REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

# Role of Epidermal Growth Factor Receptor Inhibitors in The Treatment of Lung Cancer

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## Abstract

Lung cancer is one of the types of human tumors that is characterized by a high rate of incidence and prevalence. The epidermal growth factor receptor (EGFR), which is a transmembrane protein and a subclass of receptor tyrosine kinase, has a major role in the carcinogenesis and metastasis of lung tumors. Therefore, the study of EGFR signaling pathways and their activity is crucial for the development of cytotoxic drugs that could provide high response rates with minimum range of side effects. Drugs that inhibit the activity of EGFR could be divided into first-generation, second-generation, and third-generation EGFR inhibitors. The three classes of EGFR differ in their affinity and selectivity. This review aims to discuss the role of EGFR in the process of lung carcinogenesis, and the effectiveness of EGFR inhibitors in the treatment of lung cancer patients.

**Keywords:** Lung cancer, Epidermal growth factor receptor (EGFR), Targeted drugs, EGFR mutations, EGFR inhibitors.

## 1. Introduction

Lung cancer is considered the highest type of cancer among men in terms of incidence and is associated with the highest death rates (**Thandra et al., 2021)**. It is also considered the second most common type of cancer for both men and women **(Laguna et al., 2024)**. Smoking represents the major risk factor for lung carcinogenesis. In addition, air pollutants, fuel consumption, radon, asbestos, and arsenic exposure could increase the risk of lung tumor incidence **(Leiter et al., 2023)**.

Lung carcinoma is a malignant disease that accounts for eighteen percent of carcinogenic tumors. A few years ago, the number of lung tumor death cases was about two million cases, mainly male patients. The TNM staging system, which consists of primary tumor size (T), regional lymph nodes invasion (N), and metastases (M), is used to classify the stage of lung cancer **(Osarogiagbon et al., 2023)**.

There are two main types of lung carcinogenic tumors, which are small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC could be further subdivided into squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma. Mutations of the epidermal growth factor receptor (EGFR) could have an influence on NSCLC patients **(Ortiz et al., 2022)**. The most common EGFR mutations are exon 21-point mutations and exon 19 deletion **(Marin-Acevedo et al., 2023)**.

## 2. Therapeutic Protocols

For most patients, NSCLC is discovered at advanced stage, therefore it is considered one of the

most difficult types of cancer in terms of treatment. Treatment methods of lung cancer include radiotherapy, surgery, and chemotherapy **(Alduais et al., 2023)**.

Patients who are diagnosed with stage one or stage two NSCLC are major candidates of surgical treatment. The surgical removal of one lobe, which is known as lobectomy, is considered the best treatment option for patients who are at the early stage, as it is has no effect on the function of the lung **(Uslenghi et al., 2023)**.

Radiation therapy is useful for treating early-stage lung cancer patients. Radiation that is stereotactic ablative is considered beneficial for inoperable patients. However, this type of radiation is often associated with tumor recurrence. Moreover, tissue fibrosis and post radiation effects could occur after radiotherapy **(Allignet et al., 2023)**.

A combination of platinum compounds, like cisplatin and carboplatin, and third generation chemotherapeutic drugs, like gemcitabine, vinorelbine, paclitaxel, or docetaxel, represents the first line chemotherapy treatment. In addition, the first line treatment option for non-squamous NSCLC is a combination of bevacizumab, vascular endothelial growth factor (VEGF) inhibitor, paclitaxel and carboplatin. However, patients who express positive K-ras mutation could experience treatment failure with platinum compounds. Moreover, paclitaxel and docetaxel are not considered suitable therapeutic options for patients who express beta-tubulin positive mutation **(Araghi et al., 2023)**.

The major choice of treating NSCLC patients are the drugs that act by inhibiting EGFR tyrosine kinase. The currently used EGFR tyrosine kinase inhibitors (TKIs) are divided into first generation TKIs, second generation TKIs, and third generation TKIs. First generation TKIs include gefitinib, erlotinib, and icotinib, second generation TKIs are afatinib and dacomitinib, and third generation TKI is osimertinib, which is effective in treating central nervous system (CNS) metastases **(John et al., 2022)**.

# 3. Epidermal growth factor receptor (EGFR)

## 3.1. Signaling pathways

The development of lung carcinogenesis, particularly NSCLC, could be induced by EGFR mutations. The EGFR pathway is encoded by tyrosine kinase, a transmembrane enzyme that consists of intracellular and extracellular domains. The transduction of signaling pathways is induced mainly by three pathways; PI3K/AKT/mTOR, RAS/RAF/MAPK and JAK/STAT pathways **(Oprita et al., 2021)** (**Figure 1)**.

Many carcinogenic processes are regulated by EGFR, including cellular proliferation, differentiation, survival, and metastasis **(Chhouri et al., 2023)**. Phosphoinositide 3-kinase (PI3K), an enzyme that has a major role in the synthesis of lipids, is responsible for activating the protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway. PI3K is a protein that consists mainly of two subunits; P110 and P85 subunits. The phosphorylation process of PI3K is activated when the extracellular stimuli (growth factors) bind to their receptors, such as the G-protein coupled receptor. The catalytic subunit of PI3K, P110, is responsible for the phosphorylation of phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 3,4,5-trisphosphate (PIP3), which then activates phosphoinositide-dependent kinase-1 (PDK1) and the downstream signaling pathway of serine/threonine kinase (AKT). AKT could induce carcinogenic processes, including cellular invasion, proliferation, and metastasis, by the activation of downstream signaling pathways **(Iksen et al., 2021)**.

Carcinogenesis could be induced by overstimulation of receptor tyrosine kinase, inactivation of tumor suppressor genes (PTEN), or the deregulation process of PI3K/AKT/mTOR pathway caused by gene mutation. Furthermore, apoptosis inactivation and resistance to chemotherapy could result from over-activation of the PI3K/AKT/mTOR signaling pathway. The over-activation of AKT pathway can cause inhibition of the activity of Bcl-2 proteins, which have a major role in apoptosis, therefore resulting in induction of the carcinogenic process **(Oprita et al., 2021)**.

Tumor metastasis could be induced by the PI3K/AKT/mTOR signaling pathway through the stimulation of receptor tyrosine kinase and cytokines. AKT induces the migration of cancerous cells by activating the phosphorylation of serine subunit (ser507) **(Iksen et al., 2021)**.

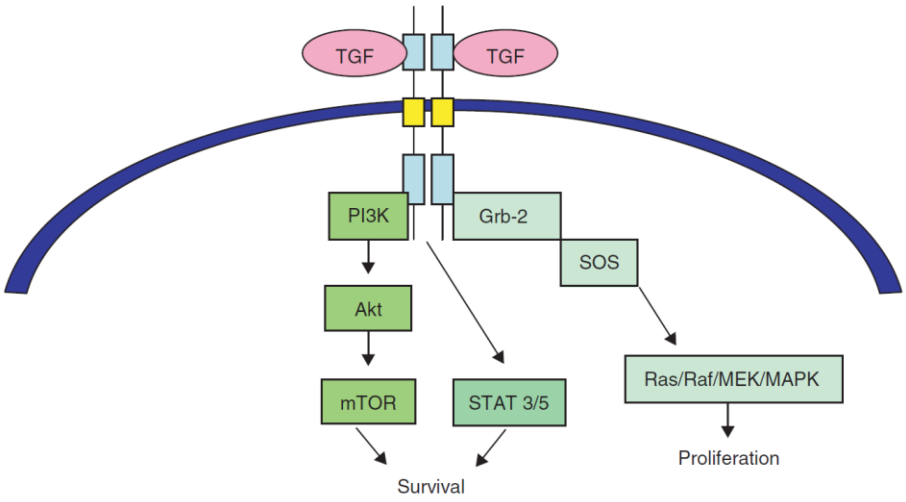


**Figure 1. Signaling pathway of EGFR (Tang et al., 2006).** Induction of EGFR signaling pathway, through binding of EGFR ligand, which is transforming growth factor (TGF-α), to the extracellular domain, leading to autophosphorylation process through downstream signaling pathways. PI3K: Phosphoinositide 3-kinase; AKT: protein kinase (B); mTOR: mammalian target of rapamycin; Grb: Granzyme-b; STAT: signal transducer and activator of transcription; sos: guanine nucleotide exchange factor; Ras/Raf/MEK/MAPK: a cellular signaling pathway involved in progression and proliferation of cancer.

There are two main pharmacological classes that act by targeting EGFR, which are monoclonal antibodies (Mabs) and inhibitors of EGFR enzymatic activity. Mabs are considered active against the EGFR extracellular domain. Although TKIs inhibit the intracellular domain by suppressing its autophosphorylation, they have low selectivity, which could result in inhibiting other EGFR family members **(Zubair & Bandyopadhyay, 2023)**.

## 3.2. EGFR Inhibitors

The anticarcinogenic activity of EGFR inhibitors involves antiproliferation with arrest of the cell cycle at G0-G1 phase, inhibition of angiogenesis, suppressing the tumor invasion and its metastasis, and the augmentation of the anticarcinogenic effect of chemotherapy drugs **(Janani et al., 2022)**.
A group of chemotherapy drugs, called EGFR inhibitors, is considered a standard group for treating lung cancer patients. It acts by inhibiting the signaling pathway of EGFR through inhibiting the action of tyrosine kinase (TK) enzyme, as summarized in **Table 1**. Erlotinib and Gefitinib were the first developed drugs that act by this mechanism of action **(Ayati et al., 2020)**.

EGFR inhibitors, particularly Erlotinib and Gefitinib, could be administered by oral route. Moreover, their administration is associated with low adverse effects profile, presented as fatigue, rash, diarrhea, and rarely occurring pneumonitis **(Zubair & Bandyopadhyay, 2023)**. Drugs that act by inhibiting EGFR are considered targeted therapy, and therefore result in increasing the overall survival (OS) rate for lung tumor patients **(Ayati et al., 2020)**.

Drugs that inhibit certain signaling pathway, such as PI3K (buparlisib), mTOR (sirolimus), are considered effective for treating lung cancer. However, there are some cases that do not respond to targeted therapy; including carcinogenic tumor that lack the target upon which the drug acts, and tumors which the target does not have major role for their carcinogenesis **(Iksen et al., 2021)**.

EGFR inhibitors resistance could be classified into two main types; intrinsic resistance and acquired resistance. Intrinsic resistance is the failure of EGFR inhibitors to achieve positive therapeutic outcome, while acquired resistance is the worsening of the lung tumors after having positive therapeutic outcome at the first period of treatment **(Laface et al., 2023)**.

Acquired resistance to EGFR inhibitors was an emerging problem that needed to be resolved by the development of second-generation EGFR inhibitors, which act by irreversible binding to EGFR-HER1 receptor domain. Moreover, acquired resistance led to the development of third generation EGFR inhibitors that are characterized by wide therapeutic range and low side effects

**Table 1. EGFR inhibitors in terms of mechanism of action, indications, and side effects**

| Drug | Mechanism of action | Indication | Side effects |
|---|---|---|---|
| Erlotinib | Inhibiting intracellular phosphorylation, through tyrosine kinase inhibition. | Lung and pancreatic cancer. | Rash and diarrhea. |
| Gefitinib | EGFR reversible inhibition; first registered targeting agent. | Third line therapy for treating chemo-resistant NSCLC, could be used in combination with carboplatin or paclitaxel. | Rash and diarrhea. |
| Osimertinib | Third generation EGFR inhibitor. | First line or second line therapy against resistance and sensitizing mutations. | Minimal gastric and skin side effects. |
| Cetuximab | Monoclonal antibody that inhibits IgG1 anti-EGFR. | Treating lung cancer and considered first-line treatment for colorectal metastatic RAS wild-type cancer. | Follicle inflammation and flushing. |

profile **(Marin-Acevedo et al., 2023)**.

Some patients develop resistance to TKIs due to EGFR secondary mutations, particularly (T790M) mutation, which represents 50% of acquired resistance to TKIs **(Zubair & Bandyopadhyay, 2023)**.

NSCLC patients with mutated EGFR showed better treatment response with first generation inhibitors, compared to conventional chemotherapeutic methods. Erlotinib and Gefitinib, which are first generation inhibitors of EGFR, act by binding reversibly to wild-type EGFR and mutant EGFR **(Ayati et al., 2020)**. Side effects affecting the skin and gastrointestinal mucosa could result from binding to wild EGFR. On the other hand, Afatinib and dacomitinib, which are second generation inhibitors of EGFR, bind irreversibly to EGFR. Compared to gefitinib, dacomitinib caused better overall survival for NSCLC patients with mutant EGFR. However, second generation drugs cause low inhibiting effect of T790M EGFR, and could result in side effects, including diarrhea and rash **(Du et al., 2023)**.

### 3.2.1. Erlotinib

Erlotinib is a quinazoline derivative that reversibly and selectively inhibits the EGFR tyrosine kinase, which is accompanied by inhibiting its intracellular phosphorylation **(Figure 2)**. It is also available as oral dosage form **(Pourmadadi et al., 2024)**.

Erlotinib is considered a useful drug in the treatment of both lung cancer and pancreatic cancer and is used for the treatment of advanced NSCLC. It is also considered effective when used in combination with Gemcitabine for treating pancreatic cancer **(Zubair & Bandyopadhyay, 2023)**. The maximum recommended dose of Erlotinib for treating lung cancer is 150 mg per day. Erlotinib based therapy was accompanied by side effects, such as rash and diarrhea, without causing high degree of hair loss, neuropathy, or bone marrow suppression like other chemotherapy drugs **(Lee et al., 2020)**.

### 3.2.2. Gefitinib

Gefitinib, which is considered third-line therapy for the treatment of NSCLC patients who showed chemoresistance, is the first registered drug that targets EGFR, with symptom improvement rate ranging between 30% and 50%. Moreover, it acts by EGFR reversible inhibition, and it is available as oral preparation. In addition, it showed activity against brain metastatic tumors, therefore, it is useful for patients who suffer from both brain cancer and lung cancer. However, its administration was associated with some reversible dose dependent side effects, such as diarrhea and rash. Untreated NSCLC patients, stage 3B or stage 4, could be treated with a combination therapy of gefitinib and carboplatin-paclitaxel, without affecting the clearance of paclitaxel or carboplatin **(Marin-Acevedo et al., 2023)**.

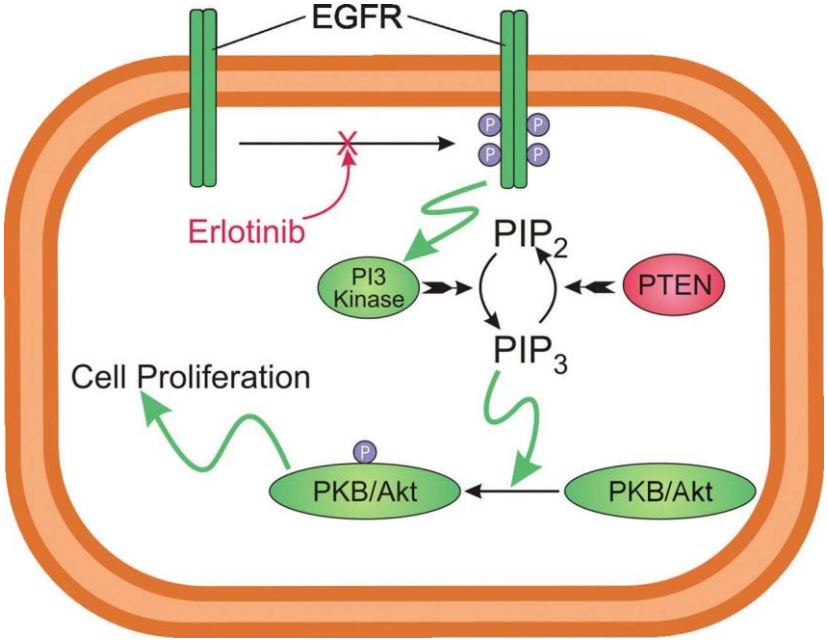


**Figure 2. The mechanism of action of Erlotinib (Krueger & Srivastava, 2006).** Mode of action of Erlotinib by inhibiting the intracellular phosphorylation of tyrosine kinase, therefore inhibiting the downstream signaling pathway. PIP3: Phosphatidylinositol-3,4,5-trisphosphate; PI3K: phosphatidylinositol-3 kinase; PKB/Akt: protein kinase B; PTEN: Phosphatase and TENsin homolog deleted on chromosome 10.

### 3.2.3. Osimertinib

Osimertinib, which is a third generation EGFR inhibitor, is considered an effective drug in terms of pharmacological activity and toxicity. It is an acceptable drug either as first-line therapy or second-line therapy due to its efficacy against both resistance mutations and sensitizing mutations. In addition, it causes minimal gastric and skin side effects due to its low effect on wild EGFR. However, patients who expressed T790M mutation showed 71 percent response rate and 10.1 median progression free survival (PFS), while those who did not express T790M mutation showed 21 percent response rate and 2.8 months median PFS, therefore Osimertinib is recommended more for patients who are T790M positive. Moreover, patients developed acquired resistance to treatment by Osimertinib, which could be classified as EGFR pathway dependent resistance and EGFR independent resistance **(Lee et al., 2020)**.

### 3.2.4. Cetuximab

Cetuximab is a monoclonal antibody that acts by inhibiting the IgG1 anti-EGFR. Its loading dose is 400 mg/m$^2$, and its maintenance dose is 250 mg/m$^2$. In addition, cetuximab can be used in combination with other chemotherapy regimens, resulting in positive treatment outcomes **(Janani et al., 2022)**. Moreover, it is considered first-line treatment for colorectal metastatic RAS wild type cancer **(Saoudi González et al., 2024)**. However, its administration was followed by some adverse reactions, including follicle inflammation and flushing **(Alexandris et al., 2023)**.

## 4. Conclusion

The epidermal growth factor receptor plays a pivotal role in the treatment of NSCLC. The development of EGFR tyrosine kinase inhibitors is considered a successful therapeutic method for the inhibition of lung tumor angiogenesis and metastasis. EGFR, which is encoded by tyrosine kinase enzyme, could be subdivided into wild-type and mutated-type which is responsible for lung carcinogenesis.

Chemotherapy drugs that target the EGFR to suppress tumor progression could be divided mainly into two groups, which are monoclonal antibodies and EGFR inhibitors.

Drugs that inhibit EGFR are subdivided into first-generation, second-generation, and third-generation drugs. The mechanism of action of EGFR tyrosine

kinase inhibitors depends mainly upon inducing the process of apoptosis and inhibiting the phosphorylation process, therefore this pharmacological class provides acceptable positive therapeutic outcomes with high treatment response, and low side effects profile. The administration of combination of EGFR inhibiting regimens could provide better therapeutic response than single-agent therapy.

The study of EGFR and its role in lung carcinogenesis is crucial for the development of proper treatment methods. EGFR-TKI inhibitors provide a promising treatment option for NSCLC patients, therefore the development of chemotherapy drugs that belong to this class could provide alternative treatment methods that provide better treatment response in terms of the overall survival and the progression free survival period.

## References

Alduais, Y., Zhang, H., Fan, F., Chen, J., & Chen, B. (2023). Non-small cell lung cancer (NSCLC): A review of risk factors, diagnosis, and treatment. Medicine, 102(8), e32899.

Alexandris, D., Alevizopoulos, N., Palamaris, K., Gakiopoulou, C., & Theocharis, S. (2023). Pinnae and facial hypertrichosis induced by cetuximab. Journal of Oncology Pharmacy Practice, 29(3), 731-737.

Allignet, B., De Ruysscher, D., Martel-Lafay, I., & Waissi, W. (2023). Stereotactic body radiation therapy in unresectable stage III non-small cell lung cancer: A systematic review. Cancer Treatment Reviews, 118, 102573.

Araghi, M., Mannani, R., Heidarnejad maleki, A., Hamidi, A., Rostami, S., Safa, S. H., Faramarzi, F., Khorasani, S., Alimohammadi, M., & Tahmasebi, S. (2023). Recent advances in non-small cell lung cancer targeted therapy; an update review. Cancer Cell International, 23(1), 162.

Ayati, A., Moghimi, S., Salarinejad, S., Safavi, M., Pouramiri, B., & Foroumadi, A. (2020). A review on progression of epidermal growth factor receptor (EGFR) inhibitors as an efficient approach in cancer targeted therapy. Bioorganic chemistry, 99, 103811.

Chhouri, H., Alexandre, D., & Grumolato, L. (2023). Mechanisms of acquired resistance and tolerance to EGFR targeted therapy in non-small cell lung cancer. Cancers, 15(2), 504.

Du, Z., Sun, J., Zhang, Y., Hesilaiti, N., Xia, Q., Cui, H., Fan, N., & Xu, X. (2023). Structure-guided strategies of targeted therapies for patients with EGFR-mutant non–small cell lung cancer. Biomolecules, 13(2), 210.

Iksen, Pothongsrisit, S., & Pongrakhananon, V. (2021). Targeting the PI3K/AKT/mTOR Signaling Pathway in Lung Cancer: An Update Regarding Potential Drugs and Natural Products. Molecules, 26(13), 4100.

Janani, B., Vijayakumar, M., Priya, K., Kim, J. H., Prabakaran, D., Shahid, M., Al-Ghamdi, S., Alsaidan, M., Othman Bahakim, N., & Hassan Abdelzaher, M. (2022). EGFR-Based targeted therapy for colorectal cancer—Promises and challenges. Vaccines, 10(4), 499.

John, T., Taylor, A., Wang, H., Eichinger, C., Freeman, C., & Ahn, M.-J. (2022). Uncommon EGFR mutations in non-small-cell lung cancer: A systematic literature review of prevalence and clinical outcomes. Cancer Epidemiology, 76, 102080.

Krueger, K. E., & Srivastava, S. (2006). Posttranslational protein modifications: current implications for cancer detection, prevention, and therapeutics. Molecular & Cellular Proteomics, 5(10), 1799-1810.

Laface, C., Maselli, F. M., Santoro, A. N., Iaia, M. L., Ambrogio, F., Laterza, M., Guarini, C., De Santis, P., Perrone, M., & Fedele, P. (2023). The resistance to EGFR-TKIs in non-small cell lung cancer: from molecular mechanisms to clinical application of new therapeutic strategies. Pharmaceutics, 15(6), 1604.

Laguna, J. C., García-Pardo, M., Alessi, J., Barrios, C., Singh, N., Al-Shamsi, H. O., Loong, H., Ferriol, M., Recondo, G., & Mezquita, L. (2024). Geographic differences in lung cancer: focus on carcinogens, genetic predisposition, and molecular epidemiology. Therapeutic Advances in Medical Oncology, 16, 17588359241231260.

Lee, C.-S., Sharma, S., Miao, E., Mensah, C., Sullivan, K., & Seetharamu, N. (2020). A comprehensive review of contemporary literature for epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer and

their toxicity. Lung Cancer: Targets and Therapy, 11, 73-103.

Leiter, A., Veluswamy, R. R., & Wisnivesky, J. P. (2023). The global burden of lung cancer: current status and future trends. Nature Reviews Clinical Oncology, 20(9), 624-639.

Marin-Acevedo, J. A., Pellini, B., Kimbrough, E. O., Hicks, J. K., & Chiappori, A. (2023). Treatment strategies for non-small cell lung cancer with common EGFR mutations: a review of the history of EGFR TKIs approval and emerging data. Cancers, 15(3), 629.

Oprita, A., Baloi, S.-C., Staicu, G.-A., Alexandru, O., Tache, D. E., Danoiu, S., Micu, E. S., & Sevastre, A.-S. (2021). Updated insights on EGFR signaling pathways in glioma. International Journal of Molecular Sciences, 22(2), 587.

Ortiz, A. F. H., Camacho, T. C., Vásquez, A. F., del Castillo Herazo, V., Neira, J. G. A., Yepes, M. M., & Camacho, E. C. (2022). Clinical and CT patterns to predict EGFR mutation in patients with non-small cell lung cancer: A systematic literature review and meta-analysis. European Journal of Radiology Open, 9, 100400.

Osarogiagbon, R. U., Van Schil, P., Giroux, D. J., Lim, E., Putora, P. M., Lievens, Y., Cardillo, G., Kim, H. K., Rocco, G., & Bille, A. (2023). The International Association for the Study of Lung Cancer Lung Cancer Staging Project: overview of challenges and opportunities in revising the nodal classification of lung cancer. Journal of Thoracic Oncology, 18(4), 410-418.

Pourmadadi, M., Mohammadzadeh, V., Mohammadi, Z. S., Poorkhalili, P., Afjoul, N., Behzadmehr, R., Fathi-Karkan, S., Rahdar, A., & Ghotekar, S. (2024). Advances in erlotinib delivery systems: Addressing challenges and exploring opportunities in EGFR-targeted cancer therapies. Inorganic Chemistry Communications, 161, 112114.

Saoudi González, N., Ros, J., Baraibar, I., Salvà, F., Rodríguez-Castells, M., Alcaraz, A., García, A., Tabernero, J., & Élez, E. (2024). Cetuximab as a Key Partner in Personalized Targeted Therapy for Metastatic Colorectal Cancer. Cancers, 16(2), 412.

Tang, P. A., Tsao, M.-S., & Moore, M. J. (2006). A review of erlotinib and its clinical use. Expert opinion on pharmacotherapy, 7(2), 177-193.

Thandra, K. C., Barsouk, A., Saginala, K., Aluru, J. S., & Barsouk, A. (2021). Epidemiology of lung cancer. Contemporary Oncology/Współczesna Onkologia, 25(1), 45-52.

Uslenghi, C., Casiraghi, M., Spaggiari, L., & Bertolaccini, L. (2023). Next-generation Lung Cancer Surgery: a brief trip into the future of the Research. Journal of Clinical Medicine, 12(10), 3479.

Zubair, T., & Bandyopadhyay, D. (2023). Small molecule EGFR inhibitors as anti-cancer agents: discovery, mechanisms of action, and opportunities. International Journal of Molecular Sciences, 24(3), 2651.