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# A Review of Targeted Therapies for Non-Small Cell Lung Cancer Treatment

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## ABSTRACT

Non-small cell lung cancer (NSCLC) accounts for around 80-90% of all lung cancers as well as for most cancer related deaths in men. Targeted therapies play a crucial role in the treatment of NSCLC. This literature review explores the effectiveness of three targeted therapies: Crizotinib, bevacizumab, and osimertinib. Crizotinib targets anaplastic lymphoma kinase (ALK) and mesenchymal epithelial transitional (MET) alterations, while bevacizumab inhibits vascular endothelial growth factor (VEGF) to impede angiogenesis. Osimertinib, a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), targets epidermal growth factor receptor (EGFR) mutations, particularly T790M. Each therapy targets distinct molecular pathways involved in NSCLC progression and resistance mechanisms. Understanding the comparative efficacy of these targeted therapies is essential for optimizing treatment strategies and improving patient outcomes.

## INTRODUCTION

Non-small cell lung cancer (NSCLC) makes up around 80-90% of all lung cancers and accounts for most lung cancer related deaths in men[1,2]. It consists of three main subtypes: adenocarcinoma (ADC), large cell carcinoma (LCC), and squamous cell carcinoma (SCC). Treatment for NSCLC has historically consisted of systemic cytotoxic chemotherapy. Systemic cytotoxic chemotherapy works by the non-selective killing of both malignant tumour cells and normal, dividing or growing cells in the body[3]. NSCLC treatments are generally known to lower the risk of cancer relapse, but often result in undesirable adverse effects, including anemia, fatigue, nausea, and appetite loss[3]. Side effects caused by other immunotherapies can be severe, for example, bowel perforations, renal insufficiency, and pericardial effusions[4,5,6].

Molecular pathways play a crucial role in the development and treatment of NSCLC, forming the basis for current therapeutic strategies and our understanding of NSCLC[7]. Studies have highlighted the significance of identifying driver gene mutations, such as the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) rearrangements, and Kirsten rat sarcoma viral oncogene (KRAS) mutations, in NSCLC patients to promote targeted therapy and improve patient outcomes[8]. Additionally, dysregulation of signalling cascades due to genetic modifications contributes to cancer initiation,

progression, and drug resistance in NSCLC[9]. Transcriptome profiling has been utilized to identify key dysregulated pathways and genes associated with different histological subtypes of NSCLC, including ADC and SCC, aiding in the understanding of biological functions and potential therapeutic targets[7].

This understanding of the molecular pathways that drive malignancy in NSCLC has enabled scientists to identify enzymes and their specific functions, which is particularly important when identifying cancer cells. One of the novel treatments that has been developed is the use of targeted therapy. Targeted therapy involves the use of drugs or other substances that inhibit specific molecular pathways and proteins responsible for cancer cell growth, division and survival[10,11]. Targeted therapies can vary widely, but they often focus on molecular and genetic factors specific to the lung cancer cells, such as certain proteins or gene mutations[12]. Targeted therapies are associated with a lower incidence of high-grade adverse events, with toxicity profiles depending on the drug's specific mechanism[13].

For example, in NSCLC, targeted therapies might inhibit the action of the vascular endothelial growth factor (VEGF) or ALK in patients whose tumours have mutations in these genes, as shown by Waarts et al.[14,15,16].This precision medicine approach allows for more individualized treatment plans with the potential for improved outcomes such as improved survival rates and better quality of life, as well as reduced side effects compared to more traditional chemotherapy-based treatment approaches[17].

Crizotinib is a biology-based biomarker, and has demonstrated a favorable toxicity profile[18]. Patients with lung squamous cell cancer (LSCC) have shown promising responses to osimertinib. The treatment has also been proven to improve survival in advanced lung cancer with EGFR mutation[19].A statistically significant and clinically meaningful survival benefit was found in patients who received bevacizumab along with chemotherapy as compared to those who did not[20].

Although bevacizumab, crizotinib and osimertinib are all used in the treatment of NSCLC, they differ fundamentally in their chemical composition and biological mechanism of action[1]. Bevacizumab is a monoclonal antibody targeting extracellular, thereby inhibiting angiogenesis VEGF, whereas crizotinib and osimertinib are small molecule TKIs that act intracellularly on oncogenic driver mutations[4,11].

In this article, we conduct a literature review of clinical and experimental research for three targeted therapies - osimertinib, crizotinib and bevacizumab - and evaluate their efficiency in treating NSCLC. We expect to reveal significant differences in the efficacy, relapse rate, and overall therapeutic benefit of these drugs when they are used to treat NSCLC. This paper aims to provide a concise way for the reader to compare these targeted therapies, and to be able to follow the contents of the paper with ease. We will begin with an introduction to each of these targeted therapies, and then provide details as to how they work, their efficiency, their side effects and an insight as to which targeted therapy may be best for treatment of NSCLC.

Targeted Therapies:

*Crizotinib*

Crizotinib is an orally administered drug that works by blocking signals caused by alterations in the genes ALK and ROS1, inhibiting oncogenic signalling pathways, and resulting in tumour growth suppression. It is used for the treatment of ALK positive NSCLC. In a study done by Lowe et al., where crizotinib was used in patients with ALK positive cancer, the rate of event free survival in the paediatric patients was 76.8%. 15 patients out of the 66 relapsed[21]. According to a study done by the South Asian Journal of Cancer, there are long-term beneficial effects of crizotinib in ALK positive NSCLC as well as a favourable toxicity profile[22].

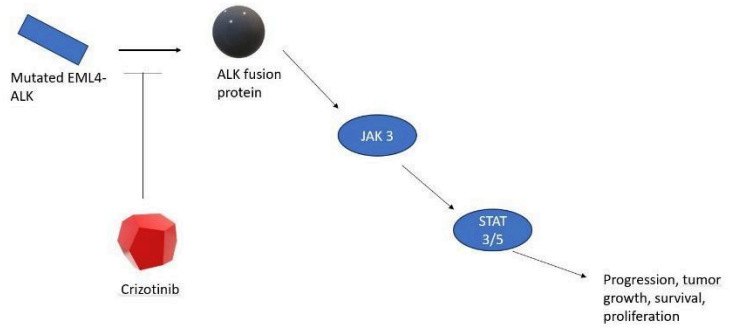


Figure 1. Simplified version of an image produced by Ando et al.,[23].This diagram illustrates how the Janus kinase/signal transducer and activator of transcription JAK/STAT signalling cascades are affected by ALK gene translocation. It is the activation of this signalling pathway, as well as the RAS and PI3K-AKT signalling pathways that influences not only cancer development but also influences tumour growth and metastases of cancer cells[23] [Figure 1].

*Osimertinib*

Osimertinib is a targeted therapy drug that works by blocking the EGFRs and is used to treat EGFR positive non-small cell lung cancer. It is orally administered. It has been shown that osimertinib demonstrated an adequate safety profile with manageable toxicities, leading to a low treatment discontinuation rate and no reported fatal adverse events[24].

*Bevacizumab*

Bevacizumab is a drug which is administered via infusion. It works by selectively binding circulating VEGF, thereby inhibiting the binding of VEGF to its cell surface receptors. It is often used in combination with chemotherapy or other targeted therapies. Bevacizumab combined with chemotherapy is a safe and effective treatment for non-squamous cell NSCLC[25]. According to Yue, Zhou., et.al, bevacizumab increases objective response rate, overall survival, and prolongs progression free survival in NSCLC patients[26]. However, bevacizumab also increased hypertension and haemorrhagic events rates in patients[26].

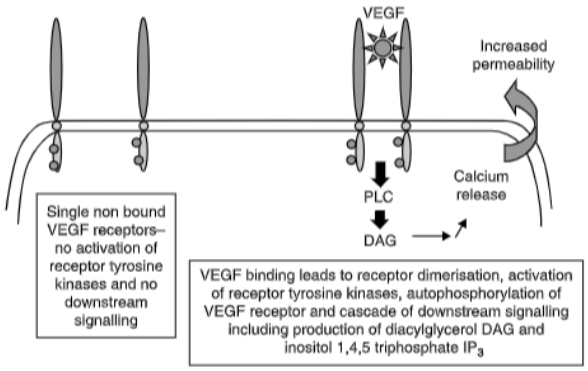


Figure 2. Adapted from Midgley and Kerr.[27] VEGF-A (represented by the central circle and triangles pointing outwards) and its receptor (VEGF receptor 2) (represented by oblong shapes on both sides of VEGF-A, with an intracellular tail). The binding of VEGF-A to VEGF receptor-2, triggers a cascade of signalling events within the endothelial cells, leading to processes that promote angiogenesis. VEGF activation leads to downstream effects such as calcium release and increased permeability in capillaries, mediated by factors such as VEGF receptor-2 [Figure 2].

*Research Question*

*Which targeted therapy (osimertinib, bevacizumab, crizotinib) is most effective in treating non-small cell lung cancer while minimizing side effects?*

## METHODS

To understand the effectiveness of each targeted therapy in terms of treatment effectiveness, measured here in terms of the chance of relapse, mortality, as well as the occurrence of side effects, we conducted a literature review on published clinical and experimental studies. We obtained research papers, articles, case studies, and published databases from the following sources: Google Scholar, PubMed, National Cancer Institute GDC Database, Medline, and other Internet search engines. We used keywords such as "Osimertinib," "Bevacizumab," "Crizotinib," and "Targeted Therapy" to identify relevant material.

All of the material obtained was gathered in a spreadsheet, and then organized with respect to different aspects of each research paper, for example, the medication, the mutation targeted, whether it was used in combination or alone.

After analysing all the material, a detailed comparison was done between therapies, evaluating the following aspects: side effects; relapse rate; mortality; cost effectiveness and access; time taken to develop drug resistance; and overall efficiency.

## RESULTS

We had a total of 18 research papers; 4 reviewed crizotinib, 6 reviewed osimertinib, 6 reviewed bevacizumab, 1 reviewed both osimertinib and bevacizumab, and 1 was a general analysis of targeted therapies, with focus on crizotinib. 13 papers discussed side effects. Among these 13 papers, 2 papers did not clearly mention the side effects, however, their seriousness (Grade 1, 2 or 3; grade 1 being mild or asymptomatic findings with minimal or no functional limitations, grade 2 being moderate symptoms that limit instrumental activities of daily living or require medical intervention, and grade 3 being severe and medically significant, often requiring hospitalization or urgent intervention) and how often they occurred was discussed. Efficacy of each targeted therapy was discussed in all 18 papers, covering different age groups and gene mutations in NSCLC like EGFR, ALK, VEGF, and ROS1. 8 papers discussed the mortality and relapse rate in detail and provided estimated data, while 6 other papers mentioned the increase or decrease in mortality and relapse rate when a given targeted therapy was used. All 18 papers reported drug resistance development in patients, and 10 reported the approximate duration it takes to develop drug resistance in an individual being treated.

### *Efficacy*

Osimertinib emerges as a highly effective targeted therapy for NSCLC, particularly in patients with EGFR mutations. The FLAURA trial demonstrated significant improvements in progression-free survival (PFS) with osimertinib compared to standard EGFR TKIs[28,29,30]. Additionally, osimertinib shows promising results in overall survival, with lower adverse events and higher continuation rates compared to other EGFR-TKIs. First-line osimertinib demonstrated a median overall survival of 38.6 months, compared with 31.8 months for first-generation EGFR-TKIs, corresponding to a 6.8-month absolute survival gain and a 20% reduction in the risk of death. In contrast, chemotherapy, the previous mainstay for NSCLC treatment, has limitations such as strong adverse reactions and a shorter survival period[28]. Osimertinib's efficacy is further supported by its ability to overcome resistance mutations like EGFR C797S, making it a valuable first-line option[30].

In the phase III FLAURA trial, first-line osimertinib demonstrated a median overall survival of 38.6 months, compared with 31.8 months for first-generation EGFR-TKIs, corresponding to a 6.8-month absolute survival gain and a 20% reduction in the risk of death[28].

### *Side effects*

Osimertinib stands out as a targeted therapy with relatively fewer side effects compared to other therapies like bevacizumab. Clinical trials have shown that osimertinib has a lower incidence of adverse events, with diarrhoea, skin toxicity, nausea, and decreased appetite being the most common but mostly grade 1 or 2 in severity[28,31]. In contrast, bevacizumab, when used in combination therapies, has been associated with significant side effects such as hypertension, proteinuria, thromboembolic events, gastrointestinal perforation, and wound healing complications[29]. Crizotinib has also shown various side effects, such as grade-3 adverse events that included neutropenia, raised ALT and pneumonitis[32]. The improved safety

profile of osimertinib makes it a favourable option in the treatment of NSCLC, offering efficacy with a lower burden of adverse effects.

*Relapse rate*

Osimertinib, a third-generation EGFR-TKI, has shown promising results with a lower relapse rate in patients with EGFR-mutated NSCLC[28]. Studies have demonstrated a significant improvement in progression-free survival (PFS) and overall survival (OS) with osimertinib compared to standard EGFR-TKIs and certain other targeted therapies, indicating its efficacy in reducing relapse rates[28,29,33]. Additionally, osimertinib has been associated with a lower incidence of adverse events compared to other treatments, further supporting its role as a preferred targeted therapy option[28]. However, bevacizumab has also been very effective in non-small cell lung cancer patients with brain metastases, with no reported episodes of a CNS haemorrhage greater than Grade 2, also making it a viable option[7].

*Drug resistance*

In the realm of targeted therapy for drug resistance, osimertinib, a potent EGFR inhibitor, stands out as a promising option. It has shown efficacy in overcoming resistance mechanisms such as the T790M mutation, which is a common cause of resistance to other EGFR inhibitors[30,34]. Additionally, osimertinib's ability to target specific mutations like C797S and T790M contributes to its effectiveness in combating drug resistance[30]. Furthermore, the combination of osimertinib with other agents like bevacizumab has shown promise in inhibiting tumour growth and improving outcomes in certain EGFR-mutant NSCLC patients[35] . Overall, osimertinib's superior potency against resistance mechanisms and its selectivity make it a frontrunner in the battle against drug resistance in targeted therapy for NSCLC. The approximate duration taken to develop drug resistance to osimertinib, it takes 10-18 months, while crizotinib and bevacizumab each take around 12 months.

*Mortality rate*

Osimertinib, a third-generation EGFR-TKI, stands out for its lower mortality rate compared to standard EGFR-TKIs in the treatment of advanced NSCLC. Studies have shown that patients on osimertinib had a median overall survival of 38.6 months, with a hazard ratio for death of 0.80, indicating a significant survival benefit[28]. Additionally, the data reveals that adverse events of grade 3 or higher were reported in 42% of patients on osimertinib, which was lower than the 47% reported in the comparator group[28]. Osimertinib also demonstrated an impressive objective response rate of 80% and a disease-control rate of 97%, showcasing its efficacy and favourable safety profile[29]. Bevacizumab, when used along with chemotherapy, was associated with an improvement in overall survival, and it reduced mortality risk, compared with chemotherapy alone[39]. Crizotinib has demonstrated a reduction in mortality compared with platinum-based chemotherapy in ALK-positive NSCLC, however long-term overall survival benefits are limited by the relatively rapid development of acquired resistance[40]. Across major clinical trials, osimertinib demonstrates a greater mortality benefit than both bevacizumab-based chemotherapy and crizotinib, achieving a significantly longer median overall survival (38.6 months), whereas bevacizumab

confers only modest survival improvements and crizotinib shows limited overall survival benefit due to early resistance development[28,41]. Osimertinib provides a substantial survival advantage over chemotherapy in EGFR-mutated NSCLC, achieving median overall survival exceeding 3 years compared with approximately 2 years with chemotherapy-based regimens[28]. These findings collectively position osimertinib as a targeted therapy with a notably lower mortality rate in the management of NSCLC.

## CONCLUSION

As a targeted treatment for non-small cell lung cancer, osimertinib demonstrates superior efficacy in EFGR-mutated NSCLC, with comparatively lower relapse and mortality rates. It has also proven to be effective in combating drug resistance and inhibiting tumour growth. However, each targeted therapy has its own positive and negative aspects, and combinatorial treatment strategies, like the use of chemotherapy with bevacizumab, have demonstrated therapeutic benefits, especially in those cases where patients develop drug resistance. The continuous development and exploration of targeted therapies in non-small cell lung cancer indicate a promising future and have potential for further advancement and new treatment strategies.

| Feature | Osimertinib | Crizotinib | Bevacizumab |
|---|---|---|---|
| *Drug class/ nature* | Small-molecule tyrosine kinase inhibitor (3rd-generation EGFR-TKI) | Small-molecule tyrosine kinase inhibitor | Humanized monoclonal antibody |
| *Primary molecular target* | EGFR activating mutations; activity against T790M resistance mutation | ALK and ROS1 rearrangement | Vascular endothelial growth factor A (VEGF-A) |
| *Cellular site of action* | Intracellular (EGFR kinase domain) | Intracellular (ALK/ROS1 kinase domains) | Extracellular (circulating VEGF ligand) |
| *Progression-free survival benefit* | Marked and sustained improvement vs earlier EGFR-TKIs and chemotherapy | Significant improvement vs chemotherapy, but shorter durability | Modest improvement when combined with chemotherapy |
| *Impact on mortality risk* | Substantial reduction in risk of death compared with chemotherapy and earlier EGFR-TKIs | Reduced mortality compared with chemotherapy, limited by resistance | Modest reduction in mortality risk vs chemotherapy alone |
| *Time to* | 10–18 months | ~12 months | ~12 months |

| | | | |
|---|---|---|---|
| *resistance (approximated)* | | | |
| *Severity of adverse effects* | Generally mild to moderate; low discontinuation rates | Moderate; grade 3 toxicities reported | Potentially severe, particularly vascular-related toxicities |
| *Overall clinical role* | Most effective option for EGFR-mutated NSCLC with longest survival benefit | Effective targeted option for ALK-positive NSCLC with intermediate survival benefit | Adjunct therapy providing incremental benefit rather than durable disease control |

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