Review Article

Breaking Barriers in Non-Small Cell Lung Cancer Treatment: Ceritinib Role in Advancing Targeted Therapy

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ABSTRACT

Lung cancer remains the leading cause of cancer-related death globally, with non-small cell lung cancer (NSCLC) accounting for most cases. A critical subset of NSCLC is characterized by anaplastic lymphoma kinase (ALK) gene rearrangements, which drive tumor growth and progression. Targeting this genetic alteration, Ceritinib, a second-generation ALK inhibitor, has shown significant efficacy in both treatment-naive patients and those who have progressed on prior ALK inhibitor therapy. Ceritinib disrupts downstream signaling pathways essential for cancer cell proliferation and survival by inhibiting the ALK fusion protein. Clinical trials such as ASCEND-4 and ASCEND-5 have demonstrated Ceritinib's superiority over standard chemotherapy, offering improved progression-free G1202R and objective response rates. Despite its benefits, patients often develop resistance to Ceritinib, necessitating ongoing research into combination therapies and next-generation ALK inhibitors. Promising strategies include combining Ceritinib with MEK inhibitors, PD-1/PD-L1 inhibitors, and anti-angiogenic agents to overcome resistance and enhance therapeutic efficacy. Personalized medicine approaches, guided by molecular profiling, are also crucial in optimizing treatment regimens.

Moreover, Ceritinib's potential extends beyond NSCLC, showing promise in treating other ALK-altered malignancies, thereby broadening its clinical applicability. This review comprehensively examines the mechanism of action, clinical efficacy, safety profile, and future perspectives of Ceritinib in managing ALK-positive NSCLC. By highlighting Ceritinib's pivotal role, we underscore its importance in advancing therapeutic strategies and improving patient care.

Keywords: Non-Small Cell Lung Cancer (NSCLC); ALK-positive NSCLC; Ceritinib; ALK Inhibitor; Anaplastic Lymphoma Kinase (ALK); Targeted Therapy

1. INTRODUCTION

Lung cancer remains a formidable global health challenge, being the second most diagnosed malignancy and the leading cause of cancer-related mortality[1]. In 2020 alone, lung cancer was responsible for approximately 1.8 million deaths worldwide, underscoring its deadly impact. The disease is broadly categorized into two primary types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately 85% of all lung cancer cases[2]. NSCLC is a heterogeneous group of cancers that includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, each with distinct pathological and clinical characteristics[3]. The high mortality rate, which is about 18% associated with lung cancer, is mainly due to its tendency to be diagnosed at an advanced stage when curative treatment options are limited.

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases. Despite significant advancements in detection and treatment, the prognosis for NSCLC remains poor, especially for patients diagnosed at an advanced stage. This poor prognosis can be attributed to several factors, including late diagnosis, tumor heterogeneity, limited screening, resistance to treatment, and the complexity of managing the disease[4].The overall 5-year survival rate for NSCLC is less than 18%, primarily because many patients are diagnosed at advanced stages. This rate decreases even further for those with advanced disease, reflecting the significant challenges in treating late-stage NSCLC effectively[5]. Traditional treatments for NSCLC include surgery, chemotherapy, and radiotherapy, but these approaches have limited effectiveness in advanced stages[6]. Over the past decade, understanding the molecular underpinnings of NSCLC has revolutionized its management, paving the way for targeted therapies. These therapies inhibit critical molecules involved in cancer growth and progression, offering more effective and personalized treatment options.

A critical breakthrough in the molecular characterization of NSCLC was the discovery of rearrangements in the anaplastic lymphoma kinase (ALK) gene. ALK is a transmembrane receptor tyrosine kinase that belongs to the insulin receptor superfamily[7]. In normal adult tissues, ALK expression is minimal; however, when the ALK gene is aberrantly activated through rearrangements, it can drive oncogenesis[8]. ALK rearrangements are present in approximately 2-7% of NSCLC cases, which translates to a significant number of patients given the high incidence of lung cancer globally[9]. One of the most common ALK rearrangements in NSCLC is the fusion of the ALK gene with the echinoderm microtubule-associated protein-like 4 (EML4) gene, resulting in the EML4-ALK fusion protein[10]. This fusion protein exhibits constitutive kinase

activity, activating multiple downstream signaling pathways, such as PI3K/AKT, RAS/RAF/MEK/ERK, and JAK/STAT. Dysregulation or constant activation of these pathways can produce pro-inflammatory cytokines and mediators, promoting inflammation within the tumor microenvironment. This inflammation can further contribute to tumor progression and therapy resistance[11].

Identifying ALK rearrangements in NSCLC has enhanced an understanding of the disease's biology by revealing how these genetic changes drive cancer progression through specific signaling pathways. This knowledge helps develop targeted therapies tailored to each patient's genetic profile, improving treatment effectiveness. The first ALK inhibitor to receive FDA approval was crizotinib in 2011, demonstrating significant clinical benefits in patients with ALK-positive NSCLC[12]. However, despite initial responses, most patients eventually develop resistance to crizotinib, necessitating the development of next-generation ALK inhibitors. One such next-generation ALK inhibitor is Ceritinib. Ceritinib is designed to overcome resistance to crizotinib in ALK-positive NSCLC by targeting specific secondary mutations such as L1196M, G1269A, I1171T, and S1206Y, which allows it to overcome resistance that develops during crizotinib treatment[13]. It has shown efficacy in both treatment-naive patients and those who have progressed on crizotinib[14]. By binding to the ATP-binding pocket of the ALK protein, Ceritinib inhibits its kinase activity, thereby blocking the downstream signaling pathways that promote cancer cell survival and proliferation[15]. Moreover, Ceritinib has demonstrated the ability to penetrate the central nervous system (CNS), effectively treating brain metastases, a common complication in ALK-positive NSCLC[16].

In summary, the advent of ALK inhibitors like Ceritinib represents a significant advancement in treating ALK-positive NSCLC, offering hope for improved outcomes in this subset of lung cancer patients. This review will delve into the mechanism of action, clinical efficacy, safety profile, and future perspectives of Ceritinib in managing ALK-positive NSCLC, highlighting its pivotal role in enhancing therapeutic strategies and patient care.

2. MECHANISM OF ACTION OF CERITINIB

The discovery of the EML4-ALK fusion gene has significantly advanced our understanding of non-small cell lung cancer (NSCLC). This fusion results from a chromosomal rearrangement that combines the ALK gene with the EML4 gene, forming a constitutively active tyrosine kinase, the EML4-ALK fusion protein. This aberrant protein drives oncogenesis by activating multiple downstream signaling pathways in cell growth and survival[10]. Ceritinib, a next-generation ALK inhibitor, targets and inhibits the activity of the EML4-ALK fusion protein by binding to its ATP-binding site, preventing downstream signaling necessary for tumor proliferation and survival.

Ceritinib's potent antitumor activity has been demonstrated in preclinical models and clinical trials, effectively reducing tumor size and delaying disease progression in ALK-positive NSCLC patients[17]. Its inhibition of ALK signaling disrupts crucial pathways like RAS/RAF/MEK/ERK and PI3K/AKT/mTOR, which are essential for tumor growth and metastasis, thereby impeding tumor progression and metastatic spread, contributing significantly to its therapeutic efficacy in ALK-positive NSCLC[15]. Ceritinib effectively overcomes crizotinib resistance in ALK-positive NSCLC due to its distinct binding profile and potent ALK inhibition. It offers a valuable alternative for patients resistant to crizotinib, enhancing treatment options and improving outcomes[18].

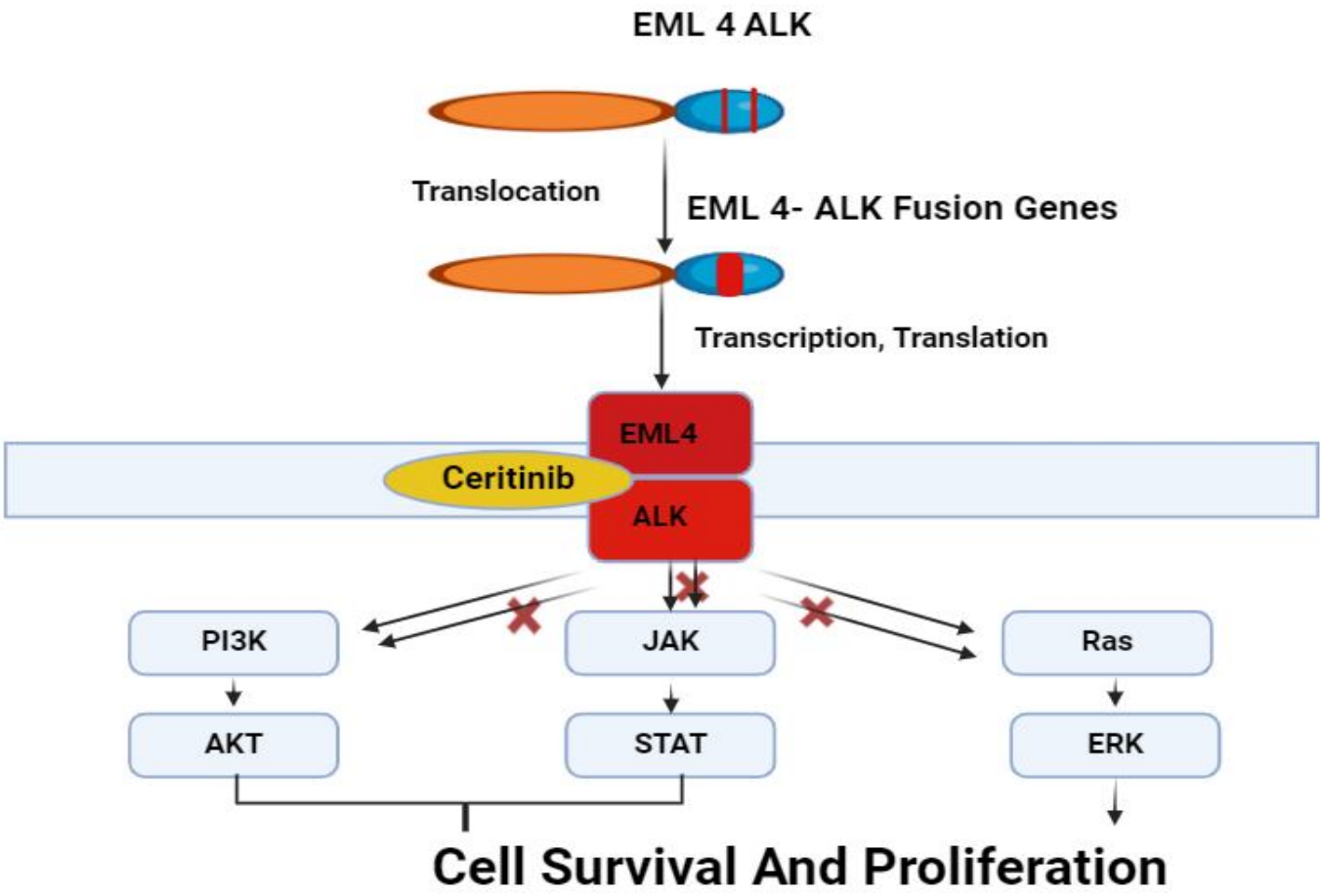

Figure 1: Ceritinib inhibiting phosphorylation of the EML4–ALK kinase and deactivating downstream growth pathways.

EML4-ALK-Echinoderm Microtubule-associated-protein-Like 4-Anaplastic Lymphoma Kinase; ERK- extracellular-signal-regulated kinase; JAK- Janus kinase; PI3K- AKT-Phosphoinositide 3-kinase /protein kinase B; STAT- Signal transducer of activation

2.1 Mechanism of Ceritinib in Overcoming ALK Resistance

Ceritinib is specifically designed to overcome resistance mechanisms seen with first-generation inhibitors like crizotinib. It achieves this by targeting a broader range of ALK mutations, including key resistance mutations such as G1202R and L1196M, which limit the efficacy of other inhibitors. With its stronger binding affinity to the ALK kinase domain, Ceritinib more effectively inhibits ALK-driven tumor growth, even in resistant cases. Additionally, Ceritinib disrupts critical downstream ALK-dependent signaling pathways, reducing tumor proliferation and inducing apoptosis. A significant advantage of Ceritinib is its superior central nervous system (CNS) penetration, making it effective against brain metastases—a common challenge in ALK-positive non-small cell lung cancer (NSCLC). Furthermore, its higher dose tolerability enables treatment at therapeutically effective levels, addressing complex resistance mechanisms. These attributes position Ceritinib as a potent option for patients who have developed resistance to other ALK inhibitors, offering a more comprehensive approach to treatment[19].

3. CLINICAL EFFICACY & SAFETY PROFILE

3.1 Efficacy in treatment-naive patients

Ceritinib, a potent second-generation ALK inhibitor, has showcased remarkable efficacy in various settings of ALK-positive non-small cell lung cancer (NSCLC). In the pivotal ASCEND-4 trial involving treatment-naive patients, Ceritinib demonstrated superior progression-free survival (PFS) compared to standard chemotherapy, with a median PFS of 16.6 months versus 8.1 months for the chemotherapy group ($p < 0.001$)[20]. Moreover, Ceritinib exhibited a significantly higher objective response rate (ORR), indicating a more substantial tumor burden reduction. The NCCN panel recommends Ceritinib for ALK-positive NSCLC patients who progress after Crizotinibor those intolerants to Crizotinib. A phase II trial (ASCEND-2) showed Ceritinib effective in patients with brain metastases who had ≥2 prior treatments and crizotinib progression[21].

Furthermore, in patients with disease progression after prior ALK inhibitor therapy, such as Crizotinib, the ASCEND-5 trial demonstrated Ceritinib's efficacy as a second-line therapy, with a median PFS of 5.4 months compared to 1.6 months for

Parameter	Crizotinib	Alectinib	Brigatinib	Ceritinib	Lorlatinib

standard chemotherapy ($p < 0.001$). These findings collectively underscore Ceritinib's role as a promising treatment avenue across various stages of ALK-positive NSCLC, offering both enhanced efficacy and improved GI safety, particularly in Asian populations, and as an effective second-line option post-crizotinib treatment[22]**.**

3.2 Comparison of safety and efficacy with other ALK inhibitors

Comparing Ceritinib with other ALK inhibitors like Crizotinib, Alectinib, and Brigatinib, its unique efficacy profile and ability to manage specific resistance mutations provide clinical flexibility. Unlike the broader resistance mechanisms seen with some treatments, resistance to ceritinib is not a class effect, allowing it to manage distinct mutation patterns**.**HenceCeritinib remains a potent alternative, especially for patients with resistance mutations that may not respond as effectively to other ALK inhibitors. Also, Ceritinib is a cost-effective option for treatment-naïve patients with ALK-positive advanced NSCLC. Summary of Ceritinib vs other first line ALK inhibitors is shown in table 1

Table 1: Summary of Ceritinib vs other first-line ALK inhibitors

Overall Response Rate (ORR)	60%	75.00%	71%	68%	76%
Progression-Free Survival (PFS)	10.8 months(ASCEND-4 trial)[24]	34.8 months (ALEX trial)[25]	24 months (ALTA-1L trial)[26]	17 months (ASCEND-4 trial)[24]	25.7 months (CROWN trial)[27]
CNS Activity	Poor CNS activity	Effective CNS (38%)	Moderate CNS activity(28%)	Superior CNS activity(51.5%)	Best-in-class CNS activity(71%)
Side effects	Hypercholesterolemia (4%), hypertriglyceridemia (6%), edema (39%), increased weight (13%), peripheral neuropathy (15%), cognitive effects (6%), anemia (8%),	Anemia (20%), myalgia (16%), increased blood bilirubin (15%), increased weight (10%), musculoskeletal pain (7%), and photosensitivity reaction (5%)	Increase in creatine kinase level (39%), cough (25%), hypertension (23%), increased lipase level (19%), nausea (26%), diarrhea (49%), constipation (15%), peripheral edema (4%), vomiting (18%),	Nausea (in 82%), diarrhea (75%), vomiting (65%), fatigue (47%), increased alanine aminotransferase levels (35%)	Hypercholesterolemia (70%), hypertriglyceridemia (64%), edema (55%), increased weight (38%), peripheral neuropathy (34%), cognitive effects (21%), anemia (19%)

3.3 Common adverse reactions & management of side effects

Common adverse reactions to Ceritinib include gastrointestinal issues such as nausea, diarrhea, and vomiting, which are reported in a significant proportion of patients. Hepatotoxicity, characterized by elevated liver enzymes, and

hyperglycemia are also notable side effects**[28]**. Management strategies for these adverse reactions involve dose modifications, supportive care, and regular monitoring. For gastrointestinal symptoms, antiemetic and antidiarrheal medications are commonly used. Hepatotoxicity is managed through routine liver function tests and adjusting the Ceritinib dose if significant elevations in liver enzymes are detected. Hyperglycemia is managed through regular blood glucose monitoring and appropriate antidiabetic medications**[29]**.Summary of landmark trial for Ceritinib is shown in table 2

Table 2: Summary of landmark trialfor Ceritinib (ASCEND trials)

Clinical trial	ORR (%)	IORR (%)	PFS (months)	Most common AEs (any grade)	Most common AEs (grade 3 or 4)
ASCEND-1 Phase I n = 246 prior ALKi prior CT.**[30]**	54.6 in ALK pretreated, 66.3 in ALK naive	36 in ALK pretreated, 63 in ALK naive	18.4 in ALK pretreated 63 in ALK naive	Nausea (82%), diarrhea (75%), vomiting (65%), fatigue (47%), increased ALT (35%), constipation (32%), abdominal pain (30%)	Increased ALT (21%), increased AST (11%), diarrhea (7%), increased lipase (7%), nausea (5%), fatigue (5%), vomiting (5%)
ASCEND-2 Phase II n = 140 prior ALKi prior CT.**[31]**	38.6	45	5.7	Nausea (81%), diarrhea (80%), vomiting (63%), increased alt (44%), decreased appetite (41%), fatigue (36%), weight decreased (34%), increased AST (32%)	Increased ALT (17%), nausea (6%), diarrhea (6%), fatigue (6%), increased AST (5%), vomiting (4%), weight decreased (4%)

ASCEND-3 Phase II n = 124 ALKi-naive prior CT.**[32]**	63.7	20	NA	Diarrhea (82%), nausea (74%), vomiting (67%), decreased appetite (49%), increased ALT (40%), abdominal pain (33%), fatigue (32%)	GGT increased (18%), ALT increased (15%), AST increased (7%), blood ALP increased (7%), fatigue (6%)

Alt- Alanine aminotransferase, AST- Aspartate aminotransferase, ALP- Alkaline phosphatase, GGT- Gama glutamyl transferase,

ORR- Objective response rate, IORR- Informed objective response rate,PFS- Progression free survival

4. PATIENT SELECTION CRITERIAAND MONITORING STRATEGIES FOR CERITINIB THERAPY

4.1 Patient selection criteria

Ceritinib is a targeted therapy primarily used for the treatment of patients with ALK-positive non-small cell lung cancer (NSCLC). Patient selection criteria for Ceritinib therapy are crucial to ensure optimal outcomes and minimize unnecessary risks. The primary criterion for selecting patients for Ceritinib treatment is the presence of ALK rearrangements, which can be identified through molecular testing such as fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), or next-generation sequencing (NGS)[17]. Additionally, Ceritinib is often considered for patients who have progressed on or are intolerant to crizotinib, the first-line ALK inhibitor. Clinicians must also evaluate the patient's overall health status, liver function, and any pre-existing conditions that Ceritinib could exacerbate, as these factors can influence the efficacy and safety of the treatment.

4.2 Monitoring strategies for Ceritinib therapy

Monitoring patients on Ceritinib therapy is crucial for managing side effects and assessing treatment efficacy. Regular liver function tests (LFTs) are necessary due to the risk of hepatotoxicity, with tests at baseline, biweekly for the first two months, then monthly. Gastrointestinal side effects like diarrhea, nausea, and vomiting require proactive management with antiemetics and antidiarrheals[33]. Periodic electrocardiograms (ECGs) and electrolyte monitoring are essential due to the risk of QT interval prolongation, especially in patients with cardiac histories[34]. Regular imaging studies, such as CT scans or MRIs every 6 to 12 weeks, track the tumor's response. Patient-reported outcomes and quality-of-life

assessments help manage side effects and ensure overall well-being[35]. Dosage adjustments based on these evaluations aim to maximize efficacy while minimizing disruptions to the patient's quality of life.

5. CURRENT ROLE OF CERITINIB IN MANAGEMENT STRATEGY OF NSCLC

5.1 Role of Ceritinib in treatment modalities

Ceritinib is pivotal in treating ALK-positive non-small cell lung cancer (NSCLC). Its integration into treatment modalities is guided by its demonstrated efficacy in both treatment-naive patients and those who have progressed on prior ALK inhibitor therapy, particularly crizotinib. Ceritinib acts as a non-competitive inhibitor of the ATP-hydrolyzing ectonucleotides CD39, showing micromolar potency. It, therefore, results in decreased extracellular concentrations of immunosuppressive, cancer-promoting adenosine. In contrast to other investigated kinase inhibitors, Ceritinib may have additional immunotherapeutic effects. Moreover, the Ceritinib scaffold could be further optimized to obtain more potent CD39 inhibitors for the immunotherapy of cancers[36]. Below is a detailed exploration of Ceritinib's role within various treatment guidelines

5.2 As second-line therapy

Ceritinib is a highly recommended second-line therapy for patients who have experienced disease progression following initial ALK inhibitor therapy, particularly crizotinib [37]. The ASCEND-5 trial provided compelling evidence for Ceritinib's efficacy in this context, showing a median PFS of 5.4 months (95% CI: 4·1 to 6·9) compared to 1.6 months (1·4-2·8) with chemotherapy [HR 0·49 (0·36-0·67); p<0·0001]. The ORR of 39.1% further supports Ceritinib's role in managing disease progression after crizotinib failure[22]. Clinical guidelines suggest transitioning to Ceritinib in patients resistant to first-line ALK inhibitors. The NCCN guidelines include Ceritinib as a preferred option for second-line therapy following crizotinib[38].

5.3 Treatment in the context of brain metastases

Patients with ALK-positive NSCLC frequently develop brain metastases, which pose significant therapeutic challenges. Ceritinib has demonstrated central nervous system (CNS) activity, making it a valuable option for patients with brain metastases[39]. Studies like ASCEND-7 have shown that Ceritinib can penetrate the blood-brain barrier and achieve meaningful intracranial responses. This property positions Ceritinib as a suitable therapy for managing brain metastases in ALK-positive NSCLC patients as a first-line treatment and subsequent therapy lines [40].

5.4 Combination Therapy

Recent studies have explored the efficacy of combination therapies in advanced ALK-rearranged non–small cell lung cancer (NSCLC), revealing promising outcomes. One study assessed the combination of ceritinib, an ALK inhibitor, with Ribociclib, a CDK4/6 inhibitor, demonstrating notable clinical activity with a recommended phase II dose of 300 mg/day ceritinib and 200 mg/day Ribociclib, yielding an objective response rate (ORR) of 50% and a median progression-free survival (mPFS) of 24.8 months(95% CI, 5.5 to 25.1), all within a manageable safety profile[41]. Another study evaluated ceritinib combined with nivolumab, a PD-1 inhibitor, showing an ORR of 83%(95% CI: 35.9 to 99.6) in ALK inhibitor-naive patients and up to 64% (95% CI: 35.1 to 87.2)response in those with PD-L1 expression ≥1%. Although this combination presented a higher toxicity profile, including a 64% incidence of all-grade rash, it suggests significant potential for improving outcomes in patients with advanced ALK-rearranged NSCLC[42]. These findings underscore the importance of combination therapies in enhancing treatment efficacy while necessitating a careful balance between effectiveness and toxicity.

5.5 Ceritinib Resistance and Strategies to Overcome It

Ceritinib, is effective in treating ALK-positive NSCLC but can face resistance over time due to mechanisms such as secondary ALK mutations (e.g., G1202R, F1174C), activation of alternative signaling pathways (EGFR, MET), histologic transformation (to small cell lung cancer), increased drug efflux, and tumor heterogeneity. To overcome this resistance, strategies include using third-generation ALK inhibitors like lorlatinib, combination therapies with EGFR, MET, or mTOR/PI3K inhibitors, targeting drug efflux mechanisms, sequential ALK inhibitor therapy, and employing liquid biopsy and genetic profiling for personalized treatment. Additionally, combining immunotherapy with ALK inhibitors and managing histologic transformation through tailored therapies or chemotherapy offer further avenues to combat Ceritinib resistance[17].

5.6Dosing and Administration

Ceritinib is typically administered at a dose of 750 mg orally once daily with food, which has been shown to optimize its bioavailability and minimize gastrointestinal side effects. Food increases ceritinib exposure. A high-fat meal increases AUC by 73% and Cmax by 41%, while a low-fat meal increases AUC by 58% and Cmax by 43% compared to fasting. A 600 mg or higher dose with food may result in greater exposure than a 750 mg dose taken fasting, possibly increasing adverse reactions.The dosing regimen may be adjusted based on patient tolerance and the presence of adverse effects.

Monitoring liver function tests, blood glucose levels, and electrocardiograms (ECGs) is recommended to manage and mitigate potential side effects effectively[36].

Ceritinib is primarily metabolized by CYP3A4, and its efficacy and safety can be significantly influenced by concomitant use of drugs affecting this enzyme[43]. CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, can increase Ceritinib metabolism, leading to decreased plasma concentrations and reduced therapeutic efficacy. Conversely, CYP3A4 inhibitors, including ketoconazole, itraconazole, and grapefruit juice, can elevate Ceritinib levels, raising the risk of adverse effects like gastrointestinal disturbances and liver toxicity. Drugs with moderate CYP3A4 effects, such as diltiazem and erythromycin, may also alter Ceritinib levels but to a lesser extent. To manage these interactions, therapeutic drug monitoring is crucial, and dose adjustments may be necessary[44]. Clinicians should screen for potential drug interactions, regularly monitor Ceritinib levels, and educate patients about the impact of over-the-counter medications and dietary factors on Ceritinib metabolism. This approach ensures optimal efficacy and minimizes risks for ALK-positive NSCLC patients.

6. FUTURE PERSPECTIVES & RESEARCH

Exploring combination therapies with ceritinib for ALK-positive NSCLC holds significant promise for improving treatment outcomes. Combining ceritinib with MEK inhibitors targets key cancer survival pathways, potentially overcoming resistance and enhancing efficacy[45]. Additionally, pairing ceritinib with PD-1/PD-L1 inhibitors leverages the immune system to boost antitumor responses. At the same time, the combination with anti-angiogenic agents aims to restrict tumor growth by cutting off its blood supply[46]. Combining ceritinib with anti-angiogenic agents like bevacizumab may enhance treatment by restricting tumor blood supply while inhibiting ALK signaling[47]. Additionally, combining ceritinib with chemotherapy agents like pemetrexed and cisplatin is being studied for its potential to provide synergistic effects, especially in patients resistant to ceritinib alone or with aggressive disease requiring multiple therapies[48]. Research also investigates combining ceritinib with traditional chemotherapy, particularly for patients who have developed resistance to ceritinib alone. Personalized approaches are being developed by targeting specific genetic mutations, enabling more tailored and effective treatments.

CONCLUSION

Ceritinib has solidified its role as a vital targeted therapy for ALK-positive NSCLC, particularly for patients resistant to first-generation ALK inhibitors like crizotinib. As a second-generation inhibitor, it significantly improves progression-free survival and overall response rates, with the added benefit of CNS penetration to manage brain metastases. Despite

associated side effects such as gastrointestinal toxicity and hepatotoxicity, Ceritinib remains an effective alternative for refractory patients, enhancing the treatment landscape of ALK-positive NSCLC.

CONSENT

Nil

ETHICAL APPROVAL

This article is based on previous studies and contains no new studies with human participants or animals performed by any authors**.**

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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