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Review Article

Recent Clinical Trials and Industry Updates on EGFR Inhibitors (2024-2025)

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ABSTRACT

The Epidermal Growth Factor Receptor (EGFR) signaling pathway has been and still is essential in the genesis and therapy of several solid tumors, the most famous among them being Non-Small Cell Lung Cancer (NSCLC) and Metastatic Colorectal Cancer (mCRC). Major changes in clinical practice and regulatory approvals have been made as a result of the recent progress from 2024 till 2025. In NSCLC, the LAURA trial showed the advantage of osimertinib as consolidation therapy after chemoradiation in unresectable stage III disease, whereas the FLAURA2 trial confirmed that the combination of osimertinib and chemotherapy was more effective as first-line metastatic setting, thus the indication was extended. The MARIPOSA study gave the green light to the combination of amivantamab with lazertinib as a new first-line treatment, and the PAPILLON study supported the employment of amivantamab in combination with platinum-pemetrexed for the tumors carrying the EGFR exon 20 insertion mutation. Furthermore, sunvozertinib was granted accelerated approval for the treatment of patients with exon 20 insertion-positive NSCLC who had undergone prior therapy, and some newly-developed fourth-generation EGFR inhibitors, like the ones targeting resistance C797S, are already in the process of being further developed. On the other hand, mCRC progressed in parallel with the unveiling of updated results of the PARADIGM trial that demonstrated the effectiveness of anti-EGFR antibodies in RAS wild-type left-sided tumors and with data from prospective studies showing the practicality of ctDNA-guided rechallenge in later-line settings. Altogether, these developments highlight the fact that precision medicine is continuously optimizing EGFR-targeted therapies in various cancer types, thus, not only are patients being presented with new treatment options and doses of hope but also coming possibilities of drug discovery are being informed.

Keywords: Osimertinib, FLAURA2 Trial, LAURA Trial, Amivantamab, Lazertinib, MARIPOSA Trial, PAPILLON Trial.

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INTRODUCTION

Epidermal Growth Factor Receptor (EGFR) signal transduction system is essential in controlling the growth, differentiation, and survival of the cells. In such cases, where the pathway is disrupted due to activating mutations or overexpression of the receptor, the changes in the pathway will result in the breaking of control and the development of neoplasms (Zhou *et al*., 2023). Mutations in the Epidermal Growth Factor Receptor (EGFR) in Non-Small Cell Lung Cancer (NSCLC) are mainly linked to the histology of adenocarcinoma, the status of no smoking and the origin of the Asian population, thus indicating the peculiar epidemiologic patterns which affect clinical management (New England Journal of Medicine [NEJM], 2024). On the other hand, colorectal cancer is devoid of EGFR mutations; however, receptor expression, as well as downstream activation, remains of clinical significance, especially when considering the selection of targeted therapy (JAMA, 2023).

Firstly, the introduction of EGFR-targeted treatments was among the most outstanding events in the history of precision oncology. First-generation TKIs (tyrosine kinase inhibitors), including gefitinib, erlotinib, and afatinib, showed to the patients a substantial clinical benefit but were unfortunately fallible in the long run with the development of resistance, the secondary T790M mutation being the most frequent one (Therapeutic Advances in Medical Oncology, 2024).

The beginning of the third-generation TKI osimertinib marked a turning point, as it was the perfect solution for T790M-caused resistance, besides, it showed great CNS (Central Nervous System) performance and survival benefits to a high degree (U.S. FDA, 2024a).

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However, even with the development of the above technologies, the end of resistance to osimertinib is still a reality, different mechanisms, and hence the next therapeutic options are urgently needed (Cancer Treatment Reviews, 2024).

Monoclonal antibodies directed against EGFR, such as cetuximab and panitumumab, are still relevant agents in mCRC for patients with RAS wild-type tumors. Their therapeutic benefit has been even more developed based on molecular and clinical knowledge, such as identifying the predictive role of primary tumor location (sidedness) and the emerging use of circulating tumor DNA (ctDNA) profiling to inform rechallenge strategies (JAMA Network Open, 2024).

Collectively, these advances illustrate how EGFR-targeted approaches continue to evolve, offering new opportunities to improve outcomes while addressing emerging resistance mechanisms.

Key clinical trials and regulatory approvals

LAURA: Osimertinib Following Definitive Chemoradiotherapy in Patients With Non-Small Cell Lung Cancer III / IIIA (Primary).

The LAURA phase III trial demonstrated that consolidation osimertinib following chemoradiotherapy significantly prolonged PFS in patients with inoperable stage III EGFR-mutated NSCLC (National Cancer Institute, 2024). These results reaffirmed the FDA approval of osimertinib in this context in 2024 (FDA, 2024d).

Osimertinib Plus Chemotherapy in First-Line Metastatic NSCLC (FLAURA2)

In a trial, FLAURA2, the patients diagnosed with newly advanced EGFR-mutated NSCLC were given either a dosage of osimertinib alone or a combination of osimertinib and chemotherapy. Chemotherapy also increased the Overall Survival (OS) and PFS and the combination regimen was approved by FDA in 2024 (AstraZeneca, 2025; FDA, 2024a).

Amivantamab Plus Lazertinib in First-Line NSCLC (MARIPOSA)

MARIPOSA trial compared amivantamab combined with lazertinib with osimertinib in patients with EGFR-mutated NSCLC, in the initial line of treatment. The dual-targeted strategy demonstrated a longer PFS with a tolerable safety profile (NEJM, 2024), which led to the combination receiving approval in 2024 by the FDA (FDA, 2024b).

Amivantamab Plus Platinum-Based Chemotherapy for Exon 20 Insertions (PAPILLON).

The PAPILLON study proved amivantamab plus carboplatin and pemetrexed to be a better choice among patients with NSCLC whose tumors contain EGFR exon 20 insertions. The regimen almost doubled PFS compared with chemotherapy alone (Zhou *et al*., 2023). This combination was later approved by FDA (FDA, 2024c). Pretreated Exon 20 Insertion NSCLC on Sunvozertinib. Sunvozertinib, an oral tyrosine kinase inhibitor with specific activity against EGFR insertions at exon 20, showed long-lasting response in patients who had developed following earlier treatment. Based on these data, the FDA gave accelerated approval in 2025 (OncLive, 2025; FDA, 2025).

EMERGING THERAPIES AND FUTURE DIRECTIONS

New studies are going on to identify novel ways of overcoming resistance mechanisms in EGFR-mutated cancers. These are fourth-generation TKIs of the C797S mutation, antibody drug conjugates and bispecific antibodies. These methods are likely to increase treatment choices in the next several years.

Fourth-Generation EGFR Inhibitors

C797S mutation is one of the most common mechanisms of resistance to the use of osimertinib. To counter this, a number of fourth generation EGFR blockers are under development. Some agents like BLU-945 and BBT-176 are specifically designed to bypass resistance of C797S. Initial findings of SYMPHONY trial have reported an initial clinical activity with BLU-945 (Blueprint Medicines, 2024; Therapeutic Advances in Medical Oncology, 2024). On the same note, BBT-176 and its subsequent analogue molecule BBT-207 have delivered promising results in both preclinical and early clinical trials (Cancers, 2023; Clinical Trials Arena, 2024).

Combinatorial Strategies

Along with next-generation inhibitors, combination strategies are being explored to increase the efficacy of treatment and extend disease control. These involve combining the EGFR inhibitors with MET inhibitors, and their use with immune checkpoint inhibitors. The purpose of such strategies is to slow or even avoid resistance and enhance long-term patient outcomes (Cancer Treatment Reviews, 2024).

Advances in Colorectal Cancer

Anti-EGFR strategies have been refined to a large extent in metastatic Colorectal Cancer (mCRC). The PARADIGM trial proved that panitumumab combined with chemotherapy provided a survival benefit compared with bevacizumab-based regimens in the patients with left-sided, RAS wild-type tumors (JAMA, 2023). Moreover, ctDNA-guided rechallenge of anti-EGFR has also shown to be promising and is now able to induce reintroduction of EGFR antibodies in patients with RAS/BRAF wild-type disease at progression and thus extend disease control (JAMA Network Open, 2024).

INDUSTRIAL DEVELOPMENTS AND MARKET TRENDS

EGFR-targeted therapies remain the core of the oncology pipeline maintained by pharmaceutical companies, which consider them indispensable assets in the age of the precision medicine era. Multiple expansions of astrazeneca label into the space with both early-stage and metastatic NSCLC have further cemented their leadership in the space. Another significant player that has surfaced is Janssen, which has received regulatory approvals of amivantamab-based combinations that cover the treatment of not only classical EGFR mutations but also exon 20 insertions, thus increasing the variety in treatment choices in a wide range of patient subgroups. Meanwhile, Asian companies in biotechnology, and especially China, are on the rise and medicines like sunvozertinib are making their way into the global market via expedited FDA approval by 2025. Such trends not only echo the trend of growing globalization of EGFR drug innovation, but also a move toward competitive diversification, as both multinational pharmaceutical and regional biotech companies are stepping forward with these developments. Combined, these initiatives emphasize the active and fast-changing character of EGFR inhibitor landscape, where there is a competition that leads to innovation, and new agents keep on transforming care standards (OncLive, 2025).

EGFR-targeted therapies have a significant intellectual property contribution to their development and commercialization. Core composition-of-matter and method-of-use patents claim first-, second-, and third-generation tyrosine kinase inhibitors and monoclonal antibodies and fourth-generation agents in development. Table 1 below lists some illustrative patents of clinically relevant EGFR inhibitors, such as osimertinib, amivantamab, lazertinib and sunvozertinib, their assignees, jurisdictions and first references. This summary explains why drug manufacturers and biotechnology companies are establishing strong patent platforms in order to stay on the top of the EGFR inhibitors market.

Recent Advances in EGFR Inhibitors (2024-2025)

Various clinical trial disclosures and regulatory measures in the last two years have redefined the treatment model of EGFR-mutated Non-Small Cell Lung Cancer (NSCLC) and broadened the area of anti-EGFR medication.

Osimertinib consolidation therapy following chemoradiotherapy in unresectable stage III EGFR-mutated NSCLC as assessed in the LAURA trial showed a significant clinically measurable increase in progression-free survival (PFS). These figures were the basis of regulatory clearances such as the U.S. FDA and the CDSCO in India in 20242025, which made osimertinib the new standard of care in this environment globally (AstraZeneca, 2025a).

The FLAURA2 trial of osimertinib with platinum-based chemotherapy showed significant improvements in Overall Survival (OS) and PFS over osimertinib in first-line metastatic disease and resulted in an expansion of the label in 2024 (OncLive, 2025). Similar neoadjuvant trials are looking at using osimertinib earlier in the disease course, though questions regarding the duration and order remain (Oncology News Central, 2025).

Other than osimertinib, bispecific antibody regimens are still being developed. A new standard based on amivantamab with platinum/pemetrexate was established with the trials in the so-called exon 20 insertion-positive NSCLC; The trial PAPILLON established the superiority of amivantamab plus platinum/pemetrexate (AstraZeneca, 2025a; AstraZeneca, 2025b). The combination of amivantamab with lazertinib (MARIPOSA) was shown to be better than Osimertinib.

Small-molecule inhibition is active in the exon 20 insertion space. In 2025, Sunvozertinib was given accelerated approval by the FDA to use in previously treated patients and showed sustainable responses, and the other drugs, including zorifertinib, are in the phase III trials (Wikipedia, 2025a, 2025b).

The fourth-generation (4G) EGFR-inhibitor pipeline has been rendered more competitive, to overcome resistance via the C797S mutation. Early data were reported to be promising with BLU-945 (SYMPHONY), BBT-176 and with in development molecules like J INTS Bio, JIN-A02 and BI-4732 being included (Biospace, 2025; opnMe, 2024). Simultaneously, the globalization of 4G EGFR drug development is reflected in new inhibitors by CCM Biosciences and Black Diamond Therapeutics, some of which are discussed at ASCO 2025 (Business Wire, 2025; Trial Med Path, 2025).

In summary, EGFR inhibitors will continue to be a mainstay of precision oncology and the current practice of innovation includes antibody therapies, combination regimens, and resistance-guided next-generation agents. These developments strengthen EGFR as one of the most active therapeutic targets in thoracic cancer.

Recent Market Coverage of EGFR Inhibitors (2024-2025)

The osimertinib (Tagrisso) by AstraZeneca has remained a leader in the EGFR inhibitors worldwide market. After the label expansions in 2024, Tagrisso earned about 6.6 billion in global sales, and the demand was high in the United States, Europe, China, Japan and South Korea (FiercePharma, 2025).

EGFR-mutant NSCLC Sir This marked a significant milestone to Johnson & Johnson with first-line FDA approval of amivantamab-lazertinib in August 2024. By 2025, the regimen had already earned approximately 320 million sales of its products worldwide, and almost 80 percent of the sales were in the U.S. market (FDA, 2024; Yuhan, 2025).

Sunvozertinib (developed by Dizal) was acceleratedly approved by the U.S. FDA in July 2025, in the exon 20 insertion NSCLC

segment, but previously in China. The drug has now been established as a significant oral therapy to patients with an exon 20 deletion disease previously treated (Oncology Nursing Society, 2025; Association of Community Cancer Centers, 2025).

Meanwhile, anti-EGFR monoclonal antibodies are also proving to have a long lasting market in the Metastatic Colorectal Cancer (mCRC). As a reminder of the long-term relevance of these compounds in RAS wild-type disease, cetuximab (Erbitux) of Merck KGaA earned sales of €1.162 billion and panitumumab (Vectibix) of Amgen sold 1.045 billion in 2024, with both drugs being used in the disease worldwide (Merck KGaA, 2025; Amgen, 2025).

Anti-EGFR monoclonal antibodies including cetuximab and panitumumab are still useful treatment agents in patients with RAS/ BRAF wild-type, left-sided metastatic colorectal cancer. The clinical benefit is, however, frequently constrained by the evolution of acquired resistance in the form of emergent mutations in the RAS, BRAF, or the EGFR ectodomain. Recent developments in circulating tumor DNA (ctDNA) have opened up the opportunity to research rechallenge models, providing the chance to re-institute EGFR blockade following a drug-free period when resistant clones have been destroyed.

A number of phase II trials have offered support to this strategy. Such trials as CHRONOS and CRICKET proved that patients who were positively ctDNA-confirmed as having RAS/BRAF wild-type status responded to rechallenge with panitumumab or cetuximab in a manner significant to the clinical response (Cremolini *et al.*, 2019; Parseghian *et al.*, 2022). The value of rechallenge in such biomarker-selected population was recently validated by a pooled study of four Italian prospective trials (CAVE, VELO, CRICKET, CHRONOS) involving 114 patients. Overall Response Rate (ORR) in this analysis was 17.5, disease control rate was 72.3, median Progression-Free Survival (PFS) was 4.0 months and median Overall Survival (OS) was 13.1. Notably, the lack of liver metastases was linked to better PFS and OS, which showed that the presence of heterogeneity in the area of the disease affects the treatment effect (Ciardiello *et al.*, 2024).

Table 1: Patents for EGFR Inhibitors.

Drug/Program	Core Patent(s)	Assignee(s)	Scope	Reference (APA style)
Osimertinib (AZD9291)	WO2013014448; WO2015101791; WO2017134051	AstraZeneca AB	Composition of matter, crystalline forms, formulations	AstraZeneca AB. (2013). Compounds for the treatment of cancer (WO2013014448A1). World Intellectual Property Organization. https://patentscope.wipo.int
Amivantamab (EGFR×MET bispecific mAb)	WO2014081954	Genmab A/S; Janssen Biotech, Inc.	Bispecific antibodies targeting EGFR and MET	Genmab A/S, & Janssen Biotech, Inc. (2014). Bispecific anti-EGFR and anti-MET antibodies (WO2014081954A1). World Intellectual Property Organization. https://patentscope.wipo.int
Lazertinib (YH-25448)	WO2016060443	Yuhan Corporation; Janssen Biotech, Inc.	Composition of matter for 3rd-generation EGFR-TKIs	Janssen Biotech, Inc., & Yuhan Corporation. (2016). Compounds and compositions for modulating mutant EGFR (WO2016060443A2). World Intellectual Property Organization. https://patentscope.wipo.int
Sunvozertinib (DZD9008)	WO2019149164	Dizal (Jiangsu) Pharmaceutical Co., Ltd.	EGFR inhibitors selective for exon 20 insertions	Dizal (Jiangsu) Pharmaceutical Co., Ltd. (2019). EGFR exon 20 insertion inhibitors (WO2019149164A1). World Intellectual Property Organization. https://patentscope.wipo.int
BLU-945	WO2021133809; CA3210395	Blueprint Medicines Corporation	Fourth-generation EGFR inhibitors active against T790M/C797S	Blueprint Medicines Corporation. (2021). Compounds for mutant EGFR inhibition (WO2021133809A1). World Intellectual Property Organization. https://patentscope.wipo.int
BBT-176/ BBT-207	(Various filings across KR/WO; early disclosures 2020–2023)	Bridge Biotherapeutics, Inc.	Fourth-generation EGFR inhibitors targeting C797S-mediated resistance	Bridge Biotherapeutics, Inc. (2023). Fourth-generation EGFR inhibitors for resistant cancers [Patent filings and clinical program data]. Retrieved from https://clinicaltrials.gov/ct2/show/NCT04820023

In addition to these data, a meta-review and meta-analysis, which was published in late 2024, synergized accessible phase II data. The combination of the outcomes was an ORR of about 20.5%, a disease control rate of about 67, median PFS of 3.5 months, and median OS of about 9.8 months (da Silva *et al*., 2024). These data indicate that although the rechallenge rates are small in comparison with initial treatment, patient selection based on ctDNA enriches significantly in terms of responders and disease control in comparison with non-selected strategies.

The clinical evidence was further enhanced by the abstracts that were discussed at ASCO 20242025 and ESMO 2024. Such reports highlighted the reality of serial ctDNA monitoring to identify rechallenge candidates and to follow the dynamics of resistance, which supports the presence of liquid biopsy as a new clinical standard (Sartore-Bianchi *et al*., 2024; Taieb *et al*., 2024).

Together, these results indicate that ctDNA-guided anti-EGFR rechallenge is a rationale and evidence-based approach in later-line mCRC treatment. Despite a moderate clinical benefit, such a course is a personalized treatment option in patients with small choices. Further investigation needs to be concerned with randomized trials of ctDNA-guided rechallenge vs standard late-line therapy and integrating approaches (e.g., anti-EGFR antibodies with immune checkpoint inhibitors or chemotherapy) to enhance response durability.

CONCLUSION

During the last two years, therapeutic landscape of EGFR driven cancers has changed significantly. Osimertinib-based consolidation therapy, new first-line combinations and exon 20 insertion-targeting agents have quickly transformed clinical practice in NSCLC. At the same time, the discovery of fourth-generation EGFR inhibitors provides a possible way out of the resistance effects, including the C797S mutation. In metastatic colorectal cancer, molecular stratification and personalization of treatment remains under evolution to enhance the use of anti-EGFR treatment. All these advancements are a considerable move in the right direction and the initial stage of a new age of precision oncology of EGFR driven malignancies.

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ABBREVIATIONS

ctDNA: Circulating tumor DNA; **EGFR:** Epidermal growth factor receptor; **ex20ins:** Exon 20 insertion; **FDA:** U.S. Food and Drug Administration; **LAURA:** Osimertinib after chemoradiotherapy in unresectable stage III EGFR-mutated NSCLC trial; **mCRC:** Metastatic colorectal cancer; **NSCLC:** Non–small cell lung cancer; **PAPILLON:** Amivantamab plus chemotherapy for EGFR exon 20 insertion–positive NSCLC trial; **FLAURA2:** Osimertinib plus chemotherapy in first-line EGFR-mutated NSCLC trial; **MARIPOSA:** Amivantamab plus lazertinib vs osimertinib in first-line EGFR-mutated NSCLC trial; **PARADIGM:** Panitumumab vs bevacizumab plus chemotherapy in RAS wild-type mCRC trial.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

SUMMARY

The Epidermal Growth Factor Receptor (EGFR) pathway has been a primary mediator of tumorigenesis and an invaluable precision therapy in solid tumors, with specific reference to Non-Small Cell Lung Cancer (NSCLC) and metastatic colorectal cancer (mCRC). The 2024-2025 time frame has been particularly productive, and several landmark trial decisions and regulatory achievements redefined clinical practice. The LAURA trial consolidated the use of osimertinib after chemoradiotherapy in unresectable stage III disease in the context of the NSCLC, which was subsequently adopted as a new standard of care and met regulatory approval. Likewise, the FLAURA2 trial results validated the findings, showing that the use of osimertinib and chemotherapy in the first-line metastatic milieu increased clinical benefit with an ensuing label expansion by the FDA and intensified treatment in the relevant patient groups.

MARIPOSA trial further advanced the frontline management with the proof of the effectiveness of amivantamab combined with lazertinib, and the final decision was the regulatory approval of the dual-targeted regimen. Simultaneously, the PAPILLON study confirmed the advantage of the combination of amivantamab with a platinum and pemetrexed combination in patients with ex20ins mutations, leading to changes in the drug labeling and recommendations. The other milestone was the expedited approval of sunvozertinib, which offered a viable treatment alternative to patients with ex20ins NSCLC who had previously been treated- a historically underserved clinical area.

In addition to these developments, fourth-generation EGFR inhibitors to overcome acquired resistance are being developed through early-phase studies, including the C797S mutation that limits the tolerability of osimertinib treatment. These new agents have potential to overcome one of the most difficult resistance

mechanisms and form a major horizon in EGFR-directed drug development.

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