Original article

Intracranial effect of osimertinib in relapsed *EGFR*-mutated T790M-positive and –negative non-small cell lung cancer patients: results from a phase II-study

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Abstract

Introduction

Osimertinib is effective for relapsed T790M-positive patients with brain metastases. The high brain permeability suggests that also such patients without T790M could benefit. Therefore, we evaluated the effect of osimertinib on brain metastases in both T790M-positive and -negative patients.

Methods

The TREM-study was an investigator-initiated phase II, single-arm, multi-institutional clinical trial conducted in Northern Europe. Patients with resistance to prior EGFR-TKIs received osimertinib until radiological progression, unacceptable toxicity or death. Baseline brain scans were performed in patients with known or suspected brain metastases and repeated every 8-12 weeks. We assessed intracranial efficacy in patients with baseline brain metastases.

Results

Brain metastases were detected in 48/199 patients at baseline. Of these, 63% were T790M-positive, 27% -negative and 10% had unknown T790M-status. The majority (73%) of the patients had received prior whole brain radiotherapy and additionally 8% had received stereotactic radiosurgery (SRS).

Brain scans were available for review for 42 patients. The intracranial progression free survival was 39.7 vs 3.5 months for T790M+ and T790M- patients, respectively ($p<0.001$).

The overall intracranial disease control rate (iDCR) was 81%, and for T790M+ and T790M- patients the DCR was 89% vs 55%, respectively.

The estimated risk of CNS progression was 0.8% at 6 months and 6% at 12 months for T790M-positive patients, and 14% and 17% at 6 and 12 months, respectively, for the T790M-negative.

Conclusion

This subgroup analysis confirms CNS efficacy of osimertinib in patients with the T790M resistance mutation, while other treatment options should be considered for EGFR-TKI relapsed T790M-negative patients with brain metastases.

Key words

EGFR, osimertinib, brain metastases, non-small cell lung cancer, T790M

1 Introduction

Brain metastases frequently occur in lung cancer. Of all patients with non-small cell lung cancer (NSCLC), around 10-15% have brain metastases and 25-30% of patients who present with metastatic disease have metastases to the brain at the time of diagnosis [1-3]. For oncogenic driven lung cancers with mutations in the epidermal growth factor receptor (EGFR) gene or anaplastic lymphoma kinase (ALK) rearrangements, as many as 50-60% of patients develop brain metastases during the course of their disease [4]. This may lead to increased morbidity, decline in neurocognitive function and reduced quality of life [5,6]. Although the survival for patients with brain metastases has increased in the recent years, and especially in the presence of molecular alterations, patients with poor prognostic factors still have a dismal outcome [1,2,7].

Current treatment options for brain metastases are surgery or stereotactic radiation therapy in the case of a single or a few metastases, or whole brain radiotherapy (WBRT) for multiple metastases [8]. There is, however, an ongoing debate about the efficacy of WBRT, and a recent randomized phase III-study did not show any difference in quality of life or overall survival between WBRT plus steroids and best supportive care plus steroids [6]. The efficacy of most systemic therapies is limited by their poor ability to cross the blood-brain barrier (BBB) [9].

An activating *EGFR*-mutation is present in around 10% of patients with non-small cell lung cancer in Western countries and 40-50% of Asian patients. These mutations are predictive of response to tyrosine kinase inhibitors (EGFR-TKI) [10,11]. Even though first- and second-generation EGFR-TKIs, such as erlotinib, gefitinib and afatinib, have a low BBB-penetrance,

clinical data indicate some activity in the central nervous system (CNS) [12-14]. Given the high incidence of brain metastases in this patient population, there is a need for more effective treatments [4].

Osimertinib is a third generation EGFR-TKI with activity towards both the activating mutations and the T790M resistance mutation, which emerges in about 50-60% of patients at the time of progression on first- or second-generation EGFR-TKIs [15,16]. Preclinical data suggest that osimertinib has a better BBB-penetrance than the first- or second-generation EGFR-TKIs [17]. In the randomized AURA3-study, osimertinib improved progression free survival (PFS) compared to chemotherapy as second line treatment in patients with the T790M-mutation [18]. A subgroup analysis of patients with brain metastases from this trial demonstrated that osimertinib was superior also in terms of intracranial objective response rate (iORR) and intracranial PFS (iPFS) [19]. Given as upfront therapy, patients treated with osimertinib had longer PFS and OS than patients who received first-generation EGFR-TKIs [20]. Also in this setting, osimertinib showed superior iORR and iPFS in the subgroup of patients with CNS-disease [21].

In a recent investigator-initiated multi-center, single-arm trial (TREM), we evaluated the effect of osimertinib in patients with resistance to first- or second-generation EGFR-TKIs, regardless of T790M-status [22]. In the T790M-positive cohort, there was no significant difference in PFS or OS between patients with or without brain metastases at baseline, but the T790M-negative patients with brain metastases had a worse outcome than T790M-negative patients without CNS-disease (PFS 1.6 vs 5.6 months and OS 7.5 vs 17.0 months).

In this exploratory analysis of patients with baseline brain metastases in the TREM-study, we aimed to investigate the efficacy of osimertinib on intracranial clinical endpoints in pretreated patients, with or without the T790M-mutation. Given the high intracerebral exposure of osimertinib, the poor overall outcome for the T790M-negative patients with brain metastases was surprising. Therefore, a second aim for this analysis was to provide an explanation for the observed discrepancy between the T790M-positive and –negative patients with intracerebral disease.

2 Material and methods

2.1 Trial design and participants

The TREM-trial was an investigator-initiated phase II, single-arm, multi-centre clinical trial conducted in Northern Europe. Detailed methodology has been published previously [22]. In brief, patients had to be over 18 years of age, have locally advanced or metastatic non-small cell lung cancer harbouring a sensitising *EGFR*-mutation and having progressed on at least one previous EGFR-TKI. Furthermore, they had to have measurable disease by the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines version 1.1 and have an Eastern Cooperative Oncology Group (ECOG) status of 0-2. Patients with brain metastases could be included if asymptomatic and on stable steroid dose the last two weeks prior to enrolment.

2.2 Procedures

A rebiopsy was done before commencement on osimertinib, but patients were enrolled regardless of the presence of T790M. If a tissue biopsy was not considered feasible, a plasma sample could be analysed for mutations. T790M-negativity was defined as negative in tissue

biopsy. In cases where a tissue biopsy were insufficient for assessing mutational status and a supplementary liquid biopsy negative or not available, T790M-status were regarded unknown. All patients received treatment with osimertinib 80 mg administered orally once daily. Toxicity-triggered dose reduction to 40 mg daily was allowed. Treatment continued until radiological progression according to RECIST 1.1 or death. Treatment beyond RECIST-defined progression was allowed if the patient was deemed by the investigator to derive clinical benefit. A baseline MRI or CT scan of the brain was mandated in cases with known or suspected brain metastases. If presence of brain metastases was confirmed, the brain scan was to be repeated at the time for overall tumour assessments every 8 weeks the first year and thereafter every 12 weeks until progression at any site.

We collected brain scans for independent central radiological review and evaluated them according to RECIST 1.1. The radiologist was blinded for clinical data. Previously irradiated lesions were considered non-target lesions unless the lesion had progressed after radiotherapy. Data cut-off for this analysis was January 2019.

2.3 Outcomes and statistical analysis

Intracranial efficacy of osimertinib in terms of iORR and iPFS was assessed in the subgroup of patients with baseline brain metastases. iORR was defined as the proportion of patients with a confirmed partial or complete response of brain lesions. Intracranial disease control rate (iDCR) was defined as all patients with either complete response, partial response or stable disease. iPFS was defined as the time from start of treatment to intracranial progression or death. For patients with only non-target intracranial lesions, progression was defined as described in RECIST 1.1 as either an increase in tumour burden equivalent to a 20% increase

in tumour diameter had there been measurable lesions, emergence of new lesions or an increase in disease burden leading to change of systemic therapy or application of local therapy. Patients without brain progression were censored at the date of the latest assessment before data cut-off. Time-to-event analyses were performed with the Kaplan-Meier method and groups were compared by the log-rank test. Risk of CNS progression in the full study population was evaluated by a competing risk analysis where intracranial progression was considered the event in interest and extracranial progression and death were considered competing events. Patients without events were censored at the time of their last assessment. For all analyses, a two-sided p-value < 0.05 was considered statistically significant. The statistical analyses were conducted with IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp.) and R version 3.6.1.

2.4 Ethics

All patients gave written informed consent, and the study was conducted in accordance with the Good Clinical Practice-guidelines and the Declaration of Helsinki. The study was approved by the National Ethics Committees in each participating country. The trial is registered with ClinicalTrials.gov (NCT02504346). Oslo University Hospital was sponsor for this study, and it was designed by the principal investigators. Funding was provided by Astra Zeneca and the South-Eastern Norway Regional Health Authority. The funding sources did not have any role in the collection of data, analyses or interpretation of the results, nor did they participate in writing of the manuscript. The study is reported according to the CONSORT-guidelines where applicable (Supplementary Material).

3 Results

3.1 Patients

A total of 199 patients were included in the TREM-study. At baseline, 48 patients (24%) had brain involvement including one with only leptomeningeal disease. Brain CT or MRI scans were available for central review for 42 of the patients (Fig. 1). The baseline characteristics of the patients with CNS metastases are summarized in Table 1. At inclusion, 30 of the patients with CNS metastases had a T790M-mutation (in whom 3 were detected in plasma due to lack of tissue, and 27 in tissue biopsies), 13 patients were T790M-negative and five patients had unknown T790M-status (Table 1). The baseline characteristics of the cohort with CNS metastases were similar to those of the patients without known disease in the CNS, with the exception that patients with CNS metastases were younger with a median age of 61.5 years versus 68.0 years, and the proportion of patients in poor performance status was larger (25% versus 12% with ECOG 2, respectively) (Suppl. Table 1).

Of patients with CNS disease, 46% had three or less brain metastases at inclusion (Table 2). Multiple brain metastases (>10) were found in 17% of the patients. The majority of the patients (81%) had received brain radiotherapy prior to inclusion (73% whole brain radiotherapy and 8% stereotactic radiosurgery) and only seven patients (15%) had not received any local treatment to the brain. The median time from local treatment for brain metastases to inclusion was 10 months.

3.2 Efficacy

The median follow up for iPFS was 13.5 months. The overall iPFS was 19.1 months (95% CI, 8.7 to NR) (Fig. 2A). For the T790M-positive patients the iPFS was 39.7 months (95% CI, 19.1 to NR) vs 3.5 months (95% CI, 1.0 to NR) for the T790M-negative, $p < 0.001$ (Fig. 2B).

The iORR for all patients with brain metastases was 10% overall. For the T790M-positive group the iORR was 7% vs 9% for the T790M-negative group, respectively, p=0.100 (Table 3). The iDCR was 81% overall, and 89% vs 55% (p=0.031) for the T790M-positive and T790M-negative patients, respectively. Of the patients with only non-target lesions at baseline (n=35), two patients achieved a complete intracranial response (both were T790M-positive), and 25 patients had non-CR/non-PD as their best response. Seven patients had measurable disease at baseline as defined by RECIST 1.1 [23] (due to the high number of patients previously treated with whole brain radiotherapy). The median number of brain metastases at baseline for these patients was 2 (range 1-15) and the median sum of the diameter of target lesions at baseline was 28 mm (range 21-67 mm) (Suppl. Table 2). The iORR among those with measurable disease at baseline (n=7) was 29% and the iDCR 100%. Two patients had an intracranial partial response (PR) as their best overall response and five patients had stable disease (SD) (Table 3 and Suppl. Figure 1). None of the seven had progressive disease (PD) as their best response.

The overall median duration of disease control was 19.1 months (95% CI, 13.2 to NR). For T790M-positive patients, the median duration of disease control was 39.7 months (95% CI, 19.1 to NR) vs 5.2 months (95% CI, 3.5 to NR) for T790M-negative, p = 0.006 (Suppl. figure 2A-B). The duration of the two partial responses was 9.7 months (ongoing at data cut-off, T790M-status unknown) and 3.8 months (T790M-negative). Furthermore, the two T790M-positive patients who achieved a complete response had a duration of response of 17.3 months and 34.4 months, respectively.

Within the group of patients with baseline brain metastases, 14/48 (29%) developed progression in the brain during the course of the study, whereas 7/151 (5%) of the patients without baseline brain metastases experienced progression in the brain (Suppl. Figure 3). In a competing risk analysis including the full study cohort the estimated risk of CNS progression at 6 months was 0.8% for T790M-positive patients and 14% for T790M-negative patients (Fig. 2C). At 12 months, the estimated risk was 6% vs 17% for the T790M-positive and –negative, respectively.

To further explore the differences between T790M-positive and –negative patients, we also performed a competing risk analysis including only the patients with pre-existing brain metastases. In the T790M-positive group, the risk of progression in the brain at 6 months was 0% vs a 17% risk of extracranial progression (Fig. 2D). At 12 months, the estimated risk of CNS progression was 13% vs 40% for non-CNS-progression. For the T790M-negative patients, the risk of CNS-progression vs non-CNS-progression was 39% vs 31% at 6 months and not calculable at later time points.

4 Discussion

In this subgroup analysis of 48 patients with brain metastases, we have demonstrated that osimertinib has intracranial activity in pretreated patients and confers durable disease control in the brain.

The median iPFS of 39.7 months for T790M-positive patients in this study was longer than previously reported [19]. Furthermore, the iDCR were high (100% for the 7 patients with

measurable disease, 81% for the total cohort and 89% for the T790M-positive group) and in line with the iDCR reported in other studies (87-95% in the AURA-trials [19,24], 97% in another recent study with 38 T790M-positive patients with brain metastases treated with osimertinib [25]). In this setting, where extensive use of prior radiotherapy precludes the interpretation of the isolated effect of osimertinib on intracerebral response, disease control is a clinically meaningful endpoint. Indeed, the disease control in the brain for the patients in the TREM-study was durable, especially in the T790M-positive group with an impressive median duration of intracranial disease control of 39.7 months.

The iORR was modest in the present study, and lower than in the AURA-studies evaluating T790M-positive patients [19,24]. However, according to clinical practice in the years before initiation of this trial, as many as 73 % of the patients had received WBRT prior to inclusion. Because of this, few patients had truly measurable disease at baseline when adhering strictly to the RECIST-criteria [23]. Thus, the iORR based on the patients who were evaluable for response (2/7, 29%) must be interpreted with caution due to the small sample size. When considering all the patients with brain scans available for review, the iORR (4/42, 10%) was lower, mainly because of the high number of patients with only non-target lesions who are designated the response “non-CR/non-PD” instead of PR or SD, respectively. In the AURA3-study, the iORR for patients with or without measurable CNS-disease in the osimertinib-arm was 40%, but a smaller proportion of these patients had received prior radiotherapy (37%) [19]. In the pooled analysis of the patients with brain metastases in the AURA2-study and the AURA-extension study, 73% of the patients defined as having measurable disease had received prior radiation therapy to the brain. Thus, different use of brain irradiation makes cross-trial comparisons of response rates difficult.

We also found that the risk of progression in the brain was only 6% at 12 months for the T790M-positive patients in the full study cohort. Taking into account that similar to the AURA3-study [19], brain imaging was not mandated for patients without known brain lesions at baseline and hence small asymptomatic new CNS-lesions might not be discovered in all patients, this analysis could be under-estimating the true risk. On the other hand, the majority of these patients were far down the trajectory of their disease, and as the incidence of brain metastases increases during the course of *EGFR*-mutated disease [4], they had a high risk of developing symptomatic as well as asymptomatic brain metastases. Thus, the low risk of progressive brain disease probably reflects a protective effect of osimertinib and is of clinical value for the individual patients.

To our knowledge, this is the first study to evaluate the effect of osimertinib on brain metastases in EGFR-TKI refractory patients without T790M (defined as T790M-negative in extracranial tissue biopsies). Due to the high permeability of osimertinib over the BBB we originally hypothesized that T790M-negative patients with brain metastases could have a clinical benefit of this drug [17]. Furthermore, some studies demonstrated that a large proportion of patients with brain metastases and T790M-positive extracranial tumors are T790M-negative in the cerebrospinal fluid [25,26]. Still, they had an excellent intracranial effect of osimertinib [25]. This could suggest an effect also in cases negative for T790M both extra- and intracranially. However, we have previously shown that T790M-negative patients with brain metastases have shorter overall PFS and OS than T790M-negative patients without brain metastases (PFS 1.6 vs 5.6 months and OS 7.5 vs 17.0 months, respectively) [22]. In the present analysis, T790M-negative patients who had progressed on previous EGFR-TKI treatment had an inferior outcome across all the intracranial endpoints, and although one of the patients with a partial intracranial response was T790M-negative, the duration of this

response was only 3.8 months. Furthermore, the T790M-negative patients with pre-existing brain metastases had a similar risk of progression intra- and extracranially, whereas the T790M-positive patients had a clear benefit of osimertinib in terms of reduced risk of brain progression compared to extracranial progression. This suggests that the probable explanation for the observed short PFS and OS in T790M-negative patients is lack of treatment effect within the brain, and emphasizes the challenge of treating brain metastases in patients with non-T790M-mediated resistance to EGFR-TKIs. The biological mechanisms underlying this possible lack of benefit of osimertinib in the brain remain unknown. However, this finding is contrary to the 1st line setting where the CNS-effect of osimertinib is well established [21].

A limitation to this analysis is that the single-arm design does not allow firm conclusions to be drawn. However, the results for the T790M-positive patients are in line with previously published data from both randomized and non-randomized trials. Furthermore, the follow-up time for iPFS is substantially longer in our study than in the AURA-trials, suggesting a sustained CNS protection with osimertinib. Further studies are needed to determine the role of osimertinib in treating brain metastases in combination with or without radiotherapy.

To conclude, this subgroup analysis adds to existing data on the effect of osimertinib in treating brain metastases and preventing disease progression in the CNS in patients with T790M-mediated resistance to prior EGFR-TKI treatment. However, the poor OS for pretreated T790M-negative patients with brain metastases in this study seems to be driven by minimal intracranial efficacy of the drug in this group.

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Disclosure Statement

HG, ÅH, SE, KHH, JBS and SC have nothing to disclose. IJZE has received honoraria for lectures or advisory boards for Novartis and Boehringer-Ingelheim. AM has received grants from AstraZeneca. 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 honoraria for lectures or advisory boards from AstraZeneca and grants from Roche, Pfizer and Astra Zeneca.

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Figure legends

Figure 1. Overview of patient flow.

Figure 2 (A) Intracranial progression free survival (iPFS). **(B)** iPFS by T790M-status. **(C)** Cumulative incidence of CNS progression in the full study cohort. **(D)** Cumulative incidence of CNS progression in patients with baseline brain metastases.

Supplementary figure 1. Best percentage change in target lesions for patients with measurable disease.

Supplementary figure 2 (A). Duration of disease control, overall. **(B)** Duration of disease control by T790M.

Supplementary figure 3. Proportion of patients with progression in the CNS in the full study cohort, regardless of T790M. *BM – brain metastases*