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OSIMERTINIB-BASED COMBINATION THERAPY FOR EGFR-MUTANT NSCLC WITH BRAIN METASTASES: A CLINICAL CASE IN THE CONTEXT OF THE FLAURA2 STUDY

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Abstract. This article presents a clinical case of treating a female patient with EGFR-mutant non-small cell lung cancer (NSCLC) with brain metastases using osimertinib-based combination therapy. Following disease progression after afatinib therapy, third-generation tyrosine kinase inhibitor (osimertinib) targeted therapy was initiated, followed by combination treatment in accordance with the FLAURA2 study protocol. This included osimertinib, chemotherapy (carboplatin + pemetrexed), and bevacizumab. Significant regression of cerebral metastases and disease stabilization were observed. The article discusses practical aspects of applying FLAURA2 data in real-world clinical settings and explores the potential for implementing a personalized approach to oncology, even under budget constraints. The importance of molecular diagnostics and physicians' clinical awareness in making therapeutic decisions is emphasized.

Keywords: EGFR-mutant NSCLC, osimertinib, FLAURA2, brain metastases, targeted therapy, pemetrexed, carboplatin, bevacizumab, personalized oncology, clinical case.

EGFR-мутантты ұсақ жасушалы емес өкпе обыры мен ми метастаздарындағы осимертинибке негізделген біріктірілген терапия: FLAURA2 зерттеуінің контексіндегі клиникалық жағдай

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Аңдатпа. Мақалада миға метастаздары бар EGFR-мутантты ұсақ жасушалы емес өкпе обырын (ҰЖЕӨО) емдеу бойынша клиникалық жағдай ұсынылған. Осимертинибке негізделген біріктірілген терапия қолданылды. Афатинибпен емделгеннен кейін аурудың үдеуі байқалған соң, үшінші буын тирозинкиназа тежегішімен (осимертиниб) мақсатты терапия басталды, кейіннен - FLAURA2 зерттеуінің хаттамасына сәйкес біріктірілген ем жүргізілді. Бұл емге осимертиниб, химиотерапия (карбоплатин + пеметрексед) және бевацизумаб кірді. Нәтижесінде ми метастаздарының айқын регрессі мен үдерістің тұрақтануы байқалды. FLAURA2 деректерін нақты клиникалық тәжірибеде қолданудың практикалық аспектілері, сондай-ақ шектеулі бюджет жағдайында да онкологияда жекелендірілген тәсілді енгізу мүмкіндіктері талқыланады. Терапиялық шешім қабылдауда молекулалық диагностиканың және дәрігерлердің клиникалық хабардарлығының маңыздылығы атап өтіледі.

Түйін сөздер: EGFR-мутантты ҰЖЕӨО, осимертиниб, FLAURA2, ми метастаздары, мақсатты терапия, пеметрексед, карбоплатин, бевацизумаб, жекелендірілген онкология, клиникалық жағдай.

Комбинированная терапия на основе осимертиниба при EGFR-мутантном немелкоклеточном раке лёгкого с метастазами в головной мозг: клинический случай в контексте исследования FLAURA2

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Аннотация. В статье представлен клинический случай лечения пациентки с EGFR-мутантным немелкоклеточным раком лёгкого (НМРЛ) с метастазами в головной мозг, на фоне применения комбинированной терапии, основанной на осимертинибе. На фоне прогрессирования заболевания после терапии афатинибом была начата таргетная терапия ингибитором тирозинкиназы 3-го поколения (осимертиниб), а в дальнейшем — комбинированное лечение в соответствии с протоколом исследования FLAURA2, включающее осимертиниб, химиотерапию (карбоплатин + пеметрексед) и бевацизумаб. Наблюдался выраженный регресс церебральных метастазов и стабилизация процесса. Обсуждаются практические аспекты применения данных FLAURA2 в реальной клинической практике, а также возможности внедрения персонализированного подхода в онкологии даже в условиях ограниченного бюджета. Подчёркивается значимость молекулярной диагностики и клинической осведомлённости врачей в принятии терапевтических решений.

Ключевые слова: EGFR-мутантный НМРЛ; осимертиниб; FLAURA2; метастазы в головной мозг; таргетная терапия; пеметрексед; карбоплатин; бевацизумаб; персонализированная онкология; клинический случай.

Introduction. EGFR-mutant non-small cell lung cancer (NSCLC) is a subtype of NSCLC characterized by mutations in the epidermal growth factor receptor (EGFR) gene. The frequency of EGFR mutations varies but is typically:

- Approximately 10–15% among patients in the United States, more commonly in cases of adenocarcinoma [1]
- Up to 30–50% in Asian populations, including about 38% in China [2]
- Around 20% of all adenocarcinoma cases in NSCLC in Russia [3]

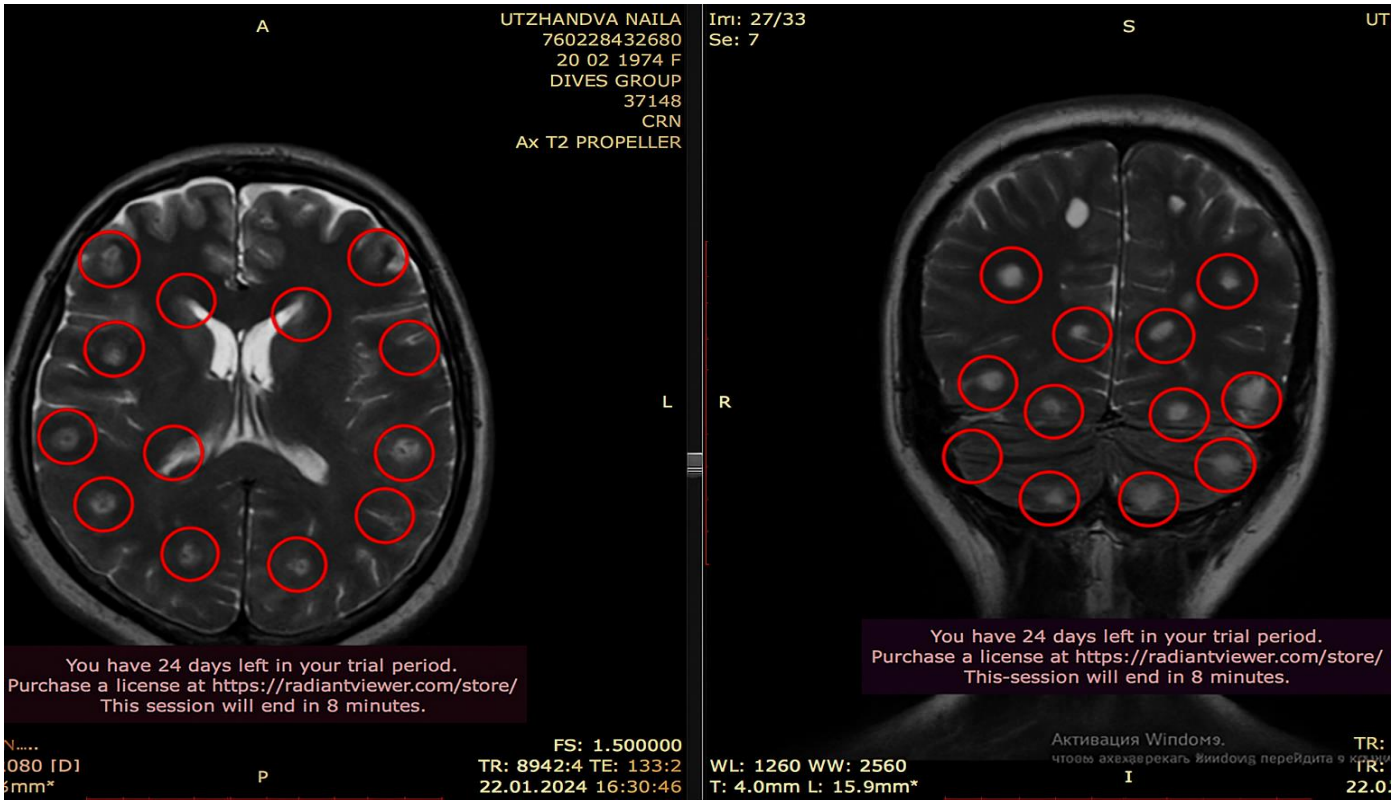
Thus, on average, EGFR mutations are found in approximately 20% of all NSCLC cases, particularly in the adenocarcinoma subtype, and more frequently among women and non-smokers [4].

Until recently, Osimertinib was the standard first-line therapy. However, results from the “FLAURA-2” study [5, 6] demonstrated a significant improvement in progression-free survival with the addition of chemotherapy to Osimertinib, especially in patients with brain metastases. Below is a clinical case illustrating the application of this treatment regimen.

Clinical Case. Patient U., 49 years old. Under follow-up at the Regional Clinical Hospital of Turkestan Region since July 20, 2022. Discussed at the Multidisciplinary Team (MDT) meeting on June 17, 2022. Recommendation: diagnostic thoracotomy. The patient was admitted to the City Oncology Center in Shymkent to the Thoracoabdominal Surgery Department for operative treatment. On July 12, 2022, the patient underwent a video-assisted thoracoscopic surgery (VATS) on the left side with a lung lesion biopsy. Postoperative histological report No. 11224-25 dated July 19, 2022: moderately differentiated adenocarcinoma, G-II. Discussed at MDT on July 20, 2022. Recommendation: EGFR mutation testing via molecular genetic analysis; dynamic PET/CT scan. From July 21 to July 29, 2022, the patient received courses of neoadjuvant chemotherapy. Molecular genetic analysis of EGFR (report No. 257 dated August 2, 2022): EGFR Exon 19 deletion mutation detected. Beginning in August 2022, the patient started targeted therapy with “Afatinib”. In August 2023, disease progression was noted in the form of brain metastases. As a

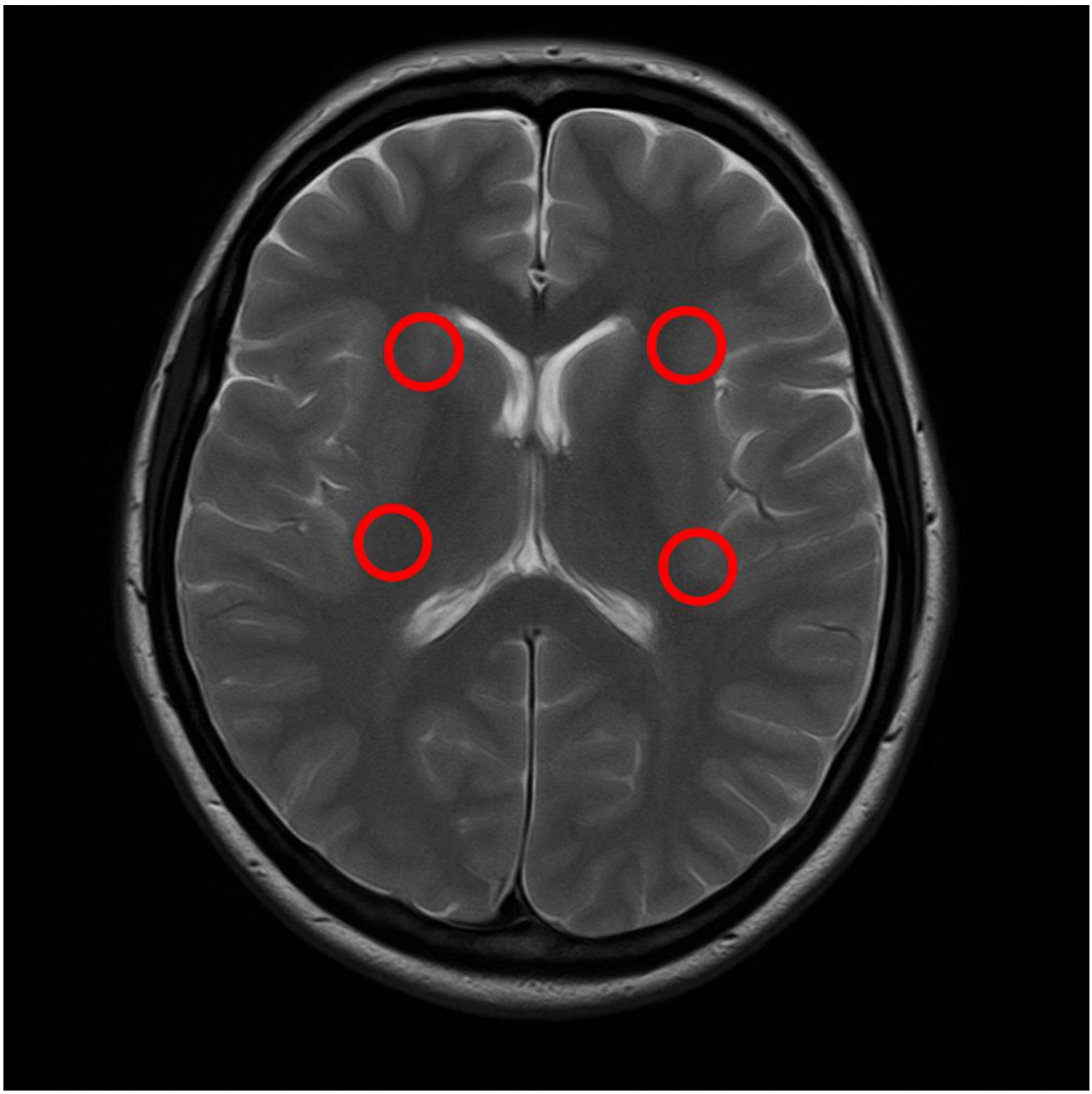
result, on August 11, 2023, the MDT recommended initiating targeted therapy with the EGFR inhibitor Osimertinib.

Protocol of Magnetic Resonance Imaging of the Brain and Intracranial Arteries dated 22.01.2024



In both cerebral hemispheres and cerebellar hemispheres, multiple lesions are observed - approximately 15 in total - round in shape, with a homogeneous structure, measuring up to 2.2 × 1.6 cm, surrounded by a perifocal zone of vasogenic edema. Conclusion**:** Multiple lesions in both cerebral hemispheres and cerebellar hemispheres (differential diagnosis: metastases).

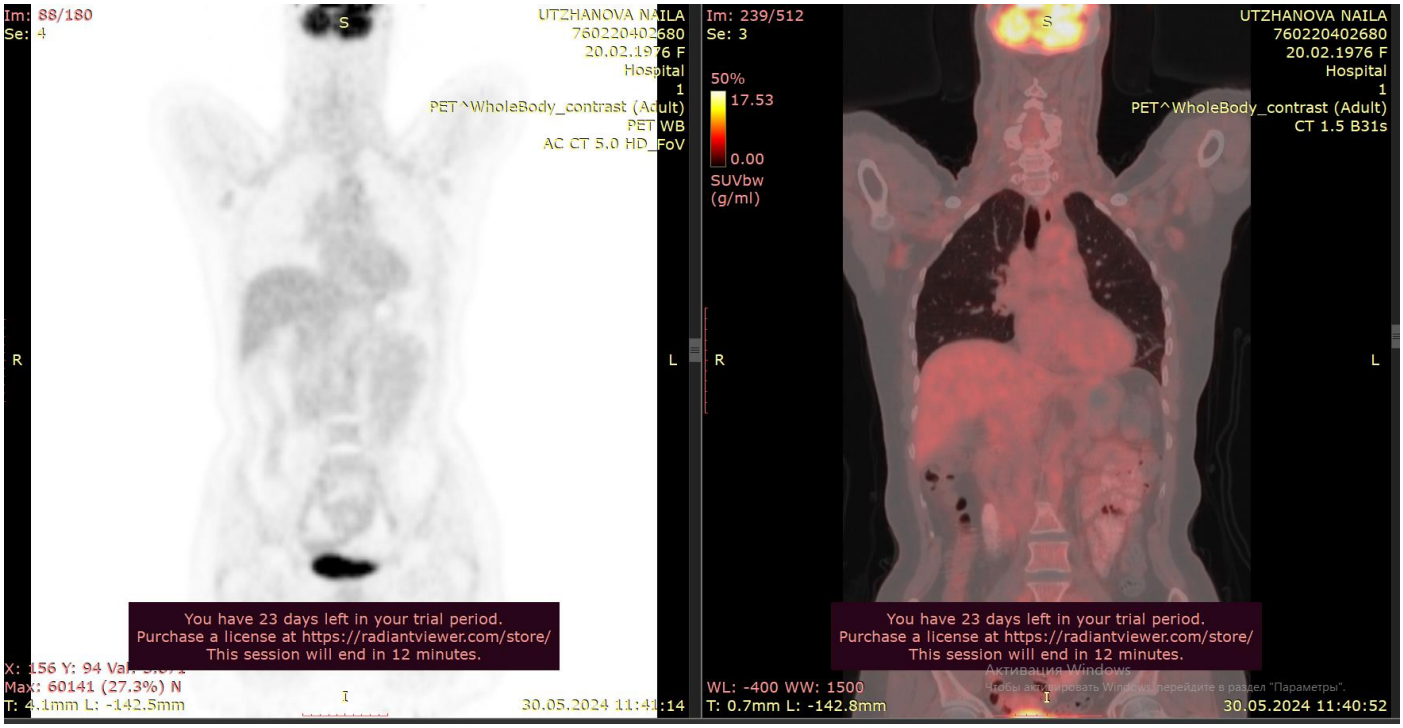
A follow-up magnetic resonance imaging (MRI) of the brain was performed. Protocol of Brain MRI dated 18/03/2024: on a series of MR images, hyperintense foci are identified on T2-weighted and FLAIR sequences in the frontal and parietal lobes of both cerebral hemispheres. The lesions are round to oval in shape, measuring up to 2.6 × 1.4 cm, with no signs of surrounding perifocal edema. (*Images not provided; visualization generated using artificial intelligence.*)



Until May 2024, the patient received targeted therapy with a third-generation tyrosine kinase inhibitor (TKI), Osimertinib.

In May 2024, difficulties arose with access to the medication. Given the presence of metastatic brain involvement, the patient was recommended to undergo Targeted therapy with a VEGF inhibitor (Bevacizumab) in combination with chemotherapy using the Pemetrexed + Carboplatin regimen. However, the patient declined chemotherapy courses, opting instead to continue with targeted therapy alone and wait for the availability of her original medication.

/CT Scan dated 30.05.2024:



PET/CT dated 30.05.2024: Conclusion: no convincing PET/CT evidence of a metabolically active ^{18}F-FDG-avid tumor process was detected. Axillary lymphadenopathy on the right side.

From May 13, 2024, to July 24, 2024, the patient received courses of targeted therapy with the VEGF inhibitor Bevacizumab.

Given the PET/CT findings showing no convincing evidence of a metabolically active ^{18}F-FDG-avid tumor process, and based on the published data from the “FLAURA-2” clinical trial, the case was reviewed by the MDT. By decision of the MDT on August 23, 2024, considering the patient’s young age and the presence of cerebral metastases, it was recommended that she undergo courses of TT with protein kinase inhibitors combined with VEGF inhibitors, along with 6 cycles of chemotherapy using the carboplatin + pemetrexed regimen, followed by maintenance therapy with pemetrexed.

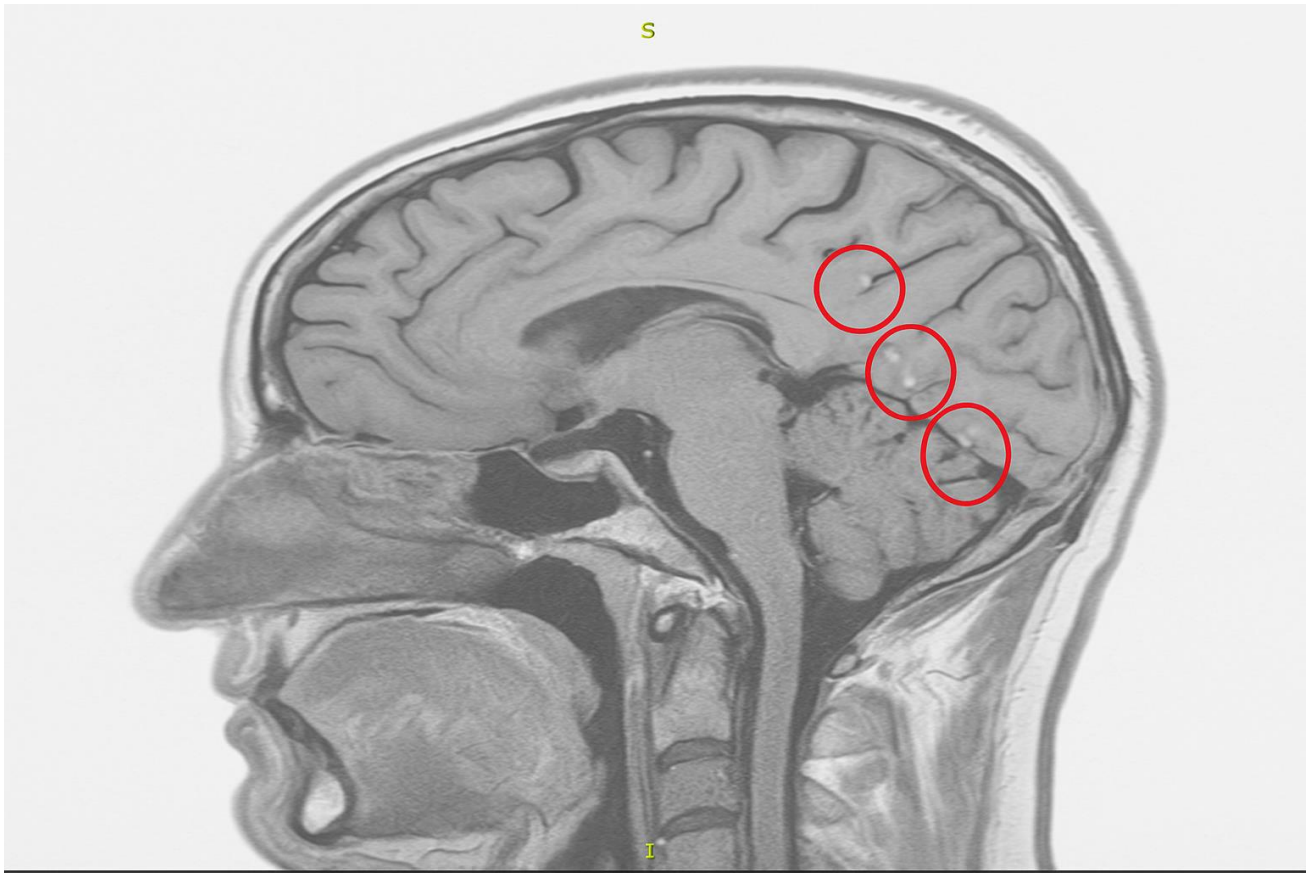
Considering the published data from the “FLAURA-2” study, the patient agreed to undergo chemotherapy. At that time, she also regained access to the third-generation tyrosine kinase inhibitor (TKI), Osimertinib.

From August 28, 2024, to December 30, 2024, the patient received 6 cycles of palliative polychemotherapy according to the “RR” regimen:

- **Pemetrexed** 500 mg/m² = 800 mg, administered intravenously (IV) by infusion
- **Carboplatin** AUC 4 = 450 mg, administered IV by infusion

The patient underwent regular follow-up examinations, with a particular focus on the brain.

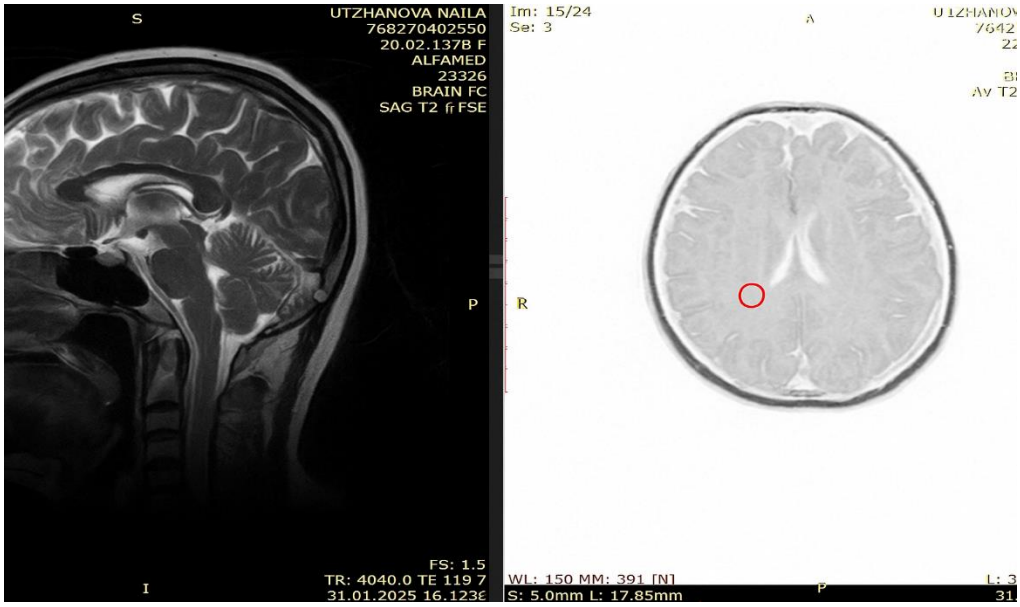
MRI of the Brain with Contrast — October 24, 2024:



Against the background of periventricular leucomalacia, hyperintense foci are observed on T2-weighted and FLAIR sequences in the parietal and occipital lobes of both cerebral hemispheres. The lesions are round to oval in shape, measuring up to 3.6 × 2.1 mm, with no signs of surrounding perifocal edema.

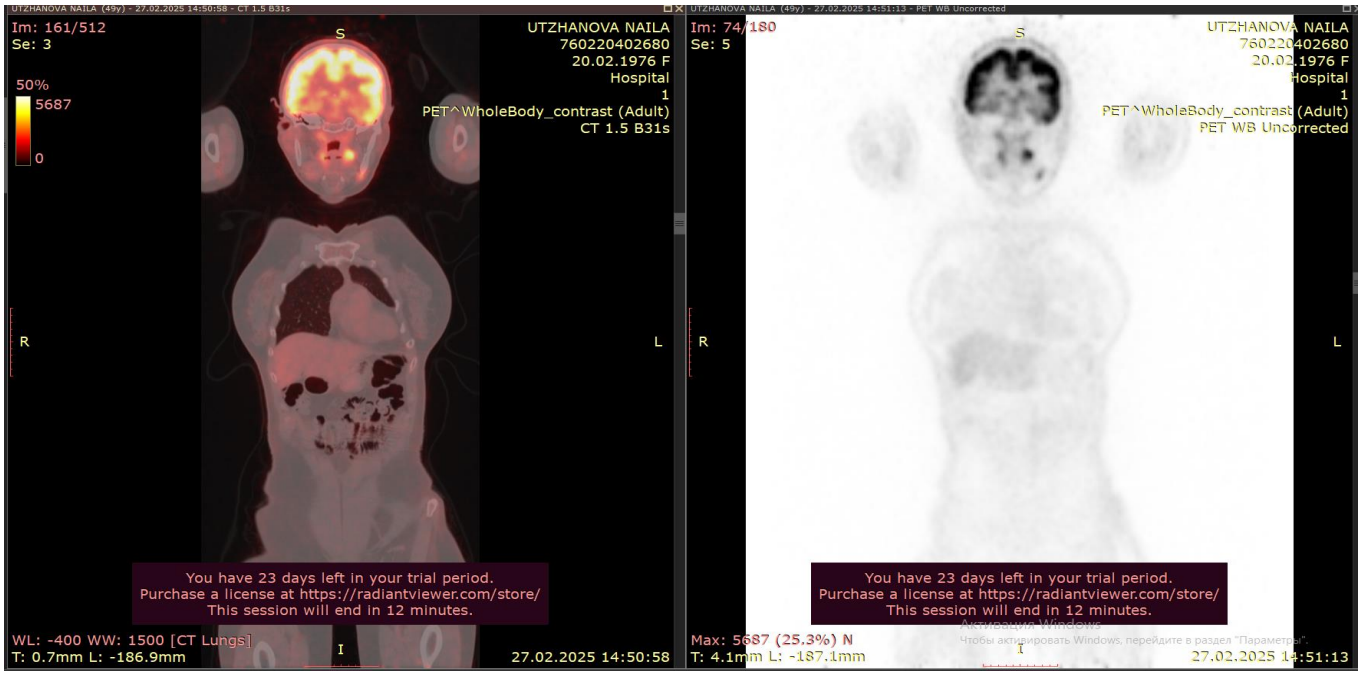
The patient completed chemotherapy courses in December 2024 and subsequently underwent follow-up examinations.

MRI of the Brain with Contrast – January 31, 2025.



In the subcortical and periventricular regions of both cerebral hemispheres, single hyperintense foci are observed on T2-weighted and T2 FLAIR images, measuring up to 0.55 mm. No diffusion restriction is noted on diffusion-weighted images, and no accumulation of paramagnetic contrast agent is seen on post-contrast scans. Conclusion**:** solitary foci, most likely of vascular origin, without accumulation of paramagnetic contrast agent, located in the subcortical and periventricular regions of both cerebral hemispheres.

PET/CT dated February 27, 2025. Conclusion:



- No definitive PET/CT evidence of a local recurrence of the primary oncological disease in the left lung with high metabolic activity was detected.
- PET/CT signs of symmetrical increased tracer uptake in the lymph nodes of the head, neck, and mediastinum (bronchopulmonary group on both sides), possibly corresponding to reactive changes, warrant dynamic observation.
- PET/CT findings of a nodular lesion in the left lobe of the thyroid gland (no significant changes compared to previous scans). Endocrinologist consultation and ultrasound follow-up are recommended.
- A hypervascular mass in the left lobe of the liver without metabolic activity, most consistent with a hemangioma (stable compared to previous scans).

Compared to the PET/CT results from May 30, 2024, there is newly observed increased metabolic activity in the lymph nodes of the retropharyngeal, submandibular, and bronchopulmonary groups on both sides. No isotope uptake is noted in the axillary lymph nodes in the current scan.

- As of February 2025, the primary lesion remains stable, and there is regression of the metastatic brain lesion.
- The patient continues on maintenance therapy with pemetrexed.

Discussion. The FLAURA2 study demonstrated that adding 4 cycles of chemotherapy (carboplatin + pemetrexed) to osimertinib:

- increases median progression-free survival (PFS) to 25.5 months compared to 16.7 months with monotherapy (Hazard Ratio [HR] 0.62),
- is particularly effective in cases with CNS metastases (24.9 months vs. 13.8 months, HR 0.47),

- has a manageable toxicity profile.

In patient U., a clinical response was observed that aligns with the findings of the study: significant regression of CNS metastatic lesions, disease control, and symptom improvement. The initiation of maintenance therapy with pemetrexed alongside ongoing osimertinib treatment is consistent with the FLAURA2 protocol.

Conclusion. The presented clinical case highlights not only the clinical significance of identifying an EGFR mutation in a patient with non-small cell lung cancer (NSCLC) and cerebral metastases, but also underscores the importance of increasing clinician awareness of contemporary clinical trials such as FLAURA and FLAURA2. These studies have fundamentally changed the treatment paradigm for EGFR-positive NSCLC, demonstrating the efficacy of third-generation tyrosine kinase inhibitors (e.g., osimertinib) and their combination with chemotherapy in improving progression-free survival and achieving effective control of cerebral lesions.

In resource-limited countries with strict financial constraints, the implementation of personalized medicine is often perceived as an unaffordable luxury. However, even a minimal level of molecular profiling (such as testing for EGFR, ALK, and ROS1 mutations) can fundamentally alter the therapeutic strategy, improve treatment effectiveness, and ultimately reduce overall costs by enabling more rational use of high-cost drugs and decreasing the number of hospitalizations.

It is important to emphasize that knowledge of, and active engagement with, the results of international clinical trials enables physicians to make well-informed decisions, adapting global standards to local realities. In this way, professional awareness and analytical competence among clinical oncology specialists become essential resources for implementing the principles of personalized care—even within the constraints of limited budgets.

The FLAURA2 study may serve as a basis for reconsidering first-line treatment standards for this category of patients.

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