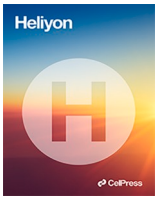
Heliyon 10 (2024) e24378

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

An epidermal growth factor receptor-mutated lung adenocarcinoma patient with brain lesions resisted to osimertinib monotherapy but achieved more than 4 years of survival in osimertinib plus bevacizumab metronomic treatment

Jie Liu [a], Xiao Han [b], Xiufeng Hu [a], Yuange He [c], Yijia Shao [c], Yanyan Yang [c], Kai Wang [c], Yanqiu Zhao [a,*]

[a] Department of Internal Medicine, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, 450008, China
[b] Department of Obstetrics and Gynecology, The Third Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, China
[c] Geneplus-Beijing, Beijing ,102206, China

ARTICLE INFO

Keywords:
Non-small cell lung cancer (NCSLC)
EGFR mutation
Osimertinib
Bevacizumab

ABSTRACT

Background: Epidermal growth factor receptor (EGFR) mutations have been identified as promising therapeutic targets for non-small cell lung cancer. Osimertinib, a third-generation EGFR-tyrosine kinase inhibitor-targeting drug, has good anti-tumor ability and excellent intracranial effects. However, management of osimertinib resistance is a clinical challenge. The clinical benefit of osimertinib combined with the antiangiogenic drug, bevacizumab, remains to be determined.

Case presentation: A 40-year-old female with right lung adenocarcinoma (cT2aN3M1c, IVb) was confirmed positive for EGFR exon 19 deletion mutation (c.2235_2249del, 1.3%). After receiving 5 months of osimertinib (80 mg, qd) therapy, the patient's disease progressed and she subsequently accepted treatment with osimertinib (80 mg, qd) plus bevacizumab (15 mg/kg, q21d) and achieved notable clinical remission for 23 months until renal impairment occurred, after which bevacizumab was discontinued. The patient had 6 months of remission before progression, after which bevacizumab was added again. To date, the disease has been under control. The brain lesion showed partial response again, and the side effects of bevacizumab were tolerable. The overall survival time exceeded 4 years.

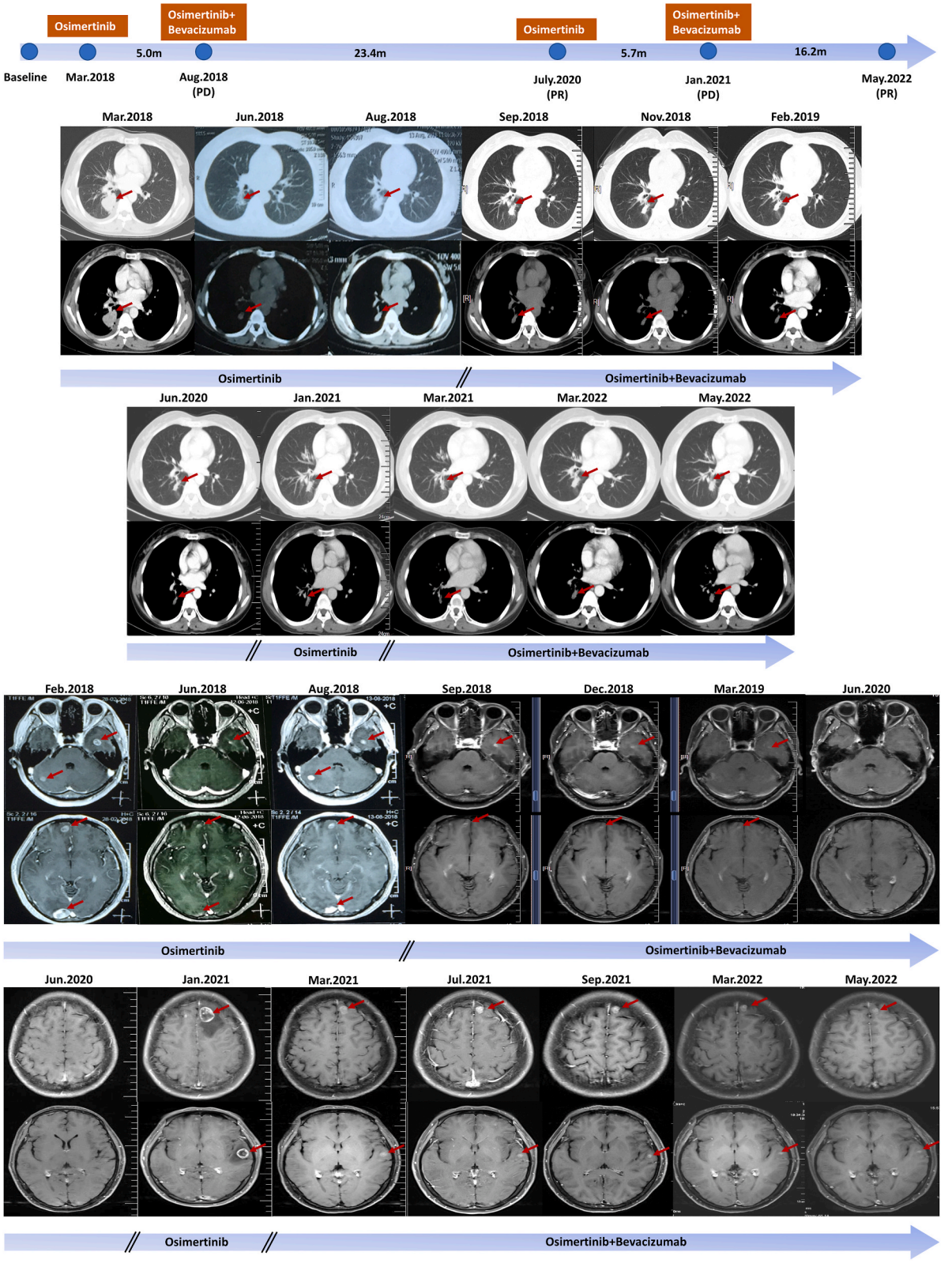
Conclusion: This case report describes a treatment strategy for osimertinib-resistant patients with EGFR exon 19 deletion mutations. Metronomic treatment with osimertinib plus bevacizumab was achieved for more than 4 years.

1. Introduction

Lung cancer is the most frequent cause of cancer-related death worldwide [1]. Epidermal growth factor receptor (EGFR) mutations occur in 10~20% of patients with non-small cell lung cancer (NSCLC) in Caucasians and approximately 40% of the Asian population [2,3]. EGFR-tyrosine kinase inhibitor (TKI) sensitizing mutations are most frequently seen in exon 19 (deletions) or in exon 21

* Corresponding author. 127 Dongming Road, Jinshui District, Zhengzhou, China.
E-mail address: zlyyzhaoyanqiu0366@zzu.edu.cn (Y. Zhao).

https://doi.org/10.1016/j.heliyon.2024.e24378
Received 7 August 2023; Received in revised form 18 December 2023; Accepted 8 January 2024
Available online 11 January 2024



(caption on next page)

Fig. 1. Time course depicting treatment process and radiological evaluation from 2018 to 2022. The PFS1 of osimertinib was 5 months. And the PFS2 of osimertinib plus bevacizumab was 27 months, during which bevacizumab was discontinued for 11 months while the disease was in remission. The patient is at present still on treatment and is receiving osimertinib plus bevacizumab. PR, partial response; PD, progressive disease; CT, computed tomography; MRI, magnetic resonance imaging.

(Leu858Arg), and the subsequent development of targeted therapy with small-molecule EGFR-TKIs has dramatically revolutionized the treatment landscape of these tumors. Several large phase III trials have demonstrated the superior efficacy of first-, second-, and third-generation TKIs compared to standard platinum-based chemotherapy in advanced NSCLC with EGFR mutations [4].

Osimertinib, a representative EGFR-TKI, has been shown to have better clinical benefits than first-generation EGFR-TKIs (gefitinib or erlotinib) in first-line monotherapy [5]. In light of its promising clinical trial results, osimertinib was approved as a first-line treatment for advanced EGFR-mutated NSCLC, regardless of T790 M mutation status [5]. However, almost all medicated patients develop drug resistance. The common mechanisms of drug resistance are acquired EGFR mutations and mesenchymal epithelial transition amplification, but more than half of the mechanisms are still unknown [6]. For targets with clear resistance mechanisms, there is still a lack of drugs with clear efficacy.

Moreover, nearly 30–50% of patients with NSCLC have brain metastases and poor prognosis. The prognosis has been reported to be approximately 2 months with the best supportive care, and only 3–6 months with conventional surgery, stereotactic radiation therapy, or whole brain radiation therapy [7]. However, there is no clinically effective and optimal treatment for patients with NSCLC with central nervous system (CNS) metastasis, which greatly reduces the survival benefit of these patients. The National Comprehensive Cancer Network (NCCN) guidelines recommend that osimertinib should be considered for patients with EGFR mutations who have progressive CNS or leptomeningeal disease; however, the treatment of patients with brain metastases after osimertinib resistance remains a challenge. Multiple clinical trials have shown that the combination of the antiangiogenic agent, bevacizumab, and a first-generation TKI as first-line treatment for advanced NSCLC can prolong PFS compared with TKI monotherapy [8]. However, the efficacy of bevacizumab combined with osimertinib is controversial according to recently published phase I or II clinical studies, and lacking data from phase III clinical trials [9,10].

Here, we report a case to provide unequivocal clinical evidence for osimertinib and bevacizumab effectiveness in lung adenocarcinoma patient. It isa case of lung adenocarcinoma with CNS metastases harboring EGFR exon 19 deletion that responded to metronomic therapy with osimertinib and bevacizumab for more than 4 years. Interestingly, this metronomic therapy modality appears to confer significant survival benefits to patients.

2. Case presentation

A 40-year-old female patient presented to Henan Cancer Hospital on March 7, 2018, complaining of an irritating dry cough for 3 months, blurred vision, and chest tightness for 1 week. She had visited another hospital 10 days prior and found multiple intracranial metastases on brain magnetic resonance imaging (MRI) (the largest brain lesion was 27× 16 mm).

A pathological diagnosis by electronic bronchoscopy revealed adenocarcinoma in the lower lobe of the right lung. Immunohistochemical results showed that the tumor cells were CD56 (−) , P40 (−) , CK7(+) , Ki-67 (+5%) , Napsin-A (+) , P63 (−) , and TTF-1 (+). The patient underwent emission computed tomography (CT) examination with whole-body bone scintigraphy on March 8, 2018 and showed no obvious abnormal radiation distribution. Chest CT revealed a mass with multiple inflammatory changes in the lower lobe of the right lung (34 × 31 mm) and multiple small nodules in both the lungs. Multiple lymph nodes were observed in the right hilum, mediastinum, and right supraclavicular area, some of which were swollen. The lung puncture pathology was diagnosed as adenocarcinoma (cT2aN3M1c, IVb).

With informed consent, the patient underwent eight lung cancer-related gene tests on March 20, 2018 and the results showed a non-frameshift deletion mutation in EGFR exon 19 (c.2235_2249del). The patient received osimertinib (80 mg qd) as first-line therapy on March 16, 2018 with no obvious adverse reactions. The lung lesions were reduced (23 × 12 mm) and the brain lesions were first reduced (8 × 6 mm) and then enlarged (16 × 11 mm). The overall efficacy was considered to be progressive disease (PD), according to RECIST1.1. The progression-free time was 5.0 months.

Considering local progression and osimertinib resistance, the patient refused further chemotherapy and radiotherapy. Secondary biopsy specimens were not readily available. In view of the better brain control efficacy of bevacizumab in the early stages, bevacizumab was added after full consultation with the patient [11]. Therefore, the patient was treated with second-line osimertinib (80 mg, qd) plus bevacizumab (15 mg/kg, q21d). Until July 27, 2020, the patient underwent routine urine examination and the results showed urinary protein +∼++ and that 24-h urinary protein was less than 2 g, which was considered to be due to a possible renal injury from bevacizumab [12]. The lung lesions shrank (16 × 8 mm) and all brain lesions disappeared. The overall efficacy was evaluated as partial response (PR) and the time without disease progression was 23.4 months.

Bevacizumab was discontinued and the patient was treated with osimertinib alone because she was concerned about worsening toxicity with bevacizumab. It was not until 6 months later (January 19, 2021) that PD occurred. Lung lesions enlarged (20 × 9 mm) and multiple new brain lesions occurred (the largest lesion was 22 × 10 mm). The overall curative effect was PD and the progression-free time was 5.7 months. After PD occurred, the peripheral blood samples were used for genetic testing. EGFR was wild-type, and no clear drug resistance gene was found; therefore, osimertinib treatment continued.

The repeated 24-h urinary protein level was less than 2 g, which met the safety requirements of continuing bevacizumab [12]. In view of the previously reported good efficacy, bevacizumab was re-added to the treatment after full consultation with the patient. The

lung lesions measured 17 × 9 mm and the brain lesions shrunk (the largest lesion was 8 × 5 mm). The overall curative effect was PR and the progression-free time was 16.2 months. There was no further severe nephrotoxicity (urinary protein +~++, 24-h urinary protein less than 2 g) while continuing bevacizumab. Disease-free remission occurred for more than 4 years after metronomic therapy, which has benefited the patient to date. The treatment process and radiological evaluation are summarized in Fig. 1.

3. Discussion

We described a patient with lung adenocarcinoma with CNS metastases harboring an EGFR exon 19 deletion mutation that achieved the longest survival to date with osimertinib and bevacizumab therapy.

The FLAURA study reported that patients with EGFR-sensitive mutations could benefit from osimertinib with 18.9 months of PFS [13]. However, this patient progressed to PD after only 5 months of osimertinib therapy. As the NCCN guidelines suggest that radiotherapy and continued use of osimertinib can be considered after first-line treatment with osimertinib for advanced NSCLC, the patient received second-line osimertinib combined with bevacizumab therapy. In a retrospective study, a rechallenge with osimertinib combined with bevacizumab after the first-line progression of osimertinib resulted in a median PFS of 7.0 months [14]. The efficacy evaluation for the combined therapy in our patient was PR and the PFS was 23.4 months. After considering the possible renal injury from bevacizumab, osimertinib monotherapy was reinitiated and achieved a remission of 5.7 months after symptomatic progression in lung and brain lesions. The combination of osimertinib and bevacizumab was then reintroduced and achieved a PFS of 16.2 months. The patient achieved an overall survival of more than 4 years with osimertinib and bevacizumab combination therapy.

To our knowledge, this is the longest surviving case to date of osimertinib plus bevacizumab for lung adenocarcinoma with CNS metastases carrying EGFR 19 exon deletion, with an overall survival time of more than 4 years so far. In clinical practice, the efficacy of bevacizumab combined with osimertinib is controversial in previous reports. However, in this study, the lung adenocarcinoma patient achieved long term survival through osimertinib and bevacizumab combination therapy, which may provide clinical evidence for osimertinib and bevacizumab effectiveness in lung adenocarcinoma patient. If similar cases are encountered in the future, our treatment strategy may have implications for these patients and their treating clinicians.

Management of osimertinib resistance is a clinical challenge, especially in patients with brain metastases [14]. Several prospective randomized trials have demonstrated the effect of a dual EGFR/vascular endothelial growth factor (VEGF) pathway to prolong PFS in advanced EGFR-mutated NSCLC [8,15]. In the phase II JO25567 study, the PFS of erlotinib plus bevacizumab versus erlotinib alone as first-line therapy in advanced EGFR-mutated NSCLC was 16.4 months versus 9.8 months [16]. Similar results were found in the large phase III NEJ026 study of erlotinib plus bevacizumab versus erlotinib as first-line therapy in advanced EGFR-mutated NSCLC where they obtained a PFS of 16.9 months versus 13.3 months [17]. In the phase III Artemis-CTONG1509 study, bevacizumab plus erlotinib not only prolonged PFS in the overall population, but also significantly benefited PFS in the brain metastasis subgroup, compared with erlotinib [8].

The aforementioned studies focused on the efficacy of antiangiogenic drugs combined with first-generation EGFR-TKIs; however, bevacizumab combined with osimertinib was quite different from what we expected. In a phase I/II single-arm trial of 49 patients, osimertinib plus bevacizumab as first-line therapy for EGFR-mutated advanced NSCLC resulted in a median PFS of 19 months [18]. Results from the WJOG9717L study showed there was no statistically significant difference in PFS between osimertinib plus bevacizumab and osimertinib alone in second-line treatment (PFS 22.1 months vs. 20.2 months) [10]. Another study from Japanese scholars on EGFR-TKI-resistant patients with secondary T790 M mutation showed that the total effective rate was higher in the osimertinib combined with bevacizumab group (71.8% vs. 55.0%), but that the PFS and time to treatment failure were shorter than in those with osimertinib monotherapy [9].

These studies on the clinical benefits of the combination of osimertinib and bevacizumab are still controversial. In the present case, the additional bevacizumab seemed to reverse the resistance of osimertinib monotherapy. With the application of the combination of osimertinib and bevacizumab, the overall survival of our patient has been more than 4 years. We speculated that sequential osimertinib combined with bevacizumab after osimertinib resistance is more effective than direct combination therapy, and that patients with brain metastasis are the dominant beneficiaries of this sequential therapy, the mechanism of which requires further research.

In 2000, Kerbel et al. proposed a new concept of metronomic chemotherapy (MCT) based on numerous studies [19]. In multiple subsequent clinical trials, MCT alone or in combination with other treatments has shown certain advantages, especially in terms of lower toxicity and higher tolerability. At the same time, this metronomic treatment also showed higher efficacy. In a phase II trial of MCT plus bevacizumab for stage IV NSCLC, the median PFS was 9 months and median OS was 30 months, and the authors hypothesized that the addition of bevacizumab to MCT may result in enhanced antiangiogenic effects and clinical benefits [20]. Here, we propose a new modality similar to metronomic chemotherapy, namely, metronomic therapy with osimertinib plus bevacizumab. We speculate this rhythmic administration of bevacizumab resulted in a surprising clinical benefit, while reducing adverse effects.

The mechanism of osimertinib in combination with bevacizumab is still under investigation. VEGF and EGFR share many overlapping and parallel downstream pathways [21]. The inhibition of both signaling pathways can improve the efficacy of anti-tumor therapy and eliminate resistance to EGFR inhibition [22,23]. Bevacizumab enhances the anti-tumor effect of osimertinib by reducing the expression of VEGF and microvessel density in tumors, thereby improving the tumor microenvironment. Osimertinib and bevacizumab cross the blood-brain barrier and have comparable effectiveness in the CNS [24]. A study has shown that this combination therapy may be more effective and more protective against CNS progression [18].

In conclusion, we report the longest survival to date with osimertinib combined with bevacizumab using metronomic-like therapy. The patient achieved long term survival through osimertinib and bevacizumab combination therapy and this metronomic therapy may prolong the benefit of osimertinib, but large cohort clinical studies are needed to confirm this.

4. Conclusion

This case report describes a treatment strategy for osimertinib-resistant patients with EGFR exon 19 deletion mutations. Metronomic treatment with osimertinib plus bevacizumab was achieved for more than 4 years.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013). The written informed consent was obtained from the patient.

Date availability statement

Data include in article/supp. material/referenced in article.

CRediT authorship contribution statement

Jie Liu: Writing – original draft, Writing – review & editing, Resources, Funding acquisition, Formal analysis, Conceptualization. **Xiao Han:** Resources, Formal analysis. **Xiufeng Hu:** Resources, Formal analysis. **Yuange He:** Writing – original draft. **Yijia Shao:** Writing – original draft. **Yanyan Yang:** Writing – original draft. **Kai Wang:** Writing – original draft, Writing – review & editing. **Yanqiu Zhao:** Writing – review & editing, Supervision, Resources, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

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.

Acknowledgments

This research was funded by the National Natural Science Foundation of China (No. 82102916 to JL), the Medical Science and Technology Planning Project of Henan Province (No. LHGJ20210176), and the Beijing Science and Technology Innovation Medical Development Foundation (KC2021-JX-0186-44).

References

[1] F.R. Hirsch, G.V. Scagliotti, J.L. Mulshine, et al., Lung cancer: current therapies and new targeted treatments, Lancet 389 (10066) (2017) 299–311.
[2] A.S. Tsao, G.V. Scagliotti, P.J. Bunn, et al., Scientific Advances in lung cancer 2015, J. Thorac. Oncol. 11 (5) (2016) 613–638.
[3] R. Rosell, E. Carcereny, R. Gervais, et al., Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial, Lancet Oncol. 13 (3) (2012) 239–246.
[4] G. Recondo, F. Facchinetti, K.A. Olaussen, et al., Making the first move in EGFR-driven or ALK-driven NSCLC: first-generation or next-generation TKI? Nat. Rev. Clin. Oncol. 15 (11) (2018) 694–708.
[5] J.C. Soria, Y. Ohe, J. Vansteenkiste, et al., Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer, N. Engl. J. Med. 378 (2) (2018) 113–125.
[6] A. Leonetti, S. Sharma, R. Minari, et al., Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer, Br. J. Cancer 121 (9) (2019) 725–737.
[7] O. Arrieta, C. Villarreal-Garza, J. Zamora, et al., Long-term survival in patients with non-small cell lung cancer and synchronous brain metastasis treated with whole-brain radiotherapy and thoracic chemoradiation, Radiat. Oncol. 6 (2011) 166.
[8] Q. Zhou, C.R. Xu, Y. Cheng, et al., Bevacizumab plus erlotinib in Chinese patients with untreated, EGFR-mutated, advanced NSCLC (ARTEMIS-CTONG1509): a multicenter phase 3 study, Cancer Cell 39 (9) (2021) 1279–1291.
[9] H. Akamatsu, Y. Toi, H. Hayashi, et al., Efficacy of osimertinib plus bevacizumab vs osimertinib in patients with EGFR T790M-mutated non-small cell lung cancer previously treated with epidermal growth factor receptor-tyrosine kinase inhibitor: west Japan Oncology group 8715L phase 2 randomized clinical trial, JAMA Oncol. 7 (3) (2021) 386–394.
[10] H. Kenmotsu, K. Wakuda, K. Mori, et al., Randomized phase 2 study of osimertinib plus bevacizumab versus osimertinib for untreated patients with nonsquamous NSCLC harboring EGFR mutations: WJOG9717L study, J. Thorac. Oncol. 17 (9) (2022) 1098–1108.
[11] A. Ilhan-Mutlu, M. Osswald, Y. Liao, et al., Bevacizumab prevents brain metastases formation in lung adenocarcinoma, Mol. Cancer Therapeut. 15 (4) (2016) 702–710.
[12] X. Zhu, S. Wu, W.L. Dahut, et al., Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis, Am. J. Kidney Dis. 49 (2) (2007) 186–193.
[13] M. Dyer, M. Green, S. Jones, et al., Estimating long-term survival of previously untreated patients with EGFR mutation-positive (EGFRm) advanced non-small cell lung cancer (NSCLC) who received osimertinib in the FLAURA study[EBOL], J. Clin. Oncol. 37 (15) (2019) e20560.
[14] Q. Cui, Y. Hu, Q. Cui, et al., Osimertinib rechallenge with bevacizumab vs. Chemotherapy plus bevacizumab in EGFR-mutant NSCLC patients with osimertinib resistance, Front. Pharmacol. 12 (2021) 746707.
[15] K. Nakagawa, E.B. Garon, T. Seto, et al., Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Oncol. 20 (12) (2019) 1655–1669.
[16] T. Seto, T. Kato, M. Nishio, et al., Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study, Lancet Oncol. 15 (11) (2014) 1236–1244.
[17] H. Saito, T. Fukuhara, N. Furuya, et al., Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial, Lancet Oncol. 20 (5) (2019) 625–635.

[18] H.A. Yu, A.J. Schoenfeld, A. Makhnin, et al., Effect of osimertinib and bevacizumab on progression-free survival for patients with metastatic EGFR-mutant lung cancers: a phase 1/2 single-group open-label trial, JAMA Oncol. 6 (7) (2020) 1048–1054.
[19] G. Klement, S. Baruchel, J. Rak, et al., Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumor regression without overt toxicity, J. Clin. Invest. 105 (8) (2000) R15–R24.
[20] C.L. Marquette, S.C. Grant, M. DeShazo, et al., Phase II study of metronomic chemotherapy (MC) with bevacizumab (B) in patients (Pts) with advanced (Adv) nonsquamous non-small cell lung cancer (NS-NSCLC), J. Clin. Oncol. 31 (15) (2013), 8057-8057.
[21] K. Perdrizet, N.B. Leighl, The role of angiogenesis inhibitors in the era of immune checkpoint inhibitors and targeted therapy in metastatic non-small cell lung cancer, Curr. Treat. Options Oncol. 20 (3) (2019) 21.
[22] A. De Luca, A. Carotenuto, A. Rachiglio, et al., The role of the EGFR signaling in tumor microenvironment, J. Cell. Physiol. 214 (3) (2008) 559–567.
[23] J. Tabernero, The role of VEGF and EGFR inhibition: implications for combining anti-VEGF and anti-EGFR agents, Mol. Cancer Res. 5 (3) (2007) 203–220.
[24] T. Reungwetwattana, K. Nakagawa, B.C. Cho, et al., 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, J. Clin. Oncol. (2018) O2018783118.