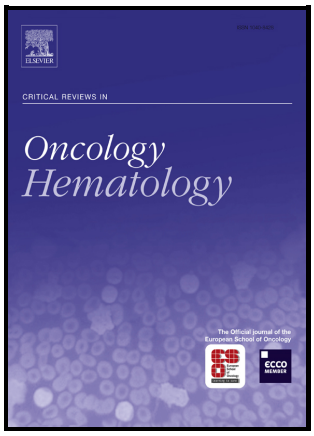
Journal Pre-proof



Role of osimertinib plus brain radiotherapy versus osimertinib single therapy in EGFR-mutated Non-Small-Cell Lung Cancer with brain metastases: a meta-analysis and systematic review.

Alessandro Nepote, Stefano Poletto, Valentina Bertaglia, Simona Carnio, Carlo Piumatti, Cristina Lanzetta, Ornella Cantale, Giorgio Saba, Paolo Bironzo, Silvia Novello, Antonino Carmelo Tralongo

PII: S1040-8428(24)00283-X

DOI: https://doi.org/10.1016/j.critrevonc.2024.104540

Reference: ONCH104540

To appear in: *Critical Reviews in Oncology / Hematology*

Received date: 17 May 2024
Revised date: 14 October 2024
Accepted date: 18 October 2024

Please cite this article as: Alessandro Nepote, Stefano Poletto, Valentina Bertaglia, Simona Carnio, Carlo Piumatti, Cristina Lanzetta, Ornella Cantale, Giorgio Saba, Paolo Bironzo, Silvia Novello and Antonino Carmelo Tralongo, Role of osimertinib plus brain radiotherapy versus osimertinib single therapy in EGFR-mutated Non-Small-Cell Lung Cancer with brain metastases: a meta-analysis and systematic review., *Critical Reviews in Oncology / Hematology,* (2024) doi:https://doi.org/10.1016/j.critrevonc.2024.104540

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2024 Published by Elsevier.

Journal Pre-proof

Role of osimertinib plus brain radiotherapy versus osimertinib single therapy in EGFR-mutated Non-Small-Cell Lung Cancer with brain metastases: a meta-analysis and systematic review.

Alessandro Nepote[a1], Stefano Poletto[a1], Valentina Bertaglia[a*], Simona Carnio[a], Carlo Piumatti[a], Cristina Lanzetta[a], Ornella Cantale[a], Giorgio Saba[b], Paolo Bironzo[a], Silvia Novello [a2] and Antonino Carmelo Tralongo[c2]

[a]Oncology Unit, San Luigi Gonzaga Hospital, Department of Oncology, University of Turin, Regione Gonzole 10, 10043, Orbassano, Italy.
[b]Medical Oncology Unit, University Hospital and University of Cagliari, 09042 Cagliari, Italy.
[c]Medical Oncology Unit, Umberto I Hospital, Azienda Sanitaria Provinciale (ASP) Siracusa, 96100 Siracusa, Italy

Correspondence to: Oncology Unit, San Luigi Gonzaga Hospital, Department of Oncology, University of Turin, Regione Gonzole 10, 10043, Orbassano (TO), Italy.
E-mail address: valentina.bertaglia@gmail.com (V.Bertaglia)
[1]Equal contribution
[2]Co-last authors

Keywords:
Non small cell lung cancer, targeted therapy, osimertinib, brain metastases, brain radiotherapy, meta-analysis

Short biography

Alessandro Nepote was born in Turin, where, after completing his medical degree, he is currently doing his residency in medical oncology. Since 2021 he started working with patients affected by melanoma with an advanced disease at Candiolo IRCCS institute (Candiolo). Afterwards he spent one year at San Luigi Gonzaga hospital (Orbassano), where he was involved as a clinician and as a youg researcher in the prestigious Lung Cancer Unit, directed by Prof.ssa Novello.
During his career, he has followed some melanoma clinical trials as a sub-investigator, including phase 1-2 clinical trials. Now, he is focusing on translational research, especially on melanoma brain metastasis at the Baggiolini Lab (Institute of Oncology Research) in Bellinzona (CH)

Stefano Poletto, MD, is a Clinical Research Fellow in the Department of Oncology, University of Turin, and A.O.U. San Luigi Orbassano, Turin, Italy. Previously he completed his fellowship in Medical Oncology at the IRCCS Candiolo Cancer Institute in Turin, Italy. His main topics of research

Journal Pre-proof

include the immunotherapy in the treatment of hematologic and solid tumors, with a particular focus on skin and thoracic cancer.

Valentina Bertaglia, MD, PhD, is a Medical Oncologist at the Thoracic Oncology Unit of San Luigi Hospital, Orbassano (Turin). In 2009, she graduated in Medicine and Surgery from the University of Turin. In 2015 she completed her specialist training in Medical Oncology and PhD programme in Experimental Medicine and Therapy at the University of Turin. She specialises in the treatment of thoracic malignancies and geriatric oncology.

Simona Carnio, MD, is a Medical Oncologist at the Thoracic Oncology Unit of San Luigi Hospital, Orbassano (Turin) with clinical and research focus on thoracic malignancies and palliative care.

Carlo Piumatti, MD, is a fellow in Medical Oncology at the University of Turin. He graduated in Medicine at the University of Torino. He is involved in clinical management as well as research in solid tumors.

Cristina Lanzetta, MD, is a fellow in Medical Oncology at the University of Turin. She graduated in Medicine at the University of Torino. She is involved in clinical management as well as research in solid tumors.

Ornella Cantale, MD, is a fellow in Medical Oncology at the University of Turin. She graduated in Medicine at the University of Catania. She is involved in clinical management as well as research in solid tumors.

Giorgio Saba, MD, is a fellow in Medical Oncology at the University of Cagliari (Italy). He is involved in clinical management as well as research in lung cancer and breast cancer.

Paolo Bironzo MD, PhD, is Assistant Professor of Medical Oncology at the Department of Oncology of the University of Turin. His main research areas are thoracic tumors, especially lung cancer and pleural mesothelioma. He is a member of the European Organisation for the Research and Treatment of Cancer (EORTC) Lung Cancer Group Board and scientific secretary of the Italian Association of Medical Oncology (AIOM) Clinical Practice Guidelines on Pleural Mesothelioma. He is actively involved in clinical and translational research, including international collaborations, mainly on thoracic tumors. He is author and co-author of several works in peer-reviewed journals. He is member of the Italian Association of Medical Oncology (AIOM), International Association for the Study of Lung Cancer (IASLC), and European Society of Medical Oncology (ESMO).

Journal Pre-proof

Silvia Novello MD, PhD is Full Professor of Medical Oncology at the Department of Oncology of the University of Turin. She earned her medical degree and completed the postgraduate training in Respiratory Medicine and Medical Oncology at the University of Turin and partially at the Institut Gustave Roussy, in France. Currently, she is head of the Medical Oncology and Thoracic Oncology Unit at the San Luigi Hospital, Orbassano (Turin), where she also tutors medical students and Postgraduate students in Respiratory Medicine and Medical Oncology. Prof. Novello's research interests include thoracic malignancies, primary prevention, gender differences in lung cancer, basic, translational and clinical applied research on lung cancer and mesothelioma, including pharmacogenomics. She is involved as PI in many international and national controlled clinical trials evaluating new approaches in diagnosis and lung cancer therapy. From July 2012 until 2016, Prof Novello has been a Member of the Board of Directors of the International Association for the Study of Lung Cancer and since October 2016 Member of the Board of Directors of the Italian Association of Medical Oncology, past Secretary and now part of the EORTC Lung Cancer Group and member of several scientific societies including the American Society of Clinical Oncology, American Thoracic Society and the European Society of Medical Oncology. Currently, she is the President of WALCE (Women Against Lung Cancer in Europe), a non profit European Association founded in 2006 in Turin, Italy, part of the scientific Committee of LuCe (Lung cancer Europe) and also member of the Scientific Committee of Bonnie J Addario Lung Cancer Foundation and Member of the Scientific Committee of ICAPEM (Investigación sobre Cáncer de Pulmón en Mujeres). She is the author or co-author of over 150 publications in peer-reviewed journals.

Antonino C Tralongo, MD, is specialist in Clinical Oncology and practices at the Umberto I Hospital in Syracuse. His main field of interest concerns thoracic and skin cancers (he is the referent of lung pathology in the Oncology Department where he works). His training also includes scientific research, primarily based on research methodology. He currently works within the Laboratory of Methodology of Systematic Reviews and Production of Guidelines, in the Department of Oncology of the Mario Negri Institute in Milan, where he contributes to the production and updating of the Italian Association of Medical Oncology (AIOM) guidelines. He is a member of the European Society of Medical Oncology. He is the author and co-author of several publications in peer- reviewed journals.

Journal Pre-proof

Abstract

Single-agent osimertinib has improved outcomes in EGFR-mutated lung cancer patients with brain metastases (BMs), but still, 40% of them will experience an intracranial progression. We performed a systematic review to evaluate the role of brain radiotherapy upfront plus osimertinib. We

evaluated articles comparing the use of osimertinib versus osimertinib plus brain radiotherapy. We included 897 patients from nine retrospective studies. Patients treated with combination therapy had an improvement in intracranial progression-free survival (HR 0.76; 95% CI 0.61-0.94) and overall survival (HR 0.56; 95% CI 0.36-0.87) with an acceptable safety profile. Osimertinib with upfront brain radiotherapy may be a suitable first-line treatment option for EGFR mutated patients with BMs at diagnosis. The main limitations of this analysis are the retrospective nature and the inability to control for a single variable of interest. Despite that, the combination of osimertinib and upfront brain radiotherapy is a treatment strategy that deserves further prospective trials.

1. Introduction

Brain metastases (BMs) represent a main issue in the treatment of non-small-cell lung cancer (NSCLC). About 10-25% of the patients with advanced disease present BMs at the initial diagnosis, and up to 50% of the patients eventually develop BMs during the entire course of the disease. (Riihimäki et al., 2014; Ulahannan et al., 2017). Furthermore, BMs incidence shows an increasing trend due to the development of more accurate diagnostic procedures and new treatment options leading to better control of extracranial disease. However, the development of BMs still results in a poor clinical outcome with a median overall survival (OS) that ranged from 3 to 15 months. (Achrol et al., 2019; Sperduto et al., 2012)

Epidermal growth factor receptor (*EGFR*) mutations are common in patients with advanced NSCLC, with a frequency of approximately 50% in Asian populations and 15% in Caucasian patients. Patients with EGFR-mutated NSCLC present a higher propensity to develop BMs (Berger et al., 2013; Melosky et al., 2022; Rangachari et al., 2015; Rosell et al., 2009). In particular, BMs are detected in 24.4% of EGFR-mutated patients at the time of diagnosis and in 46.7% within 3 years from the diagnosis, respectively. (Rangachari et al., 2015) EGFR tyrosine kinase inhibitors (EGFR-TKIs) are the standard treatment for advanced NSCLC with EGFR mutations (Hendriks et al., 2023). The third-generation TKI osimertinib demonstrated to improve progression-free survival (PFS) as compared to first-generation TKIs (gefitinib and erlotinib) and is the preferred first-line treatment to date. (Soria et al., 2018). Moreover, the phase III FLAURA trial confirmed the efficacy of osimertinib in patients with asymptomatic brain metastases (BMs) with a CNS objective response rate (ORR) that ranged from 66% to 91%, depending on the presence or not of measurable lesions. This led to an improvement in intracranial PFS (icPFS) (58% vs 40% at 18 months) as well, due to the ability to cross the blood-brain barrier (BBB) compared to first-generation TKIs (Reungwetwattana et al., 2018).

Loco-regional treatments are another cornerstone of BMs management, encompassing both neurosurgical approaches and radiotherapy (RT). Specifically, RT could be delivered either as whole-brain radiotherapy (WBRT) or as stereotactic radiosurgery (SRS) (Mantovani et al., 2021). Few retrospective studies and meta-analyses reported the longest median OS in patients receiving upfront SRS followed by TKI in EGFR-mutated NSCLC with baseline brain metastases, suggesting a possible role of combining these two strategies. (Magnuson et al., 2017; Soon et al., 2015).

However, the role of combining upfront brain RT with more brain-penetrating drugs such as osimertinib is not well established. For this reason, we conducted a meta-analysis to better define the possible benefits of upfront brain RT concurrent with the start of the third-generation TKI osimertinib in all line settings.

2. Material and methods

We conducted a comprehensive literature search using PubMed, EMBASE, and the Cochrane Library from September 1, 2023, to October 31, 2023. We did an update of the literature search in March 2024, screening for the articles published in the meantime. We ended the literature research on March 31, 2024. We followed and reported guidelines from the PRISMA checklist (Page et al., 2021) (Supplementary File 1). The protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) CRD42024469153 and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42024469153.

2.1 Search strategy

The search utilized the following combination of keywords: (Lung cancer or non-small cell lung cancer or adenocarcinoma or NSCLC or lung neoplasm) AND (radiotherapy or cranial radiotherapy or radiation therapy or whole brain radiation therapy or WBRT or whole brain radiotherapy or stereotactic radiotherapy or stereotactic radiosurgery or SRS or radiosurgery or intracranial) AND (TKI or osimertinib or tyrosine kinase inhibitor or EGFR or targeted therapy or epidermal growth factor receptor) AND (brain metastases or CNS metastases) [MeSH Terms]. (see Supplementary File 1)

The inclusion criteria for literature selection were defined using the Population, Intervention, Control, Outcomes (PICO) method (**Fig. 1**).

2.2 Study selection

Inclusion criteria for the quantitative meta-analysis involved studies with data on: (1) patients diagnosed with EGFR-mutated NSCLC with brain metastases; (2) reporting or extractable data on either median PFS or OS and the related hazard ratio (HR); (3) treatment with osimertinib in whichever line settings and brain RT (either SRS or WBRT) as an upfront treatment strategy; (4) studies in which a minority of patients in the experimental arm (SRS or WBRT + TKI) underwent brain surgery as local treatment were included.

Exclusion criteria were: (1) studies in which RT was considered as a salvage therapy or as consolidative therapy in the combination arm; (2) studies including surgery as the only treatment option in the experimental arm; (3) studies including patients treated with first-generation TKIs or studies in which it was not possible to extrapolate outcome single data regarding osimertinib use; (4) studies written in a language other than English; 5) articles published before January 1, 2014.

A total of 1,258 abstracts were initially reviewed independently by two authors (A.N., V.B.), using dual data extraction through Ryyaan software. Before the screening, 28 articles were automatically excluded as duplicates and one was excluded because the work was not published in English. Of the remaining 1,229 articles screened, 45 full-text articles were assessed for eligibility. A third reviewer (S.P.) cross-checked the articles selected by the first two authors, confirming eligibility and resolving disagreements. Ultimately, 9 articles were considered eligible for quantitative meta-analysis The full list of all excluded articles is available as an online library through the link reported in Supplementary File 1. We described the selection algorithm based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (**Fig. 2**)

2.3 Data extraction and risk of bias assessment

We used Microsoft Excel for data collection. For each study, we extracted data about the number of patients included in each arm, line setting, median follow-up, patients with less than three metastases in each arm, intracranial overall response rate, median progression-free survival, and median overall survival for each arm, rate of adverse events. The quality of the studies included was evaluated through the Newcastle-Ottawa scale (NOS) for cohort studies. (**Table 1**).

2.4 Outcome measures

Journal Pre-proof

The primary outcomes of the study were icPFS and OS. Secondary outcomes were intracranial overall response rate (icORR) and the rate of adverse events (AEs). OS was defined as the survival time between the start of third-generation TKI and death from any cause. Intracranial PFS was defined as failure of local control of known brain metastases or development of new brain metastases following initial therapy with third-generation TKI. IcORR was defined as the rate of complete response plus partial response at the intracranial level.

We assessed the overall certainty of the evidence for each outcome using the GRADE domains according to the GRADE approach (Balshem et al., 2011). The existing evidence was summarised in a Summary of Findings (SoF) table, which provides critical information about the magnitude of the interventions' relative effects, as well as the quantity and certainty of available evidence.

2.5 Statistical Analysis

The inverse variance method was assessed to analyze time-to-event outcomes, producing a pooled effect estimate and using Hazard Ratio and their related 95% confidence intervals. When studies did not provide any direct information about the Hazard Ratio of the outcomes of interest, we obtained the log Hazard Ratio and the Standard Error through p-value and/or Confidence Interval, as suggested by the Cochrane guidelines and scientific literature. (Higgins et al., 2023; Parmar et al., 1998) . A random effect model was performed for all analyses due to potential heterogeneity among the studies. Statistical heterogeneity was evaluated using the I^2 statistic, which assesses the appropriateness of pooling the individual study results. The I^2 value provides an estimate of the amount of variance across the studies as a result of heterogeneity rather than chance: $I^2 < 30\%$ indicates mild, 30–50% moderate, and > 50% severe heterogeneity. Reports of the rate of adverse events and ic ORR were descriptive, as only three studies reported these data and meta-analysis was not feasible. Results were depicted as conventional meta-analysis forest plots using RevMan 5.4 software.

3. Results

Nine retrospective studies were included in the final analysis for a total of 897 patients, with a median follow-up time ranging from 14.0 and 40.0 months (Gu et al., 2021; Niu et al., 2024; Thomas et al., 2022; Tozuka et al., 2024; Xie et al., 2019; Yu et al., 2021; Zhai et al., 2021; Zhao et al., 2022; Zhou et al., 2023). The studies included were published from 2019 to 2024. Patients belonged to an Asian ethnicity in 8 out of 9 studies. Data on primary outcomes as well as main patient characteristics are listed for each study in Table 2. Gu et al. and Zhao et al. evaluated patients treated with every generation of EGFR-directed TKIs in first line. However, a subgroup analysis assessed the outcome for patients treated with osimertinib. In the study of Gu et al., more patients in the RT group had neurological symptoms (68.3% vs 33.3%) and more than three brain metastases (43.3% vs 23.1%). Gu et al. reported in detail subsequent treatments after intracranial progression and only two out of thirteen patients treated with first-line third-generation TKI alone received subsequent salvage brain RT.

Three studies evaluated patients treated with third-generation TKIs in first-line (Niu et al., 2024; Tozuka et al., 2024; Zhou et al., 2023). Niu et al. also included patients treated with aumolertinib, while osimertinib was the only evaluated EGFR-inhibitor in the other two studies. In the study of Niu et al., all patients presented neurologic symptoms, and more patients in the combination group presented an oligo BM number (59.5% vs 36.4%), even if this difference was not statistically significant. In the study of Zhou et al., the RT group had a higher prevalence of patients with symptomatic BM (55.2% vs 20.5%) while no differences were seen in other patient characteristics, such as the number of brain metastases or the presence of extracranial metastases. In the study of Tozuka et al., patients receiving osimertinib plus local treatment upfront presented a higher median of the largest BM diameter (15 vs 8 mm), a higher proportion of symptomatic BMs (42% vs 9%), more frequently received steroids (27% vs 8%, p=0.008), and more likely had only intracranial disease.

In the remaining studies, patients treated with osimertinib in all-line settings were evaluated, including patients with acquired T790M mutation. (Thomas et al., 2022; Xie et al., 2019; Yu et al., 2021; Zhai et al., 2021) It is worth mentioning that Thompson et al. also enrolled 4 patients treated with the third-generation TKI rociletinib, and patients in the RT+TKI arm more frequently exhibited more than ten brain metastases (44.2% vs. 30.8%). Zhai et al. showed no differences in the number of brain metastases and symptomatic patients between the two treatment arms. Yu et al. reported no differences in the two arms in the number of brain metastases and the other reported characteristics, while more symptomatic patients were treated with osimertinib+RT.

We should highlight that three of the studies included in this analysis also enrolled a minority of patients who received surgery as local treatment. (Niu et al., 2024; Tozuka et al., 2024; Zhao et al., 2022). In the study of Zhao et al., 24 patients were enrolled in the combination group but authors did not specify if they received SRS or surgery. Furthermore, Niu et al. enrolled 14 patients receiving surgery, while in the study of Tozuka et al., one patient received WBRT+SRS, 3 patients had surgery, and 2 patients had both SRS + surgery.

3.1 Primary outcomes

OS data were evaluable for 8 studies. (Gu et al., 2021; Niu et al., 2024; Tozuka et al., 2024; Xie et al., 2019; Yu et al., 2021; Zhai et al., 2021; Zhao et al., 2022; Zhou et al., 2023), showing a significant improvement in patients treated with third-generation TKI plus radiotherapy, as compared with TKI alone, with an HR of 0.56 (95% CI 0.36- 0.87; certainty of evidence: very low). Heterogeneity in the included studies was 56%. (Figures 3, 5)

Final analysis of the co-primary endpoint icPFS was obtained from 7 studies with available data. (Gu et al., 2021; Niu et al., 2024; Thomas et al., 2022; Tozuka et al., 2024; Yu et al., 2021; Zhai et al., 2021; Zhou et al., 2023). The study of Xie et al. was excluded from the final analysis on icPFS because only systemic PFS was reported. Patients treated with third-generation TKI plus radiotherapy experienced a significantly longer icPFS, as compared with patients treated with third-generation TKI alone (HR 0.76, 95% CI 0.61-0.94; certainty of evidence: very low). Heterogeneity among the studies was low (I^2 = 0%). (Figures 4-5)

3.2 Secondary outcomes

Three studies (Zhai et al. 2021, Thomas et al., 2022 and Niu et al.,2024) reported data on icORR. In the first study, the icORR was 38.1% in the osimertinib plus RT group and 42.5% in the osimertinib alone group, but this difference was not statistically significant (P = 0.740). Among patients who received osimertinib plus RT, 2 patients (9.5%) achieved a complete response of the intracranial metastases. In the second study, the icORR was similar between the TKI alone and TKI+RT arms (73.1% vs 74.4%), with no patients achieving a complete response. In the third study, the two groups experienced similar icORR (59.1% vs 61.9%) and intracranial disease control rate (88.6% vs 92.9%). Only four studies (Zhou et al., 2024, Zhai et al., 2021, Niu et al., 2024 and Tozuka et al., 2024) described treatment toxicities. In the study of Zhai et al., the rate of AE was 32.5% in the osimertinib alone group and 47.6% in the osimertinib plus RT group. The rate of grade 3-4 (G3-4) adverse events was more than doubled in the osimertinib plus RT group (19.0% vs 7.5%), but this difference was not statistically significant (p = 0.220). The most common G3-4 AEs in the combination group was leukoencephalopathy in 14.2% of patients, but only patients treated with WBRT eventually experienced leukoencephalopathy. Niu et al. and Tozuka et al. reported no significant difference in adverse reactions between the two groups. In the study of Niu et al., more patients in the TKI + RT arm experienced leukoencephalopathy (16.5% vs 4.6%) and oral ulcer (14.3% vs 4.5%), while in the study of. Tozuka et al. only two patients had AEs related to local treatment, including one case of radionecrosis. Zhou et al. reported similar TKI-related AEs in both treatment arms (75% vs 73.5%). Also, they described AEs related to brain RT. The

incidence of AEs was higher in patients with multiple BMs as compared with patients with an oligometastatic brain disease (51.3% vs 85.7%, P < 0.001). Also, patients with multiple brain metastases experienced more frequently dizziness (31.9% vs 53.1%, P = 0.036), headache (27.7% vs 51.1%, P = 0.019), radiation dermatitis (17.0% vs 47.3%, P = 0.002) and neurocognitive dysfunction (32% vs 85.7%, P < 0.001). The incidence of grade 3-4 AEs was similar (2.1% vs 4.1%)

4. Discussion

To our knowledge, this is the first meta-analysis to evaluate the role of adding upfront brain radiotherapy in patients with EGFR-mutated NSCLC and BMs treated with third-generation TKIs.

The introduction of osimertinib completely changed clinical practice due to its ability to overcome BBB with an important improvement in icPFS as compared to first-generation TKIs. However, almost half of the patients relapse at the 2-year landmark time point. (Ramalingam et al., 2020). Multiple mechanisms of resistance to osimertinib have been identified, such as *MET* proto-oncogene amplification, secondary *EGFR* mutations, and histologic transformation. As of today, chemotherapy represents the preferred treatment option at the time of progression.

In this scenario, patients with BMs at diagnosis still represent a difficult-to-treat subgroup, leading to a poorer prognosis and potentially affecting quality of life in the case of local progression. (Roper et al., 2020).

Therefore, understanding the optimal timing of brain radiotherapy is crucial to improving patient outcomes and maximizing osimertinib efficacy.

Our analysis included almost 900 patients with metastatic EGFR-mutated NSCLC and treated with upfront SRS or WBRT in addition to a third-generation TKI, showing a statistically significant improvement in terms of OS and icPFS, with a 44% decreased risk of death and a 24% decreased risk of intracranial progression. This may reflect on one side the effective role of RT in treating a poor prognostic disease site and, on the other, a negligible additive effect in reducing the risk of the appearance of new BMs. Of note, in the combination arm, only a minority of patients were treated with WBRT with an expected prophylactic effect. (Reungwetwattana et al., 2018; Wu et al., 2020). The addictive effect of brain radiotherapy may also contribute to delaying cloning selection due to the drug pressure, reducing the risk of rapid resistance and progression of the existing lesions at the beginning of the systemic treatment.

However, our study has some limitations. First, all of the included studies are retrospective with the intrinsic possibility of selection bias, possibly affecting treatment choice based on the CNS tumor burden. In addition, studies where a minority of patients in the experimental arm underwent brain surgery as local treatment were not excluded. However, less than 5% of patients received surgery as local treatment. Second, all but one study was conducted in the Asian region, limiting the reproducibility of these results in other populations. Third, since single patient-level data are lacking, we were unable to control for covariates of interest, such as gender differences, presence of neurologic symptoms, type of EGFR mutation, number of brain metastases, tumor burden, and specific radiotherapy protocols. Finally, the heterogeneity of the studies included in the OS analysis was high, and for this reason, this data should be interpreted with caution.

With these limitations, our findings support the use of upfront radiotherapy, although based on case-by-case discussion, and confirm the pivotal importance of multidisciplinary management of these patients. The certainty of evidence analysis of the two primary endpoints was classified as “very low”, highlighting the difficulty of conducting studies in this field. Randomized clinical trials are needed to confirm our findings and better define the subgroup of patients that could benefit the most from a combination approach. A multicenter randomized phase II trial evaluating osimertinib alone compared

to osimertinib plus SRS in patients with ≤ 10 brain or brainstem metastases is ongoing and results are expected in 2025 (NCT03769103).

A potential issue of combining different treatment regimens is the increased toxicity. Only four studies reported data about toxicities and adverse events. (Zhou et al., 2024, Zhai et al., 2021 Niu et al. 2024 and Tozuka et al.,2024) Zhai et al. showed that the rate of G3-4 AEs was higher in the osimertinib plus brain radiotherapy group, even if the difference was not statistically significant. Also, six cases of leukoencephalopathy were registered, all in the WBRT plus osimertinib group. (Zhai et al., 2021) Leukoencephalopathy was also reported by Niu et al., with a higher risk in the combination treatment, even if the overall rate of adverse events was similar between treatment arms. Zhou et al. reported an increased rate of AEs in patients with multiple brain metastases, suggesting a subgroup of patients at higher risk. We should highlight that adverse events were underreported in the selected studies and for this reason, a formal comparison was not feasible. Data from the literature are missing and mostly refer to the safety of the combination between first- or second-generation EGFR-TKIs and RT, showing an absent or modest increment of G3-4 AEs. (Jiang et al., 2016; Luo et al., 2015; Zhou et al., 2022).

In a systematic review by Hendriks et al. evaluating the combination of TKI with cranial radiotherapy in ALK-rearranged or EGFR-mutated NSCLC patients, no cases of leukoencephalopathy were mentioned. However, neurotoxicity such as brain radionecrosis was reported in the experimental arm. (Hendriks et al., 2015), as with one patient in the study of Tozuka et al. Although conclusions cannot be drawn, the safety profile is another crucial aspect that should be investigated in future prospective clinical trials.

Systemic treatment for patients with metastatic EGFR-mutated NSCLC is continuously evolving and new options for patients with brain metastases are emerging. In the phase 3 randomized FLAURA-2 trial, osimertinib + platinum–pemetrexed chemotherapy was shown to be superior to osimertinib alone, with a maintained benefit even in the subgroup of patients with baseline brain metastases (24.9 vs 13.8 months; HR 0.47 (95% CI, 0.33–0.66).

Preliminary data of the MARIPOSA trial showed that the combination of lazertinib and amivantamab led to a benefit in mPFS also in the subgroup of patients with a history of BMs (18.3 vs 13.0 months; HR 0.69, 95% CI 0.53–0.92) as compared to osimertinib single agent in first line. In the interim analysis, the combination arm also trends favorably toward a benefit in OS in the overall population. (Cho et al., 2023). However, 75% of patients experienced a grade ≥3 adverse event, with a more than doubled discontinuation rate (35% vs 14%) in the combination arm.

In this changing landscape, osimertinib plus concomitant brain radiotherapy still represents a valid option that deserves further evaluation and could be an interesting first-line approach, especially in patients with comorbidities that could not be suitable for more intensive treatments.

5. Conclusion

In summary, this is the first meta-analysis showing an iPFS and OS benefit in patients with metastatic EGFR-mutated NSCLC with BM treated with osimertinib and concomitant upfront brain radiotherapy, showing a significant synergistic effect between the two treatments. Osimertinib and concomitant brain radiotherapy may be a first-line treatment option for NSCLC patients with EGFR mutation and BMs at diagnosis. Future clinical trials should confirm these results and explore whether certain subgroups may benefit more from this approach.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Journal Pre-proof

Credit authorship contribution statement

AN: Conceptualization, Methodology, Writing-Original draft preparation, visualization, Writing - Reviewing and Editing. SP: Conceptualization, Methodology, Data curation, Writing- Original draft preparation, Visualization, Writing -Reviewing and Editing. VB: Methodology, data curation, writing-Original draft preparation. ACT: Methodology, Formal Analysis, Supervision. SC, CL,CP,OC,GS: Reviewing. PB, SN, ACT: supervision, Writing- Reviewing and Editing.

Conflict of interest statement

Authors declare no conflicts of interests.

Acknowledgements

None

References

Achrol, A.S., Rennert, R.C., Anders, C., Soffietti, R., Ahluwalia, M.S., Nayak, L., Peters, S., Arvold, N.D., Harsh, G.R., Steeg, P.S., Chang, S.D., 2019. Brain metastases. Nat Rev Dis Primers 5, 5. https://doi.org/10.1038/s41572-018-0055-y

Balshem, H., Helfand, M., Schünemann, H.J., Oxman, A.D., Kunz, R., Brozek, J., Vist, G.E., Falck-Ytter, Y., Meerpohl, J., Norris, S., 2011. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64, 401–406. https://doi.org/10.1016/j.jclinepi.2010.07.015

Berger, L.A., Riesenberg, H., Bokemeyer, C., Atanackovic, D., 2013. CNS metastases in non-small-cell lung cancer: Current role of EGFR-TKI therapy and future perspectives. Lung Cancer 80, 242–248. https://doi.org/10.1016/j.lungcan.2013.02.004

Cho, B.C., Felip, E., Spira, A.I., Girard, N., Lee, J.-S., Lee, S.-H., Ostapenko, Y.V., Danchaivijitr, P., Liu, B., Alip, A., Korbenfeld, E.P., Dias, J., Sun, T., Martinez, M., Bauml, J.M., Shreeve, M., Sethi, S., Knoblauch, R.E., Hayashi, H., Lu, S., 2023. Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Primary results from MARIPOSA, a phase III, global, randomized, controlled trial. Annals of Oncology 34, S1306. https://doi.org/10.1016/j.annonc.2023.10.062

Gu, Y., Xu, Y., Zhuang, H., Jiang, W., Zhang, H., Li, X., Liu, Y., Ma, L., Zhao, D., Cheng, Y., Yu, Y., Liu, P., Qin, J., Chen, X., Gao, J., Wang, M., Liang, L., Cao, B., 2021. Value and significance of brain radiation therapy during first-line EGFR-TKI treatment in lung adenocarcinoma with EGFR sensitive mutation and synchronous brain metastasis: Appropriate timing and technique. Thorac Cancer 12, 3157–3168. https://doi.org/10.1111/1759-7714.14169

Hendriks, L.E., Kerr, K.M., Menis, J., Mok, T.S., Nestle, U., Passaro, A., Peters, S., Planchard, D., Smit, E.F., Solomon, B.J., Veronesi, G., Reck, M., 2023. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology 34, 339–357. https://doi.org/10.1016/j.annonc.2022.12.009

Journal Pre-proof

Hendriks, L.E.L., Schoenmaekers, J., Zindler, J.D., Eekers, D.B.P., Hoeben, A., De Ruysscher, D.K.M., Dingemans, A.-M.C., 2015. Safety of cranial radiotherapy concurrent with tyrosine kinase inhibitors in non-small cell lung cancer patients: A systematic review. Cancer Treat Rev 41, 634–645. https://doi.org/10.1016/j.ctrv.2015.05.005

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook., n.d.

Jiang, T., Min, W., Li, Y., Yue, Z., Wu, C., Zhou, C., 2016. Radiotherapy plus EGFR TKIs in non-small cell lung cancer patients with brain metastases: an update meta-analysis. Cancer Med 5, 1055–1065. https://doi.org/10.1002/cam4.673

Luo, S., Chen, L., Chen, X., Xie, X., 2015. Evaluation on efficacy and safety of tyrosine kinase inhibitors plus radiotherapy in NSCLC patients with brain metastases. Oncotarget 6, 16725–16734. https://doi.org/10.18632/oncotarget.4264

Magnuson, W.J., Lester-Coll, N.H., Wu, A.J., Yang, T.J., Lockney, N.A., Gerber, N.K., Beal, K., Amini, A., Patil, T., Kavanagh, B.D., Camidge, D.R., Braunstein, S.E., Boreta, L.C., Balasubramanian, S.K., Ahluwalia, M.S., Rana, N.G., Attia, A., Gettinger, S.N., Contessa, J.N., Yu, J.B., Chiang, V.L., 2017. Management of Brain Metastases in Tyrosine Kinase Inhibitor–Naïve Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis. Journal of Clinical Oncology 35, 1070–1077. https://doi.org/10.1200/JCO.2016.69.7144

Mantovani, C., Gastino, A., Cerrato, M., Badellino, S., Ricardi, U., Levis, M., 2021. Modern Radiation Therapy for the Management of Brain Metastases From Non-Small Cell Lung Cancer: Current Approaches and Future Directions. Front Oncol 11. https://doi.org/10.3389/fonc.2021.772789

Melosky, B., Kambartel, K., Häntschel, M., Bennetts, M., Nickens, D.J., Brinkmann, J., Kayser, A., Moran, M., Cappuzzo, F., 2022. Worldwide Prevalence of Epidermal Growth Factor Receptor Mutations in Non-Small Cell Lung Cancer: A Meta-Analysis. Mol Diagn Ther 26, 7–18. https://doi.org/10.1007/s40291-021-00563-1

Niu, L., Wu, H., Gao, R., Chen, L., Wang, J., Duan, H., Long, Y., Xie, Y., Zhou, Q., Zhou, R., 2024. Optimal sequence of LT for symptomatic BM in EGFR-mutant NSCLC: a comparative study of first-line EGFR-TKIs with/without upfront LT. J Cancer Res Clin Oncol 150. https://doi.org/10.1007/s00432-023-05538-9

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. The BMJ. https://doi.org/10.1136/bmj.n71

Parmar, M.K.B., Torri, V., Stewart, L., 1998. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17, 2815–2834. https://doi.org/10.1002/(SICI)1097-0258(19981230)17:24<2815::AID-SIM110>3.0.CO;2-8

Ramalingam, S.S., Vansteenkiste, J., Planchard, D., Cho, B.C., Gray, J.E., Ohe, Y., Zhou, C., Reungwetwattana, T., Cheng, Y., Chewaskulyong, B., Shah, R., Cobo, M., Lee, K.H., Cheema, P., Tiseo, M., John, T., Lin, M.-C., Imamura, F., Kurata, T., Todd, A., Hodge, R., Saggese, M., Rukazenkov, Y., Soria, J.-C., 2020. Overall Survival with

Journal Pre-proof

Osimertinib in Untreated EGFR-Mutated Advanced NSCLC. New England Journal of Medicine 382, 41–50. https://doi.org/10.1056/NEJMoa1913662

Rangachari, D., Yamaguchi, N., VanderLaan, P.A., Folch, E., Mahadevan, A., Floyd, S.R., Uhlmann, E.J., Wong, E.T., Dahlberg, S.E., Huberman, M.S., Costa, D.B., 2015. Brain metastases in patients with EGFR -mutated or ALK -rearranged non-small-cell lung cancers. Lung Cancer 88, 108–111. https://doi.org/10.1016/j.lungcan.2015.01.020

Reungwetwattana, T., Nakagawa, K., Cho, B.C., Cobo, M., Cho, E.K., Bertolini, A., Bohnet, S., Zhou, C., Lee, K.H., Nogami, N., Okamoto, I., Leighl, N., Hodge, R., McKeown, A., Brown, A.P., Rukazenkov, Y., Ramalingam, S.S., Vansteenkiste, J., 2018. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 36, 3290–3297. https://doi.org/10.1200/JCO.2018.78.3118

Riihimäki, M., Hemminki, A., Fallah, M., Thomsen, H., Sundquist, K., Sundquist, J., Hemminki, K., 2014. Metastatic sites and survival in lung cancer. Lung Cancer 86, 78–84. https://doi.org/10.1016/j.lungcan.2014.07.020

Roper, N., Brown, A.-L., Wei, J.S., Pack, S., Trindade, C., Kim, C., Restifo, O., Gao, S., Sindiri, S., Mehrabadi, F., El Meskini, R., Ohler, Z.W., Maity, T.K., Venugopalan, A., Cultraro, C.M., Akoth, E., Padiernos, E., Chen, H., Kesarwala, A., Smart, D.K., Nilubol, N., Rajan, A., Piotrowska, Z., Xi, L., Raffeld, M., Panchenko, A.R., Sahinalp, C., Hewitt, S., Hoang, C.D., Khan, J., Guha, U., 2020. Clonal Evolution and Heterogeneity of Osimertinib Acquired Resistance Mechanisms in EGFR Mutant Lung Cancer. Cell Rep Med 1, 100007. https://doi.org/10.1016/j.xcrm.2020.100007

Rosell, R., Moran, T., Queralt, C., Porta, R., Cardenal, F., Camps, C., Majem, M., Lopez-Vivanco, G., Isla, D., Provencio, M., Insa, A., Massuti, B., Gonzalez-Larriba, J.L., Paz-Ares, L., Bover, I., Garcia-Campelo, R., Moreno, M.A., Catot, S., Rolfo, C., Reguart, N., Palmero, R., Sánchez, J.M., Bastus, R., Mayo, C., Bertran-Alamillo, J., Molina, M.A., Sanchez, J.J., Taron, M., 2009. Screening for Epidermal Growth Factor Receptor Mutations in Lung Cancer. New England Journal of Medicine 361, 958–967. https://doi.org/10.1056/NEJMoa0904554

Soon, Y.Y., Leong, C.N., Koh, W.Y., Tham, I.W.K., 2015. EGFR tyrosine kinase inhibitors versus cranial radiation therapy for EGFR mutant non-small cell lung cancer with brain metastases: A systematic review and meta-analysis. Radiotherapy and Oncology 114, 167–172. https://doi.org/10.1016/j.radonc.2014.12.011

Soria, J.-C., Ohe, Y., Vansteenkiste, J., Reungwetwattana, T., Chewaskulyong, B., Lee, K.H., Dechaphunkul, A., Imamura, F., Nogami, N., Kurata, T., Okamoto, I., Zhou, C., Cho, B.C., Cheng, Y., Cho, E.K., Voon, P.J., Planchard, D., Su, W.-C., Gray, J.E., Lee, S.-M., Hodge, R., Marotti, M., Rukazenkov, Y., Ramalingam, S.S., 2018. Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. New England Journal of Medicine 378, 113–125. https://doi.org/10.1056/NEJMoa1713137

Sperduto, P.W., Kased, N., Roberge, D., Xu, Z., Shanley, R., Luo, X., Sneed, P.K., Chao, S.T., Weil, R.J., Suh, J., Bhatt, A., Jensen, A.W., Brown, P.D., Shih, H.A., Kirkpatrick, J., Gaspar, L.E., Fiveash, J.B., Chiang, V., Knisely, J.P.S., Sperduto, C.M., Lin, N., Mehta, M., 2012. Summary Report on the Graded Prognostic Assessment: An Accurate and Facile Diagnosis-Specific Tool to Estimate Survival for Patients With Brain Metastases. Journal of Clinical Oncology 30, 419–425. https://doi.org/10.1200/JCO.2011.38.0527

Thomas, N.J., Myall, N.J., Sun, F., Patil, T., Mushtaq, R., Yu, C., Sinha, S., Pollom, E.L., Nagpal, S., Camidge, D.R., Rusthoven, C.G., Braunstein, S.E., Wakelee, H.A., McCoach, C.E., 2022. Brain Metastases in EGFR- and ALK-Positive NSCLC: Outcomes of Central Nervous System-Penetrant Tyrosine Kinase Inhibitors Alone Versus in Combination With Radiation. Journal of Thoracic Oncology 17, 116–129. https://doi.org/10.1016/j.jtho.2021.08.009

Tozuka, T., Noro, R., Mizutani, H., Kurimoto, F., Hakozaki, T., Hisakane, K., Naito, T., Takahashi, S., Taniuchi, N., Yajima, C., Hosomi, Y., Hirose, T., Minegishi, Y., Okano, T., Kamio, K., Yamaguchi, T., Seike, M., 2024. Osimertinib plus local treatment for brain metastases versus osimertinib alone in patients with EGFR-Mutant Non-Small Cell Lung Cancer. Lung Cancer 191. https://doi.org/10.1016/j.lungcan.2024.107540

Ulahannan, D., Khalifa, J., Faivre-Finn, C., Lee, S.-M., 2017. Emerging treatment paradigms for brain metastasis in non-small-cell lung cancer: an overview of the current landscape and challenges ahead. Annals of Oncology 28, 2923–2931. https://doi.org/10.1093/annonc/mdx481

Wu, Y.-L., Tsuboi, M., He, J., John, T., Grohe, C., Majem, M., Goldman, J.W., Laktionov, K., Kim, S.-W., Kato, T., Vu, H.-V., Lu, S., Lee, K.-Y., Akewanlop, C., Yu, C.-J., de Marinis, F., Bonanno, L., Domine, M., Shepherd, F.A., Zeng, L., Hodge, R., Atasoy, A., Rukazenkov, Y., Herbst, R.S., 2020. Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer. New England Journal of Medicine 383, 1711–1723. https://doi.org/10.1056/NEJMoa2027071

Xie, L., Nagpal, S., Wakelee, H.A., Li, G., Soltys, S.G., Neal, J.W., 2019. Osimertinib for EGFR -Mutant Lung Cancer with Brain Metastases: Results from a Single-Center Retrospective Study . Oncologist 24, 836–843. https://doi.org/10.1634/theoncologist.2018-0264

Yu, F., Ni, J., Zeng, W., Zhou, Y., Guo, T., Zeng, Y., Zhao, Y., Li, S., Li, Yida, Yang, X., Zou, L., Wang, S., Liu, Q., Li, Yuan, Chu, L., Chu, X., Ye, L., Yu, W., Zhu, Z., 2021. Clinical Value of Upfront Cranial Radiation Therapy in Osimertinib-Treated Epidermal Growth Factor Receptor–Mutant Non-Small Cell Lung Cancer With Brain Metastases. Int J Radiat Oncol Biol Phys 111, 804–815. https://doi.org/10.1016/j.ijrobp.2021.05.125

Zhai, X., Li, W., Li, J., Jia, W., Jing, W., Tian, Y., Xu, S., Li, Y., Zhu, H., Yu, J., 2021. Therapeutic effect of osimertinib plus cranial radiotherapy compared to osimertinib alone in NSCLC patients with EGFR-activating mutations and brain metastases: a retrospective study. Radiation Oncology 16. https://doi.org/10.1186/s13014-021-01955-7

Zhao, Y., Li, S., Yang, X., Chu, L., Wang, S., Tong, T., Chu, X., Yu, F., Zeng, Y., Guo, T., Zhou, Y., Zou, L., Li, Y., Ni, J., Zhu, Z., 2022. Overall survival benefit of osimertinib and clinical value of upfront cranial local therapy in untreated EGFR-mutant nonsmall cell lung cancer with brain metastasis. Int J Cancer 150, 1318–1328. https://doi.org/10.1002/ijc.33904

Zhou, J., Zhou, Y., Sun, Y., Xiao, L., Lu, H., Yin, X., Fan, K., 2023. The efficacy of upfront craniocerebral radiotherapy and epidermal growth factor receptor-tyrosine kinase inhibitors in patients with epidermal growth factor receptor-positive non-small cell lung cancer with brain metastases. Front Oncol 13. https://doi.org/10.3389/fonc.2023.1259880

Zhou, K., Cai, X., Wang, X., Lan, X., Zhang, X., 2022. Efficacy and safety of WBRT + EGFR-TKI versus WBRT only in the treatment of NSCLC patients with brain metastasis: An

Journal Pre-proof

updated meta-analysis. Thorac Cancer 13, 563–570. https://doi.org/10.1111/1759-7714.14299

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

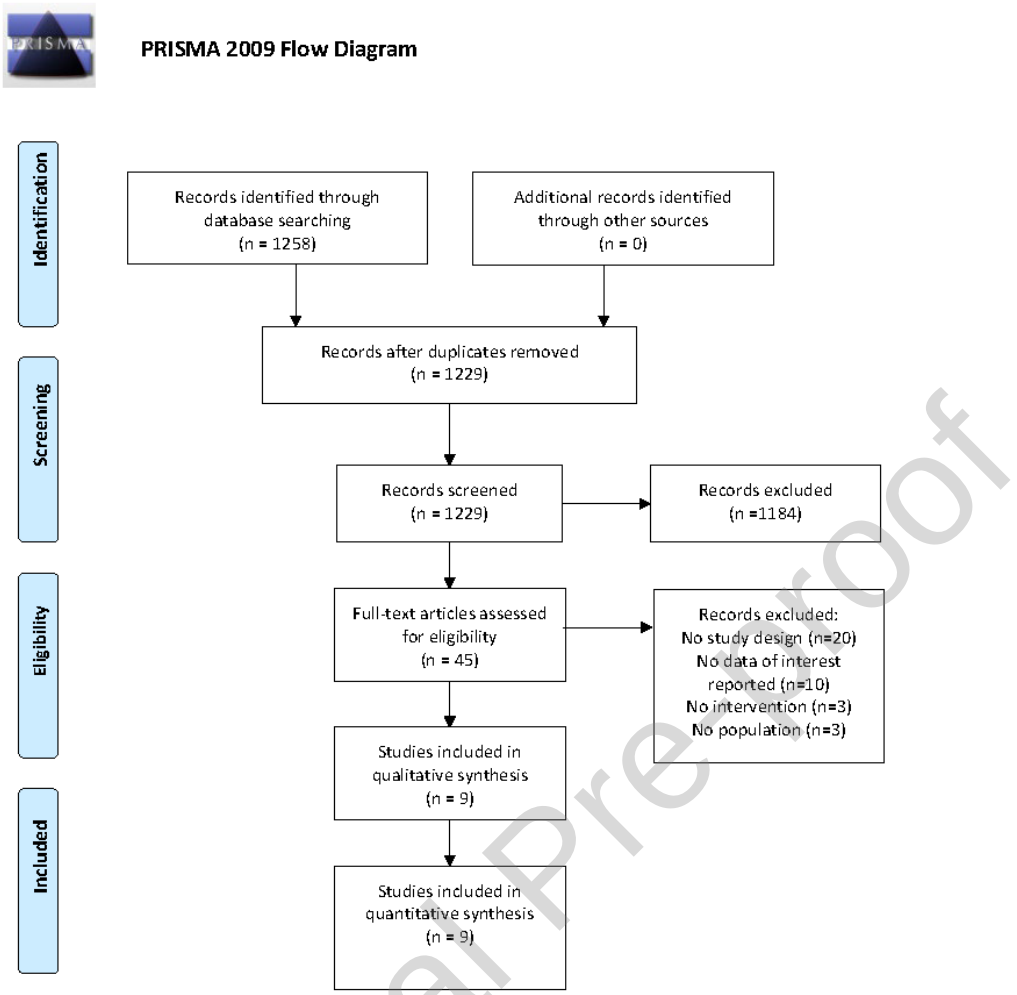
☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Figure 1 - Population, Intervention, Control, Outcomes (PICO) Structure for Study Selection. NSCLC: non-small cell lung cancer; SRS: stereotactic radiosurgery; TKI: tyrosine-kinase inhibitors; WBRT: whole brain radiotherapy

P	**Population**	EGFR-mutated NSCLC with brain metastases in all lines setting, candidate for an EGFR TKI treatment.
I	**Intervention**	Combination of osimertinib and SRS or/and WBRT
C	**Comparison**	osimertinib
O	**Outcome(s)**	Progression free survival and Overall Survival

Figure 2 - Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart of the Selection Process.

Journal Pre-proof



Journal Pre-proof

Figure 3 – Overall survival in patients treated with tyrosine-kinase inhibitor plus radiotherapy (TKI + RT) versus TKI alone (TKI).

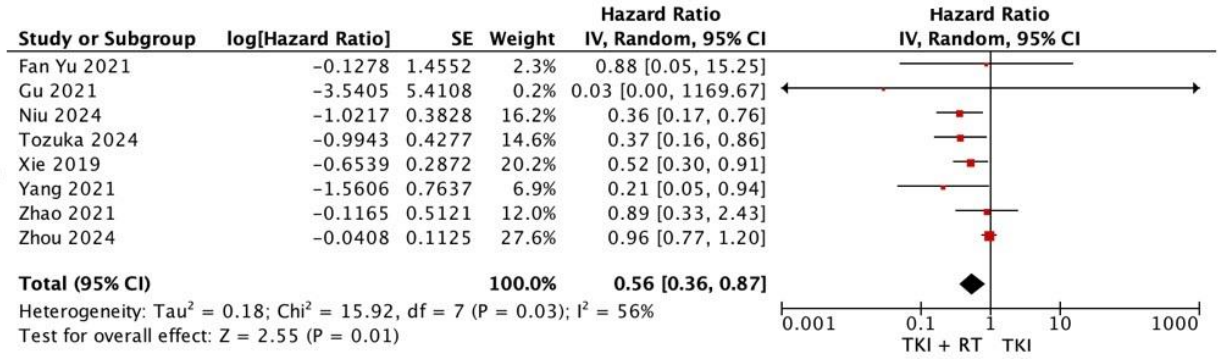
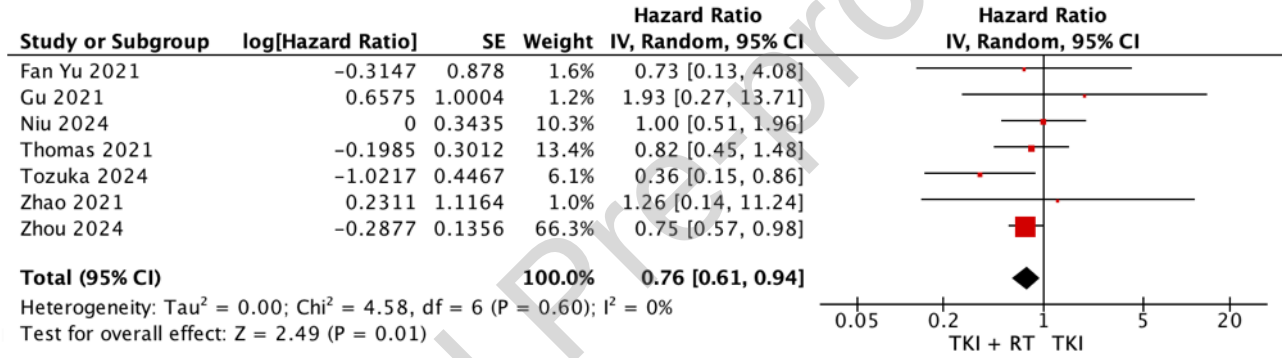


Figure 4 – Intracranial progression-free survival in patients treated with tyrosine-kinase inhibitor plus radiotherapy (TKI + RT) versus TKI alone (TKI)



Journal Pre-proof

Figure 5- Summary of Finding with certainty of evidence through GRADE methodology.

Summary of findings

RT + osimertinib vs osimertinib alone in EGFR-mutated NSCLC with brain metastases under treatment in all lines setting

Patients or population: EGFR-mutated NSCLC with brain metastases under treatment in all lines setting, candidate for a EGFR TKI treatment.
Setting: outpatients
Intervention: RT + osimertinib
Comparison: osimertinib

Outcomes	Anticipated absolute effect (95% CI)		Relative effect (95% CI)	№ of partecipants (studies)	Certainty of evidence (GRADE)	
	Risk with third generation TKI	Risk with RT + third generation TKI				
Overall survival follow up: 14 - 40 months (interval)	NA	NA	**HR 0.56** (0.36 a 0.87)	(8 observational studies)	⨁◯◯◯ Very low [a,c]	
Progression free survival follow up: 14- 40 months (interval)	NA	NA	**HR 0.76** (0.61 a 0.94)	(7 observational studies)	⨁◯◯◯ Very low [b]	

CI: Confidence interval; **HR:** Hazard Ratio
NA: not available

Explanations

a. The certainty of evidence was downgraded for imprecision, due to wide confidence interval.
b. The certainty of evidence was downgraded for performance and detection bias due to study design.
c. The certainty of evidence was downgraded for heterogeneity among the studies.

HR: hazard ratio; NA: not available; NSCLC: non-small cell lung cancer; RT: radiotherapy; TKI: tyrosine-kinase inhibitor.

Table 1: Quality assessment of clinical trials performing Newcastle-Ottawa Scale (NOS)

Author	Year	Selection				Comparability	Outcome			Score
		1	2	3	4	5	6	7	8	
Xie et al.	2019	*	*	*	*		*			**5**
Zhai et al.	2021	*	*	*	*	**	*			**7**
Gu et al.	2021	*	*	*	*	**	*	*		**8**
Thomas et al.	2021	*	*	*	*	**	*		*	**8**
Fan Yu et al.	2021	*	*	*	*	**	*		*	**8**
Zhao et al.	2021	*	*	*	*	**	*			**7**
Zhou et al.	2024	*	*	*	*	**	*		*	**8**
Niu et al.	2024	*	*	*	*	**	*		*	**8**
Tozuka et al.	2024	*	*	*	*	**	*	*		**8**

Table 2 – Summary of main patient characteristics and primary outcome in the included studies.

Journal Pre-proof

Study	Study design	Line	N. patients	N. TKI alone arm	N. RT + TKI arm (SRS/SRT+TKI, WBRT+TKI)	Median follow-up (months)	N. brain mts <=3 TKI alone (%)	N. brain mts <=3 TKI + RT (%)	Median icPFS TKI alone vs RT + TKI (months, HR 95% CI)	Median OS TKI alone vs RT + TKI (months, HR 95% CI)
Zhai et. 2021	Retrospective	All	61	40	21 (2, 19)	15.3	37.5%	38.1%	16.7 vs 13.5 (1.26, 0.14-11.24)	26.1 vs 29.2 (0.89, 0.33-2.43)
Gu et al. 2021	Retrospective	First	16	13	3 (NA, NA)	40.0	NA	NA	(1.93, 0.27-13.71)	(0.03, 0-1169.67)
Thomas et al. 2021	Retrospective	All	95	52	43 (34, 9)	16.8	46.2%	27.9%	14.8 vs 20.5 (0.82, 0.45-1.48)	NA
Xie et al. 2019	Retrospective	All	20	11	9 (9,0)	NA	NA	NA	NA	NR vs 16.2 (0.52, 0.30-0,91)
Fan Yu et al. 2021	Retrospective	All	205	157	48 (24, 24)	14	39.5%	43.2%	17.7 vs 24.1 (0.73, 0.13-4.08)	24.5 vs 27.8 (0.88, 0.05-15.25)
Zhao et al. 2021	Retrospective	First	80	56	24 (24 *, 0)	15.2	NA	NA	NA	26.7 vs 38.9 (0.21, 0.05-0.94)
Zhou et al. 2024	Retrospective	First	213	117	96 (NA, NA)	18.6 and 16.4	49%	41.9%	37.6 vs 36.2 (0.75,0.57-0.98)	29.7 vs 21.8 (0.96,0.77-1.20)
Niu et al. 2024	Retrospective	First	86	44	42 (14, 14) **	17.0	36.4%	59.5%	24 vs 21 (1.00, 0.51–1.96)	43 vs. 28 (0.36, 0.17–0.76)
Tozuka et al. 2024	Retrospective	First	121	45	76 (32, 7) ***	26.3	57%	29%	NR vs NR (0.36, 0.15-0.86)	NR vs 31.2 (0.37, 0.16-0.86)

HR: hazard ratio; icPFS: intracranial progression-free survival; NA: not available; OS: overall survival; RT: radiotherapy; SRS: stereotactic radiosurgery; SRT: stereotactic radiotherapy; TKI: tyrosine-kinase inhibitor; WBRT: whole-brain radiotherapy. * SRS or surgery. ** 14 patients received surgery. *** 1 patient received WBRT+SRS, 3 patients surgery; 2 patients SRS + surgery.

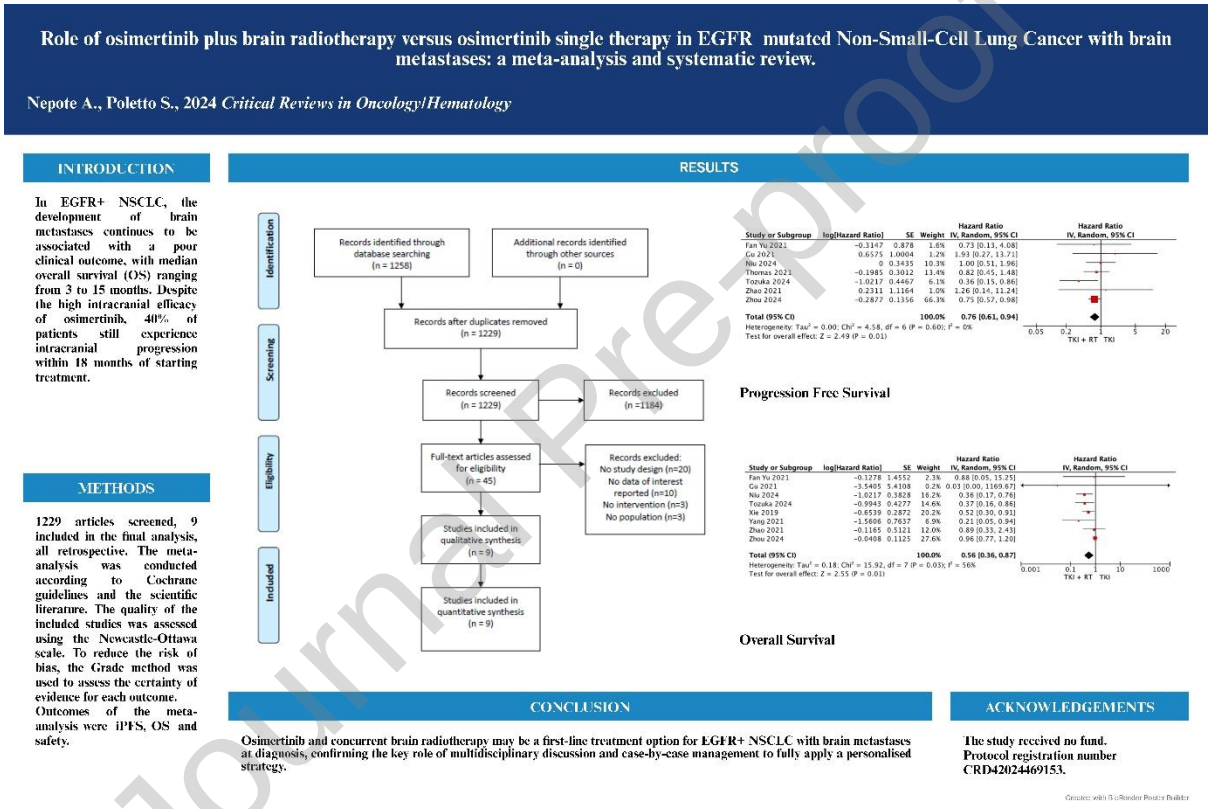
Journal Pre-proof

Highlights

The role of combining upfront brain radiotherapy upfront with a third-generation EGFR-TKI is not well established.

Patients treated with combination therapy had an improvement in intracranial progression free survival (HR 0.76; 95% CI 0.61-0.94) and overall survival (HR 0.56; 95% CI 0.36-0.87) with an acceptable safety profile.

This treatment strategy deserves further studies in prospective trials.



Journal Pre-proof