Treatment of Brain Metastases in Non-Small Cell Lung Cancer

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Abstract. Non-small cell lung cancer is the most common subtype of lung cancer, and brain metastases are a frequent and devastating complication with poor prognosis. The blood-brain barrier and blood-tumor barrier limit intracranial drug delivery, resulting in suboptimal therapeutic effects. Recent advances in molecular targeted therapy and immunotherapy have markedly improved survival, particularly in patients harboring EGFR or ALK alterations, where next-generation tyrosine kinase inhibitors demonstrate strong intracranial activity. Radiotherapy remains essential for local control, while chemotherapy contributes mainly to systemic disease management. Increasingly, multidisciplinary and combination strategies are shaping the treatment paradigm. Nevertheless, challenges such as drug resistance, BBB limitations, and neurocognitive preservation persist. This review summarizes current therapeutic strategies for NSCLC with brain metastases, highlights their strengths and limitations, and discusses future directions for optimizing patient outcomes.

Keywords: Non-Small Cell Lung Cancer; Brain Metastases; Treatment; Targeted Therapy.

1. Introduction

Lung cancer is the most common malignant tumor worldwide, among which non-small cell lung cancer (NSCLC) accounts for approximately 85% [1]. The brain is one of the most common metastatic sites, affecting 10–25% of patients at diagnosis and more than half during the course of disease [2]. Brain metastases (BM) often cause intracranial hypertension and focal neurological deficits, severely compromising quality of life and survival. Without treatment, median overall survival is only about one month [3].

The blood–brain barrier (BBB), composed of endothelial cells, tight junctions, pericytes, astrocytes, and the basement membrane, maintains central nervous system homeostasis. In the setting of brain metastases, structural and functional changes give rise to the blood–tumor barrier (BTB). Although more permeable than the BBB, the BTB exhibits marked heterogeneity, leading to uneven drug distribution and limited efficacy of systemic therapies [4].

Current treatment options include surgery, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), chemotherapy, targeted therapy, and immunotherapy, most of which are applied in combination. Advances in molecular profiling and targeted agents have shifted the treatment paradigm from purely palliative local interventions toward individualized, multidisciplinary strategies integrating systemic and local therapies. Systematically summarizing the progress and shortcomings in this field is of great significance for optimizing clinical decision-making and improving patient prognosis.

2. Therapeutic Mechanisms

The blood–brain barrier plays a pivotal role in maintaining intracerebral homeostasis. Its barrier function is reflected in two main aspects: first, tight junctions between endothelial cells form a **physical barrier** that prevents macromolecules and most drugs from entering the brain; second, a system of uptake and efflux transporters regulates transmembrane exchange, allowing essential nutrients in while expelling potentially harmful substances. Following the development of brain

metastases, the BBB undergoes structural and functional changes, evolving into the blood–tumor barrier. Although the BTB exhibits higher permeability than the intact BBB, persistent efflux transporter activity results in limited intracranial drug accumulation, thereby restricting the efficacy of chemotherapy and certain targeted agents [5] (Figure 1).

Molecular targeted therapies inhibit oncogenic signaling pathways driven by alterations such as EGFR and ALK, thereby blocking tumor cell survival and proliferation at their source. For instance, EGFR mutations activate downstream PI3K/AKT/mTOR and RAS/RAF/MEK/ERK cascades, which are closely associated with tumor growth and cell cycle progression. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) suppress tumor growth by inhibiting EGFR activation and subsequent signaling (Figure 2). New-generation TKIs not only enhance systemic efficacy but also penetrate the BBB effectively, demonstrating superior activity against brain metastases.

In contrast, most conventional chemotherapeutics have poor BBB penetration due to high molecular weight and low lipophilicity, limiting their intracranial effect. Consequently, they are primarily applied for systemic control. Consequently, they are primarily applied for systemic control. Intrathecal administration can bypass the BBB entirely, enabling direct drug delivery into cerebrospinal fluid and offering therapeutic benefits for leptomeningeal metastases.

Radiotherapy remains a cornerstone of local treatment by inducing DNA damage with high-energy radiation, leading to rapid tumor shrinkage and symptom relief. Whole-brain radiotherapy (WBRT) is suited for diffuse or multiple metastases, whereas stereotactic radiosurgery (SRS) delivers precise high-dose radiation to limited lesions, striking a balance between tumor control and preservation of neurological function [6].

Immune checkpoint inhibitors (ICIs) reactivates anti-tumor immunity by blocking PD-1/PD-L1 or CTLA-4 signaling. Disruption of the BBB in metastatic lesions facilitates immune cell infiltration, thereby enabling ICIs to produce durable responses both intracranially and systemically [7].

3. Treatment

3.1 Monotherapy

3.1.1. Molecular Targeted Therapy

Molecular targeted therapy has brought major breakthroughs for patients with NSCLC brain metastases, significantly improving intracranial disease control and overall survival (OS) in populations with driver gene mutations.

3.1.1.1. EGFR-TKIs

EGFR is one of the most critical targets in NSCLC brain metastases. Approximately 50% of Asian patients and 10%-15% of Caucasian patients carry EGFR mutations [8]. EGFR-targeted agents have undergone several generations of development. First-generation TKIs (gefitinib, erlotinib and icotinib) are reversible TKIs, second-generation TKIs (afatinib and dacomitinib) are irreversible inhibitors with additional HER2 activity, third-generation osimertinib not only target sensitive mutations and the T790M resistance mutation but also demonstrate superior BBB penetration.

Studies have shown that all generations of EGFR-TKIs exhibit intracranial efficacy in patients with brain metastases. With first-generation TKIs, patients with baseline brain metastases achieve a median intracranial progression-free survival (miPFS) of approximately 9 months and a median OS of 26–29 months [9-11]. In real-world studies, the second-generation agent afatinib yielded an mPFS of 13–14 months and an OS of nearly 30 months, though it was associated with relatively high incidences of diarrhea and rash [12].Among all EGFR-TKIs, osimertinib demonstrates significantly superior intracranial disease control compared with earlier generations. Its miPFS is three times longer than that of gefitinib, with manageable toxicity, and it has become a first-line standard regimen recommended by international guidelines [13, 14].

3.1.1.2. ALK-TKIs

ALK fusions are detected in 4% of NSCLC patients [15]. First-generation crizotinib has limited central nervous system (CNS) penetration and low intracranial efficacy, second-generationTKIs such as alectinib and brigatinib offer improved CNS activity and markedly enhance intracranial disease control, third-generation lorlatinib covers a broad spectrum of resistance mutations and possesses the strongest BBB penetration and CNS activity among ALK inhibitors.

In patients with brain metastases treated with crizotinib, the mPFS is only 6–11 months, with limited intracranial activity and a high risk of resistance [16, 17]. In contrast, when alectinib is used in patients with baseline BM, the mPFS extendes to 27.7 months, significantly reducing the risk of intracranial progression [18, 19]. Brigatinib achieves a 3-year intracranial progression-free survival (iPFS) rate of 31% and a 3-year OS rate exceeding 74%, and both alectinib and brigatinib have been recommended as first-line treatment options [20]. Lorlatinib provides durable intracranial control, with a 5-year iPFS rate of 83%, making it particularly suitable for patients with brain metastases or drug resistance [17, 21].

3.1.1.3. Inhibitors for Other Mutations

Some targeted drugs for rare driver mutations also demonstrate CNS activity. For patients with ROS1 fusions (1%-2%), entrectinib and repotrectinib achieve an intracranial objective response rate (iORR) exceeding 50% [22, 23]. For BRAF V600E mutation (1%-2%), combined BRAF/MEK inhibitors such as dabrafenib plus trametinib has shown efficacy [24, 25]. Although NTRK fusions are rare, entrectinib and larotrectinib both exhibit favorable CNS activity [26]. In METex14 skipping mutations (3%-4%), capmatinib demonstrates a high iORR [27, 28]. For RET fusions (1%-2%), selpercatinib achieves an iORR of more than 80% [29]. Moreover, novel antibody-drug conjugates (ADCs), such as the HER2-targeted drug trastuzumab deruxtecan, have shown promising activity against intracranial lesions [30]. In contrast, KRAS G12C-targeted agents have limited efficacy, and immunotherapy or chemotherapy remains the mainstay of treatment for such patients.

Overall, new-generation EGFR-TKIs and ALK-TKIs provide excellent intracranial control and durable survival benefits. Landmark phase III trials, such as AENEAS and CROWN studies, have established the pivital role of osimertinib and lorlatinib in the management of driver gene-positive NSCLC brain metastases. For rare driver gene mutations, studies such as TRIDENT-1 have also shown encouraging efficacy. Therefore, molecular targeted therapy has become the cornerstone of treatment for NSCLC patients with brain metastases harboring driver gene alterations.

3.1.2. Chemotherapy

The overall efficacy of systemic chemotherapy in NSCLC brain metastases remains limited. Most chemotherapeutic agents penetrate the BBB poorly, and efflux transporters further reduce their intracranial concentrations, resulting in insufficient activity against CNS lesions. Moreover, patients with brain metastases are often excluded from large-scale clinical trials, leading to relatively scarce high-quality evidence in this population. Commonly used agents include platinum-based compounds, taxanes, and pemetrexed, which are mainly primarily administered for the control of extracranial disease.

Several studies have indicated that chemotherapy achieves only modest outcomes in patients with brain metastases. For instance, in trials such as KEYNOTE-021, 189, and 407, patients with BM had an mPFS of 4.1 months and an OS of 7.6 months [31]. Among patients with KRAS G12C mutation and CNS involvement, docetaxel resulted in an mPFS of 2.9 months [32]. Similarly, the combination of pemetrexed plus carboplatin resulted in an mPFS of approximately 4.1 months in those with BM [33]. Although systemic chemotherapy has limited impact on intracranial disease control, it remains a viable option when targeted therapies or immunotherapies are unavailable.

Intrathecal injection aims to bypass the BBB by directly delivering drugs into the cerebrospinal fluid, thereby achieving high local drug exposure for patients with leptomeningeal metastases. Intrathecal pemetrexed, for example, has shown clinical benefit in certain patients with EGFR-mutant leptomeningeal metastases, leading to symptom relief and prolonged survival [34]. However,

common adverse effects include myelosuppression and nausea, while additional risks such as infection, bleeding, and neurological injury require careful monitoring. Although intrathecal administration offers particular advantages for leptomeningeal disease, its efficacy against parenchymal brain metastases is limited, and clinical application necessitates a cautious balance between therapeutic benefit and potential risks.

3.1.3. Radiotherapy

Radiotherapy is a key local treatment option for NSCLC brain metastases, primarily including whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS).

WBRT enables simultaneous coverage of multiple lesions, with reported intracranial response rates of 70%–90%. It can prolong PFS to some extent and alleviate neurological symptoms, however, long-term use is associated with risks of cognitive decline and high recurrence rates [35, 36]. Consequently, WBRT is mainly reserved for patients with multiple or diffuse brain metastases, particularly those requiring rapid symptom relief.

SRS delivers highly precise, focused radiation to tumor sites while sparing surrounding normal brain tissue. It can be applied as a standalone treatment, in combination with WBRT, or as an adjuvant therapy following surgery, and is generally more suitable for patients with a limited number of lesions. Retrospective analyses show a mOS of approximately 8 months for patients receiving single-session SRS, while those undergoing multiple SRS sessions may achieve survival exceeding 3 years, underscoring its potential role in long-term intracranial control [37].

In summary, radiotherapy remains an indispensable component of NSCLC brain metastasis management. Evidence from studies such as HYBRID suggests that SRS provides superior intracranial disease control and better preservation of neurocognitive function, whereas WBRT remains more appropriate for patients with diffuse or extensive metastatic disease.

3.1.4. Immunotherapy

Immune checkpoint inhibitors (ICIs) restore antitumor immunity by blocking the PD-1/PD-L1 or CTLA-4 pathways, thereby reactivating exhausted T cells. Patients with NSCLC brain metastases may be more responsive to ICIs due to BBB disruption and increased immune cell infiltration. Multiple studies have confirmed that ICIs exert durable intracranial activity and provide meaningful survival benefits. In particular, PD-1/PD-L1 inhibitors have shown clear efficacy, and their combination with chemotherapy or radiotherapy can further enhance both intracranial and systemic responses.

Among PD-1 inhibitors, nivolumab was the first to be applied in patiens with brain metastases. Retrospective cohort studies have reported an mPFS of approximately 3 months and an mOS of nearly 15 months, while clinical studies demonstrated an mOS exceeding 9 months with favarable safety profiles [38, 39]. Pembrolizumab, in phase II studies, achieved an intracranial PFS of about 2 months, however, real-world data suggest that when administered as first-line therapy, PFS can be extended to 10 months , indicating greater benefits with earlier use [40, 41].

The PD-L1 inhibitor atezolizumab, when conbined with chemotherapy and bevacizumab, achieved an OS of 11 months in patients with baseline brain metastases. As monotherapy, atezolizumab also conferred survival benefits in this subgroup, with good overall tolerability [42, 43].

CTLA-4 inhibitors have limited efficacy as monotherapy but demonstrate synergistic effect when combined with PD-1 inhibitors. For instance, the combination of nivolumab and ipilimumab resulted in an mOS of 17 months in patients with brain metastases, outperforming single-agent regimens [44].

In conclusion, representative studies such as the KEYNOTE series and CheckMate 227 highlight that immunotherapy can induce durable intracranial and extracranial responses in selected patients with NSCLC brain metastases, offering the potential for long-term survival.

3.2 Combined Therapy

Combined therapy plays an important role in the management of NSCLC brain metastases. Monotherapy has clear limitations: although targeted agents are effective, resistance inevitably

depelops; chemotherapy and immunotherapy are hindered by BBB penetration; and radiotherapy is associated with considerable adverse effects. By integrating different treatment modalities, combination strategies can improve intracranial control rates, prolong survival, and enhance overall prognosis.

Combining TKIs directed against the same molecular target results in overlapping mechanisms, which increase toxicity without conferring meaningful benefits. Therefore, current research emphasizes combinations targeting distinct pathways. For example, MET amplification is a key mechanism of resistance to EGFR-TKIs. The combination of tepotinib and osimertinib has been shown to improve the iORR in patients with baseline brain metastases [45]. Retrospective studies of EGFR-TKI combined with VEGFR-TKI have reported an mPFS of 18.8 months, while the FL-ALTER trial also demonstrated a significant PFS benefit [46, 47]. Although this approach shows promise for intracranial control, its safety profile and long-term efficacy remain to be further validated.

The combination of EGFR-TKIs and chemotherapy has also demonstrated clinical benenfit, In patients with brain metastases, gefitinib plus chemotherapy prolonged mPFS to 16.3 months and the mOS to 35.0 months [10]. Similarly, osimertinib combined with chemotherapy yielded an mPFS of 24.9 months, which was significantly superior to osimertinib monotherapy [14]. However, the incidence of grade ≥3 adverse events increased to 64% in the combination group, presominantly hematologic and cardiac toxicities. Such regimens may be more appropriate for patients with a high tumor burden or those who have not received prior local therapy.

Combining TKIs with radiotherapy can further enhance local control. A meta-analysis revealed that third-generation TKIs plus radiotherapy significantly improved intracranial disease control and OS [48]. The URBO-NSCLC study suggested that combining TKI with SRS increased local control rate in patients with large lesions [49]. Nevertheless, study outcomes remain inconsistent, and treatment-related toxicity is increased, underscoring the importance of carful patient selection.

In patients with EGFR mutations, the efficacy of PD-1/PD-L1 inhibitors is limited. The combination of TKIs with ICIs has not demonstrate consistent clinical benefit, with low ORR and high rates of severe adverse events. As such, this approach is not recommended for routine use in patients with NSCLC-BM [50].

Anti-vascular endothelial growth factor (VEGF) drugs may normalized tumor vasculated and improve drug delivery. The combination of erlotinib and bevacizumab was shown to extend both mPFS and mOS. Similarly, osimertinib plus bevacizumab as first-line treatment achieved a CNS mPFS of 26.7 months, while combinations of ALK inhibitor with bevacizumab also demonstrated improve disease control [11, 51, 52]. However, attention must be paid to the risks of bleeding and vascular-related toxicities.

4. Discussion

Lung cancer remains one of the most common malignancies worldwide. With the rising incidence of brain metastases, treatment strategies have continued to evolve. Third-generation EGFR-TKIs such as osimertinib and ALK-TKIs such as lorlatinib have significantly improved intracranial disease control rates and overall survival due to their strong BBB penetration and high intracranial activity, but acquired drug resistance remains a major challenge. Fourth-generation EGFR-TKIs, such as BLU-945, have shown preliminary anti-tumor activity in early clinical trials and may be combined with osimertinib, yet their safety and intracranial efficacy still require further validation [53].

Radiotherapy remians indispensable for local control, sympton relief, and prevention of new lesions. SRS, with its high precision and ability to spare normal brain tissue, has become the standard for patients with oligometastases, while WBRT is reversed for diffuse or multiple brain metastases, albeit at the cost of a high risk of cognitive decline. Memory-preserving WBRT can mitigate neurotoxicity, and hypofractionated SRS may be applied to larger lesions or those located in critical brain regions.

For patients without actionable driver gene mutations but with high PD-L1 expression, ICI, either alone or combined with chemotherapy or CTLA-4 inhibitors, can provide durable systemic and intracranial responses. However, patients with EGFR or ALK alterations derive limited benefit from ICIs, and evidence for combining ICIs with TKIs is scarce and associated with significant toxicity, making this approach not currently recommended.

Systemic chemotherapy is limited by poor intracranial response rates due to the BBB. Pemetrexed and platinum-based regimens can be combined with TKIs or ICIs, but systemic toxicity requires close monitoring. Intrathecal therapy is particularly important for leptomeningeal metastases, yet its efficacy against parenchymal metastases is modest, and it carries risks of procedural complications and neurotoxicity.

Monotherapy is often insufficient for durable disease control, highlighting the importance of combinaton strategies. Combining targeted therapy with chemotherapy can prolong PFS and OS; pairing targeted therapy and anti-angiogenic agents may further improve outcomes, though at the cost of increased toxicity. The benefit of combining targeted therapy with radiotherapy depends on lesion size and treatment timing, requiring individualized planning. By contrast, combining targeted therapy with immunotherapy remains poorly supported by current evidence and is accociated with high toxicity, and thus s not recommended in routine practice. Key challenges of combination therapy include accurate patient selection, optimizion of drug choice, and sequencing, as well as management of cumulative toxicity and financial burden. SRS offers both efficacy and cost-effectiveness in patients with oligometastases, whereas hippocampal-avoidant WBRT (HA-WBRT) can preserve cognitive function but increases economic burden. Bevacizumab may relieve radiation necrosis, yet its cost alsolimits widespread use [54-56]. Therefore, in clinical decision-making, efficacy, safety, and cost-effectiveness must be carefully balanced to formulate individualized treatment strategies tailored to survival expectations and resource accessibility.

Future research should focus on overcoming drug resistance and BBB-related barriers, advancing next-generation targeted therapies, exploring rational combination regiments to bypass resistance, and developing innovative drug delivery systems to enhance intracranial efficacy. Dynamic monitoring of circulating tumor DNA (ctDNA) in plasma or cerebrospinal fluid may also enable more precise and individualized treatment. Although significant progress has been made in the management of NSCLC-BM, challenges remain, including resistance mechanisms, optimization of combination approaches, preservation of neurocognitive function, and treatment of patients with complex resistance patterns. Moving forward, individualized strategies that integrate novel drug development, advanced diagnostic and therapeutic technologies, and multidisciplinary collaboration will be critical to improving both survival and quality of life in this population.

5. Conclusion

This study systematically reviews the comprehensive treatment strategies for non-small cell lung cancer with brain metastases. With the growing understanding of molecular driver genes and the advancement of therapeutic approaches, the management of NSCLC-BM has evolved from palliative local therapy to a multidisciplinary model integrating local and systemic treatments. Molecular targeted agents, particularly third-generation EGFR-TKIs and ALK-TKIs, have become preferred first-line options owing to their superior blood–brain barrier penetration and robust intracranial efficacy. Radiotherapy remains indispensable for local control and symptom relief, while immune checkpoint inhibitors provide durable benefit in patients with high PD-L1 expression and no driver mutations. Chemotherapy and intrathecal therapy also retain value, particularly for systemic disease control and leptomeningeal metastases.

Nevertheless, significant challenges persist, including blood–brain barrier limitations, acquired resistance, optimization of combination strategies, scarcity of dedicated evidence-based data, and risks of long-term neurotoxicity. Future research should prioritize strategies to overcome BBB-related barriers and resistance mechanisms, refine individualized combination regimens, generate high-

quality data specific to brain metastasis populations, and balance efficacy with safety. These efforts will be critical to further improving prognosis and quality of life for patients with NSCLC-BM.

Declarations

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Author Contributions

Yuzhu Chen: Data curation; Resources; Writing, review & editing.
Ziyu: Writing – review & editing.

Competing Interests

The authors declare that there is no conflict of interest.

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Availability of Data and Materials

Table 1. Clinical Trials of Targeted Therapy for Brain Metastases in Non-Small Cell Lung Cancer

References	Registration number	Study name	Intervetion group	Control group	Study design	N	Intracranial/ CNS efficacy	Systemic efficacy
[9]	NCT03849768	AENEAS	Aumolertinib	Gefitinib	phase III	51 (CG:55)	mCNS PFS:29.0m(CG:8.3m) CNS ORR:62.7%(CG:49.1%) CNS DCR:94.1%(CG:96.4%) mCNS DoR:27.7m(CG:6.9m)	6-month PFS:86.0%(CG:71.8%) 12-month PFS:72.5%(CG:30.4%) 18-month PFS:59.9%(CG:8.9%) 24-month PFS:56.8%(CG:8.9%)
[10]	NCT01951469	GAP BRAIN	Gefitinib plus chemotherapy	Gefitinib	phase III	80 (CG:81)	miPFS:15.6m(CG:9.1m) iORR:85.0%(CG:63.0%) iDCR:95.0%(CG:93.8%)	mPFS:16.3m(CG:9.3m) mOS:35.0m(CG:28.9m) ORR:76.3%(CG:58.0%) DCR:97.5%(CG:95.1%)
[47]	NCT04028778	FL-ALTER	Gefitinib plus anlotinib	Gefitinib	phase III	49 (CG:50)	-	mPFS:13.8m(CG:8.3m)
[11]	NCT02759614	ARTEMIS-CTONG1509	Erlotinib plus bevacizumab	Erlotinib	phase III	44 (CG:47)	-	mPFS:17.9m(CG:11.1m) mOS:31.6m(CG:26.8m)
[13, 14]	NCT04035486	FLAURA2	Osimertinib plus chemotherapy	Osimertinib	phase III	118 (CG:104) 116 (CG:110)	mCNS PFS:30.2m(CG:27.6m) CNS ORR:73%(CG:69%) CNS DCR:91%(CG:93%) mCNS DoR:NR(CG:26.2m)	mPFS:24.9m(CG:13.8m)
[16]	NCT04632758	INSPIRE	Iruplinalkib	Crizotinib	phase III	37 (CG:44)	iORR:90.9%(CG:60.0%) miDoR:20.1m(CG:9.3m)	mPFS:22m(CG:11m) 24-month PFS:49.0%(CG:4.4%) 24-month OS:85.6%(CG:84.0%)
[17, 21]	NCT03052608	CROWN	Lorlatinib	Crizotinib	phase III	38 (CG:40)	5-year iPFS:83%(CG:NE) iORR:92%(CG:33%)	mPFS:NR(CG:6.0m) 12-month PFS:78%(CG:22%) 5-year PFS:53%(CG:NE)
[18, 19]	NCT02075840	ALEX	Alectinib	Crizotinib	phase III	64 (CG:58)	CNS ORR:81.0%(CG:50.0%)	mPFS:27.7m(CG:7.4m)
[20]	NCT02737501	ALTA-1L	Brigatinib	Crizotinib	phase III	47 (CG:49)	3-year miPFS:31%(CG:9%) 4-year miPFS:22%(CG:NE) miDoR:27.9m(CG:9.2m)	3-year OS:74%(CG:55%) 4-year OS:71%(CG:44%)
[22]	NCT02097810 NCT02568267 EudraCT, 2012-000148-88	STARTRK-1 STARTRK-2 ALKA-372-001	Entrectinib	-	phase I phase II phase I	23	miPFS:7.7m iORR:55% miDoR:12.9m	mPFS:13.6m

Continue from Table 1								
[23]	NCT03093116	TRIDENT-1	Repotrectinib (ROS1 TKI-naïve)	Repotrectinib (ROS1-TKI pretreated and chemotherapy-naïve)	phase II	17 (CG:26)	iORR:89%(CG:38%)	-
[57]	NCT02576431 NCT02122913	-	Larotrectinib	-	phase II phase I	10	CNS ORR:63%	-
[58]	NCT02864992	VISION	Tepotinib	-	phase II	23	-	mPFS:9.5m
[29]	NCT04194944	-	Selpercatinib	Pemetrexed plus platinum therapy	phase III	17 (CG:12)	iORR:82%(CG:58%)	-
[30]	NCT03505710	DESTINY-Lung01	Trastuzumab deruxtecan	-	phase II	33	-	mPFS:7.1m mOS:13.8m
CNS, central nervous system; PFS, progression free survival; ORR, objective response rate; DCR, disease control rate; DoR, duration of response; OS, overall survival								

Table 2. Clinical Trials of Chemotherapy for Brain Metastases in Non-Small Cell Lung Cancer

References	Registration number	Study name	Intervetion group	Control group	Study design	N	Systemic efficacy
[31]	NCT02039674 NCT02578680 NCT02775435	KEYNOTE-021 KEYNOTE-189 KEYNOTE-407	Pembrolizumab Plus Platinum-Based Chemotherapy	Platinum-Based Chemotherapy	phase III	105 (CG:66)	mPFS:6.9m(CG:4.1m) mOS:18.8m(CG:7.6m)
[33]	NCT05184712	HARMONi-A	Ivonescimab plus pemetrexed and carboplatin	Pemetrexed and carboplatin	phase III	35 (CG:37)	mPFS:5.75m(CG:4.14m)
[34]	ChiCTR1800016615	-	Intrathecal Pemetrexed	-	phase II	132	mOS:12.0m
PFS, progression free survival; OS, overall survival							

Table 3. Clinical Trials of Radiotherapy for Brain Metastases in Non-Small Cell Lung Cancer

References	Registration number	Study name	Intervention group	Control group	Study design	N	Intracranial efficacy	Systemic efficacy
[36]	NCT02882984	HYBRID	WBRT	SRS	phase III	41 (CG:44)	month iPFS:91.7%(CG:91.1%) miPFS:21.4m(CG:22.3m)	2-year OS:75.6%(CG:90.9%) 3-year OS:36.6%(CG:52.3%)
[59]	NCT01887795	-	WBRT plus erlotinib	WBRT	phase III	109 (CG:115)	miPFS:11.2m(CG:9.1m)	mPFS:5.3m(CG:4.0m)
[60]	NCT03614065	-	Rh-endostatin plus WBRT	WBRT	phase III	19 (CG:24)	miPFS:11.6m(CG:4.8m)	mPFS:8.1m(CG:4.9m) mOS:14.2m(CG:6.4m)
WBRT, whole brain radiation therapy; SRS, Stereotactic Radiosurgery; PFS, progression free survival; OS, overall survival								

Table 4. Clinical Trials of Immunotherapy for Brain Metastases in Non-Small Cell Lung Cancer

References	Registration number	Study name	Intervetion group	Control group	Study design	N	Intracranial/ CNS efficacy	Systemic efficacy
[40]	NCT02085070	-	Pembrolizumab	-	phase II	42	Medium CNS PFS:2.3m	mPFS:1.9m 1-year OS:40% 2-year OS:34% mOS:9.9m
[44]	NCT02477826	CheckMate 227	Nivolumab plus ipilimumab	Platinum-doublet chemotherapy	phase III	68 (CG:66)	5-year iPFS:16%(CG:6%)	5-year PFS:12%(CG:0%) mOS:17.4m(CG:13.9m) 5-year OS:23%(CG:13%)
CNS, central nervous system; PFS, progression free survival; OS, overall survival								

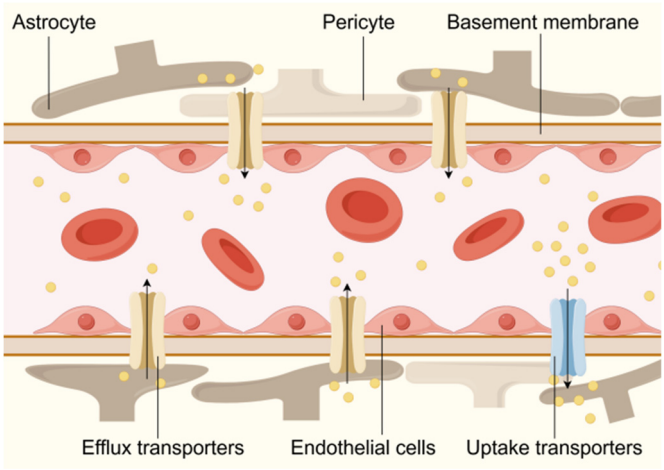

Figure 1. | Schematic representation of the structure and function of the blood–brain barrier (BBB). The BBB is primarily composed of brain microvascular endothelial cells, pericytes, astrocytes, and the basement membrane. Tight junctions between endothelial cells establish a physical barrier, while uptake and efflux transporters regulate transmembrane substance exchange. This highly selective system restricts the entry of harmful compounds while permitting essential nutrients to maintain cerebral homeostasis. During tumorigenesis and the development of brain metastases, structural and functional alterations in the BBB lead to the formation of the blood–tumor barrier (BTB), which exhibits distinct permeability and transport properties compared with the normal BBB.

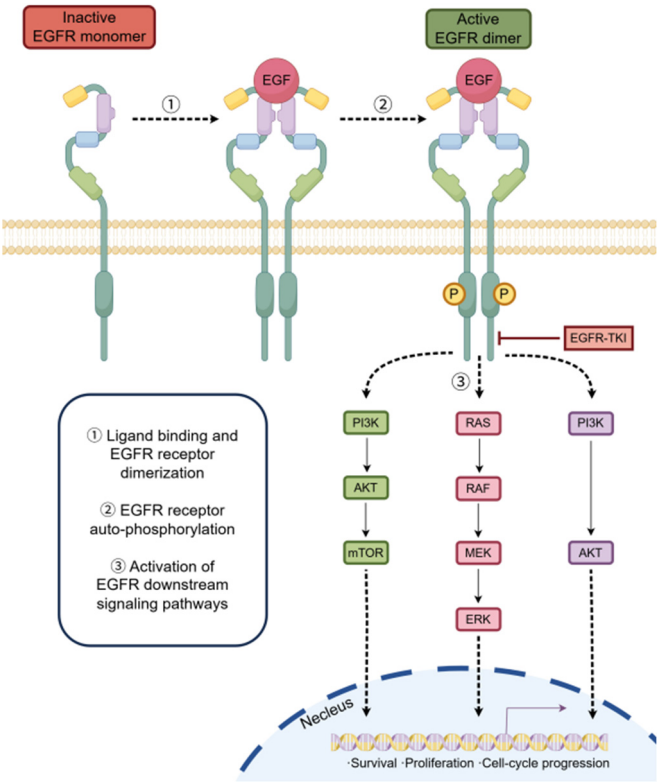

Figure 2. | Epidermal growth factor receptor (EGFR) signaling pathway and the mechanism of action of tyrosine kinase inhibitors (EGFR-TKIs). Ligand binding induces EGFR dimerization and autophosphorylation, which subsequently activate multiple downstream pathways, including PI3K/AKT/mTOR and RAS/RAF/MEK/ERK. These cascades regulate cell survival, proliferation, and cell-cycle progression. EGFR-TKIs exert antitumor effects by blocking EGFR activation and downstream signal transduction, thereby suppressing tumor growth and progression.