Title

Osimertinib in T790M-positive and -negative patients with *EGFR*-mutated advanced non-small cell lung cancer (the TREM-study)

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Abstract

Objectives

In non-small cell lung cancer patients with acquired resistance to first- or second-generation EGFR-TKIs, osimertinib is approved in the presence of the T790M resistance mutation. We assessed the efficacy of osimertinib in both T790M-positive and T790M-negative patients.

Materials and Methods

The TREM-study is an investigator-initiated, multi-centre, single-arm, phase 2 clinical trial conducted in five Northern European countries. Patients with progression on at least one

previous EGFR-TKI were assigned to treatment with 80 mg of osimertinib daily until radiological progression or death. Patients were included regardless of the presence of T790M. The primary endpoint was objective response rate (ORR).

Results

Of 199 included patients, 120 (60%) were T790M-positive, 52 (26%) were T790M-negative and 27 (14%) had unknown T790M-status. 24% had brain metastases and 15% had an ECOG performance status of 2. Overall ORR was 48% (95% CI, 41%-55%), 60% (51%-69%) for T790M-positive patients and 28% (15%-41%) for T790M-negative patients, p<0.001. ORR for patients with co-occurring del19 vs L858R was 61% vs 32%, p=0.001. Duration of response was similar between the T790M-positive and –negative groups (11.8 vs 10.7 months, p=0.229). Overall median progression-free survival (PFS) was 8.9 months (95% CI, 7.4-10.5), and 10.8 vs 5.1 months for T790M-positive vs –negative patients (HR 0.62, p=0.007). Median overall survival (OS) was 17.9 months (95% CI, 14.4-21.3). For T790M-positive vs –negative median OS was 22.5 vs 13.4 months, (HR 0.55, p=0.002).

Conclusions

This study confirms the efficacy of osimertinib for T790M-positive patients. There was also clinically significant activity of osimertinib in a proportion of T790M-negative patients.

Clinical trial registration

This trial is registered with ClinicalTrials.gov (NCT02504346).

Key words: Non-small cell lung cancer, epidermal factor growth receptor (EGFR), T790M, tyrosine kinase inhibitor, osimertinib, survival, clinical trial, brain metastases

1 Introduction

Lung cancer is one of the most common cancers worldwide, and by far the most fatal with 1.8 million cancer-related deaths yearly [1]. The majority of patients have advanced disease at the time of diagnosis and hence a poor prognosis. Mutations in the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) gene act as oncogenic drivers and are present in about 10 % of patients with non-squamous non-small cell lung cancer (NSCLC) in Western countries [2-6]. *EGFR*-mutations are predictive of response to first- and second-generation tyrosine kinase inhibitors (EGFR-TKIs) such as erlotinib, gefitinib, afatinib or dacomitinib, with response rates of around 70 %. Unfortunately, all patients inevitably develop resistance to these drugs within a median of 9-15 months [7-10]. The most frequent resistance mechanism is the point mutation T790M on exon 20, which is detectable in about 60 % of patients at the time of progression [11].

Osimertinib is a third generation, irreversible EGFR-TKI, targeting both the sensitizing mutations and the T790M resistance mutation [12]. In patients harbouring the T790M-mutation after progressing on a first- or second-generation EGFR-TKI, osimertinib was superior to platinum doublet chemotherapy with a higher response rate (71 % vs 31 %) and longer progression free survival (10.1 vs 4.4 months, $p < 0.001$) [13]. The median overall survival was 26.8 vs 22.5 months, $p = 0.277$ [14]. In a phase 1 study which, in addition to T790M-positive patients, also included EGFR-TKI pre-treated patients without the T790M-mutation, the latter group demonstrated an overall response rate of 21 % and a median PFS of 2.8 months, indicating some activity of osimertinib despite the absence of T790M [15]. In the phase 3 FLAURA-study, osimertinib achieved both a longer median PFS and OS than first-generation EGFR-TKIs in the first-line setting (median PFS 18.9 vs 10.2 months, $p < 0.001$ and median OS 38.6 vs 31.8 months, $p = 0.0462$), thus establishing osimertinib as an option not only at the time of resistance, but also as the primary treatment of advanced *EGFR*-mutated NSCLC [16, 17].

We conducted this single-arm prospective clinical study to evaluate the efficacy of osimertinib in patients progressing on standard EGFR-TKI treatment regardless of T790M-status. We hypothesized that osimertinib would have similar activity in a Northern European cohort of patients as previously shown in studies with a high proportion of Asian patients [13], and that some patients without detectable T790M-mutation would benefit.

2 Material and methods

2.1 Trial design

The TREM-study is an investigator-initiated, multi-institutional, single-arm, phase 2 clinical trial conducted in 14 centres in five Northern European countries (Norway, Sweden, Denmark, Finland and Lithuania).

2.2 Patients

Eligible patients were over 18 years old with advanced (stage IIIB or IV) histologically or cytologically confirmed non-small cell lung cancer with a documented sensitizing *EGFR* mutation. They had radiologically assessed disease progression on or after at least one previous EGFR-TKI. There had to be measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) guidelines version 1.1 at baseline, an Eastern Cooperative Oncology Group (ECOG) status of 0-2 and a life expectancy of minimum 12 weeks. Patients with asymptomatic brain metastases on stable steroid dosage the last two weeks before start of study treatment could be enrolled. Patients could have had more than one line of TKI-treatment or other systemic anticancer therapies prior to study entry. Patients also had to have adequate liver, kidney and bone marrow function.

Exclusion criteria included current or previous interstitial lung disease or radiation pneumonitis, prolonged QTc-interval or treatment with osimertinib or other EGFR-TKIs with

similar profile prior to inclusion. Any remaining toxicity from previous treatment had to be less than Common Terminology Criteria for Adverse Events (CTCAE v4.0) grade 2 (except alopecia).

2.3 Ethics

All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and the ICH-guidelines of Good Clinical Practice, and according to regulatory requirements and individual Ethics Committees approval in the countries of each participating site. The trial is registered with ClinicalTrials.gov (NCT02504346).

2.4 Roles of the sponsor, authors and the funding sources

This was an academic study designed by the principal investigators and Oslo University Hospital was sponsor. Neither the sponsor nor the participating sites had any financial benefit from the study. The funding sources did not have access to data, nor did they take part in analyses, interpretation of the results or writing of the manuscript.

2.5 Assessments and procedures

Eligible patients received osimertinib with a starting dose of 80 mg orally once daily until radiological progression by RECIST v 1.1 or death, whichever occurred first, or unacceptable toxicity. Patients could continue treatment beyond radiological progression if they had clinical benefit, as judged by the investigator. Archival tumour material from the time of diagnosis was collected, and a rebiopsy to determine mutational status was required prior to the first dose of osimertinib. If a biopsy was not possible to obtain, a plasma sample for mutational analysis could be collected if methods for analysing plasma were available at the study centre in question. T790M-negative status was defined as absence of T790M in the presence of an activating *EGFR*-mutation in tissue. In the case of a negative plasma sample and no tissue sample available, the mutational status was regarded as unknown. Analysis for *EGFR*-status in tissue or blood at inclusion was done per local practice at the different centres, and methods included

mainly quantitative PCR and in a few cases next generation sequencing. Patients received osimertinib regardless of T790M-status.

Adverse events were graded according to the CTCAE version 4.0. A first visit for toxicity assessment was done two weeks after commencing osimertinib. Tumour assessments were done with CT-scans of the thorax and abdomen every 8 weeks the first 48 weeks of treatment, thereafter every 12 weeks. MRI of the brain was done at baseline in patients with known or suspected brain metastases, and repeated in the same intervals as the CT-scans if there were brain involvement. Patients who discontinued treatment for other reasons than progression or death, continued assessments until disease progression. Biochemistry, tumour markers, electrocardiogram-recordings and toxicity assessment were done at each visit. At every visit including baseline, blood was collected and stored for analyses of liquid biopsies and other translational research purposes (not reported here). At progression on osimertinib, the patients were asked to undergo a new biopsy sampling for molecular profiling and exploratory research.

2.6 Outcomes

The primary endpoint was objective response rate (ORR) defined as the percentage of patients with partial or complete response according to RECIST v 1.1, assessed by the investigators. All responses were confirmed with a subsequent scan at least 4 weeks after the response was first assessed. Secondary endpoints were progression-free survival (PFS), duration of response (DoR), disease control rate (DCR), overall survival (OS) and safety. Progression-free survival was defined as the time from start of treatment until progression or death in absence of progression, whichever occurred first. Duration of response was defined as the time from a response was first assessed (and later confirmed) until progression. Disease control rate was the proportion of patients who achieved at least stable disease as best overall response (stable disease, partial response or complete response). Overall survival was defined as the time from start of treatment until death of any cause.

2.7 Statistical methods

All time-to-event endpoints were calculated with the Kaplan-Meier method. Univariate comparisons were done with the log-rank test. The Cox proportional hazards model were used to calculate hazard ratios and to perform multivariate analyses. Categorical data were analysed with the chi-square test or the Fisher's exact test. The Student's t-test was used for continuous data. Logistic regression modelling was done to evaluate subgroups of response rates. For all analyses a two-sided p-value less than 0.05 was considered statistically significant. No formal power calculation was done, but a sample size of 200 patients was considered adequate to establish evidence on efficacy and to provide robust material for translational research. All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.).

3 Results

3.1 Patients

199 patients were included from July 2015 to November 2017. Baseline characteristics are summarized in table 1. The median age was 66 years, 70 % were female and 52 % never-smokers. 15 % had an ECOG status of 2. 24 % of the patients had brain metastases including one patient with leptomeningeal disease. 25 % had had more than one line of EGFR-TKI and 44 % also had had at least one line of other systemic cancer therapy, mainly chemotherapy, prior to study entry.

All patients had a documented *EGFR*-mutation before treatment prior to the study. *EGFR*-mutational status was assessable in rebiopsies in 172 of the 199 patients (in tissue from 157 patients and in plasma from 15 patients) at inclusion. 120 (60 %) patients were T790M-positive and 52 (26 %) T790M-negative. Reasons for unknown mutational status (27 patients, 14 %) included not enough biopsy material available, biopsy considered not feasible for technical or

safety reasons, or only liquid biopsy with no mutation detected. In more than 95 % of the patients, the activating mutation found at diagnosis was retained at inclusion.

The most common sensitizing mutations at baseline were deletions in exon 19 (del19) (53 %) and the L858R point mutation in exon 21 (26 %). There was a statistically significant lower prevalence of the L858R-mutation in the T790M-positive group vs the T790M-negative group (23 % vs 44 %, p = 0.006). The other baseline characteristics were equally distributed between T790M-positive and -negative patients.

3.2 Response rates and duration of response

Data cut-off was January 7, 2019. The median follow-up was 27.0 months and the median duration of treatment was 11.8 months (range 0-40.6+ months). 191 patients were evaluable for response, defined as patients with measurable disease at baseline. The overall response rate was 48 % (95 % CI, 41 to 55 %) (table 2). Among the T790M-positive patients, 60 % (95 % CI, 51 to 69 %) achieved an objective response vs 28 % (95 % CI, 15 to 41 %) in the T790M-negative patients (p < 0.001). There was a statistically significant difference between the ORR in patients with del19 and L858R, 61 % vs 32 % respectively, p = 0.001 (figure 1A). Within the T790M-positive group, the ORR for patients with del19 and L858R was 70 % vs 44 % (p = 0.017) and in the T790M-negative group 33 % vs 15 % (p = 0.162). The ORR for patients with baseline brain metastases was 55 % vs 46 % for patients without brain metastases, p = 0.296 (figure 1B). The T790M-positive patients with and without brain metastases had an ORR of 66 % vs 58 %, respectively, p = 0.471. In the T790M-negative group the ORR was 33 % for patients with brain metastases vs 26 % for patients without, p = 0.718. There were no statistically significant differences in ORR between the other subgroups.

The disease control rate was 83 % (95 % CI, 77 to 88 %) overall, 91 % (95 % CI, 85 to 96 %) for T790M-positive patients and 64 % (95 % CI, 50 to 78 %) for T790M-negative patients, $p < 0.001$ (table 2).

A logistic regression model including T790M-status, gender, smoking history, age, ECOG status, del19/L858R, baseline brain metastases, 1 vs 2 or more previous lines of therapy and previously only TKI or TKI and chemotherapy was fitted to identify independent predictors of response. T790M-positive status (OR 4.0, $p = 0.001$) and del19 (OR 3.2, $p = 0.002$) were the only variables significantly associated with ORR.

The overall median duration of response was 10.7 months (95 % CI, 8.5 to 12.9). There was no statistically significant difference between the T790M-positive and -negative groups with a DoR of 11.8 vs 10.7 months, respectively, $p = 0.229$ (figure 2). However, DoR differed between patients with del19 and L858R (12.0 vs 8.9 months, $p = 0.042$) (data not shown).

3.3 Progression-free survival

The median progression-free survival for all patients (n = 199) was 8.9 months (95 % CI, 7.4 to 10.5) (figure 3A). Median PFS for T790M-positive patients was 10.8 months vs 5.1 months for T790M-negative, HR 0.62 (95 % CI, 0.43 to 0.88), $p = 0.007$ (figure 3B). For patients with del19 mutation, the median PFS was 11.3 vs 7.3 months for patients with L858R, HR 0.55 (95 % CI, 0.38 to 0.80), $p = 0.001$. In the T790M-positive group, the median PFS for patients with del19 vs L858R was 12.6 vs 10.6 months, HR 0.61 (95 % CI, 0.38 to 0.99), $p = 0.044$, whereas in the T790M-negative group it was 5.7 vs 1.7 months, HR 0.61 (95 % CI, 0.32 to 1.13), $p = 0.112$ (figures 3C-3D). For patients with brain metastases at baseline, the median PFS was 7.3 vs 9.1 months for patients without brain metastases, HR 1.28 (95 % CI, 0.90 to 1.82), $p = 0.165$, regardless of T790M-status. There was also no significant difference in PFS for T790M-positive

patients with or without brain metastases, but in the T790M-negative group the median PFS was significantly shorter for patients with brain involvement than without (1.6 vs 5.6 months, HR 2.46 (95 % CI, 1.23 to 4.93), p = 0.009) (figures 3E-3F). We performed a multivariate analysis including T790M-status, age, gender, smoking-status, ECOG-status, CNS-metastases, del19 or L858R, one or more prior lines of treatment and duration of previous treatment. The variables that were significantly associated with PFS were T790M-positive status (HR 0.49 (95 % CI, 0.33 to 0.73), p < 0.001), del19 (HR 0.52 (95 % CI, 0.35 to 0.78), p = 0.002) and longer duration of previous treatment (HR 0.52 (95 % CI, 0.34 to 0.80), p = 0.003). We also performed multivariate analyses for the T790M-negative and -positive groups separately. The only statistically significant variable in the T790M-negative group was presence of CNS metastases (HR 2.95 (95 % CI, 1.37 to 6.33)), p = 0.006. In the T790M-positive group, the statistically significant variables were longer duration of previous treatment (HR 0.51 (95 % CI, 0.30 to 0.86)), p = 0.011, more than one previous line of treatment (HR 1.98 (CI 95 %, 1.17 to 3.35), p = 0.011 and del19-mutation (HR 0.50 (95 % CI, 0.30 to 0.84), p = 0.008.

3.4 Overall survival

At the data cut-off, 127 of 199 (64 %) patients had died. The median overall survival for the whole study cohort was 17.9 months (95 % CI, 14.4 to 21.3) (figure 4A). The survival rates at 12 and 24 months were 67 % and 39 %, respectively. The median OS for T790M-positive vs -negative patients was 22.5 vs 13.4 months, HR 0.55 (95 % CI, 0.37 to 0.81), p = 0.002 (figure 4B).

For patients with del19 or L858R mutations, the median overall survival was 21.8 vs 15.2 months, respectively, HR 0.65 (95 % CI, 0.43 to 1.00), p = 0.046. However, no such difference in median OS was seen with regards to sensitizing mutations within the T790M-positive or the T790M-negative groups (figure 4C-4D).

There was no statistical difference in median OS for patients with or without brain metastases overall, 15.2 months vs 20.2 months, HR 1.33 (95 % CI 0.89 to 1.98), p = 0.162, but for patients with T790M-negative status and brain metastases the median OS was substantially worse than for T790M-negatives without brain metastases (7.5 vs 17.0 months, HR 3.08 (95 % CI 1.46 to 6.51), p = 0.002) (figure 4F). For the T790M-positives the median OS was similar regardless of brain involvement, 21.8 vs 22.5 months, HR 0.87 (95 % CI, 0.50 to 1.51), p = 0.611 (figure 4E).

There was a markedly shorter median overall survival for patients in poor performance status, 20.8 months (ECOG 0-1) vs 5.6 months (ECOG 2), p = 0.001 (data not shown). This difference was also seen in the T790M-positive and -negative groups with a median OS of 24.2 vs 9.4 and 13.7 vs 2.0 months, respectively, although the difference was not statistically significant in the T790M-negative group.

There were no statistically significant differences in median OS across other subgroups.

3.5 Safety

196 of 199 (98.5 %) patients experienced an adverse event, most of which were of grade 1-2. The most commonly reported adverse events were fatigue (67 %), decreased appetite (45 %), dyspnoea (44 %), rash (43 %), paronychia (42 %) and diarrhoea (42 %). 29 % of the patients had an adverse event of grade 3 or higher. 10 patients (5 %) needed a permanent dose reduction and only five patients (2.5 %) discontinued treatment due to adverse events (three with pneumonitis, one with ventricular tachycardia and one with cerebral ischemia). There were 14 cases of QTc-prolongation, all grade 1 except one grade 2 event, and 8 cases of pneumonitis, one grade 3 and the rest of lower grades. There were no treatment-related deaths.

4 Discussion

Osimertinib has emerged as a new standard of care in patients with advanced *EGFR*-mutated NSCLC, both in the first-line setting and after acquired resistance against first- and second-generation EGFR-TKIs in patients with the resistance mutation T790M [13, 16]. In the present study, we demonstrated the efficacy of osimertinib in a Northern European population of patients with advanced *EGFR*-mutated NSCLC with acquired resistance to first- or second-generation EGFR-TKIs, regardless of the presence of the T790M-mutation.

The patients in the current cohort were heavily pre-treated. In contrast, 96 % of the patients in AURA3 had received only one line of prior treatment. Furthermore, 15 % of the patients in our trial had an ECOG performance status of 2 while in the AURA-studies only patients in good performance status (PS 0-1) were included. The median age (66 years) was also higher than in the AURA-trials (60-63 years). Despite this, the ORR for T790M-positive patients in our study (60 %) is only slightly lower than in the AURA3-study (71 %) and comparable to the ORR in AURA1 (61 %) [13, 15]. The DCR of 91 % is similar to the DCR in AURA3 (93 %). The median PFS of 10.8 months for the T790M-positive patients is in line with the median PFS observed in the AURA-studies, and the median OS of 22.5 months mirrors the OS in AURA3 (26.8 months) [14]. Thus, the study population in our trial is a less selected group, which better represents real world-patients. Still, the efficacy of osimertinib in T790M-positive patients is in line with previous reports, and is consistent with population-based observational studies [18, 19].

Interestingly, osimertinib also showed clinically relevant activity in the T790M-negative group. To date, there are few approved treatment options for patients without the T790M-mutation who are refractory to EGFR-TKIs, except chemotherapy or, in some countries, a combination of chemotherapy and immunotherapy [20] for fit patients. Immunotherapy alone seems less effective in this population [21]. In our material, the T790M-negative cohort had a response rate (28 %) and PFS (5.1 months) comparable to that of the chemotherapy-arm in the randomized AURA3-study. Furthermore, the duration of response in the present study was similar for

T790M-positive and -negative patients, suggesting that despite the lower likelihood of response for T790M-negative patients, those who achieve a response, have a similar benefit as T790M-positive patients. Our trial is the second study to evaluate the effect of osimertinib in T790M-negative patients. In the phase 1 AURA1-trial, 61 T790M-negative patients achieved an ORR of 21 % and a median PFS of 2.8 months [15]. However, this trial was a dose expansion trial, and 20 of the patients received daily doses lower than the recommended 80 mg, which might explain the lower efficacy compared to our study.

The reason for this observed activity of osimertinib in patients without the T790M-mutation remains unclear, but might at least in part be due to false negative biopsies because of tumour heterogeneity. To minimize the number of false negatives, a negative tissue biopsy could be followed by mutation testing in plasma [22]. However, the prevalence of the T790M-mutation in our material is similar to what has previously been reported [11], and the testing was done with methods available in routine practice at the different centres. Thus, we have no reason to believe that the rate of false negatives should be higher in our cohort than in a clinical setting. Taking into consideration that osimertinib is a less toxic treatment than combination chemotherapy, and appears to have similar efficacy, osimertinib might represent an attractive treatment option for selected T790M-negative patients. Still, there is a need for additional approaches to identify those who remain EGFR-dependent and therefore are most likely to respond to continued EGFR-inhibition.

In the present study, the response rate for patients harbouring a sensitizing deletion in exon 19 was higher than for patients with L858R, both overall and within the T790M-positive and -negative cohorts. The association with a better response rate remained significant when adjusted for other factors. The tendency of a more favourable outcome for patients with del19-mutation compared to patients with L858R was also seen across other efficacy endpoints such as PFS and OS. Existing data suggest that patients with del19-mutations have longer PFS when

treated with first- or second-generation TKIs in the first line setting [23-25]. Moreover, in a pooled analysis of two trials comparing the second generation TKI afatinib with chemotherapy, there was a statistically significant survival benefit for patients with del19 treated with afatinib, but not for patients with L858R [26]. Similarly, in the setting of acquired resistance to first-line EGFR-TKIs and presence of T790M, patients with co-occurring del19-mutation treated with osimertinib tended to have a higher response rate, longer PFS and OS [18, 27, 28]. In our material, the prevalence of T790M is higher in patients with del19 than with L858R, consistent with previously reported data, indicating that the T790M mutation is more likely to emerge in the context of a del19-mutation [29, 30]. Thus, our results add to the growing body of evidence that del19 and L858R are distinct subtypes of *EGFR*-mutated NSCLC with different prognosis and response to treatment with EGFR-TKIs.

Both preclinical and clinical data have demonstrated that osimertinib is effective in the CNS [31, 32]. Consistent with this, there were no differences in response rate, PFS or OS for patients with or without brain metastases at study entry. This was also true within the T790M-positive cohort, but for patients without the T790M-mutation, both PFS and OS were worse for patients with brain involvement. Furthermore, the presence of brain metastases was the only variable statistically significantly associated with the outcome in multivariate analysis. This might reflect the lower probability of overall response in the T790M-negative cohort, combined with the in general worse prognosis for patients with brain metastases.

The adverse events reported in this trial were mainly of mild character and in line with that observed previously. Some of the most frequent adverse events like fatigue and dyspnoea could be related to symptoms from the disease itself rather than being a side effect of the drug. Overall, there were no new safety signals.

In conclusion, this study confirms the efficacy and tolerability of osimertinib as second or later line treatment in patients with advanced *EGFR*-mutated NSCLC in a Northern European cohort. For T790M-positive patients, the results are consistent with the existing evidence, from both clinical trials and real-world data, and show similar efficacy in patients with and without brain metastases. Osimertinib also exhibits activity in the T790M-negative cohort, and might be a treatment option for selected patients in whom EGFR-TKI resistance is not due to T790M-mutation.The ongoing translational analyses based on this study might contribute to elucidate this.

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Conflicts of Interest Statement

IJZE, ÅH, SE and SC have nothing to disclose. AM has received grants from AstraZeneca. KHH has received honoraria for lectures or advisory boards for Takeda, Roche, MSD, AstraZeneca, Pierre Fabre and BMS. JK has received honoraria for lectures or advisory boards from AstraZeneca, BMS, Boehringer-Ingelheim, MSD and Roche. BHG has received honoraria for lectures and advisory boards for AstraZeneca. OTB has received grants from Roche and Pfizer.

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