Chapter 11

ALK and ROS1-Positive Non-Small Cell Lung Cancer: Molecular Characteristics, Diagnostic Strategies, and Targeted Therapeutic Approaches

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Abstract

Non-small cell lung cancer (NSCLC) cases with ALK or ROS1 rearrangements represent distinct molecular entities, often identified in younger, never-smoker female patients exhibiting adenocarcinoma subtype. These oncogenic fusions drive constitutive tyrosine kinase activation, promoting tumor growth, survival, and metastasis through pathways such as PI3K/AKT/mTOR, MAPK/ERK, and JAK/STAT.

Accurate detection of ALK and ROS1 alterations is essential for treatment planning and is routinely performed using immunohistochemistry, fluorescence in situ hybridization (FISH), or next-generation sequencing (NGS). In ALK-positive disease, second- and third-generation tyrosine kinase inhibitors (TKIs)—including alectinib, brigatinib, and lorlatinib—have demonstrated superior efficacy compared to chemotherapy, particularly in central nervous system (CNS) control. Lorlatinib offers significant benefit in the presence of resistant mutations (e.g., G1202R) and brain metastases.

In ROS1-rearranged NSCLC, crizotinib and entrectinib are established first-line therapies, while repotrectinib has emerged as a promising option for patients harboring solvent-front mutations such as ROS1 G2032R. Although generally well tolerated, each TKI presents unique toxicity profiles, including neurocognitive effects and hyperlipidemia with lorlatinib.

Guidelines now emphasize not only biomarker-driven systemic therapy but also the integration of local treatments for patients with oligometastatic or CNS involvement. With sequential targeted therapy, median overall survival in ALK-positive NSCLC exceeds seven years, underscoring the transformative impact of precision oncology in this subgroup.

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1. The Biology and Pathogenic Role of ALK and ROS1 Genes

A subset of non-small cell lung cancer (NSCLC) patients harbors ALK or ROS1 rearrangements, representing a small but clinically relevant molecular group. ALK fusions are most frequently observed in 3–7% of cases, predominantly among tumors with adenocarcinoma features. ROS1 rearrangements are less frequent, accounting for about 1–2% of non-squamous NSCLC cases. Despite differences in prevalence, both alterations share overlapping clinical, histopathological, and molecular characteristics. They are most commonly identified in younger patients, female individuals, and those without a history of smoking.

These gene rearrangements result in constitutive activation of tyrosine kinase domains, which promotes oncogenic signaling pathways involved in cellular proliferation, survival, and metastatic capacity. This molecular background underlies the tumors' sensitivity to targeted therapies with ALK and ROS1 tyrosine kinase inhibitors [1-3]. ALK and ROS1 gene rearrangements are most frequently observed in NSCLC subtypes with adenocarcinoma histology. These genetic alterations are more commonly identified in younger patients, females, and individuals with no or minimal history of tobacco exposure. ALK fusion-positive NSCLC is characteristically seen in patients under the age of 50, female, and never-smokers, although it can occasionally be detected in elderly populations as well. Similarly, ROS1 rearrangements exhibit comparable demographic and clinical features. Patients with ROS1-positive NSCLC are typically younger, female, and have adenocarcinoma histology, with a majority lacking any significant smoking history. ALK and ROS1 fusions are considered biologically mutually exclusive events and are rarely found concurrently within the same tumor specimen. This distinction holds clinical significance in selecting the appropriate targeted therapy based on molecular profiling [4, 5]. The ALK gene, located at 2p23, encodes a tyrosine kinase involved in embryonic neural development. In adult lungs, its expression is nearly absent. A chromosomal inversion can lead to fusion with the EML4 gene, generating a constitutively active EML4-ALK protein that contributes to oncogenesis in lung adenocarcinoma. The EML4-ALK fusion leads to continuous activation of the ALK kinase domain without the need for ligand binding. This dysregulated signaling engages key intracellular pathways—including RAS/MAPK, PI3K/AKT, and JAK/STAT—promoting uncontrolled cell growth, resistance to apoptosis, and oncogenic transformation [2, 6, 7].

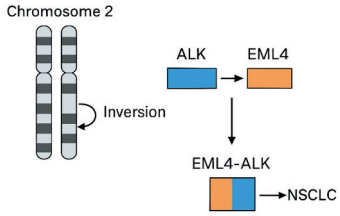

Figure 1. Schematic representation of the ALK gene and the EML4-ALK fusion (Adapted from Soda M et al., Nature, 2007) [7].

Under physiological conditions, the ALK receptor forms homodimers upon binding to its specific ligands, thereby activating its tyrosine kinase domain and initiating downstream signaling cascades that promote cell growth and survival. The EML4-ALK fusion protein is capable of autonomous dimerization and continuous activation in the absence of ligand interaction.. This oncogenic protein continuously activates key signaling pathways such as MAPK/ERK, PI3K/AKT/mTOR, and STAT3, leading to sustained cellular proliferation and survival. As a result, the EML4-ALK fusion drives uncontrolled cell growth in pulmonary epithelial cells and contributes to tumor development. EML4 represents the predominant fusion partner in ALK-rearranged NSCLC, accounting for roughly 80–90% of such cases. While alternative partners such as KIF5B, KLC1, TFG, and TPR have also been documented, they occur far less frequently [8-10]. Tumors harboring ALK rearrangements are predominantly of the adenocarcinoma subtype, often displaying mucinous features or a characteristic signet-ring cell morphology. The EML4-ALK oncogene represents the first identified fusion kinase in lung cancer that is amenable to targeted therapy. Constitutive ALK signaling driven by this fusion not only promotes proliferation and survival but also affects cytoskeletal organization, cellular migration, and metabolic regulation, collectively contributing to a highly aggressive tumor phenotype. ALK-positive NSCLC frequently presents with a more aggressive clinical course, characterized by advanced-stage diagnosis and a distinct pattern of metastasis involving the central nervous system, hepatic parenchyma, pleural surfaces, and pericardial structures, in contrast to tumors driven by other molecular alterations [5, 8, 11]. ROS1 gene rearrangements represent a rare but actionable molecular alteration in NSCLC, occurring in approximately 1–2% of cases. Located at chromosome 6q22, ROS1 encodes an orphan receptor tyrosine kinase with significant homology to ALK. While its physiological ligands remain unclear, ROS1 is thought to contribute to

embryogenesis and cellular signaling. The most frequent fusion variants include CD74-ROS1, EZR-ROS1, and SDC4-ROS1. First identified in NSCLC cell lines in 2007, the clinical relevance of ROS1 fusions was later validated in patient cohorts. These studies established ROS1 fusions as independent oncogenic drivers, distinct from ALK and EGFR mutations. ROS1-positive tumors are typically associated with adenocarcinoma histology and are most frequently found in younger patients, females, and never-smokers. Similar to ALK fusions, ROS1 fusion proteins promote constitutive activation of intracellular signaling cascades such as MAPK/ERK, PI3K/AKT/mTOR, and JAK/STAT. Additionally, they activate other signaling intermediates including IRS-1 and SHP1/2, thereby enhancing cell proliferation, metastatic potential, and resistance to apoptosis. Through these mechanisms, ROS1 fusions exert strong oncogenic activity and contribute to lung tumorigenesis. Although molecularly distinct from ALK-rearranged tumors, ROS1-positive NSCLC exhibits a similar clinical phenotype due to its oncogene-addicted biology [2, 12, 13].

2. Molecular Diagnostic Techniques and Biomarkers

The identification of ALK and ROS1 gene rearrangements in advanced NSCLC is of critical importance for therapeutic decision-making. International guidelines, including those from NCCN and ESMO, recommend routine testing for these fusions in all advanced-stage NSCLC cases, particularly those with adenocarcinoma histology. Tumor tissue, obtained via biopsy or surgical resection, is typically used for molecular testing. However, in cases where adequate tissue is unavailable, circulating tumor DNA from plasma (liquid biopsy) may serve as an alternative source.

Detection of ALK and ROS1 gene fusions can be achieved using several molecular and histopathological tools, including IHC, FISH, RT-PCR, and NGS, each offering distinct advantages in terms of sensitivity and specificity. For ALK detection, IHC with the FDA-approved Ventana ALK (D5F3) antibody is commonly used owing to its simplicity, rapid processing time, and cost-efficiency. Strong and diffuse cytoplasmic staining is considered sufficient for diagnosis, eliminating the need for confirmatory FISH. In cases with equivocal or weak staining, FISH or NGS is recommended. FISH, once regarded as the gold standard, detects gene rearrangements using break-apart probes targeting the ALK locus.

NGS-based panels, which are increasingly utilized, offer simultaneous assessment of multiple oncogenic drivers such as ALK, ROS1, EGFR, and BRAF, and can also identify fusion partners. Accordingly, NCCN and

ESMO guidelines strongly advocate the use of panel-based NGS in advanced NSCLC when resources allow.

Similar approaches are employed for the diagnosis of ROS1 rearrangements. FISH remains a commonly used FDA-approved method, with positivity defined by break-apart signals in at least 15 percent of tumor cells. However, certain ROS1 fusion variants, such as GOPC (FIG)-ROS1, may not be reliably detected by FISH. For this reason, IHC using antibodies such as Ventana SP384 or CST D4D6 is often utilized as an initial screening tool. While ROS1 IHC demonstrates high sensitivity, its specificity is limited, and positive results must be confirmed by FISH or RNA-based NGS. DNA-based NGS may also miss certain fusion variants, making RNA-based sequencing a more sensitive option. RT-PCR is limited to detecting known fusion types and may fail to identify novel or rare partners.

Recent evidence indicates that both IHC and NGS can be applied not only to formalin-fixed tissue but also to cytological samples, including cell blocks obtained from fine needle aspiration, as well as circulating tumor DNA extracted from plasma. The identification of ALK or ROS1 rearrangements constitutes a reliable predictive biomarker for tyrosine kinase inhibitor response and is classified as ESCAT tier I-A by ESMO, confirming its established clinical utility. Another relevant biomarker is PD-L1 expression, which may exhibit heterogeneous patterns in ALK- or ROS1-positive tumors. Nonetheless, checkpoint inhibitors, such as monotherapy with pembrolizumab, generally demonstrate limited efficacy in these oncogene-driven NSCLC subtypes, regardless of PD-L1 status. Consequently, targeted TKIs remain the preferred first-line treatment.

In summary, testing for ALK and ROS1 rearrangements should be conducted regardless of patient demographics, including age, sex, or smoking status. Molecular alterations may be present even in individuals who do not exhibit classical clinical features. The identification of ALK and ROS1 fusions through immunohistochemical or molecular assays provides reliable biomarkers that support the implementation of tailored therapies with targeted agents [14, 15].

3. Therapeutic Options: Tyrosine Kinase Inhibitors and Mechanisms of Resistance

Tyrosine kinase inhibitors (TKIs) have demonstrated significant clinical advantages over standard chemotherapy in patients harboring ALK or ROS1 fusions. In advanced non-small cell lung cancer (NSCLC) with these rearrangements, treatment has shifted toward oral small-molecule agents that

selectively target the altered kinases. Despite their initial efficacy, acquired resistance remains a key challenge that can limit long-term treatment success. This section outlines the approved TKIs used in ALK- and ROS1-positive NSCLC, examines the main mechanisms underlying resistance, and explores clinical approaches aimed at managing resistance effectively.

3.1. Tyrosine Kinase Inhibitors and Resistance in ALK-Positive Non-Small Cell Lung Cancer

Crizotinib, though initially designed as a MET inhibitor, was later found to target ALK and ROS1, leading to its regulatory approval for use in ALK-positive NSCLC. Early-phase data from the PROFILE-1001 study revealed a 57% objective response rate and 72% progression-free survival at six months in patients with ALK rearrangements. These encouraging results contributed to FDA approval in 2011 for use in metastatic ALK-positive NSCLC. Later phase III studies demonstrated that crizotinib offered superior outcomes compared to standard platinum-based chemotherapy, particularly in terms of PFS.

As a multi-target tyrosine kinase inhibitor, crizotinib acts on ALK, ROS1, and MET, yet its specificity for ALK is suboptimal. Additionally, it has limited ability to cross the blood-brain barrier, which compromises its activity against CNS metastases. Most patients experience disease progression within 10 to 12 months. Around 50% to 60% of resistance events are linked to secondary ALK mutations, including L1196M, G1269A, and G1202R. In other cases, alternative resistance pathways such as EGFR or KIT amplification, or histologic transformation to small cell lung cancer, play a role [9, 16].

To address these shortcomings, second-generation ALK inhibitors—including ceritinib, alectinib, brigatinib, and ensartinib—were developed. These agents show efficacy against mutations associated with resistance to crizotinib. Ceritinib is active against specific ALK mutations like L1196M and G1269A and has some impact on brain metastases, although its use is often limited by gastrointestinal side effects at higher doses. Alectinib, in contrast, has demonstrated strong efficacy both systemically and within the CNS. In the ALEX study, it extended median PFS from 10.9 to 34.8 months and reduced the rate of CNS progression from 41% to 9%. The five-year OS rate reached 62.5% with alectinib. Brigatinib, which inhibits both EGFR and ALK, showed a 52% reduction in progression risk compared to crizotinib, as observed in the ALTA-1L trial.

Lorlatinib is a third-generation ALK-targeted agent specifically engineered to overcome mutations such as G1202R. In the CROWN trial, lorlatinib reduced disease progression by 72% in treatment-naïve patients and yielded a 12-month PFS rate of 78%. Owing to its excellent CNS penetration, it is also effective against brain metastases. However, lorlatinib's toxicity profile—which includes hyperlipidemia, neurocognitive side effects, and peripheral neuropathy—often limits its use to post-progression settings after failure of earlier-generation TKIs.

In conclusion, the stepwise application of ALK-targeted therapies has markedly improved survival outcomes in ALK-positive NSCLC. While chemotherapy provided a median survival of less than one year, current treatment algorithms incorporating ALK TKIs have extended survival to as much as seven to eight years in clinical practice [17-22].

3.2. Tyrosine Kinase Inhibitors and Resistance in ROS1-Positive Non-Small Cell Lung Cancer

Crizotinib marked the first molecularly targeted treatment approved for patients with ROS1 fusion–positive non-small cell lung cancer (NSCLC). Initially recognized for its ROS1-inhibitory capacity in the early 2010s, its clinical utility was later supported by evidence from the PROFILE 1001 study. In that trial, individuals with metastatic ROS1-positive NSCLC achieved a 72% response rate, with a median time to progression of 19.2 months and overall survival reaching approximately 51.4 months. These results formed the foundation for its FDA approval in 2016. Nonetheless, limited central nervous system (CNS) penetration of crizotinib is associated with CNS metastases in up to 40% of treated patients, and resistance to therapy generally emerges within two years of initiation.

Entrectinib, a multi-kinase inhibitor with activity against ROS1, NTRK1-3, and ALK, has shown both systemic and intracranial efficacy in early-phase trials. Combined analyses from STARTRK-1, STARTRK-2, and ALKA-372-001 studies revealed objective response rates between 62% and 67%, and median PFS ranging from 16.8 to 21 months among ROS1-positive, crizotinib-naïve patients. In patients with brain metastases, CNS response rates ranged from 49% to 64%, with several achieving durable intracranial control. In previously crizotinib-exposed patients, entrectinib yielded a 35% response rate and PFS of approximately 8.5 months. Based on these findings, entrectinib is recommended as an initial therapy, particularly when CNS involvement is present, according to both ESMO and FDA guidelines.

Despite advances, resistance mechanisms remain a clinical challenge. Among these, the ROS1 G2032R solvent-front mutation is the most frequently identified and affects approximately one-third of patients receiving crizotinib, diminishing the effectiveness of both crizotinib and entrectinib.

Repotrectinib (TPX-0005), a next-generation ROS1/TRK inhibitor, was engineered to retain activity against kinase domain alterations such as G2032R. In the TRIDENT-1 trial, treatment-naïve patients exhibited a response rate near 80%, with median duration of benefit close to 30 months, and intracranial response rates of at least 50%. In those previously treated with ROS1-targeted agents, repotrectinib achieved a 40% response rate and a median PFS of around nine months. These findings supported the regulatory approval of repotrectinib by the FDA in November 2023 for the treatment of advanced ROS1-altered NSCLC.

In clinical practice, both crizotinib and entrectinib are appropriate first-line choices, though entrectinib may be favored in patients with CNS disease. Upon disease progression, especially when G2032R or other resistance mutations are identified, repotrectinib or emerging next-generation inhibitors should be considered. If targeted options are no longer viable, systemic chemotherapy, with or without immunotherapy, remains the recommended course of action [18, 23-28].

4. Clinical Outcomes: Progression-Free Survival, Overall Survival, and Safety Profiles

4.1. Progression-Free and Overall Survival Outcomes

The implementation of ALK- and ROS1-targeted therapies has led to substantial advances in the management of advanced-stage NSCLC. In ALK-positive cases, the introduction of next-generation tyrosine kinase inhibitors (TKIs) has notably extended progression-free survival (PFS), surpassing the previously observed 8 to 12 months seen with traditional chemotherapy. For instance, the ALEX trial demonstrated that treatment with alectinib resulted in a median PFS of 34.8 months and reduced the risk of progression by 57% compared to crizotinib (hazard ratio: 0.43). After five years, 43% of alectinib-treated patients were progression-free, compared to 19% in the crizotinib cohort. Five-year overall survival (OS) rates were 62.5% versus 45.5%, respectively. Similar durable outcomes were observed in the ALTA-1L trial with brigatinib, where 36% of participants remained progression-free at four years.

Lorlatinib, a third-generation ALK TKI, has demonstrated prolonged clinical benefit, particularly in patients with brain metastases or tumors harboring resistance-associated mutations like G1202R. In the five-year follow-up of the CROWN study, the median PFS for the lorlatinib group was not reached (95% CI: 64.3 months to NR), whereas the median PFS in the crizotinib arm was 9.1 months (95% CI: 7.4–10.9). At five years, approximately 60% of lorlatinib-treated patients had no disease progression, compared to only 8% in the crizotinib arm. These findings highlight the long-term systemic and intracranial effectiveness of lorlatinib.

According to updated NCCN (2025) and ESMO (2023) guidelines, lorlatinib is recommended as a second-line therapy for patients with CNS metastases or ALK resistance mutations and may be considered in the first-line setting in selected individuals. With sequential use of ALK inhibitors, median OS in ALK-rearranged NSCLC now exceeds seven years, signifying a remarkable therapeutic advancement [29].

For patients with ROS1-rearranged NSCLC, targeted treatments have also led to improved outcomes. Crizotinib, evaluated in the PROFILE-1001 phase I trial, showed an ORR of 72%, a median PFS of 19.3 months, and an OS of approximately 51.4 months. Entrectinib, which demonstrates activity both systemically and within the CNS, has become a first-line option. In long-term pooled analyses, treatment-naïve patients receiving entrectinib achieved a median PFS of 15.7 months. Among patients with brain metastases, the intracranial ORR was 80%, and the median intracranial PFS reached 8.8 months. These results suggest a potential advantage of entrectinib over crizotinib in cases involving CNS disease.

Repotrectinib, a highly selective next-generation ROS1 inhibitor, has shown strong clinical activity in advanced disease, including tumors with resistance mutations such as ROS1 G2032R. In the TRIDENT-1 trial, treatment-naïve patients achieved an ORR of 79%, with a median duration of response (DOR) of 34.1 months and a median PFS of 35.7 months. In previously treated patients, the ORR was 38% and median PFS was 9.0 months. Among individuals harboring the G2032R mutation, the ORR reached 59%. Additionally, repotrectinib demonstrated robust CNS activity, with intracranial response rates of 89% in treatment-naïve patients and 42% in those previously exposed to TKIs. As a result of these data, repotrectinib received FDA approval in November 2023 for use in advanced ROS1-rearranged NSCLC.

Overall, the median overall survival for advanced ROS1-positive NSCLC is estimated at 4 to 5 years. Once targeted options are exhausted, both NCCN

and ESMO guidelines recommend a transition to systemic chemotherapy, with or without immunotherapy [18, 23, 24, 27, 30].

4.2. Safety Profiles

Targeted ALK and ROS1 inhibitors exhibit distinct toxicity profiles compared to traditional cytotoxic chemotherapy. These agents are generally better tolerated, with a lower incidence of classical chemotherapy-related adverse effects such as alopecia, severe nausea and vomiting, or myelosuppression. Nevertheless, each TKI has a unique safety profile, and understanding these differences is essential for appropriate treatment management. In most cases, the adverse events associated with ALK and ROS1 TKIs are grade 1 or 2 in severity and can be managed with dose modifications. The safety profiles of major ALK and ROS1 inhibitors are summarized below:

Crizotinib

The most frequently reported adverse events with crizotinib include visual disturbances (~82%, such as flashes of light and dim-light diplopia), diarrhea (44%), nausea (40%), edema (40%), constipation (34%), vomiting (34%), elevated transaminases (22%), fatigue (20%), and dysgeusia (18%). These effects are typically mild to moderate and respond to symptomatic management. Visual effects are characteristic of crizotinib and tend to improve over time.

Ceritinib

Ceritinib is associated with a higher rate of gastrointestinal toxicity compared to crizotinib. When administered at 750 mg on an empty stomach, it causes diarrhea, nausea, vomiting, and anorexia in up to 80% of patients. Currently, a 450 mg dose taken with food is preferred to improve tolerability. Given the risk of hepatotoxicity, liver function tests should be closely monitored during treatment.

Alectinib

Alectinib is a well-tolerated second-generation ALK inhibitor. Common adverse events include constipation, fatigue, myalgia, and rash. Creatine kinase (CK) and liver enzymes should be monitored periodically, as grade ≥3 CK elevation occurs in approximately 5–8% of patients, and hepatotoxicity may occasionally develop. In the ALEX trial, only 11% of patients discontinued treatment due to adverse events.

Brigatinib

Brigatinib is generally well tolerated. Its main adverse events include fatigue, nausea, diarrhea, and transient elevations in liver enzymes. Notably, early-onset pulmonary toxicity—manifesting as dyspnea, hypoxia, or pulmonary infiltrates—can occur within the first week of treatment in 2–3.5% of patients. Therefore, it is recommended to initiate therapy at 90 mg for the first seven days before escalating to 180 mg. Hypertension and temporary increases in amylase or lipase may also occur.

Lorlatinib

Lorlatinib has a distinct toxicity profile among ALK and ROS1 inhibitors. The most common adverse event is hyperlipidemia (65–70%, with grade ≥3 in 16–20%), followed by neuropsychiatric symptoms. Mild to moderate cognitive and mood changes—including memory impairment, concentration difficulties, speech disturbances, anxiety, depression, and sleep disorders—occur in 20–30% of patients. Grade ≥3 cognitive toxicity is rare. Peripheral neuropathy, such as paresthesia and altered reflexes, has been reported in about 30% of cases. These effects are typically manageable with dose reduction or temporary treatment interruption. Statin therapy may be used for hyperlipidemia, and neurological or psychiatric consultation is advised when needed.

Entrectinib

Entrectinib is generally well tolerated, although some neurological adverse effects have been reported. Common side effects include fatigue, dizziness, impaired balance, attention deficits, and taste disturbances. Weight gain may occur due to increased appetite and fluid retention. Rare cases of cardiomyopathy have been reported. In elderly patients, monitoring for cognitive effects is recommended, along with surveillance for neutropenia and elevated transaminases.

Repotrectinib

Repotrectinib, a next-generation ROS1/TRK inhibitor developed to target solvent-front mutations such as G2032R, has a distinct safety profile. During the first one to two weeks of treatment, positional dizziness and lightheadedness may occur in approximately 30% of patients; hence, a stepwise dose-escalation protocol is advised. Other adverse effects include perioral paresthesia, dysgeusia, musculoskeletal pain, fatigue, and grade ≥3 elevations in liver enzymes in 10–15% of cases. Repotrectinib is both a strong CYP3A inhibitor and substrate, and caution is warranted when co-administered with other medications metabolized by this pathway.

4.3. Conclusion and Clinical Considerations

In general, adverse events associated with ALK and ROS1 inhibitors are mild to moderate in severity and can be effectively managed with dose adjustments and supportive care. Targeted, mechanism-specific toxicities—such as hyperlipidemia, neuropsychiatric symptoms, and gastrointestinal complaints—should be recognized early and treated accordingly. Supportive measures may include the use of statins, antidepressants, antidiarrheal agents, or antidiabetic medications, depending on the clinical scenario.

In clinical practice, patient education regarding potential toxicities and close monitoring are essential to ensure adherence and optimize outcomes. For agents like lorlatinib, which are associated with complex side effect profiles, a multidisciplinary management strategy is strongly recommended. This may involve collaboration among oncologists, nurses, pharmacists, neurologists or psychiatrists, dietitians, cardiologists, and endocrinologists to provide comprehensive and individualized care [17, 18, 24, 29, 31-34].

5. Guideline Recommendations

5.1. Molecularly Targeted Systemic Therapy Algorithm

- For ALK-positive patients, second- and third-generation TKIs—such as alectinib, brigatinib, and lorlatinib—are considered first-line therapies with equivalent strength of recommendation (category 1). Crizotinib or ceritinib should only be considered when access to preferred agents is limited.
- For ROS1-positive patients, crizotinib or entrectinib are recommended as first-line options. In the presence of brain metastases, entrectinib is preferred due to its superior CNS penetration.
- Repotrectinib, approved by the U.S. FDA in 2023 but not yet by the European Medicines Agency (EMA), is recognized in the NCCN 2025 and ESMO Living Guidelines (2025) as a promising next-generation agent. These guidelines suggest that, in centers where repotrectinib is available, it may be considered even as a first-line option.

Upon disease progression, transitioning to a next-generation TKI is recommended whenever possible. Molecular testing to identify resistance mutations is encouraged; however, if genotyping is not feasible, empirical switching to an alternative TKI is considered acceptable [35].

5.2. Systemic Therapy After TKI Failure

When all targeted treatment options have been exhausted or no actionable molecular alteration is identified, the therapeutic approach reverts to conventional NSCLC treatment algorithms:

- **Platinum-based chemotherapy combined with pemetrexed** is the preferred regimen, particularly for patients with adenocarcinoma histology.
- **Immunotherapy, with or without chemotherapy**, may be considered in patients with a smoking history or those exhibiting high tumor mutational burden (TMB) or elevated PD-L1 expression.
- The efficacy of immune checkpoint inhibitors in **ALK- and ROS1-rearranged tumors** remains limited; therefore, their use in this subgroup should be approached with caution and individualized based on clinical context.

5.3. Local Treatment Options and Eligibility Criteria

Management of Brain Metastases in ALK- and ROS1-Positive Patients

- **Brain metastases** are commonly observed during the disease course in patients with ALK- or ROS1-rearranged NSCLC.
- In cases with CNS involvement, systemic TKIs with high CNS penetration (e.g., entrectinib, alectinib, lorlatinib) should be prioritized as first-line treatment.
- However, in the presence of symptomatic or bulky CNS lesions, the following local treatment options may be considered in addition to systemic therapy:
    - **Stereotactic radiosurgery (SRS):** Preferred for single or limited brain metastases due to its precision and favorable toxicity profile.
    - **Whole-brain radiotherapy (WBRT):** Considered in cases with multiple metastases, especially when CNS-penetrant TKIs are not effective or available.
    - **Surgical resection:** May be an option for large, symptomatic, or solitary lesions causing mass effect or requiring histologic confirmation.

Note: In ALK-positive patients, third-generation TKIs such as lorlatinib have demonstrated intracranial response rates exceeding 80%. Therefore,

when feasible, upfront TKI therapy may allow deferral of radiation therapy in selected cases [32, 36, 37].

Local Ablative Therapies in Oligometastatic Disease

- **Definition of oligometastatic disease:** A clinically limited metastatic state characterized by the presence of 1 to 3 discrete, controllable metastatic lesions.
- In such cases, local ablative therapies may be added to systemic treatment to improve disease control. Common approaches include:
  - **Surgical resection**, particularly for isolated metastases in the adrenal glands, brain, or lungs.
  - **Stereotactic body radiotherapy (SBRT)** for precise and high-dose local ablation of limited metastases.
  - **Radiofrequency ablation (RFA)**, especially for selected hepatic or pulmonary lesions.

Current evidence suggests that combining local ablative therapy with systemic treatment may lead to prolonged progression-free survival, and in selected cases, durable disease control can be achieved.

Central Tumors and Complicated Cases

- In cases where the tumor invades central structures such as the trachea, main bronchi, or major vessels:
  - Palliative local interventions may be considered, including:
    - § Bronchoscopic debulking
    - § Endobronchial laser therapy
    - § Cryotherapy
    - § Radiofrequency ablation
    - § Airway stenting

These approaches aim to alleviate airway obstruction, reduce dyspnea, and ultimately improve the patient's tolerance to systemic therapies [31, 38].

Conclusion: Clinical Management Perspective

In patients with ALK- or ROS1-rearranged NSCLC:

- Tyrosine kinase inhibitors (TKIs) represent the cornerstone of first-line treatment.

- Selection of agents with CNS activity is crucial, particularly in patients with or at risk for brain metastases.
- Local therapies should be considered as part of a personalized approach, especially in cases with CNS involvement, oligometastatic disease, or complications such as airway obstruction.
- Upon systemic progression after TKI therapy, treatment strategy should transition to the conventional NSCLC therapeutic algorithm, including chemotherapy ± immunotherapy based on clinical and molecular context.

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