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Review

The relationship between genetic mutations and organ metastasis in non-small cell lung cancer

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***Abstract*:** Non-small cell lung cancer is among the most prevalent cancers worldwide, with its high metastatic potential driving poor prognosis and mortality. Advances in molecular testing and high-throughput sequencing have highlighted the roles of driver genes (EGFR, ALK, KRAS) and key non-driver genes (TP53, STK11, KEAP1) in NSCLC metastasis. These mutations influence tumor invasiveness, drug resistance, and organ-specific metastatic patterns—EGFR and ALK mutations favor brain metastasis, KRAS mutations are linked to bone, liver, and multiple lung metastases, while TP53, STK11, and KEAP1 mutations increase multi-organ metastatic risk. This review summarizes the associations between genetic mutations and metastatic sites, explores underlying molecular mechanisms, and discusses mutation-based risk prediction and personalized therapeutic strategies. With multi-omics integration and further clinical research, genetic profiling may become a key tool for guiding metastasis prevention, early intervention, and treatment optimization in NSCLC.

Keywords: circulating tumor cells (CTCs), genetic mutations, non-small cell lung cancer, organ-specific metastasis, pre-metastatic niche (PMN)

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, with adenocarcinoma, squamous cell carcinoma, and large cell carcinoma as its main subtypes.[1] Despite recent advances in diagnosis and therapy, advanced NSCLC patients still exhibit poor 5-year survival, largely due to metastasis. NSCLC commonly spreads to specific organs, including the brain, bones, liver, adrenal glands, and lungs (Figure 1),[2] which not only worsen symptoms but also complicate clinical management.

High-throughput sequencing and molecular testing have revealed the pivotal roles of driver genes (e.g., EGFR, ALK, KRAS) and key non-driver genes (e.g., TP53, STK11, KEAP1) in NSCLC development and progression. These mutations influence tumor proliferation, invasion, and drug resistance, and are closely linked to organ-specific metastasis.[3] EGFR and ALK mutations are associated with brain metastasis, KRAS with multiple lung, liver, or adrenal metastases, while TP53, STK11, and KEAP1 mutations indicate higher multi-organ metastatic risk and poor prognosis.

Despite extensive research on the link between genetic mutations and NSCLC metastasis, gaps remain due to reliance on retrospective or single-center studies, small sample sizes, and a lack of large-scale prospective data. Mechanistic insights are still fragmented, and clinical translation is limited, with no established predictive models or standardized treatment protocols based on genetic profiles.[4] A systematic summary of gene–metastasis associations in NSCLC can clarify the molecular basis of tumor progression and provide guidance for metastasis risk prediction, personalized therapy, and strategies to overcome drug resistance.

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The process and mechanisms of lung cancer metastasis

Lung cancer metastasis is a complex, multi-step process involving tumor cell phenotypic changes, interactions with the extracellular matrix and immune microenvironment, and dynamic signaling regulation.[5,6] Although NSCLC subtypes differ in metastatic behavior, the process generally follows four stages: epithelial-mesenchymal transition and invasion, circulation and extravasation, metastatic microenvironment establishment, and immune evasion and colonization (Figure 2). These stages are interconnected and mutually reinforcing, enabling tumor cells to colonize specific organs.[7–9]

Epithelial-mesenchymal transition and local invasion

Epithelial-mesenchymal transition (EMT) is an early event that enables lung cancer cells to migrate and invade. During EMT, downregulation of adhesion molecules such as E-cadherin and upregulation of mesenchymal markers like N-cadherin and vimentin cause cells to lose polarity and adopt a fibroblast-like migratory phenotype.[10,11] EMT is regulated by signaling pathways including TGF-β/SMAD, Wnt/β-catenin, and Notch; mutations in driver genes such as EGFR, KRAS, and ALK can enhance EMT through downstream activation of PI3K/AKT and MAPK, thereby increasing tumor cell invasiveness.[12,13]

A key factor in local invasion is extracellular matrix (ECM) degradation, largely driven by increased expression of matrix metalloproteinases (MMPs) and cathepsins. Cancer-associated fibroblasts (CAFs) contribute by releasing MMP-2, MMP-9, and pro-inflammatory cytokines such as IL-6 and IL-8, which remodel the ECM and facilitate cancer cell invasion through the basement membrane.[14] Altered signaling from driver genes further enhances cancer cell invasiveness, enabling entry into the bloodstream or lymphatics.

Circulatory metastasis and extravasation

After breaching local tumor barriers, cancer cells enter the bloodstream or lymphatic system as circulating tumor cells (CTCs). To survive shear stress and immune attacks, CTCs employ mechanisms such as forming heterotypic aggregates with platelets to evade natural killer cell clearance.[15,16] EGFR-mutant lung cancers show higher CTC detection rates, reflecting increased hematogenous metastatic potential.[17]

Extravasation enables circulating tumor cells to colonize distant organs. This process depends on interactions between tumor cell integrins and endothelial adhesion molecules, as well as chemokine axes like CXCL12/CXCR4 that guide cells to metastatic sites.[18] Driver gene mutations can also modulate integrin expression, affecting

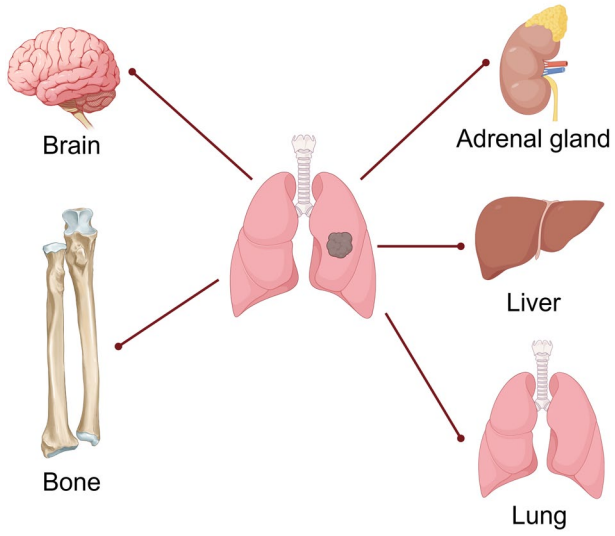

Figure 1. The common metastatic sites of non-small cell lung cancer are the brain, bone, adrenal glands, liver, and lungs.

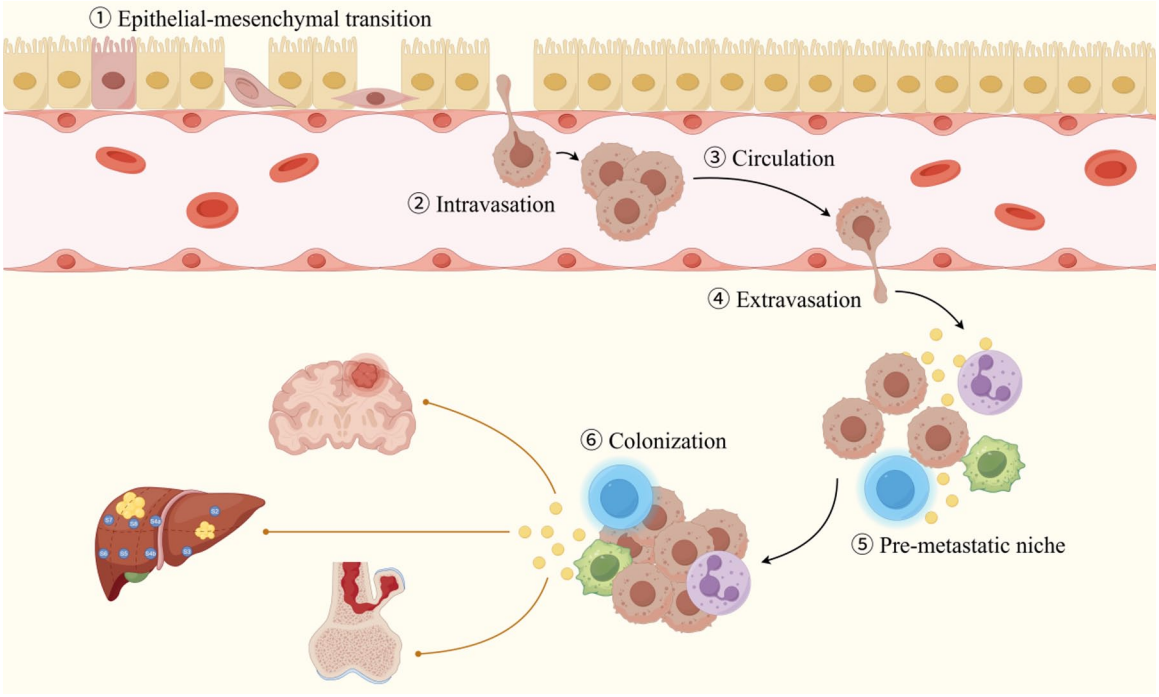

Figure 2. Lung cancer metastasis represents a complex, multistep biological cascade. Initially, tumor cells undergo epithelial-mesenchymal transition, losing polarity and acquiring migratory and invasive capacities. A subset of these cells then penetrate into the vasculature through intravasation, entering the bloodstream as circulating tumor cells. During circulation, they must withstand hemodynamic stress and evade immune surveillance, often aided by platelets and immunosuppressive factors. Subsequently, tumor cells extravasate across the vascular wall to invade distant tissues. Meanwhile, the primary tumor promotes the establishment of a pre-metastatic niche in secondary organs via exosomes, cytokines, and extracellular matrix remodeling, thereby facilitating colonization. Ultimately, cancer cells adapt to the new microenvironment, where they colonize and form macroscopic metastatic lesions.
CTCs, circulating tumor cells; EMT, epithelial-mesenchymal transition.

tumor cell retention in organ-specific microvasculature and contributing to lung cancer's organotropic metastasis.

Formation of the PMN

The pre-metastatic niche (PMN) theory suggests that primary tumors can prime distant organ microenvironments by releasing exosomes, cytokines, and growth factors before cancer cell arrival.[19] Tumor-derived exosomes, enriched in specific microRNAs and proteins, recruit myeloid-derived suppressor cells (MDSCs), promote angiogenesis, and alter matrix stiffness, creating conditions that favor cancer cell colonization.

Driver gene mutations can shape exosome content. KRAS-mutant lung cancer-derived exosomes are enriched in molecules such as miR-21 and miR-29a, which promote pre-metastatic niche formation in the liver and brain. Understanding these mechanisms can reveal organ-specific metastatic preferences of mutated lung cancers.

Immune evasion and metastasis site colonization

Immune evasion enables metastatic cancer cells to survive and form lesions in distant organs. Tumor cells can upregulate PD-L1 to suppress T cell activity or secrete immunosuppressive factors such as TGF-β and IL-10, recruiting regulatory T cells (Tregs) and M2 macrophages to weaken local anti-tumor immunity.[20]

During colonization, cancer cells must adapt to the target organ microenvironment, including oxygen levels, nutrient availability, and local cytokines. Certain mutations, such as ALK rearrangements, enhance lung cancer's ability to colonize the brain, likely by adapting to molecules

that regulate the blood-brain barrier (BBB). Cells then proliferate and partially revert to an epithelial phenotype via MET, forming clinically detectable metastases.

Key genetic mutations and metastatic target organs in NSCLC

NSCLC is a genetically heterogeneous malignancy, with driver mutations influencing tumor initiation, progression, and metastatic potential, including organ-specific spread. Advances in molecular diagnostics have clarified links between key driver genes—EGFR, KRAS, and ALK—and organotropic metastasis, while non-driver genes such as TP53 and STK11, which regulate invasiveness and metastasis, have also gained attention. This chapter systematically reviews the mutation profiles of major driver and key non-driver genes in NSCLC, examines their associations with common metastatic sites and underlying mechanisms, and summarizes mutation-based metastasis risk assessment and targeted therapy strategies, providing a foundation for precision treatment. Apparent organotropism, particularly for the central nervous system (CNS), is detection- and era-sensitive: estimates depend on routine baseline brain MRI and the availability of CNS-active targeted agents; cohorts without systematic MRI or predating these therapies may under-detect intracranial disease and are not directly comparable across eras.

EGFR mutations and metastatic target organs in NSCLC

EGFR is a key target in NSCLC, with mutations occurring in over 50% of Asian patients and 10%–15% of Caucasians.[21] These mutations mainly affect the tyrosine kinase domain (exons 18–21), with exon 19 deletions and exon 21 L858R point mutations accounting for 80%–90% of cases.[22,23] Rare mutations, including exon 20 insertions and G719X, comprise roughly 15%.[24,25] EGFR mutations are closely linked to metastasis, particularly to the brain and bones. Understanding their association with specific metastatic sites can inform patient management. The following sections review research on EGFR mutations and their relationships with brain, bone, and other metastatic targets in NSCLC.

EGFR mutations and brain metastasis. Brain metastasis is a common and clinically significant form of distant spread in EGFR-mutant NSCLC, often indicating disease progression and poor prognosis. EGFR mutations markedly increase the risk of brain metastasis, with rates 2–3 times higher than in wild-type patients.[26–28] A meta-analysis of 22 studies including 8152 NSCLC patients reported a significantly elevated risk (RR = 1.54, 95% CI 1.31–1.82, $p < 0.001$), observed at both diagnosis and post-treatment.[29] The annual incidence of brain metastasis was 15.8% in EGFR-positive patients versus 12.5% in wild-type.[30] Mutation subtype also influences risk: exon 19 deletions had the highest incidence (17.1%), followed by L858R (13.6%) and other rare mutations (13.3%), compared to 6.1% in wild-type patients.[26]

The elevated risk of brain metastasis in EGFR-mutant NSCLC is linked to dysregulated signaling pathways. Activating EGFR mutations promote brain metastasis via the ERK1/2–E2F1–WNT5A pathway: mutant EGFR continuously activates MAPK/ERK1/2, inducing E2F1 to suppress WNT5A, which reduces cell adhesion and polarity, facilitating migration, BBB penetration, and brain colonization.[31] EGFR-mutant tumors also secrete IL-11, activating astrocytes to upregulate PD-L1, suppress CD8+ T cells, and create an immunosuppressive microenvironment that supports metastatic growth.[32] Additionally, EGFR mutations enhance migration and invasion through EMT, and exosomes mediate tumor–brain microenvironment interactions, modulating BBB permeability during metastasis.[33]

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are small molecules that bind the intracellular tyrosine kinase domain of EGFR, blocking downstream signaling to inhibit tumor growth. Osimertinib, a third-generation EGFR-TKI, is the first-line standard for common sensitizing EGFR mutations. In the prespecified CNS analysis of the phase III FLAURA trial, osimertinib significantly prolonged intracranial progression free survival (PFS) versus gefitinib/erlotinib under BICR (median not reached vs 13.9 months) and achieved higher intracranial response rates.[34] FLAURA2 further showed that adding platinum–pemetrexed to osimertinib prolonged PFS, with patients who had baseline brain metastases showing a lower risk of intracranial progression or death versus osimertinib alone.[35] Nevertheless, CNS progression still occurs after osimertinib, reflecting acquired resistance

mechanisms—most commonly MET amplification or mutations.

In MET-driven resistance, adding a MET inhibitor such as capmatinib can recapture responses in selected patients.[36] Given its bispecific EGFR–MET targeting, amivantamab directly addresses this pathway and can be deployed alone or in combination. Lazertinib, a third-generation CNS-penetrant EGFR-TKI with documented intracranial activity, complements amivantamab. In MARIPOSA, first-line amivantamab + lazertinib significantly prolonged PFS versus osimertinib, with prespecified analyses indicating a reduced risk of intracranial progression.[37] In the post-osimertinib, post-platinum setting, CHRYSALIS-2 reported clinically meaningful activity of amivantamab + lazertinib (ORR ≈ 28%), including intracranial responses in subsets.[38] Accordingly, at progression on osimertinib, re-biopsy to document MET-driven resistance should guide either osimertinib + a MET inhibitor or a switch to amivantamab + lazertinib, particularly when CNS control is a priority.

EGFR mutations and bone metastasis. Bone metastasis occurs in up to 41.1% of NSCLC patients with EGFR mutations, predominantly affecting the vertebrae (76.3%) and pelvis (60.9%), while femoral involvement (20%) is associated with poor prognosis.[39] EGFR-mutant NSCLC shows higher bone metastatic rates than wild-type. PET/CT studies report 32.2% in EGFR-mutant versus 22.8% in wild-type ($p = 0.007$), with more concurrent bone and brain metastases at diagnosis (20.9% vs 7.5%, $p = 0.018$).[40] A retrospective study of 410 patients confirmed higher bone metastasis at diagnosis in EGFR-mutant cases (63.9% vs 54.4%, $p = 0.004$), with EGFR mutation identified as an independent risk factor for skeletal-related events (OR = 3.05, 95% CI 1.61–5.79, $p = 0.001$).[41]

EGFR mutations promote bone destruction in NSCLC metastasis through multiple mechanisms. EGFR signaling upregulates RANKL, stimulating osteoclast formation and activity, leading to osteolytic lesions; clinical samples show a positive correlation between EGFR and RANKL in bone metastatic tumors.[42] NSCLC-derived exosomes containing the EGFR ligand AREG activate EGFR in osteoclast precursors, upregulating genes such as RANKL, MMP9, and TRAP, thereby enhancing osteoclast differentiation and bone resorption.[43] Additionally, tumor microenvironment cytokines, including IL-6, activate STAT3 in osteoclast precursors, while TGF-β promotes osteoclast-stimulating factors and regulates tumor–osteocyte interactions, sustaining a malignant cycle of bone metastasis and exacerbating bone destruction.[44–46]

In EGFR-driven NSCLC bone metastasis, treatment primarily involves EGFR-TKIs and bone-targeted agents. EGFR-TKIs inhibit tumor proliferation and slow progression of bone lesions, while bisphosphonates and RANKL inhibitors suppress osteoclast activity, reducing bone destruction and skeletal-related events.[47,48] Combined therapy improves efficacy, delays complications, and enhances patient quality of life. Third-generation EGFR-TKIs are the standard first-line backbone in EGFR-mutated advanced NSCLC. Bone-targeted agents such as denosumab or zoledronic acid are routinely combined with calcium and vitamin D, and local measures including palliative radiotherapy and surgical or interventional stabilization are used when indicated.[49] Evidence for improvements in bone-focused endpoints—skeletal-related event (SRE) incidence or bone-PFS—with alternative EGFR-targeted strategies remains limited.

It is noteworthy that disease progression following osimertinib treatment is frequently associated with the emergence of MET amplification or mutation.[50,51] At progression, tissue re-biopsy or plasma circulating tumor DNA (ctDNA) analysis is recommended to define resistance mechanisms, with particular attention to MET activation.[52] When MEt alterations are identified, the addition of a MET inhibitor to osimertinib—such as tepotinib or capmatinib—has demonstrated clinical activity in post-osimertinib settings.[36,53] In addition, amivantamab, a bispecific antibody targeting EGFR and MET, either as monotherapy or in combination with lazertinib, has shown efficacy after osimertinib failure.[54,55] Importantly, MET-driven resistance represents a systemic mechanism of disease progression, and patients with MET amplification may benefit from these combination strategies irrespective of metastatic sites. However, the effects of MET-targeted approaches on bone-specific outcomes have not yet been prospectively established. Bone-related endpoints, including bone-specific PFS and SRE, remain underreported and should be incorporated into future studies to better characterize treatment effects on osseous disease.

EGFR mutations and other metastases. NSCLC patients with EGFR mutations are at increased risk of multiple lung metastases. Imaging studies show that EGFR-mutant tumors often present with diffuse nodules, suggesting promotion of multifocal lesions.[56] These patients also frequently develop metastases to the liver, pleura, and lymph nodes. Liver metastasis, common in advanced stages, is associated with poor prognosis; pleural metastasis can cause effusions and impair quality of life; and lymph node involvement contributes to both local progression and distant spread. Metastases to the adrenal glands and skin are less common. While EGFR mutations are linked to these patterns, the precise molecular mechanisms remain unclear, likely involving enhanced invasiveness, microenvironment modulation, and immune evasion.

KRAS mutations and metastatic sites in NSCLC

KRAS mutations and brain metastasis. In NSCLC patients with KRAS G12C mutations, the cumulative incidence of brain metastasis can reach 40%, with 35.1% presenting synchronously at diagnosis.[57] A 2023 Swedish registry study reported higher CNS metastasis at stage IV in G12C patients (28%) compared to other KRAS mutations (19%) or wild-type KRAS (18%).[58] However, real-world cohort studies found no significant differences between KRAS-mutant and wild-type patients (33% vs 40%, $p = 0.17$) or between G12C and non-G12C mutations (40% vs 41%, $p = 0.74$).[59] Thus, the impact of KRAS mutations on brain metastasis risk remains unclear.

KRAS mutations activate MAPK/ERK and PI3K pathways, promoting EMT, chemotaxis, and matrix degradation, which enhance invasiveness and facilitate BBB penetration. Co-mutations in STK11, KEAP1, and TP53 often accompany KRAS mutations, creating an immunosuppressive or highly invasive microenvironment that may impair brain control, although a direct link to brain tropism remains unconfirmed.[60]

Patients with KRAS-mutant NSCLC often have poor prognosis and limited response to conventional chemotherapy or some targeted therapies. Among approved KRAS G12C inhibitors, adagrasib provides the most robust prospective CNS evidence to date: in the phase Ib KRYSTAL-1 cohort of patients with untreated brain metastases, the confirmed intracranial ORR was 42% (95% CI 20.3–66.5) with durable control, demonstrating BBB penetration.[61] By contrast, sotorasib has emerging but more limited prospective CNS data; an exploratory post-hoc analysis of the phase III CodeBreaK 200 trial reported a reduced risk of intracranial progression versus docetaxel among patients with previously treated, stable brain metastases at baseline.[62] Next-generation G12C inhibitors such as divarasib show promising systemic activity; early studies generally excluded active, untreated brain metastases, and a phase I long-term follow-up in NSCLC is now available while robust prospective CNS-specific readouts remain pending.[63,64] However, drug resistance and limited applicability still pose challenges.[65]

KRAS mutations and bone metastasis. Clinical studies indicate that KRAS-mutant NSCLC has distinctive patterns of bone metastasis. In a study of 500 metastatic lung adenocarcinoma patients (excluding EGFR-positive), bone metastasis occurred in 26.2%, with ~28% harboring KRAS mutations; median overall survival (mOS) was lower in patients with bone metastasis (3.7 vs 9.7 months, $p = 0.003$).[66] Among KRAS subtypes, G12C patients had a higher bone metastasis rate compared to other subtypes.[67] Bioinformatics analyses show that KRAS/STK11/KEAP1 triple mutations are associated with more frequent distant metastases, particularly bone, and poorer prognosis than KRAS alone,[68] suggesting these co-mutations may synergistically enhance invasiveness and define a high-risk subgroup.

KRAS mutations promote bone metastasis via multiple pathways. KRAS activation induces EMT, reducing cell adhesion and enhancing migration and invasiveness, facilitating entry into the bloodstream and bone microenvironment. HOXC10 is upregulated in KRAS-mutant bone metastases, activating NOD1/ERK signaling by binding the NOD1 promoter, reprogramming EMT and altering the bone microenvironment.[69] Additionally, KRAS-driven secretion of CCL12 interacts with CXCR4, promoting tumor cell migration to bone and facilitating metastasis.[70]

For NSCLC patients with KRAS, especially G12C, mutations and bone metastases, targeted therapy is the main intervention. Inhibiting KRAS signaling suppresses tumor proliferation and metastasis.[66] Because STK11/KEAP1 co-mutations delineate a poor-prognosis subgroup with attenuated benefit to immune checkpoint inhibitor (ICI) monotherapy, combination

chemo-immunotherapy should be preferred over single-agent ICI, and future G12C inhibitor studies should prospectively report bone-specific endpoints to clarify osseous control.[71] KRAS-driven bone metastasis may also involve the HOXC10/NOD1/ERK pathway, and combining HOXC10 inhibition with STAT3 inhibitors could mitigate bone metastasis, suggesting potential combination therapy strategies.[69]

KRAS mutations and other metastases. KRAS-mutant NSCLC patients frequently develop metastases to the liver, adrenal glands, and multiple lung sites. A retrospective study reported liver metastasis in 11%, adrenal in 17.4%, and multiple lung metastases in 45.6% of KRAS-mutant cases.[66] These patterns may result from KRAS-driven EMT, chemokine secretion, reduced cell adhesion, and microenvironment remodeling. Co-mutations with STK11 or KEAP1 further increase the risk of liver and adrenal metastases, indicating that specific molecular subgroups have higher metastatic potential.

KRAS G12C inhibitors, such as sotorasib and adagrasib, have demonstrated objective response rates of 30%–40% in advanced or metastatic NSCLC, with some patients achieving systemic control of liver and lung metastases.[72] For cases with multiple organ progression or local threats, combining local therapies—such as radiation, ablation, or surgery—can improve disease control and patient quality of life.

ALK rearrangement and metastatic sites in NSCLC

Anaplastic lymphoma kinase (ALK) rearrangements involve fusions of ALK with genes such as EML4 or KIF5B, producing proteins with aberrant kinase activity.[73] These fusion proteins activate downstream pathways—including RAS–MAPK, PI3K–AKT, and JAK–STAT—driving abnormal proliferation and survival, and promoting tumor initiation and progression.[74,75] Identified in 2007, ALK rearrangements occur in 2%–7% of NSCLC cases and are strongly associated with brain metastasis, with some links to other metastatic sites.[76,77]

ALK rearrangement and brain metastasis. ALK-positive NSCLC patients have a high propensity for brain metastasis. Studies show that ALK rearrangements significantly increase this risk. A systematic review reported an annual incidence of 17.0% in ALK-positive patients versus 12.5% in wild-type, with a cumulative rate of 40%–60% over the disease course.[30] Retrospective analyses indicate that 20–30% of ALK-positive patients present with brain metastases at diagnosis, often with multiple lesions.[78] The incidence rises over time, underscoring the CNS as a critical site for disease progression and treatment failure.[79]

ALK-positive NSCLC brain metastasis involves multiple cellular mechanisms. ALK fusion proteins activate PI3K/AKT and MAPK pathways, enhancing tumor cell survival, migration, and adaptation in the brain microenvironment, facilitating BBB penetration.[79,80] EMT further increases invasiveness and migration through regulation of matrix metalloproteinases. Exosomes from ALK-positive cells also remodel the BBB, increasing permeability and promoting brain invasion.[81]

ALK-TKIs block the aberrant kinase activity of ALK fusion proteins, inhibiting downstream signaling and tumor cell proliferation. Alectinib has randomized phase III evidence of superior intracranial control versus crizotinib in treatment-naïve ALK-positive NSCLC. In ALEX, the 12-month cumulative incidence of CNS progression was markedly lower with alectinib across predefined subgroups (4.6% vs 31.5% without baseline CNS metastases; 16.0% vs 58.3% with baseline CNS metastases), and among patients with measurable baseline CNS lesions the intracranial ORR was 81% vs 50%.[82,83] Lorlatinib showed striking first-line CNS efficacy in CROWN and maintained durable intracranial protection on long-term follow-up.[84,85] CROWN reported an intracranial ORR of 82% versus 23% in patients with measurable brain metastases at baseline, with a time-to-intracranial-progression HR of 0.06, confirming robust CNS potency and durability.[84,85] Brigatinib also improved intracranial control versus crizotinib in ALTA-1L, supporting first-line CNS activity alongside alectinib and lorlatinib.[86]

ALK rearrangement and other target organ metastasis. Beyond brain metastasis, ALK-positive NSCLC shows a predilection for bones, pleura, liver, adrenal glands, and often presents with multi-focal lung lesions and mediastinal or distant lymph node involvement. Clinical and retrospective studies report overall metastasis rates up to 71%, with bone metastasis at 27%–32%, pleural involvement 29%–36%, and liver

metastasis 19%.[87–89] Multi-focal lung lesions and lymph node involvement are also more frequent, suggesting that peripheral organ dissemination in ALK-rearranged tumors exhibits specific "organ affinity."

EML4-ALK and other ALK fusions constitutively activate downstream pathways such as PI3K/AKT and MAPK/STAT, promoting proliferation, survival, EMT, and gene expression changes that enhance migration and invasiveness. Additionally, EML4-ALK can generate active circular RNAs and modulate exosome and chemokine secretion, remodeling distant microenvironments to facilitate tumor cell adhesion, colonization, and growth.[87]

ALK-TKIs are the main treatment for ALK-positive NSCLC with extracranial metastases. First-generation TKIs, like crizotinib, can delay progression in bone, liver, pleura, and other sites, though control of some metastases remains limited. Second-generation TKIs provide more durable control of bone, liver, and multi-organ metastases, extending PFS before resistance emerges.[86,90] Third-generation TKIs, such as lorlatinib, are effective against resistant mutations and show significant responses in bone and liver metastases.[91]

Other driver gene mutations and metastatic organs in NSCLC

In NSCLC, besides common drivers like EGFR, KRAS, and ALK, less frequent alterations—such as ROS1 fusions, BRAF mutations, and MET exon 14 skipping—also shape metastatic patterns. Though rare, these mutations can confer specific organ tropisms, influencing prognosis and treatment. Like EGFR and ALK, they activate downstream pathways including MAPK, PI3K–AKT, and JAK–STAT, promoting invasion and metastasis. Evidence suggests their extracranial metastases are more heterogeneous, often involving bone, liver, or multifocal lung lesions.

Retrospective studies have shown that the incidence of brain metastasis in ROS1-positive patients is 28%–36%, which is higher than that in wild-type patients (~20%), and the proportion of patients with brain metastasis at the time of diagnosis is approximately 12%.[92] Cohort, real-world, and imaging studies show that ROS1-positive tumors frequently metastasize to the pleura, multifocal lungs, and bones. Single-organ involvement is often higher than in wild-type cases, with some CNS involvement, though overall brain metastasis remains slightly lower than in ALK-positive tumors.[87,93] The BRAF V600E mutation in NSCLC is associated with metastatic rates of approximately 40% to the brain, 35% to the bone, and 25% to the liver.[94] BRAF V600E mutations are associated with widespread dissemination, commonly affecting bone, liver, and pleura, with metastatic patterns influenced by smoking history, PD-L1 expression, and immunotherapy response.[94] Real-world studies have shown that in patients with MET exon 14 skipping (METex14) mutations, the incidence of brain metastasis at diagnosis is 22%–27%, while the incidence of bone metastasis is 30%–35%.[95] METex14 mutations primarily metastasize to bone, pleura, lungs, liver, and mediastinal lymph nodes, with reviews noting patterns similar to advanced NSCLC overall but particularly prominent in bone and pleural involvement.[95,96]

ROS1, BRAF V600E, and MET exon 14 mutations promote tumor proliferation, invasion, and microenvironment remodeling by constitutively activating downstream pathways. ROS1 and MET signal through PI3K/AKT–MAPK, while BRAF V600E drives the RAF–MEK–ERK pathway. Co-mutations, EMT, exosome or chemokine release, and post-treatment resistant clones further influence organ-specific metastasis and tumor growth.[92]

For treatment, first-line therapy for ROS1-positive NSCLC is crizotinib, though CNS penetration is limited. Entrectinib offers superior CNS activity, making it suitable for first-line or sequential therapy[97,98]; in pooled prospective analyses, it achieved an intracranial objective response rate of 79.2% in patients with measurable baseline brain metastases with a median intracranial progression-free survival of 12.0 months, and the next-generation agent repotrectinib has demonstrated durable intracranial responses.[99,100] BRAF V600E mutations respond well to combined BRAF and MEK inhibitors, effective both post-chemotherapy and as first-line treatment, and should be prioritized; however, CNS-specific prospective datasets remain limited, and intracranial responses are mainly supported by case-level evidence.[101] Local therapies are recommended for organ-specific complications, such as fractures, pleural effusion, or liver dysfunction.[102,103] Selective MET-TKIs show promising responses and manageable safety

in MET exon 14–mutant patients, with or without brain metastases; notably, capmatinib produced intracranial responses in 7 of 13 patients with baseline brain metastases in GEOMETRY mono-1 and tepotinib showed RANO-BM–based intracranial activity in VISION.[104,105]

Non-driver key genes and metastatic sites in NSCLC

Beyond well-known driver genes, NSCLC metastatic patterns are also shaped by key non-driver genes. While not directly initiating tumors, these genes influence tumor evolution, microenvironment remodeling, and organ-specific metastasis. Recent studies highlight TP53, STK11, and KEAP1, whose alterations are often associated with poor prognosis, distinct metastatic tendencies, and treatment resistance.

TP53 mutations, which are common in NSCLC, are linked to heightened metastatic potential and poor prognosis. According to a multicenter study, TP53 mutation drives a significantly increased risk of distant metastasis in early-stage NSCLC, with a markedly higher risk of liver metastasis.[106] A genomic analysis of over 2000 lung adenocarcinomas demonstrated that TP53 inactivation correlates with a higher overall metastatic burden and significantly shorter times to lymph node metastasis.[3] A multicenter study in early-stage NSCLC further showed that TP53 mutations markedly increase the risk of distant metastasis, particularly to the liver (HR $\approx$ 2.51, 95% CI 1.07–5.93).[106] Loss of p53 function leads to genomic instability, elevated mutation load, and enhanced EMT, collectively promoting tumor cell invasion and metastasis. Although no therapies specifically target TP53 mutations, in the context of EGFR mutations, TP53 co-mutations are associated with poorer responses to TKIs and faster disease progression. Consequently, these patients often require more aggressive combination strategies, such as TKIs combined with chemotherapy or anti-angiogenic therapy.[107–109]

Research has definitively confirmed that STK11 mutations lead to primary resistance to PD-1/PD-L1 monotherapy. This is characterized by an "immune desert" phenotype in the tumor microenvironment, resulting in resistance to immune checkpoint inhibitors.[110] Real-world cohorts and meta-analyses also show reduced sensitivity to PD-1/PD-L1 monotherapy, especially in PD-L1–low/negative disease, with mechanistic data implicating AMPK pathway inactivation and STING suppression.[111–113] In KRAS-mutant lung adenocarcinoma, STK11/LKB1 co-mutation is associated with a markedly lower objective response to PD-1 blockade (~7.4%) versus KRAS-only (~28.6%) and KRAS–TP53 (~35.7%), with inferior PFS and OS.[114] Clinically, when STK11 ($\pm$ KEAP1) co-mutations are present and alternatives exist, PD-(L)1 monotherapy should generally be avoided and chemo-immunotherapy favored.[71]

KEAP1 alterations with NRF2 activation correlate with earlier/more frequent visceral metastasis (e.g., liver, nodes) and resistance to chemotherapy, radiotherapy, and immunotherapy.[3,115–117] KEAP1/NRF2-driven immune evasion—impairing dendritic-cell antigen presentation and T-cell responses—helps explain inferior outcomes on PD-(L)1 therapy and supports prioritizing combination approaches over monotherapy[118]; additional clinical observations are concordant.[119,120]

Discussion

Advances in molecular testing and high-throughput sequencing have increasingly highlighted the critical role of genetic mutations in the initiation and progression of metastasis in NSCLC. Mutations in both driver and non-driver key genes not only influence tumor biology and organ-specific metastatic tendencies but also closely impact clinical treatment responses and patient prognosis. Apparent organotropism—particularly for the CNS is detection- and era-sensitive.

In predicting metastatic risk, patients harboring EGFR or ALK mutations are more prone to developing brain metastases, whereas alterations in non-driver key genes such as TP53, STK11, and KEAP1 indicate a higher likelihood of multi-organ metastasis and poorer prognosis. Developing metastatic risk models based on mutation profiles holds promise for early identification of high-risk populations and could guide imaging surveillance and clinical interventions.[3,121] Table 1 summarizes genotype-specific organotropism and CNS-active therapies in NSCLC. In practice, standardizing baseline brain MRI in CNS-prone genotypes and aligning surveillance to genotype-specific risk make these tools clinically actionable. For osimertinib-relapsed EGFR-mutant disease, MET amplification is a key resistance mechanism; osimertinib + MET inhibition or the amivantamab–lazertinib

Table 1. Genotype-specific organotropism and CNS-active therapies in NSCLC.

Number	References	Driver gene	Main metastatic sites	Key mechanisms	CNS-active options
1	[3, 30, 34–37, 39–41]	EGFR (Ex19del/ L858R)	Brain, bone, liver	Constitutive EGFR–MAPK/ ERK signaling promotes proliferation, invasion, and survival; at resistance, MET bypass restores downstream signaling and sustains dissemination.	Osimertinib (1L; CNS efficacy); osimertinib + chemotherapy (1L; PFS/OS benefit) amivantamab + lazertinib (1L/after osimertinib; CNS activity) osimertinib + tepotinib/ capmatinib (MET-driven resistance; intracranial responses)
2	[30, 83, 84, 86, 88]	ALK fusion	Brain, pleura, bone, liver	Oncogenic ALK activation drives PI3K/AKT and MAPK pathways, fostering survival, motility, and a propensity for CNS involvement.	Alectinib (1L; RCT; CNS control) brigatinib (1L; RCT; CNS benefit) lorlatinib (1L; RCT; high intracranial ORR)
3	[61, 62, 66, 68, 71]	KRAS G12C	Brain, bone, liver, adrenal gland	KRAS–MAPK/PI3K activation drives plasticity and dissemination; STK11/KEAP1 co-mutations enforce an immune-cold state and blunt ICI response.	Adagrasib (prospective CNS activity) sotorasib (exploratory intracranial signal)
4	[92, 93, 99, 100]	ROS1 fusion	Pleura, intrapulmonary, bone, brain	ROS1 fusion kinases activate PI3K/AKT and MAPK cascades, enhancing proliferation and motility and predisposing to pleural and CNS spread.	Entrectinib (pooled/integrated CNS efficacy) repotrectinib (prospective; CNS activity)
5	[95, 104, 105]	MET exon 14 skipping	Bone, pleura, lung, liver, brain	Exon-14 skipping stabilizes MET signaling, enhancing invasion and motility and promoting visceral dissemination (bone, pleura, liver).	Capmatinib (prospective; intracranial responses) tepotinib (prospective; RANO-BM intracranial activity)
6	[94, 102, 103]	BRAF V600E	Brain, bone, liver	Constitutive RAF–MEK–ERK signaling drives proliferation and metastasis, with microenvironmental crosstalk contributing to bone and liver involvement.	Dabrafenib + trametinib (systemic efficacy; limited prospective CNS datasets)

CNS, central nervous system; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial.

combination have shown activity—including in challenging bone or CNS disease—thereby prolonging response.[36,38,54] Patients with KEAP1 or STK11 mutations typically derive limited benefit from PD-1/PD-L1 monotherapy, favoring combination strategies when feasible. Future combinatorial approaches (e.g., TKI+IO, IO+metabolic inhibitors, EGFR–MET dual blockade, and radio-sensitizing targeted/IO regimens) warrant biomarker-selected evaluation. The success of amivantamab highlights the potential of mechanism-informed, bispecific antibody approaches to preempt or tackle complex resistance patterns.

Translating these molecular insights into clinical practice is crucial for optimizing patient management. Several key recommendations can be distilled: For patients with advanced EGFR- or ALK-positive NSCLC, given their high risk of brain metastasis, baseline brain MRI and regular

asymptomatic follow-up (e.g., every 4–6 months) should be considered, with a preference for CNS-active TKIs such as osimertinib (EGFR) or alectinib/lorlatinib (ALK) in the first-line setting. For KRAS G12C with active CNS disease, prioritize CNS-active agents (e.g., adagrasib) with MRI-based follow-up. The presence of co-mutations in non-driver genes such as TP53, STK11, or KEAP1 should temper expectations for response to immune checkpoint inhibitor monotherapy and favor combination approaches (e.g., immunotherapy with chemotherapy). For rarer drivers (ROS1, BRAF V600E, METex14), baseline brain MRI and prioritization of CNS-active targeted agents (entrectinib; dabrafenib+trametinib; capmatinib) enable proactive management of metastatic risk.

Despite the substantial accumulation of data in recent years, significant limitations remain in current research. First, most studies examining the relationship between gene mutations and metastatic patterns are retrospective or single-center analyses with limited sample sizes, leading to population heterogeneity, selection bias, and a lack of large-scale prospective, multi-center validation. Non-uniform imaging (e.g., absence of routine baseline brain MRI) further biases site-specific estimates and limits cross-study comparability. Second, mechanistic studies remain fragmented; although multiple pathways—including EMT, metabolic reprogramming, exosome signaling, and the immune microenvironment—have been implicated, a unified mechanistic framework is still lacking. Third, while tools for predicting metastatic risk based on genetic mutations have been developed, they are not widely implemented in clinical practice, and most patients continue to rely primarily on imaging follow-up. Finally, although combination therapies show considerable promise, no widely accepted treatment standards exist for managing resistance-mediated progression (e.g., post-osimertinib MET amplification), and clinical decisions still rely heavily on individual physician experience. Prospective, biomarker-selected trials with predefined organ-specific endpoints and harmonized imaging are needed to validate sequencing and establish standards.

In conclusion, the association between genetic mutations and organ-specific metastasis in NSCLC illuminates the molecular mechanisms driving tumor progression and provides new opportunities for predicting metastatic risk and personalizing treatment strategies. Standardizing imaging and site-specific endpoints across trials and registries should accelerate translation and enable more rational sequencing, ultimately improving long-term survival for patients.

Conclusion

Metastasis is a major determinant of prognosis in NSCLC, with genetic mutations playing a central role. Driver mutations, such as EGFR and ALK, are strongly associated with brain metastasis, while KRAS mutations often involve bone, liver, and multiple lung sites. Non-driver genes like TP53, STK11, and KEAP1 promote multi-organ spread and poorer outcomes through genomic instability, metabolic reprogramming, and immune evasion. Clinically, mutation testing guides personalized therapy: TKIs benefit EGFR- and ALK-mutant patients, KRAS G12C inhibitors offer new options, and non-driver gene alterations often require multimodal treatment. Challenges remain, including limited prospective data and incomplete understanding of mechanisms such as EMT, exosomes, metabolism, and immune microenvironment. Integrating genetic profiles with imaging and multi-omics could improve metastatic risk prediction and therapy selection. Understanding the interplay of these mutations provides a foundation for early intervention, precision treatment, and improved patient survival.

Declarations

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References

1. Siegel RL, Giaquinto AN and Jemal A. Cancer statistics, 2024. *CA Cancer J Clin* 2024; 74(1): 12–49.
2. Gao Y, et al., Metastasis Organotropism: Redefining the Congenial Soil. *Dev Cell* 2019; 49(3): 375–391.
3. Lengel HB, et al. Genomic mapping of metastatic organotropism in lung adenocarcinoma. *Cancer Cell* 2023; 41(5): 970–985.e3.
4. Dunbar KJ, et al. Regulation of metastatic organotropism. *Trends Cancer* 2025; 11(3): 216–231.
5. Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144(5): 646–74.
6. Thiery JP, et al., Epithelial-mesenchymal transitions in development and disease. *Cell* 2009; 139(5): 871–890.
7. Fidler IJ, The pathogenesis of cancer metastasis: the "seed and soil" hypothesis revisited. *Nat Rev Cancer* 2003; 3(6): 453–458.
8. Lambert AW, Pattabiraman DR and Weinberg RA Emerging biological principles of metastasis. *Cell* 2017; 168(4): 670–691.
9. Nguyen DX, Bos PD and Massagué J. Metastasis: from dissemination to organ-specific colonization. *Nat Rev Cancer* 2009; 9(4): 274–284.
10. Nieto MA, et al., EMT: 2016. *Cell*, 2016. 166(1): 21-45.
11. Dongre A and Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. *Nat Rev Mol Cell Biol* 2019; 20(2): 69–84.
12. Yao Z, et al., TGF-beta IL-6 axis mediates selective and adaptive mechanisms of resistance to molecular targeted therapy in lung cancer. *Proc Natl Acad Sci U S A* 2010; 107(35): 15535–15540.
13. Zhang J, et al. TGF-β-induced epithelial-to-mesenchymal transition proceeds through stepwise activation of multiple feedback loops. *Sci Signal* 2014; 7(345): ra91.
14. Kalluri R. The biology and function of fibroblasts in cancer. *Nat Rev Cancer* 2016; 16(9): 582–598.
15. Labelle M, Begum S and Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. *Cancer Cell* 2011; 20(5): 576–590.
16. Schumacher D, et al. Platelet-derived nucleotides promote tumor-cell transendothelial migration and metastasis via P2Y2 receptor. *Cancer Cell* 2013; 24(1): 130–137.
17. Ilie M, et al. "Sentinel" circulating tumor cells allow early diagnosis of lung cancer in patients with chronic obstructive pulmonary disease. *PLoS One* 2014; 9(10): e111597.
18. Reymond N, d'Água BB and Ridley AJ. Crossing the endothelial barrier during metastasis. *Nat Rev Cancer* 2013; 13(12): 858–870.
19. Peinado H, et al. Pre-metastatic niches: Organ-specific homes for metastases. *Nat Rev Cancer* 2017; 17(5): 302–317.
20. Quail DF and Joyce JA, Microenvironmental regulation of tumor progression and metastasis. *Nat Med* 2013; 19(11): 1423–1437.

21. Tan DS, Mok TS and Rebbeck TR. Cancer genomics: diversity and disparity across ethnicity and geography. *J Clin Oncol* 2016; 34(1): 91–101.
22. Gazdar AF. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene* 2009; 28 (Suppl. 1): S24–S31.
23. Zhou F, et al. The changing treatment landscape of EGFR-mutant non-small-cell lung cancer. *Nat Rev Clin Oncol* 2025; 22(2): 95–116.
24. Kobayashi Y and Mitsudomi T. Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. *Cancer Sci* 2016; 107(9): 1179–1186.
25. Harrison PT, Vyse S and Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. *Semin Cancer Biol* 2020; 61: 167–179.
26. Zhang J, et al. Association between EGFR mutation types and incidence of brain metastases in postoperative patients with stage I-III NSCLC. *Tumori* 2025; 111(3): 200–209.
27. Ge M, et al. High probability and frequency of EGFR mutations in non-small cell lung cancer with brain metastases. *J Neurooncol* 2017; 135(2): 413–418.
28. Wang H, et al., Driver genes as predictive indicators of brain metastasis in patients with advanced NSCLC: EGFR, ALK, and RET gene mutations. *Cancer Med* 2020; 9(2): 487–495.
29. Li L, et al. Correlation between EGFR mutation status and the incidence of brain metastases in patients with non-small cell lung cancer. *J Thorac Dis* 2017; 9(8): 2510–2520.
30. Gillespie CS, et al. Genomic alterations and the incidence of brain metastases in advanced and metastatic NSCLC: a systematic review and meta-analysis. *J Thorac Oncol* 2023; 18(12): 1703–1713.
31. Li H, et al. E2F1-mediated repression of WNT5A expression promotes brain metastasis dependent on the ERK1/2 pathway in EGFR-mutant non-small cell lung cancer. *Cell Mol Life Sci* 2021; 78(6): 2877–2891.
32. Tang M, et al. Brain metastasis from EGFR-mutated non-small cell lung cancer: secretion of IL11 from astrocytes up-regulates PDL1 and promotes immune escape. *Adv Sci (Weinh)* 2024; 11(26): e2306348.
33. Wang H, et al. Advances in the treatment of brain metastases in EGFR-mutant non-small cell lung cancer. *Lung Cancer* 2025; 206: 108641.
34. Reungwetwattana T, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol* 2018: Jco2018783118.
35. Planchard D, et al. Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC. *N Engl J Med* 2023; 389(21): 1935–1948.
36. Wu YL, et al. Tepotinib plus osimertinib in patients with EGFR-mutated non-small-cell lung cancer with MET amplification following progression on first-line osimertinib (INSIGHT 2): a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2024; 25(8): 989–1002.
37. Cho BC, et al., Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. *N Engl J Med* 2024; 391(16): 1486–1498.
38. Besse B, et al. Amivantamab plus lazertinib in patients with EGFR-mutant NSCLC after progression on osimertinib and platinum-based chemotherapy: results from CHRYSALIS-2 cohort A. *J Thorac Oncol* 2025; 20(5): 651–664.
39. Tanaka I, et al. Femoral bone metastasis is a poor prognostic factor in EGFR-TKIs-treated patients with EGFR-mutated non-small-cell lung cancer: a retrospective, multicenter cohort study. *Ther Adv Med Oncol* 2024; 16: 17588359241303090.
40. Guan J, et al. EGFR mutations are associated with higher incidence of distant metastases and smaller tumor size in patients with non-small-cell lung cancer based on PET/CT scan. *Med Oncol* 2016; 33(1): 1.
41. Huang SM, et al. Epidermal growth factor receptor is associated with the onset of skeletal related events in non-small cell lung cancer. *Oncotarget* 2017; 8(46): 81369–81376.
42. Brouns A, et al. Association of RANKL and EGFR gene expression with bone metastases in patients with metastatic non-small cell lung cancer. *Front Oncol* 2023; 13: 1145001.
43. Taverna S, et al. Amphiregulin contained in NSCLC-exosomes induces osteoclast differentiation through the activation of EGFR pathway. *Sci Rep* 2017; 7(1): 3170.
44. Yasuda H, et al. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/

RANKL. *Proc Natl Acad Sci U S A* 1998; 95(7): 3597–602.

45. Grivennikov SI, Greten FR and Karin M. Immunity, inflammation, and cancer. *Cell* 2010; 140(6): 883–899.
46. Massagué J. TGFbeta in Cancer. *Cell* 2008; 134(2): 215–230.
47. Gen S, et al. Clinical efficacy of osimertinib in EGFR-mutant non-small cell lung cancer with distant metastasis. *BMC Cancer* 2022; 22(1): 654.
48. Hamza FN and Mohammad KS. Immunotherapy in the battle against bone metastases: Mechanisms and emerging treatments. *Pharmaceuticals (Basel)* 2024; 17(12): 1591.
49. Coleman R, et al. Bone health in cancer: ESMO clinical practice guidelines. *Ann Oncol* 2020; 31: 1650–1663.
50. Leonetti A, et al. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer* 2019; 121(9): 725–737.
51. Schoenfeld AJ, et al. Tumor analyses reveal squamous transformation and off-target alterations as early resistance mechanisms to first-line osimertinib in EGFR-mutant lung cancer. *Clin Cancer Res* 2020; 26(11): 2654–2663.
52. Rolfo C, et al. Liquid biopsy for advanced NSCLC: a consensus statement from the international association for the study of lung cancer. *J Thorac Oncol* 2021; 16(10): 1647–1662.
53. Gautschi O and Diebold J. Intracranial activity of osimertinib plus capmatinib in a patient with EGFR and MET-driven lung cancer: case report. *JTO Clin Res Rep* 2021; 2(4): 100162.
54. Cho BC, et al. Amivantamab plus lazertinib in osimertinib-relapsed EGFR-mutant advanced non-small cell lung cancer: a phase 1 trial. *Nat Med* 2023; 29(10): 2577–2585.
55. Moores SL, et al. A novel bispecific antibody targeting EGFR and cMet is effective against EGFR inhibitor-resistant lung tumors. *Cancer Res* 2016; 76(13): 3942–3953.
56. Digumarthy SR, et al. Diffuse lung metastases in EGFR-mutant non-small cell lung cancer. *Cancers (Basel)* 2019; 11(9): 1360.
57. Lamberti G, et al. Incidence of brain metastases and preliminary evidence of intracranial activity with sotorasib in patients with KRAS(G12C)-mutant non-small-cell lung cancer. *JCO Precis Oncol* 2023; 7: e2200621.
58. Isaksson J, et al. KRAS G12C mutant non-small cell lung cancer linked to female sex and high risk of CNS metastasis: population-based demographics and survival data from the national Swedish lung cancer registry. *Clin Lung Cancer* 2023; 24(6): 507–518.
59. Cui W, et al. Real world outcomes in KRAS G12C mutation positive non-small cell lung cancer. *Lung Cancer* 2020; 146: 310–317.
60. Désage AL, et al. Targeting KRAS mutant in non-small cell lung cancer: novel insights into therapeutic strategies. *Front Oncol* 2022; 12: 796832.
61. Negrao MV, et al. Intracranial efficacy of adagrasib in patients from the KRYSTAL-1 trial with KRAS(G12C)-mutated non-small-cell lung cancer who have untreated CNS metastases. *J Clin Oncol* 2023; 41(28): 4472–4477.
62. Dingemans AC, et al. Intracranial activity of sotorasib vs docetaxel in pretreated KRAS G12C-mutated advanced non-small cell lung cancer from a global, phase 3, randomized controlled trial. *Lung Cancer* 2025; 207: 108683.
63. Sacher A, et al. Single-agent divarasib (GDC-6036) in solid tumors with a KRAS G12C mutation. *N Engl J Med* 2023; 389(8): 710–721.
64. Sacher AG, et al. Single-agent divarasib in patients with KRAS G12C-positive non-small cell lung cancer: long-term follow-up of a phase I study. *J Clin Oncol* 2025; 43(30): 3249–3253.
65. Arbour KC and Riely GJ Systemic therapy for locally advanced and metastatic non–small cell lung cancer: a review. *JAMA* 2019; 322(8): 764–774.
66. Lohinai Z, et al. KRAS-mutation incidence and prognostic value are metastatic site-specific in lung adenocarcinoma: poor prognosis in patients with KRAS mutation and bone metastasis. *Sci Rep* 2017; 7: 39721.
67. Urtecho SB, et al. Decoding KRAS mutation in non-small cell lung cancer patients receiving immunotherapy: a retrospective institutional comparison and literature review. *Lung Cancer* 2025; 199: 108051.
68. Boeschen M, et al. Comparative bioinformatic analysis of KRAS, STK11 and KEAP1 (co-) mutations in non-small cell lung cancer with a special focus on KRAS G12C. *Lung Cancer* 2023; 184: 107361.
69. Li K, et al. The HOXC10/NOD1/ERK axis drives osteolytic bone metastasis of pan-KRAS-mutant lung cancer. *Bone Res* 2024; 12(1): 47.
70. Wu S, et al. Current progress and mechanisms of bone metastasis in lung cancer: a narrative review. *Transl Lung Cancer Res* 2021; 10(1): 439–451.

71. Ricciuti B, et al. Diminished efficacy of programmed death-(Ligand)1 inhibition in STK11- and KEAP1-mutant lung adenocarcinoma is affected by KRAS mutation status. *J Thorac Oncol* 2022; 17(3): 399–410.
72. Chopra D, et al. Matching-adjusted indirect comparison of sotorasib versus adagrasib in previously treated advanced/metastatic non-small cell lung cancer harboring KRAS G12C mutation. *Adv Ther* 2025; 42(9):4300-4317.
73. Arndt A, et al. Molecular tumor board: molecularly adjusted therapy upon identification and functional validation of a novel ALK resistance mutation in a case of lung adenocarcinoma. *Oncologist* 2025; 30(1); oyae143.
74. Shaw AT and Engelman JA. ALK in lung cancer: past, present, and future. *J Clin Oncol* 2013; 31(8): 1105–1111.
75. Chiarle R, et al. The anaplastic lymphoma kinase in the pathogenesis of cancer. *Nat Rev Cancer* 2008; 8(1): 11–23.
76. Soda M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007; 448(7153): 561–566.
77. Shaw AT, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009; 27(26): 4247–4253.
78. Remon J and Besse B. Brain metastases in oncogene-addicted non-small cell lung cancer patients: incidence and treatment. *Front Oncol* 2018; 8: 88.
79. Griesinger F, et al. Brain metastases in ALK-positive NSCLC - time to adjust current treatment algorithms. *Oncotarget* 2018; 9(80): 35181–35194.
80. Shreenivas A, et al. ALK fusions in the pan-cancer setting: another tumor-agnostic target? *NPJ Precis Oncol* 2023; 7(1): 101.
81. Guo F, et al. EML4-ALK induces epithelial-mesenchymal transition consistent with cancer stem cell properties in H1299 non-small cell lung cancer cells. *Biochem Biophys Res Commun* 2015; 459(3): 398–404.
82. Gadgeel S, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann Oncol* 2018; 29(11): 2214–2222.
83. Peters S, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* 2017; 377(9): 829–838.
84. Shaw AT, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *N Engl J Med* 2020; 383(21): 2018–2029.
85. Solomon BJ, et al. Lorlatinib versus crizotinib in patients with advanced ALK-positive non-small cell lung cancer: 5-year outcomes from the phase III CROWN study. *J Clin Oncol* 2024; 42(29): 3400–3409.
86. Camidge DR, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med* 2018; 379(21): 2027–2039.
87. Li Y, et al. Association of mutation profiles with metastasis in patients with non-small cell lung cancer. *Front Oncol* 2024; 14: 1451576.
88. Mendoza DP, et al. Imaging features and metastatic patterns of advanced ALK-rearranged non-small cell lung cancer. *AJR Am J Roentgenol* 2020; 214(4): 766–774.
89. Kamali C, et al. Treatment of metastatic ALK-positive non-small cell lung cancer: real-world outcomes in a single center study. *Transl Lung Cancer Res* 2024; 13(11): 2918–2933.
90. Hida T, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* 2017; 390(10089): 29–39.
91. Solomon BJ, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol* 2018; 19(12): 1654–1667.
92. Gainor JF, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. *JCO Precis Oncol* 2017; 2017: PO.17.00063.
93. Ji X, et al. Different clinical features between patients with ROS1-positive and ALK-positive advanced non-small cell lung cancer. *J Int Med Res* 2021; 49(2): 300060521993643.
94. Planchard D, et al. BRAF(V600E)-mutant metastatic NSCLC: disease overview and treatment landscape. *NPJ Precis Oncol* 2024; 8(1): 90.
95. Mazieres J, et al. MET Exon 14 skipping in NSCLC: a systematic literature review of epidemiology, clinical characteristics, and outcomes. *Clin Lung Cancer* 2023; 24(6): 483–497.
96. Oksen D, et al. Patients with advanced non-small cell lung cancer harboring MET alterations: a descriptive cohort study. *Clin Lung Cancer* 2025; 26(4): e259–e269.e5.
97. Shaw AT and Solomon BJ. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* 2015; 372(7): 683–684.

98. Drilon A, Siena S and Dziadziuszko R. Entrectinib in ROS1 fusion- positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020; 21: 261–270.

99. Dziadziuszko R, et al. Updated integrated analysis of the efficacy and safety of entrectinib in locally advanced or metastatic ROS1 fusion-positive non-small-cell lung cancer. *J Clin Oncol* 2021; 39(11): 1253–1263.

100. Drilon A, et al. Repotrectinib in ROS1 fusion-positive non-small-cell lung cancer. *N Engl J Med* 2024; 390(2): 118–131.

101. Tsakonas G, Grozman V and Ekman S. Primary CNS metastatic BRAF-mutated lung adenocarcinoma with complete intracranial response to BRAF/MEK inhibition. *Clin Lung Cancer* 2020; 21(6): e544–e546.

102. Planchard D, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol* 2017; 18(10): 1307–1316.

103. Planchard D, et al. Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: updated 5-Year survival rates and genomic analysis. *J Thorac Oncol* 2022; 17(1): 103–115.

104. Wolf J, et al. Capmatinib in MET Exon 14-mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med* 2020; 383(10): 944–957.

105. Le X, et al. Tepotinib efficacy and safety in patients with MET Exon 14 skipping NSCLC: outcomes in patient subgroups from the VISION study with relevance for clinical practice. *Clin Cancer Res* 2022; 28(6): 1117–1126.

106. Van Egeren D, et al. Genomic analysis of early-stage lung cancer reveals a role for TP53 mutations in distant metastasis. *Sci Rep* 2022; 12(1): 19055.

107. Hou H, et al. Concurrent TP53 mutations predict poor outcomes of EGFR-TKI treatments in Chinese patients with advanced NSCLC. *Cancer Manag Res* 2019; 11: 5665–5675.

108. Sun H, et al. Optimal therapy for concomitant EGFR and TP53 mutated non-small cell lung cancer: a real-world study. *BMC Cancer* 2023; 23(1): 198.

109. Liu S, et al. TP53 co-mutations in advanced EGFR-mutated non-small cell lung cancer: prognosis and therapeutic strategy for cancer therapy. *Front Oncol* 2022; 12: 860563.

110. Sitthideatphaiboon P, et al. STK11/LKB1 mutations in NSCLC are associated with KEAP1/NRF2-dependent radiotherapy resistance targetable by glutaminase inhibition. *Clin Cancer Res* 2021; 27(6): 1720–1733.

111. Boiarsky D, et al. Molecular markers of metastatic disease in KRAS-mutant lung adenocarcinoma. *Ann Oncol* 2023; 34(7): 589–604.

112. Sun L, et al. Outcomes in patients treated with frontline immune checkpoint inhibition (ICI) for advanced NSCLC with KRAS mutations and STK11/KEAP1 comutations across PD-L1 levels. *Lung Cancer* 2024; 190: 107510.

113. Ricciuti B and Garassino MC. Precision Immunotherapy for STK11/KEAP1-Mutant NSCLC. *J Thorac Oncol* 2024; 19(6): 877–882.

114. Skoulidis F, et al. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. *Cancer Discov* 2018; 8(7): 822–835.

115. Knetki-Wróblewska M, et al. Emerging insights into STK11, KEAP1 and KRAS mutations: implications for immunotherapy in patients with advanced non-small cell lung cancer. *Transl Lung Cancer Res* 2024; 13(12): 3718–3730.

116. Mitsuishi Y, Motohashi H and Yamamoto M. The Keap1-Nrf2 system in cancers: stress response and anabolic metabolism. *Front Oncol* 2012; 2: 200.

117. Galan-Cobo A, et al. LKB1 and KEAP1/NRF2 pathways cooperatively promote metabolic reprogramming with enhanced glutamine dependence in KRAS-mutant lung adenocarcinoma. *Cancer Res* 2019; 79(13): 3251–3267.

118. Zavitsanou AM, et al. KEAP1 mutation in lung adenocarcinoma promotes immune evasion and immunotherapy resistance. *Cell Rep* 2023; 42(11): 113295.

119. Scalera S, et al. KEAP1-mutant NSCLC: the catastrophic failure of a cell-protecting hub. *J Thorac Oncol* 2022; 17(6): 751–757.

120. Shiller M, et al. Clinical perspectives on the value of testing for STK11 and KEAP1 mutations in advanced NSCLC. *Front Oncol* 2024; 14: 1459737.

121. Chen S, et al. Identification of nine mutant genes and establishment of three prediction models of organ tropism metastases of non-small cell lung cancer. *Cancer Med* 2023; 12(3): 3089–3100.