Review Article

Targeting lung cancer brain metastases: a narrative review of emerging insights for anaplastic lymphoma kinase (*ALK*)-positive disease

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Background and Objective: Lung cancer is commonly associated with brain metastasis formation, and certain subtypes, such as anaplastic lymphoma kinase (*ALK*) rearranged disease, have an especially high propensity for early and frequent central nervous system (CNS) involvement for which treatment can be challenging. Historical management has centered on surgery and radiation therapy (RT), which persist as mainstays of treatment for large, symptomatic lesions and widespread CNS disease. To date, sustained disease control remains elusive, and the role for effective systemic adjunctive therapies is clear. Here we discuss the epidemiology, genomics, pathophysiology, identification, and management of lung cancer brain metastases with a particular emphasis on systemic treatment of *ALK*-positive disease according to the best available evidence.

Methods: Review of PubMed and Google Scholar databases as well as ClinicalTrials.gov provided background and seminal trials for the local and systemic management of *ALK* rearranged lung cancer brain metastases.

Key Content and Findings: The development of effective, CNS-penetrant systemic agents—including alectinib, brigatinib, ceritinib, and lorlatinib—has dramatically changed the management and prevention of *ALK* rearranged brain metastases. Most notably, there is a burgeoning role for upfront systemic therapy for both symptomatic and incidentally discovered lesions.

Conclusions: Novel targeted therapies offer patients a pathway to delay, obviate, or supplement traditional local therapies while minimizing neurologic sequelae of treatment and may reduce the risk of brain metastasis formation. However, the selection of patients to whom local and targeted treatments is offered is not trivial, and the risks and benefits of both must be weighed carefully. More work is needed to establish treatment regimens that yield durable intra- and extracranial disease control.

Keywords: Brain metastases; *ALK* rearrangement; targeted therapy

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Introduction

Background

Despite advances in systemic and molecularly targeted therapies, the development of brain metastases is common and remains associated with a poor, often terminal, prognosis. The annual incidence of brain metastases is estimated at 8 to 15 per 100,000 in the total population and 8–10% in individuals with cancer (1). These figures likely underestimate the true incidence due to increased cancer survival, the development of asymptomatic lesions, and fewer autopsies performed (2,3). Lung cancers comprise upwards of 60% of all brain metastases, and the incidence proportion of brain metastasis formation in patients with lung cancer ranges from 16% to 20% in select populations (1,2,4,5). Among lung cancer subtypes, non-small cell lung cancer (NSCLC) is disproportionately associated with brain metastasis formation, reflective of its prevalence relative to small cell lung cancer (6,7). Approximately 5% of NSCLC is associated with *ALK* rearrangement, whereas Kirsten rat sarcoma virus (*KRAS*) mutation is seen in 20–33%, epidermal growth factor receptor (*EGFR*)-positive disease in 10–15%, and both c-ros oncogene (*ROS1*) and *RET* rearrangement in ~2% of cases (8-12). Among these subtypes, patients with *EGFR* and *ALK* alterations appear to have a particularly high risk for brain metastasis formation with a majority of patients developing brain metastases within 5 years of diagnosis (13-15). This high central nervous system (CNS) tropism for *ALK*- and *EGFR*-positive disease therefore has significant implications for a patient's clinical course. Synchronous diagnosis or CNS progression within months of diagnosis is seen in 25–40% of patients with *ALK*-positive lung cancer, compared to a 20% synchronous diagnosis rate across all subtypes of NSCLC (5,13,16-23). Accordingly, early detection and management of brain metastases in patients with *ALK*-positive NSCLC represents an important opportunity for medical, neurologic, and thoracic oncologists.

Brain metastases arise through complex mechanisms that are incompletely understood. However, a prevailing hypothesis, named the metastatic cascade, suggests that neoplasms must follow a sequence of interrelated steps to deposit in distant sites such as the brain (24,25). The series of events includes: (I) proliferation and invasion of surrounding tissues including blood vessels, with lung cancers likely migrating as cohesive groups of cells (26); (II) survival within the blood stream through inactivation of natural killer immune cells in part due to interactions with platelets (27-29); (III) adherence to the endothelium facilitated by selectins on tumor-bound platelets or neutrophil-associated extracellular traps (30,31); (IV) increasing vascular permeability by binding of ATP, released by platelets, to endothelial $P2Y_2$ receptors (32); and (V) eventual transepithelial migration through complex microenvironmental signaling pathways that are again mediated through cancer cell-platelet interactions (33,34). *ALK*-positive disease likely exploits circular RNAs, specifically F-circEA-2a, produced by the *EML4-ALK* fusion gene to facilitate migration of and invasion by cancer cells (35). Expression of *EML4-ALK* also increases epithelial mesenchymal transition-inducing transcription factors, likely via Crk-like protein and MAP kinase activation, that may promote migration (36). Additionally, work by Sevenich *et al.* has demonstrated that cathepsin S, expressed by tumor cells and leading to enzymatic breakdown of the junctional adhesion molecule JAM-B, likely mediates neoplastic migration across the highly selective blood brain barrier (BBB) (37). Alternatively, access to adjacent brain parenchyma can occur when metastatic depositions within blood vessel lumina directly rupture the epithelium, including at the BBB, circumventing traditional transepithelial migration (38). Emerging data also support the role of long noncoding RNAs in essentially all of these processes, including the initiation, migration, and brain colonization of metastatic cells through interactions with tumor and microenvironmental RNA and DNA (39).

Many metastatic colonies enter a potentially prolonged dormant, stem cell-like state to avoid clearance from the new site of disease (40). This period of quiescence may represent a larger cellular program meant to facilitate metastasis or could arise from numerous factors including a hostile foreign microenvironment containing plasmin released from reactive astrocytes; local immunosuppression; and limited angiogenesis (41). Therefore, metastatic cells that survive appear to be particularly well adapted to evade immune clearance and to respond to subtle survival signals to avoid apoptosis, with evidence of contribution from serpins (41-44). The pathway allowing for emergence of dormant cancer cells into a replicative state may occur through a paradoxical, prometastatic role of astrocytes as a consequence of *de novo* cancer cell-astrocyte gap junctions (45). Through cytosolic double-stranded DNA and cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) signaling, metastatic cells precipitate the release of inflammatory cytokines and produce activation of the cyclic GMP-AMP synthase

Table 1 Methodology applied for the development of this narrative review

Items	Specification
Date of initial search	July 15, 2022
Databases and other sources searched	PubMed, Google Scholar, National Comprehensive Cancer Network, and ClinicalTrials.gov
Search terms used	Anaplastic lymphoma kinase, ALK, non-small cell lung cancer, NSCLC, lorlatinib, alectinib, brigatinib, certinib, brain metastases, radiotherapy, surgery, local therapy
Timeframe	Studies published from January 1, 2015 onward
Inclusion and exclusion criteria	Phase 1, 2, and 3 studies were considered. All literature was English language. Non-English language articles were excluded
Selection process	TAN performed the initial search with consensus reached between authors on relevant sources to include

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.

(cGAS)-stimulator of interferon genes (STING) pathway that supports cancer cell growth and facilitates colony survival (45). Successful metastatic colonies that emerge from the dormant state then proliferate. Neovascularization plays a key role in the establishment and survival of a metastatic colony, which is in part regulated by vascular endothelial growth factor (VEGF); suppression of VEGF has been shown to reduce proliferation of brain metastases (46). Combined with historically poor intracranial drug concentrations, selection for these resilient metastatic colonies reduces the efficacy of traditional treatment modalities and highlights the need for highly efficacious, brain-penetrant targeted agents.

Rationale and knowledge gap

The management of brain metastases remains challenging with poor clinical outcomes. Fortunately, molecularly targeted therapies have demonstrated improved efficacy likely owing to increased CNS penetrance, which in conjunction with local therapies of radiotherapy and surgery will continue to improve prognoses. Given the rate of development of agents and studies with heterogeneous patient populations, it can be difficult for a practicing oncologist to remain up to date on the best available evidence.

Objective

This review describes general principles of management for lung cancer brain metastases—including discussions of the role for surgery and radiation therapy (RT)—and the promising, emerging systemic treatments for *ALK*-positive NSCLC that may complement or delay traditional management strategies. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-638/rc).

Methods

Table 1 below describes the selection process for relevant references.

Management of *ALK*-positive brain metastases

Several modalities are considered for the treatment of brain metastases, with evolving knowledge of tumor molecular characteristics and genetics yielding an ever-increasing number of targeted therapies. Below we describe key management considerations, including the role of local therapies such as surgery and radiation as well as emerging data for the role of precision treatments in the management of *ALK* rearranged NSCLC.

General principles

Following lesion biopsy or resection, the diagnosis of *ALK* rearranged NSCLC requires molecular testing that may be performed through next-generation sequencing, fluorescence *in situ* hybridization, reverse transcription polymerase chain reaction, or immunohistochemistry. As this integrated diagnosis may take several weeks to return, it is useful to consider the clinical and histologic features that may suggest *ALK*-positive NSCLC. These characteristics include a younger age at diagnosis (median 6th decade of

life for *ALK*-positive disease *vs.* 8th decade among all lung cancer types); never or minimal (<10 pack-years) tobacco use history; and adenocarcinoma histology with abundant signet ring cells (47-49). Molecular characterization should not delay the initiation of indicated and urgent local therapies, such as neurosurgical resection of a symptomatic intracranial mass, though systemic therapies will ultimately require these data. In the case of delayed diagnostic information, the initiation of traditional chemotherapy is reasonable, which can be transitioned to targeted therapy when *ALK* rearrangement has been confirmed.

As part of the pre-treatment evaluation for individuals with stage II to IV NSCLC, the National Comprehensive Cancer Network (NCCN) guidelines recommend brain magnetic resonance imaging (MRI) without and with gadolinium contrast to complete systemic evaluation given the high likelihood of brain metastasis (50). This is further supported in *ALK*-positive NSCLC by the risk of synchronous or early CNS progression. Accordingly, the identification of brain metastases can occur during screening as well as on diagnostic imaging performed for incipient symptomatology. Symptoms that may implicate an intracranial lesion include neurocognitive or behavioral changes; new and often progressive weakness, numbness, or language difficulties; alterations in level of consciousness; overt seizure-like activity; and headaches of changing frequency or character.

When considering treatment for a patient with newly identified or an increasing burden of intracranial metastatic disease, a multifaceted evaluation is undertaken. This assessment includes determination of the current symptom burden, the patient's pre-morbid and current performance status, the number and location(s) of the intracranial lesion(s), and treatment received to date.

Two main scoring systems are used for performance status evaluation: the Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group (ECOG) scales. These semi-quantitative scores provide a high-level description of the patient's day-to-day function, which in concert with objective data such as age, systemic disease control, and diagnostic results including imaging and tumor genetics help clinicians formulate rough estimates of prognosis. Another tool used for prognostication is the graded prognostic assessment (GPA), which provides disease-specific median survival estimates based a cumulative score between 0 and 4 (51). The GPA for NSCLC incorporates KPS, age, number of brain metastases, presence of extracranial metastases, and *EGFR* and *ALK* aberrations in its calculation with a weighted contribution of 0-, 0.5-, or 1-point each; lower scores are associated with shorter median survival.

Where available, multidisciplinary team involvement is preferred, with input from medical and/or thoracic oncology, neurosurgery, radiation oncology, and neuro-oncology. Larger academic institutions may have tumor board meetings where a collaborative treatment plan is recommended and relevant clinical trials are considered.

Local therapies

Despite an enlarging armamentarium of molecularly targeted therapies, upfront treatment with surgical resection of and/or RT for presumed brain metastases is often considered in patients with a favorable performance status and prognosis.

The role for neurosurgery for diagnostic and therapeutic benefit is contingent on patient demographics including age, sex, and history of known primary malignancy; selection of patients to whom surgery is offered is not trivial. To help with this critical decision point, a collaborative effort between the American Society of Clinical Oncology (ASCO), Society for Neuro-Oncology (SNO), and American Society for Radiation Oncology (ASTRO) recently produced guidelines regarding patient selection and appropriateness for treatment (52). In their systematic review and expert panel, they proposed surgery be offered to patients with:

- Suspected brain metastases lacking a diagnosis of primary malignancy for whom surgery would elucidate the underlying process.
- Large tumors with mass effect.
- Multiple brain metastases whose residual intracranial and systemic disease is controllable with other measures.

The greatest benefit for surgery is likely in patients with minimal extracranial disease burden, with scant evidence for survival benefit in patients with widely metastatic disease (52).

Even in patients with an established diagnosis of NSCLC and imaging felt highly suspicious for metastasis, further tissue sampling may be appropriate for diagnostic purposes. Somatic driver mutations—such as *ALK*, *EGFR*, and *KRAS*—are, in principle, conserved in all sites of malignancy. However, pioneering work by Brastianos *et al.* demonstrated that additional, divergent genetic alterations are seen in sites of metastasis, seemingly conserved between

metastatic lesions but clonally unique from the primary tumor, which may implicate selection for or facilitation of distant spread (53). This concept was corroborated in work by Shih *et al.*, which identified candidate drivers of lung adenocarcinoma brain metastasis—specifically amplifications of *MYC*, *MMP13*, and *YAP1*—that were higher in frequency compared to control genomic data of sites of primary disease gathered from The Cancer Genome Atlas (54). By evaluating multiple tumor pairs, their team was able to assess temporal trends and determined that these amplifications tended to occur after divergence of metastatic and primary lineages, likely representing a selection of a pro-metastatic subpopulation (54). However, these alterations may be sufficient but not necessary to produce metastases, with pathways such as phenotypic transitions and epigenetics invoked as additional contributory mechanisms (55-58). Notably, these subclones may be resistant to targeted agents or reveal novel therapeutic targets. As such, early involvement by neurology or neuro-oncology, where available, and neurosurgery is strongly advised.

Following surgery, it is common to pursue RT. Although limited randomized data exist regarding the combination of surgery and RT compared to radiation alone, in patients with a single brain metastasis, results have generally favored a two-modality approach when technically feasible (59-61). For patients with one or two resected brain metastases, post-operative radiation to the resection cavity reduces the otherwise high rate of local recurrence, which is estimated to be 50–60% in one year in patients not receiving radiation (60-64). In patients with a KPS ≥70, Vogelbaum *et al.* do not specify a preferred radiation modality and consider stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), or a combination as equivalent at this time (52).

In patients for whom surgery is not reasonable due to technical limitations, extent of disease, or discordance with patient goals of care, RT or radiosurgery is considered. As with surgery, the performance status of a patient is highly relevant when balancing the risks and benefits of RT. Notably, few randomized trials of radiation treatment have enrolled patients with lower functional status, i.e., KPS <70 or ECOG >2. However, the 2016 QUARTZ trial—in which included patients were deemed unsuitable for SRS or surgery—did include a large subset (~38%) of patients with KPS <70, and on subgroup analysis demonstrated no difference in overall survival with the inclusion of WBRT as compared to optimal supportive care alone in this population (65). However, the median time from diagnosis to randomization was 25 days, and treatment was delayed (65). Despite these limitations, these results have helped inform the recommendations from ASCO-SNO-ASTRO that propose not offering radiation to patients with brain metastases as well as either (I) KPS ≤50 or (II) KPS <70 with no systemic treatment options (52). Similar to patients undergoing resection for oligometastatic disease, there is no preferred radiation modality for individuals with greater than four unresected brain metastases (52).

In individuals with sufficient performance status and oligometastatic disease—defined as one to four unresected brain metastases—SRS is preferred over WBRT or WBRT with SRS (52). This recommendation reflects the understanding that SRS is associated with fewer long-term neurocognitive effects, though there is concern that SRS may yield less durable intracranial disease control. To mitigate the risk for cognitive decline with WBRT, memantine and hippocampal avoidance have been recommended (52). These measures have demonstrated preservation of a subset of cognitive outcomes for patients without hippocampal metastases and with an expected survival of at least four months (66).

Systemic therapy

There is emerging evidence that systemic therapy may be preferred in the upfront setting over the localized therapies described above, particularly in patients with asymptomatic intracranial disease (50,52). Even in situations when local therapy would be considered standard, such as in patients with symptomatic or large brain metastases, retrospective studies suggest that tyrosine kinase inhibitors (TKIs) demonstrate significant intracranial activity with associated clinical improvement (67,68). Thus, effective systemic therapies may delay or eliminate local strategies with associated neurologic morbidity, such as WBRT. This discussion will focus on systemic management of *ALK* rearranged NSCLC according to the best available evidence and consensus recommendations from ASCO-SNO-ASTRO and the NCCN.

For patients with *ALK* rearranged NSCLC with asymptomatic brain metastases, such as those identified on screening imaging or incidentally found in work-up of another process, consensus recommendations from ASCO-SNO-ASTRO propose upfront treatment with alectinib, brigatinib, or ceritinib (52). These TKIs can be continued until evidence of intracranial progression is noted, and

in some cases it may be reasonable to continue an *ALK* inhibitor following CNS progression if deemed manageable with local therapies such as small and/or oligometastatic progression. However, it is important to note that ceritinib has lower efficacy and is generally not a preferred *ALK* TKI; lorlatinib likely represents a better upfront treatment. The data supporting these recommendations follow.

A 2019 meta-analysis pooled the results of 20 studies of treatment with various *ALK* inhibitors; 15 were single arm and five were randomized (69). Agents under investigation included crizotinib, ceritinib, entrectinib, alectinib, brigatinib, ensartinib, and lorlatinib with various comparator agents or in single arm designs. The intracranial overall response rate (iORR) for all agents was 48% with a pooled complete remission rate of 21% (69). Relevant to the current ASCO-SNO-ASTRO guidelines, the iORR for alectinib was 79%, brigatinib was 48%, and ceritinib was 45%; notably the iORR for crizotinib is 18–33% (69,70).

In CNS-specific subgroup analyses of the ALEXA and ALESIA trials, patients treated with alectinib, a second generation *ALK*-inhibitor, had improved intracranial response compared to patients who received crizotinib, a first-in-class *ALK*-inhibitor that also targets ROS1 and MET. The ALEX study compared alectinib 600 mg twice-daily (b.i.d.) to crizotinib 250 mg b.i.d. in patients without prior systemic treatment. Among the 122 patients with intracranial lesions at baseline, 59% (38/64) on alectinib experienced CNS response *vs.* 26% (15/58) on crizotinib; median duration of intracranial response was also notably longer on alectinib with 3.7 months on crizotinib against no end point reached with alectinib (23). For patients who previously received intracranial radiotherapy and with measurable CNS metastases at baseline, iORRs were 85.7% (6/7) on alectinib and 71.4% (5/7) on crizotinib (71). Furthermore, patients with measurable and non-measurable CNS disease at baseline who had not received prior RT also demonstrated much higher iORR at 74.4% (29/39) on alectinib compared to crizotinib (24.3%, 9/37) (71). For the Japanese cohort of the J-ALEX study, which compared alectinib 300 mg b.i.d. to crizotinib 250 mg b.i.d., a longer time to CNS progression was noted in patients receiving alecitinib as compared to crizotinib [hazard ratio (HR) =0.22, P value <0.0001] (72,73). The CNS outcomes analyses demonstrated a significantly lower rate of intracranial progression in patients without baseline brain metastases (HR for alectinib of 0.19, P value <0.05) as well as lower one year cumulative incidence rates of CNS progression on alectinib (5.9%) *vs.* crizotinib (16.8%), acknowledging a higher baseline rate of CNS disease for patients in the crizotinib arm (n=29 *vs.* 14) (73). These data support the idea that *ALK* inhibitors with good CNS efficacy can treat existing and potentially delay the development of brain metastases. These results were corroborated in the ALESIA study, which randomized untreated Asian patients 2:1 to either alectinib 600 mg b.i.d. or crizotinib 250 mg b.i.d. Patients receiving alectinib demonstrated superior iORR of 73% *vs.* 22% (5/23) on crizotinib; a higher complete response rate was also seen at 50% *vs.* 13% (74). A recent retrospective cohort study also evaluated the intracranial ORR of alectinib in 20 ALK-inhibitor naïve patients (cohort 1), 32 patients who developed intracranial progression with or without extracranial progression after treatment with crizotinib (cohort 2), and 13 patients with intracranial-only progression while on second-generation ALK-inhibitors other than crizotinib (cohort 3) (75). The ORRs were 81.8% in cohort 1, 76.5% in cohort 2, and 42.8% in cohort 3; most patients reported robust improvement in neurologic symptoms and the need for corticosteroids decreased significantly (75). Although these results support the role for alectinib in clinical practice, the small sample size and treatment heterogeneity necessitates cautious interpretation.

Patients with brain metastases and crizotinib-refractory disease on the ALTA trial received low- and high-dose brigatinib, with resulting iORRs of 46% on 90 mg daily and 67% on 180 mg daily dosing (76,77). In the ASCEND and ASCEND-2 trials, patients with baseline brain metastases receiving ceritinib were found to have disease control rates slightly lower than brigatinib (65–74% *vs.* 83%) with iORR of 45% among the 20 patients in ASCEND-2 with active/target brain lesions at enrollment (78,79).

The third generation *ALK/ROS1* inhibitor lorlatinib was specifically designed to penetrate the BBB and has demonstrated significant CNS activity, even in patients who have previously failed a brain penetrant TKI such as alectinib. Work by Solomon *et al.* demonstrated the potential for this agent in a single arm expansion cohort study of lorlatinib in patients with *ALK*-positive metastatic NSCLC. Among 141 patients with brain metastases, the iORR was 63% (53/84 patients with measurable intracranial disease) across all cohorts including treatment naïve participants and those with prior-TKI use (80). In another single arm trial of lorlatinib in patients with prior use of at least one *ALK* inhibitor, approximately 64% (52/81) of patients with baseline brain metastases demonstrated intracranial response with a median response duration of

12.4 months (81). The effect was further substantiated in the CROWN trial, in which 296 patients with advanced, untreated metastatic *ALK* rearranged NSCLC were randomized to receive lorlatinib or crizotinib (82). There were 38/149 (26%) patients in the lorlatinib arm with brain metastases at baseline *vs.* 40/147 (27%) on crizotinib (82). A higher proportion (66%) of patients receiving lorlatinib demonstrated intracranial response with 61% experiencing complete response; those receiving crizotinib had a much lower intracranial response at 20% (82).

A summary of key studies is seen in *Table 2*.

Attempts to compare—and potentially supplement—the effects of TKIs with RT have also been explored. A recent retrospective study of 52 patients combined *ALK*-inhibitor therapy and RT, wherein 20 patients received an *ALK*-inhibitor plus RT *vs.* 32 receiving an *ALK*-inhibitor alone (83). In this cohort, there was no significant difference in time to treatment failure between the two groups, supporting a targeted monotherapy approach to treatment that would spare the potential sequelae of RT. These data built upon two earlier series of patients with *EGFR*-positive NSCLC with brain metastases who received RT or *EGFR*-TKIs in the upfront setting; despite prolonged intracranial time to treatment failure, overall survival was not different across groups (84,85).

Of note, the aforementioned studies do not discriminate by subtypes of *ALK*-positive disease, which may have an important impact on clinical outcomes. Within *ALK*-positive NSCLC, many variants exist that appear to predict response to targeted treatment, with variants 1, 2, and 3a/b being the most common (86,87). Among these, variant 3a/b—associated with G1202R pathogenic variant—is resistant to crizotinib, ceritinib, brigatinib, and alectinib, whereas variants 1 and 2 may be relatively more sensitive to *ALK* inhibition (86-89). However, this differential response was not seen in a single institutional series of 135 patients with *ALK*-positive NSCLC receiving first-line crizotinib (n=65) or chemotherapy (n=70) when comparing all patients with variant 1 *vs.* non-variant 1 disease who received crizotinib (90). Further, in the subset of patients with baseline brain metastases treated with upfront crizotinib (n=18), there was inferior time to treatment failure for variant 1 disease, which was also noted to have more aggressive radiographic features (90). The impact of group heterogeneity and small sample size necessitates careful interpretation of these results, but more insight into the behavior of *ALK* variants will be needed to determine their implications for clinical course.

Regarding safety and tolerability, a 2019 meta-analysis evaluated 19 studies comprising 3,307 patients on *ALK*-inhibitor therapy including alectinib, brigatinib, ceritinib, and crizotinib (91). In this, they found that adverse events (AEs) were nearly universal and serious adverse events (SAEs) were seen in over 40% of participants receiving ceritinib and brigatinib (91). The most common SAEs involved the respiratory system for all four agents—including pneumonia, respiratory failure, thrombosis, and pleural effusion—followed by nervous or alimentary system sequelae; alectinib was associated with the lowest rate of SAEs overall (91). Headaches and fatigue were counted among relevant CNS AEs. The third-generation *ALK* TKI lorlatinib is associated with a high frequency of mild to potentially severe symptoms including hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, cognitive effects, fatigue, mood changes, and vision abnormalities (92). Given the relatively high proportion of patients with grade 3 or 4 AEs while on lorlatinib, patients in whom lorlatinib is considered as first-line must be carefully selected and monitored (82). Conversely, sequential *ALK* inhibitor therapy may yield a hypermutated phenomenon that could confer resistance to later lorlatinib, which therefore leads to a critical clinical decision point (93-95).

Following the ALEX trial, alectinib has become the most widely used *ALK* TKI in the upfront setting given the favorable balance of disease control and lower risk for SAEs. However, treatment resistance—and eventual disease progression—is of significant concern (87,93,96). To delay treatment resistance, combination therapy with a backbone of *ALK* inhibition has been explored. In light of the complementary action and potential efficacy of anti-VEGF therapy in reducing brain metastasis proliferation, a small, single institution phase 1/2 study recently evaluated the combination of alectinib and bevacizumab in 11 patients with *ALK* rearranged NSCLC (97). Of the 9 patients with CNS disease at baseline, iORR was 77.8% (7/9) with 44.4% (4/9) demonstrating complete CNS response; median CNS progression-free survival was not reached (97). This combination regimen was also well tolerated.

Consolidating the above, a second-generation *ALK* TKI or lorlatinib should be considered first-line therapy over other systemic agents including platinum-pemetrexed regimens and crizotinib. This is true even in patients with baseline brain metastases given good intracranial effect. These agents have demonstrated robust systemic and CNS disease control and can prevent or delay the development

Table 2 Relevant studies demonstrating comparative efficacy of *ALK*-inhibitor therapy in patients with *ALK*-rearranged NSCLC with brain metastases

Agent	Study	Author	Year	Phase	Locations	Prior TKI use	Patients	Patients with BMs	iORR
Lorlatinib	CROWN	Shaw *et al.* (82)	2020	3	International, 104 sites	None	296	78 (28 on lorlatinib)	66% *vs.* 20%
		Patients without prior treatment for metastatic disease were randomized 1:1 to lorlatinib 100 mg daily *vs.* crizotinib 250 mg b.i.d.							
		Bauer *et al.* (81)	2020	2	USA, Spain, Italy	At least 1	198	131 (81 measurable)	64%
		Patients previously treated with at least 1 ALK inhibitor/TKI (59/198 received crizotinib and 139/198 received at least one second-generation TKI) enrolled on a single-arm study of lorlatinib 100 mg daily							
		Solomon *et al.* (80)	2018	2	International, 47 sites	Mixed	228	141 (84 measurable)	63%
		Patients were grouped into six expansion cohorts based on prior treatment status including naïve (n=30), crizotinib only (n=27), crizotinib and other agent(s) (n=32), and other chemotherapy regimens including other TKIs (n=139). All received lorlatinib 100 mg daily							
Alectinib	ALESIA	Zhou *et al.* (74)	2019	3	China, South Korea, Thailand	None	187	67 (44 on alectinib)	73% *vs.* 22%
		Asian patients with previously untreated disease were randomized 2:1 to alectinib 600 mg b.i.d. *vs.* crizotinib 250 mg b.i.d.							
	ALEX	Peters *et al.* (23)	2017	3	International, 98 sites	None	303	122 (64 on alectinib)	59% *vs.* 26%
		Patients with previously untreated disease were randomized 1:1 to alectinib 600 mg b.i.d. *vs.* crizotinib 250 mg b.i.d.							
	J-ALEX	Hida *et al.* (72)	2017	3	Japan, 41 sites	None	207	43 (14 on alectinib)	NR
		Japanese patients randomized 1:1 to alectinib 300 mg b.i.d. *vs.* crizotinib 250 mg b.i.d. No iORR reported, but longer time to and lower one-year cumulative incidence rate of CNS progression noted for alectinib arm (n=103)							
Brigatinib	ALTA	Kim *et al.* (76)	2017	2	International, 71 sites	Crizotinib	222	154 (80 on 90 mg arm)	46% (90 mg) *vs.* 67% (180 mg)
		Patients with locally advanced or metastatic disease who experienced disease progression while receiving crizotinib were randomized 1:1 to receive brigatinib 90 mg daily or 180 mg daily (with 7-day lead-in period on 90 mg daily)							
Ceritinib	ASCEND-2	Crinò *et al.* (79)	2016	2	International, 51 sites	Crizotinib	140	20 (active)	45%
		Patients with locally advanced or metastatic disease who previously received at least platinum-based chemotherapy regimen and crizotinib were enrolled on the single-arm study of ceritinib 750 mg daily							
	ASCEND-1	Kim *et al.* (78)	2016	1	International, 20 sites	163/246	246	94	68%
		Patients with locally advanced or metastatic disease who failed prior standard therapy (including 163/246 having previously received ALK inhibitor treatment) or for whom no effective treatment existed (83/246 ALK-inhibitor naïve) enrolled on a dose escalation study of ceritinib with a starting dose of 750 mg daily							

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; BM, brain metastasis; iORR, intracranial overall response rate.

of new brain metastases. Our institutional experience is that alectinib is the preferred agent as it provides a favorable profile of both efficacy and tolerability, though any available second-generation agent or lorlatinib can be considered.

Symptomatic management

In the acute setting, many of the symptoms associated with brain metastases arise from or are exacerbated by peritumoral edema and mass effect. Accordingly, symptoms may be relieved by administration of corticosteroids such as dexamethasone. Despite the ubiquity of its use, the dosing and frequency of dexamethasone administration is not protocolized and varies by institution. A reasonable range of dexamethasone doses would be 4–24 mg total daily dose, which can be administered once or twice daily (98). Note that dexamethasone doses less than 16 mg daily may not be inferior for symptom relief as compared to higher doses, and brain metastasis symptoms and edema may not produce any noticeably increased response to higher doses (99). Lastly, b.i.d. dosing has demonstrated non-inferior symptom relief as compared to every six hours dosing but has a much lower incidence of side effects (100). Corticosteroids are helpful adjuncts prior to and sometimes during local and systemic therapy, but they are meant to bridge to definitive treatment.

For patients with brain metastases on *ALK* inhibitors, the neurologic side effects of TKIs such as cognitive dysfunction and peripheral can be particularly problematic. Neurologic assessment and clinical history can help tease apart the underlying etiology and whether symptoms are treatment- or disease-related. Given the frequency of these adverse effects, attention should be directed toward early screening of mood, cognitive function, pain, dysesthesias, numbness, or weakness in patients on *ALK* inhibitors. Neuropsychological evaluation and cognitive rehab may be beneficial in patients with cognitive dysfunction, and stimulants may also be considered for fatigue-related cognitive dysfunction and inattention. Neuropathy symptoms should be managed according to published guidelines (101,102); physical/occupational therapy and consideration of pharmacologic agents such as duloxetine may be helpful. Dose reduction of the TKI should also be considered.

Future directions and challenges

There are ongoing challenges to the use of systemic therapies, largely arising from limitations in crossing the BBB or the adverse effects that can develop with highly penetrant agents. Although compromise to BBB integrity accompanies larger metastatic lesions, the presence of drug efflux pumps actively limits the effective concentration of pharmacotherapy and inadvertently reinforces the metastatic niche (103). Therefore, it will be important to consider the molecular weight, lipophilicity, polar surface area, hydrogen bond donor count, permeability, and efflux for any proposed compounds (104). The development of new, highly CNS-penetrant agents will have to contend with both the BBB as well as the potential for side effects, as has been highlighted in the neurologic and extra-CNS SAE profile seen with lorlatinib.

An additional concern is the method used to determine response to treatment within studies. To facilitate comparison across trials, it will be important to use consistent and validated response criteria when assessing patients with brain metastases and their neurologic function. While many trials continue to use the one-dimensional measurements of RECIST, more recent trials incorporate the Response Assessment in Neuro-Oncology (RANO) criteria for brain metastases (105). The inclusion of neurologic outcomes data and SAEs will also allow for more nuanced agent selection in eligible patients.

Ongoing trials for *ALK* rearranged NSCLC include a study (NCT04849273) of TPX-0131, a novel oral *ALK* inhibitor, which includes patients with asymptomatic brain metastases or leptomeningeal disease, as well as an international study evaluating the use of alectinib with bevacizumab in patients with *ALK* rearranged NSCLC, including patients with treated brain metastases (NCT03779191). There is also an ongoing basket trial of entrectinib, an inhibitor of NTRK, ROS1, and ALK, which includes patients with primary or secondary CNS disease (NCT02568267).

The inclusion of patients with brain metastases in trials of *ALK* inhibitor therapy will be crucial given the propensity for CNS disease, which should include symptomatic patients who may benefit from local therapy and may help elucidate synergistic approaches with surgery and/or RT. Furthermore, the development of new studies focused on delaying resistance to *ALK* TKIs, likely through a combinatorial approach, will inform future treatment regimens.

Conclusions

The advent of targeted therapies such as alectinib,

brigatinib, ceritinib, and lorlatinib has changed the treatment paradigm for *ALK* rearranged NSCLC. These agents have yielded improved systemic and CNS disease control—including reducing the risk of developing CNS disease—and may help delay local therapies in some circumstances. Second- and third-generation *ALK* inhibitor therapy is now considered first-line for *ALK* rearranged NSCLC, but surgery and RT remain important for the control of large, widespread, and symptomatic intracranial disease. Furthermore, the development of resistance to *ALK* inhibitors will continue to affect progression-free survival unless effective combination therapies are established; some promise has been shown with bevacizumab and alectinib. Ongoing and future work will help surmount these challenges, offering hope to patients with an as-yet incurable disease.

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