (48% versus 37%). Patients at risk of progression remained only in the RWE cohort, accounting for 38% and 18%, respectively, at 32 and 48 months.

4. Discussion

Despite advances in treatment approaches over the past two decades, NSCLC imposes a considerable disease and economic burden on patients and healthcare systems. Osimertinib has emerged as an effective targeted therapy both in the first line as well as following disease progression on first- and second-generation EGFR-TKIs [15,16]. Further optimization of osimertinib-based regimens requires the acquisition and careful analysis of RWE, corroborating and expanding on the results of seminal clinical trials. Herein, we analyzed real-world data from over 10,000 patients with lung cancer. We selected the data of patients that closely matched the profiles of those enrolled in the FLAURA study in order to compare RWE outcomes. To achieve a faithful comparative analysis between real-world

Table 5. Tumor responses in the real-world cohort versus the FLAURA cohort.

Tumor response	% of RWE cohort with response (n = 303)	% of FLAURA cohort (n = 279)
Complete response	2	1
Partial response	24	13
Stable disease	63	80
Progression	11	6
ORR	26 (22–32)	14 (10–19)
CBR	89 (85–92)	94 (90–96)

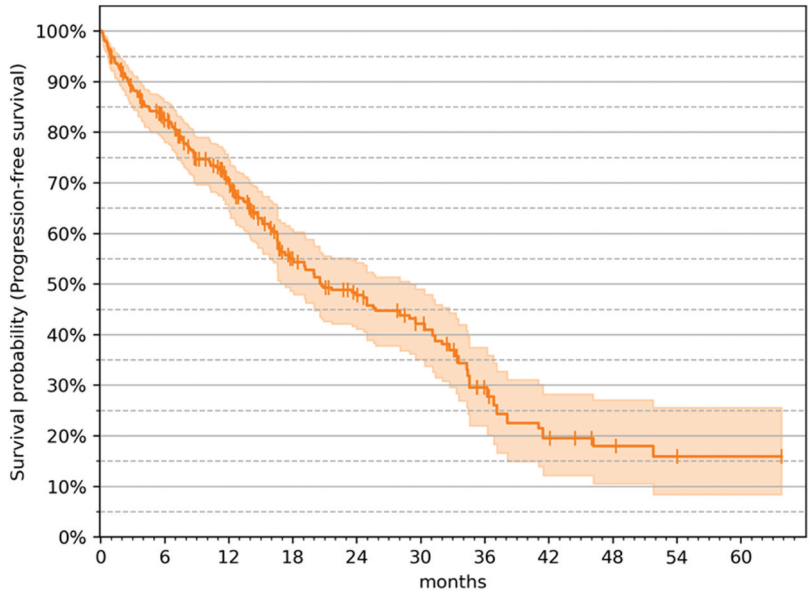

Figure 3. Progression-free survival of the Bulgarian patients on first-line osimertinib in real clinical practice.

and clinical trial data, we employed the in-house software tool Danny Analytics

RWE was obtained for the period between 1 January 2019 and 31 December 2023. IPF was performed on a set of characteristics (ECOG, age, gender, and CNS metastases) to exclude potential biases in our comparison.

Overall, the baseline characteristics of the trial and RWE cohorts were comparable, with a worse ECOG performance status noted in patients from the latter group. Comparison of treatment outcomes revealed higher rates of partial and complete responses to osimertinib in the real-world setting, in addition to a higher median PFS. Altogether, RWE aligned with results from the FLAURA trial, even exceeding trial results after the 18-month mark. These observations suggest patients in the real-world setting may experience greater clinical benefit from first-line osimertinib than initially predicted. A previous retrospective analysis of real-world patients receiving first-line osimertinib highlighted the need for designing more inclusive registration trials that would include patient and disease characteristics that are more representative of those in real clinical practice [21]. Beyond FLAURA (mPFS = 18.9 months), the disease control in our cohort was generally comparable to that previously reported in the real-world setting (19.1 months versus 16.2–22.0 months) [22–24]. Similar to our RWE, other retrospective studies also included patients with an ECOG performance status ≥2 [24]. A strength of the current work is the insight provided regarding treatment choices following first-line osimertinib, with atezolizumab being most common, either as monotherapy or in combination with chemotherapy. As continuing first-line osimertinib upon progression has been proposed to confer ongoing clinical benefit in certain patients, comparing outcomes based on post-progression osimertinib use should be considered in future studies [24].

The rate of second-line therapy initiation reported herein (3.6%) was considerably lower relative to that in other first-line osimertinib-treated cohorts (13% and 31%) [24,25]. This we attribute to the low percentage of patients experiencing disease progression on osimertinib during the study period (9.0%). It should be noted that first-line treatment choice is an important determinant of outcome in the sense that a regimen that ensures disease control and optimized patient performance can facilitate second-line systemic therapy, which is usually platinum-based, and thus requires a favorable functional status. In fact, the ability to continue osimertinib following progression in the first line and then receive second-line systemic therapy was associated with extended survival as opposed to osimertinib post-progression alone or an immediate switch to second-line systemic therapy [24]. While the current RWE does provide insight into disease progression and subsequent-line treatment, in the future, effort should be directed toward determining mechanisms of primary and acquired osimertinib resistance, as highlighted by the high incidence of cMET amplification (71%) reported in patients progressing on first-line osimertinib, who enrolled for a clinical trial [24]. cMET amplification, albeit at a considerably lower frequency (16%), was reported in a genetic analysis of first-line osimertinib resistance, in addition to the EGFR C797S mutation, while EGFR T790M-mediated resistance was not observed [26].

Finally, the growing body of RWE on osimertinib use, coupled with trials evaluating novel therapeutic regimens are essential for a faithful understanding of the efficacy of currently available treatment options and how these compare to emerging ones. More recently, the FLAURA2 clinical trial reported superior PFS in patients receiving platinum-pemetrexed plus osimertinib in the first line, when compared to those receiving osimertinib alone [27].

4.1. Study limitation

One limitation may come from the timing of the observation period which includes the COVID outbreak and consequent country lockdown leaving patients without access to planned hospital care.

All the data of interest is collected as part of the routine clinical care. Approximately 57% of all hospitals in the country

report to NHIF via online cloud connection for each admitted/discharged patients. Less than half report on a daily basis. Therefore, we do not expect missing data to hinder the analysis and interpretation to a large extent.

5. Conclusions

In summary, our retrospective analysis contributes to RWE on the efficacy of osimertinib in the first-line setting. The comparison of real-world data from the Bulgarian patients to FLAURA results corroborates conclusions from the trial, even suggesting greater efficacy in real clinical practice.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Author contributions

All the authors were involved in the conception, study design, execution, acquisition of data, analysis, and interpretation equally. All authors have contributed to the journal election and agreed to review all the stages before and after submission and have contributed to any significant change of the contents of this manuscript, as well as sharing the responsibility regarding any questions raised about the accuracy or integrity of the published work.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Reviewer disclosure

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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