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Emerging Gene Fusion Drivers in Primary and Metastatic Central Nervous System Malignancies: A Review of Available Evidence for Systemic Targeted Therapies

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Abstract

Primary and metastatic tumors of the central nervous system present a difficult clinical challenge, and they are a common cause of disease progression and death. For most patients, treatment consists primarily of surgery and/or radiotherapy. In recent years, systemic therapies have become available or are under investigation for patients whose tumors are driven by specific genetic alterations, and some of these targeted treatments have been associated with dramatic improvements in extracranial and intracranial disease control and survival. However, the success of other systemic therapies has been hindered by inadequate penetration of the drug into the brain parenchyma. Advances in molecular characterization of oncogenic drivers have led to the identification of new gene fusions driving oncogenesis in some of the most common sources of intracranial tumors. Systemic therapies targeting many of these alterations have been approved recently or are in clinical development, and the ability to penetrate the blood-brain barrier is now widely recognized as an important property of such drugs. We review this rapidly advancing field with a focus on recently uncovered gene fusions and brain-penetrant systemic therapies targeting them. ***The Oncologist*** 2018;23:1063–1075

Implications for Practice: Driver gene fusions involving receptor tyrosine kinases have been identified across a wide range of tumor types, including primary central nervous system (CNS) tumors and extracranial solid tumors that are associated with high rates of metastasis to the CNS (e.g., lung, breast, melanoma). This review discusses the systemic therapies that target emerging gene fusions, with a focus on brain-penetrant agents that will target the intracranial disease and, where present, also extracranial disease.

Introduction

Central nervous system (CNS) malignancies, including primary tumors and metastatic tumors of extracranial origin, continue to be a clinical challenge. Although some primary CNS tumors are considered low grade, they can be associated with significant morbidity. Higher-grade CNS tumors, such as glioblastoma (GBM), are aggressive and associated with an approximate overall survival (OS) of 12–17 months after multimodal treatment [1–3]. The poor prognosis of these cancers reflects, in part, the lack of systemic therapies that target the oncogenic mechanisms from which they arise. Recently, gene fusions have emerged as oncogenic drivers in GBM and other primary CNS tumors, including the neurotrophic tropomyosin receptor kinase (*NTRK*) family, the fibroblast growth factor receptor (*FGFR*) family, *c-ros oncogene 1* (*ROS1*), and *v-Raf murine sarcoma viral oncogene homolog B* (*BRAF*) [4–7]. Thus, although rare, these tyrosine kinase gene fusions are attractive targets for systemic therapies for primary CNS cancers, and efforts are underway to specifically develop small molecule tyrosine kinase inhibitors (TKIs) that penetrate the blood-brain barrier (BBB) [8].

Metastatic Disease to the CNS

Central nervous system metastases are the most common intracranial tumors in adult cancer patients [9], and they are one of the most feared complications of systemic cancer. The most common primary sources are non-small cell lung cancer (NSCLC), breast cancer, colorectal cancer, and melanoma [10, 11], which combined account for about 67%–80% of CNS

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metastases [11]. Although recent advances have extended survival in select patient groups, CNS metastases are still associated with poor prognosis, with median survival of about 7 months [12], reflecting the difficulty of disease control in these patients. In a retrospective analysis of patients with CNS metastases, intracranial progression was the direct cause of death in 57% of patients with NSCLC [13]. In NSCLC, therapies targeting epidermal growth factor receptor (EGFR) aberrations or anaplastic lymphoma kinase (ALK) fusions improve intracranial response rates and overall outcomes in patients whose tumors arise from these genetic alterations [14]. Similarly, activating mutations of BRAF occur in about half of melanomas, and BRAF inhibitors are now a standard part of the therapeutic sequence for patients with BRAF-related melanoma, including those with CNS metastases [15]. As with primary CNS malignancies, recent studies have identified recurrent gene fusions involving tropomyosin receptor kinase (TRK) and ROS1 tyrosine kinases in patients with NSCLC, breast cancer, and melanoma [16–19]. Because of the frequent occurrence of CNS metastases in these patients, intensive efforts are focused on the development of brain-penetrant therapies against these targets.

The evolution of ALK inhibitors for the treatment of NSCLC has illustrated the importance of considering CNS efficacy during drug development. Although the first U.S. approved ALK inhibitor, crizotinib, improved intracranial disease control rate versus chemotherapy, patients commonly developed new CNS metastases or intracranial progression, often attributed to the limited brain penetrance of crizotinib [20, 21]. Newer ALK inhibitors such as alectinib and ceritinib have increased CNS penetrance and can re-establish intracranial disease control in many patients [22, 23]. Thus, as research evolves in the development of TKIs targeting FGFR, TRK, and ROS1 for metastatic cancer, the ability of molecules to penetrate the brain and have resulting CNS activity is an important aspect to evaluate in the clinic. As such, clinical trials are increasingly designed to include patients with CNS metastases, whereas these patients were often excluded from older trials. A list of select TKIs studied for the treatment of CNS malignancies, with key observations regarding intracranial efficacy, is shown in Table 1.

Testing for gene fusions should be considered when there is access to relevant drugs and tumor tissue for patients with primary CNS tumors with good performance status who have exhausted standard therapy. Furthermore, in patients with CNS metastases, we recommend testing for gene fusions from the metastatic site if the patient is progressing in the brain and if there is brain metastasis tissue available for patients who have undergone surgery as part of clinical care.

It is important to appropriately identify patients who may be eligible for targeted therapies. Testing for gene fusions should be considered when there is access to relevant drugs and tumor tissue for patients with primary CNS tumors with good performance status who have exhausted standard therapy. Furthermore, in patients with CNS metastases, we recommend testing for gene fusions from the metastatic site if the patient is progressing in the brain and if there is brain metastasis tissue available for patients who have undergone surgery as part of clinical care. A number of methods are available for the identification of gene fusions, including immunohistochemistry, fluorescence in situ hybridization, next-generation sequencing, and RNA-Seq [24–26]. Each of these testing methods have specific attributes and applicable clinical scenarios that have been previously reviewed [24–26].

Several factors contribute to the challenges of developing targeted systemic therapies that are effective against CNS metastases. One factor is that mutational status may be different between primary and metastatic sites [27, 28], although the heterogeneity of gene fusions has yet to be firmly established and is an area of continued research. Complicating these differences is the fact that brain biopsy specimens are rarely available, depriving investigators and clinicians of knowledge about the molecular characteristics of CNS metastases [27]. Another factor is the brain penetrance of drugs in development, as detailed in Table 2, which can be difficult to predict from physicochemical properties or preclinical models [29]. It is also important to consider that CNS active drugs may be associated with on-target neurological side effects, such as cognitive disturbances [30]. There is a delicate balance in the development of new targeted therapies to have a high level of CNS activity as well as a safety and tolerability profile without these concerning neurologic adverse events (AEs). This review will summarize the current challenges of treating primary and metastatic CNS malignancies, and emerging targets for systemic therapies, primarily those that target gene fusions in clinical development.

The BBB and Assessment of Intracranial Responses

When the BBB is fully intact, it forms a highly restrictive barrier to the CNS for most chemotherapy drugs and large molecules [29]. Multiple factors may disrupt the BBB and affect the CNS penetrance of systemic therapies for brain malignancies, such as the formation of the blood-tumor barrier, neovascularization, and prior localized therapies allowing for altered access of drugs to the intracranial space [31–33]. Therefore, clinical trials assessing intracranial responses must take into account variables such as number, origin, and size of CNS metastases, prior therapies including radiotherapy, and traditional factors affecting the integrity of the BBB, such as patient age and performance status [34, 35].

Given the strong influence of CNS malignancies on patient survival, evaluation of intracranial responses is an essential component of clinical trials of systemic targeted therapies for primary CNS tumors and CNS metastases. Although response evaluation criteria in solid tumors (RECIST) criteria are well established for assessment of responses to oncology treatment, it is recognized that RECIST criteria have significant limitations with respect to their applicability in patients with CNS metastases [34]. As a result, international multidisciplinary efforts have led to the development of criteria for assessing intracranial responses, including Response Assessment in Neuro-Oncology criteria (RANO) and Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) [34, 35]. Although these criteria continue to evolve, they are important for standardizing the

Table 1. Intracranial activity of select tyrosine kinase inhibitors approved or in development for treatment of NSCLC, breast cancer, or melanoma

Drug	Drug class	Target	Comments on intracranial activity	Development status
Entrectinib	Small molecule TKI	TRKA/B/C, ROS1, ALK	Interim data in patients with ROS1-positive NSCLC from ongoing phase II: Intracranial ORR of 83% (5/6) in patients with measurable CNS lesions by BICR; Intracranial ORR of 71% (5/7) in patients with measurable and nonmeasurable CNS lesions by BICR [84] Responses in 5/8 patients with known primary or metastatic disease involving the brain with TRK/ROS1/ALK fusions in pooled analysis of phase I trials [73] One patient with NSCLC harboring a *SQSTM1-NTRK1* fusion achieved a complete intracranial response that was ongoing for 15 months as of the cutoff date [73] One patient in a phase I trial who had glioneuronal tumor harboring a *BCAN-NTRK1* fusion exhibited a 60% reduction in tumor volume by volumetric assessment and resolution of clinical symptoms for 11 months [7]	Ongoing phase II trial in solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK* gene fusions (NCT02568267)
Larotrectinib	Small molecule TKI	TRKA/B/C	Limited CNS penetration [75, 76] Decrease in size of intracranial lesions in one patient with brain metastases from NSCLC, although lesions were not measurable by RECIST [74] Evidence of potential treatment effect on imaging in one patient with *NTRK* fusion-positive recurrent glioblastoma [125]	Ongoing phase II in *NTRK* fusion-positive solid tumors
Lorlatinib	Small molecule TKI	ALK, ROS1	Intracranial ORR, 56% (14/25) in patients with ROS1+ NSCLC with brain metastases [86]	Ongoing phase III in ALK+ NSCLC (NCT03052608) Ongoing phase II in ALK+ or ROS+ NSCLC (NCT01970865)
Crizotinib	Small molecule TKI	ALK, ROS1	In patients with ALK+ NSCLC who had brain metastases, IDCR was significantly higher with crizotinib vs. chemotherapy (56% vs. 25% at 24 weeks) [21] Probability of brain progression was much higher than extracranial, suggesting inadequate brain penetration [20, 21]	Approved for ALK+ NSCLC
Alectinib	Small molecule TKI	ALK	Pooled analysis of CNS efficacy in two phase II single-arm trials in crizotinib-pretreated patients; measurable patients: ICRR, 64%; CDCR, 90%; duration of response, 10.8 months [23] ALEX, phase III: Alectinib vs. crizotinib; time to CNS progression for alectinib compared with crizotinib in ITT population (cause-specific HR: 0.16 vs. crizotinib; 95% CI: 0.10–0.28) [64]	Approved for ALK+ NSCLC after crizotinib
Ceritinib	Small molecule TKI	ALK	ASCEND-2 (phase II); ceritinib after chemotherapy and crizotinib. ICRR, 45%; IDCR, 80% [22] ASCEND-3 (phase II) ceritinib in ALK inhibitor-naïve; IDCR, 80% [60]	Approved for ALK+ NSCLC
Brigatinib	Small molecule TKI	ALK, EGFR	ICRR 42% (11/26) in 90-mg arm and 67% (12/18) in 180-mg arm in the ALTA phase II trial [137]	Accelerated approval (April 2017) for ALK+ NSCLC; ongoing phase III in ALK+ NSCLC (NCT02737501)
Erlotinib	Small molecule TKI	EGFR	Limited CNS penetration [52] Evidence suggests that standard dose has insufficient intracranial level to achieve disease control, but pulsatile administration of high dose improves response rates [138]	Approved for NSCLC with exon 19 deletions or exon 21 (L858R) substitution in *EGFR*

(continued)

Table 1. (continued)

Drug	Drug class	Target	Comments on intracranial activity	Development status
			Pooled analysis in NSCLC with CNS metastases; ICRR, 44.3%; IDCR, 77.8% [139]	
Gefitinib	Small molecule TKI	EGFR	Limited CNS penetration [53] Pooled analysis in NSCLC with brain metastases; ICRR, 51.8%; IDCR, 68.7% [139] Phase II trial in 41 patients with brain metastases; ICRR, 87.8% [140]	Approved for NSCLC with exon 19 deletions or exon 21 (L858R) substitution in *EGFR*
Afatinib	Small molecule TKI	EGFR	Pooled analysis in whole-body ORR reported, but ICRR not assessed [51]	Approved for NSCLC with exon 19 deletions or exon 21 (L858R) substitution in *EGFR*
Osimertinib	Small molecule TKI	EGFR (sensitizing and T790M)	In patients with CNS metastases, osimertinib had PFS of 8.5 months vs. 4.2 months for chemotherapy (HR: 0.32; 95% CI: 0.21–0.49) [141] Subgroup analysis of CNS responses in two phase II trials, ICRR, 54% (39%–68%); CNS disease control rate, 92% [142]	Approved for EGFR T790M mutation-positive NSCLC
Lapatinib	Small molecule TKI	EGFR/HER2	Lapatinib (+ capecitabine) in patients with previously untreated brain metastases from HER2+ metastatic breast cancer; ICRR, 66% [91]	Approved for HER2+ breast cancer in combination with capecitabine or letrozole
Neratinib	Small molecule TKI	EGFR/HER2	ICRR, 8% among 40 patients with HER2+ breast cancer and brain metastases, pretreated with local therapy [143]	Approved for extended adjuvant treatment of early-stage HER2+ breast cancer
AZD3759	Small molecule TKI	EGFR	Stable disease in 9/17 (53%) patients with pretreated leptomeningeal disease from NSCLC in a phase I trial [144]	Phase I
Trastuzumab	Monoclonal antibody	HER2	Limited CNS penetrance, but penetrance increased by radiotherapy [31, 145]	Approved for HER2+ breast cancer
Erdafitinib (JNJ-42756493)	Small molecule TKI	FGFR	Stable disease and minor response, respectively, in two patients with glioma treated in phase I trial [132]	Ongoing phase I trial (NCT01703481)
Dabrafenib	Small molecule TKI	BRAF	In a phase II trial: Among those with V600E mutation, 39.2% ICRR in treatment-naïve; 30.8% V600E in treatment-experienced [101]; treatment refers to local therapy for brain metastases	Approved for BRAF V600E mutation-positive malignant melanoma
Vemurafenib	Small molecule TKI	BRAF V600E mutation	ICRR, 18% (previously untreated) and 18% (previously treated) [146]	Approved for BRAF V600E mutation-positive melanoma

Abbreviations: ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CDCR, CNS disease control rate; CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ICRR, intracranial response rate; IDCR, intracranial disease control rate; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; ORR; objective response rate; PFS, progression-free survival; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.

evaluation of response rates across clinical trials. The current criteria for assessment of brain metastases from the RANO-BM group provide guidance on the selection of target and nontarget lesions and methods for imaging and measurement of tumor dimensions. They also discuss the potential confounding effects of prior treatments, such as stereotactic radiosurgery (SRS), and the preference for target lesions not previously treated with local therapy [34].

CNS Metastases

Treatment options for brain metastases generally include surgical resection, SRS, whole-brain radiation therapy (WBRT), and chemotherapy [9]. However, short-term and long-term neurological concerns associated with these therapies, including cognitive side effects and the long-term side effects of radiation [30], have prompted a search for other treatment modalities. In recent years, targeted therapies that penetrate the BBB have gained in prominence because of their ability to selectively inhibit molecular pathways promoting growth in cancer cells, while minimizing off-target side effects to normal tissues [36].

NSCLC

Among patients with NSCLC, up to 22% will have CNS metastases at initial presentation [37–40], and up to 40% will develop CNS metastases during the course of disease [41]. Gain-of-function mutations in the EGFR gene are found in about 10%–20% of NSCLC cases [42, 43]. Tyrosine kinase inhibitors

Table 2. Blood-brain barrier penetration of select agents

Drug	Target	Brain distribution	
Crizotinib	ALK, ROS1	Limited	CSF to plasma ratio of 0.0026 measured in a patient with NSCLC harboring an ALK fusion [58]
Lorlatinib	ALK, ROS1	Yes	AUC ratio of CSF to free plasma (0.31) and AUC ratio of free brain to free plasma (0.21) measure in rats after a single 10 mg/kg oral dose [147]
Entrectinib	TRK, ROS1, ALK	Yes	Brain to blood ratio [129, 148]: 0.4 in mice 0.6–1.0 in rats 1.4–2.2 in dogs
Larotrectinib (LOXO-101, ARRY-470)	TRK	Limited	50:1 plasma to CSF ratio (calculated CSF to plasma ratio of 0.02) [75, 76] High concentrations in plasma and peripheral tissues, whereas brain concentrations remain negligible at doses of 10–100 mg/kg [75, 76] 16 to 1 peripheral to CNS exposure (calculated CNS to peripheral ratio of 0.0625) [149]
Alectinib	ALK	Yes	Brain to plasma ratio at T_{max} ranged from 0.63 to 0.94 in rats treated with a single dose of ^{14}C-labeled alectinib at 1 mg/kg [150]
Ceritinib	ALK	Partial	Brain-to-blood exposure (AUC_{inf}) ratio of approximately 15% in rats (calculated brain to blood ratio of 0.15) [151]
Erdafitinib (JNJ-42756493)	FGFR	Not reported	

Abbreviations: ALK, anaplastic lymphoma kinase; AUC, area under the curve; AUC_{inf}, area under the curve from time zero to infinity; CNS, central nervous system; CSF, cerebral spinal fluid; FGFR, fibroblast growth factor receptor; NSCLC, non-small cell lung cancer; ROS1, c-ros oncogene 1; T_{max}, time of maximum concentration.

directed at EGFR are effective and recommended for treatment of NSCLC patients with EGFR mutations [44], but they have had limited success in patients who also have brain metastases [45]. The first- and second-generation EGFR TKIs (erlotinib, gefitinib, afatinib) administered either as monotherapy or in combination with WBRT have exhibited variable efficacy. Response rates ranging from 10% to 86% and median progression-free survival (PFS) of 1.6–11.1 months have been reported in patients with NSCLC, depending on the drug, study methodology, and whether overall or intracranial effects were assessed [46–51]. Furthermore, evidence suggests that erlotinib and gefitinib have limited penetration into the CNS (Table 1) [52, 53]. The irreversible third-generation EGFR TKI osimertinib, which targets activating EGFR mutations (EGFRm) and resistance mutations (T790M), has activity in the CNS both preclinically and clinically [54, 55]. The same trial also found evidence of tumor shrinkage in patients with brain metastases treated with the reversible EGFRm-inhibitor AZD3759 [56].

Another common targetable genetic alteration reported in NSCLC is a gene fusion involving ALK, which is present in approximately 3%–7% of NSCLC tumors (Table 3) [57]. Retrospective data suggest that crizotinib, a TKI targeting ALK, can initially achieve some tumor control in the CNS. However, intracranial disease progression has been frequently reported in NSCLC patients with brain metastasis treated with this agent (Table 1) [20, 58, 59], which is likely due to the limited BBB penetration of crizotinib (Table 2) [58]. Next-generation ALK TKIs such as ceritinib and alectinib have shown promising results in terms of intracranial tumor control in patients with *ALK*-positive NSCLC brain metastases [22, 60–63]. The recently reported results of the ALEX trial, a head-to-head study of alectinib versus crizotinib in previously untreated patients with *ALK*-positive NSCLC, demonstrated that time to CNS progression was significantly longer with alectinib compared with crizotinib (hazard ratio [HR]: 0.16; 95% confidence interval [CI]: 0.10–0.28) [64]. These agents also shed light on the importance of therapies that can penetrate the BBB and the benefit of using these agents in the first-line setting to treat or prevent CNS metastases and extend response to treatment. It is important to note that many patients develop acquired resistance to targeted therapies. For example, the majority of patients with NSCLC treated with crizotinib will develop disease progression within 1 year, likely due to acquired resistance [65]. The molecular mechanisms and management of secondary resistance to targeted therapies have been reviewed previously [66].

Emerging Gene Fusions as Targets

Beyond the ALK fusion pathway, other gene fusions involving tyrosine kinases are emerging as oncogenic drivers in NSCLC and other cancers with brain metastases (Table 3). Inhibitors targeting those tyrosine kinases are in development, with intracranial activity being recognized as a critical drug feature. One emerging set of genetic alterations involves the TRK family. Members of this family include the three transmembrane receptor tyrosine kinases TRKA, TRKB, and TRKC, which are encoded by the *NTRK* genes (Fig. 1; *NTRK1*, *NTRK2,* and *NTRK3*) [67, 68]. The TRK receptor tyrosine kinases are involved in development of the peripheral nervous system and in cell survival (Fig. 2) [69]. However, several aberrations of the TRK pathway have been associated with the initiation and progression of various cancers. Of those, *NTRK* gene fusions are currently the best-characterized aberrations (Table 3) [70, 71].

NTRK gene fusions have been detected at a frequency of 0.1% overall in patients with NSCLC and up to 3% in patients with NSCLC and no known oncogenic drivers [19, 70–72]. In a recent study of 1,378 patients [19], 1 of the 2 *NTRK1*-positive

Table 3. Estimated prevalence of driver gene fusions in selected malignancies

Malignancy	*NTRK1*	*NTRK2*	*NTRK3*	*ROS1*	*EGFR*	*FGFR*
Glioblastoma (adult)	1% [4, 127]	1% [128]	<1% [128]	<1% [71]	7.6% [4]	8.3% [123]
Nonbrainstem high-grade glioblastoma (pediatric)		40% [124]				
Low-grade gliomas		<1% [71]			7% [126]	3% [126]
Pilocytic astrocytoma		3% [5]				
NSCLC		<0.1%–3% [70–72]		~2% [79, 80]		
CRC		<1% [71, 152]		1% [153]		
Melanoma (spitzoid)	21% [18]			3% [154]		
Breast (secretory)			92% [16]			
Salivary (secretory [MASC])			91%–100% [155, 156]			
Papillary thyroid	<12% [157]		2%–21% [158, 159]			

Abbreviations: CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; MASC, mammary analogue secretory carcinoma; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tropomyosin receptor kinase; ROS1, c-ros oncogene 1.

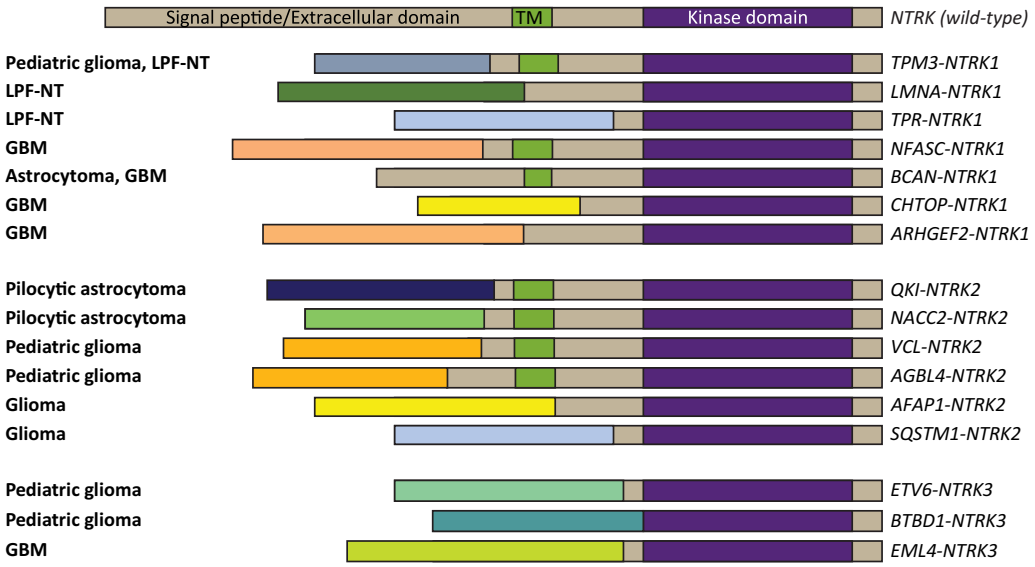

Figure 1. *NTRK* gene fusions in CNS malignancy. A depiction of *NTRK* gene fusions in various primary CNS malignancies [4, 5, 71, 124, 128, 134–136]. *NTRK* gene fusions have also been identified in CNS metastases from extracranial solid tumors, including lung, breast, and melanoma. In this case, *NTRK* is used as an illustrative example of the breadth of gene fusions that have been identified in CNS malignancies. CNS, central nervous system; GBM, glioblastoma; LPF-NT, lipofibromatosis-like neural tumor.

patients had multiple NSCLC brain metastases and was subsequently treated with entrectinib in a phase I dose-escalation study. Entrectinib is a CNS-active, potent, and selective TRK and ROS1 inhibitor. The patient had a rapid and clinically significant response and exhibited complete resolution of all brain metastases. Entrectinib was well tolerated, and the patient continued on treatment for over 6 months with an ongoing response as of the date of publication [19]. The safety profile and antitumor activity of entrectinib has been evaluated more extensively in two phase I studies (ALKA-372-001, $n = 54$ and STARTRK-1, $n = 65$) in patients with advanced solid tumors, including patients with brain metastases [73]. The predominant tumor types in these two studies were NSCLC (60%; $n = 71/119$) and gastrointestinal tumors (15%; $n = 18/119$), and 60/119 patients in the pooled cohort had gene fusions involving *NTRK1/2/3, ROS1*, or *ALK*. Of those 60 patients, 30 had received no prior TKI targeting TRK fusions, and 24 of those patients were evaluable and had tumors of extracranial origin. Entrectinib was well tolerated; the majority of treatment-related AEs (TRAEs) were less than grade 2, and all related AEs were reversible upon dose modification. The most common TRAEs were fatigue/asthenia (46%), dysgeusia (42%), paresthesias (29%), nausea (28%), and myalgias (23%) [73]. Objective responses were observed in 3/3 (100%) patients with *NTRK1/2/3*-positive tumors (NSCLC, mammary analog secretory carcinoma, colorectal cancer), 12/14 (86%) patients with *ROS1*-positive tumors (NSCLC and melanoma), and 4/7 (57%) patients with *ALK*-positive tumors (NSCLC, colorectal cancer, renal cell carcinoma). In this phase I cohort of 24 patients, 8 (32%) had known primary or secondary lesions in the brain, and intracranial responses to entrectinib were observed in 5 (63%) patients [73]. A phase II basket trial investigating entrectinib in the treatment of patients with solid tumors harboring *NTRK 1/2/3*, *ROS1*, or *ALK* gene fusions (STARTRK-2) is currently

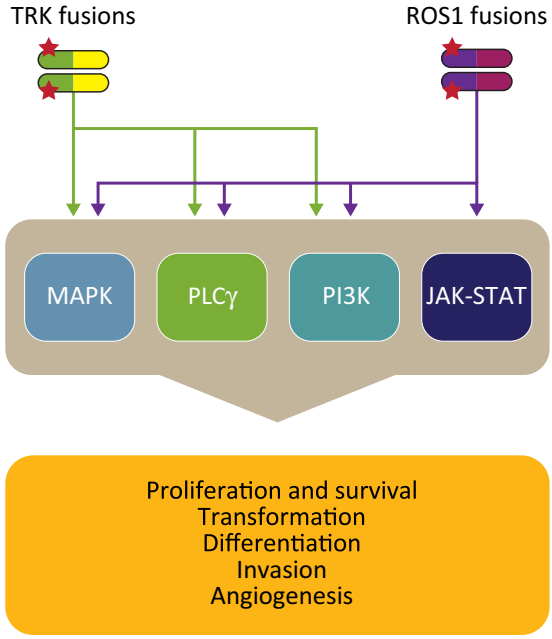

Figure 2. Cell signaling pathways activated by TRK and ROS1 kinases. Ligand-independent signaling through TRK and ROS1 fusion proteins leads to activation of multiple pathways that stimulate proliferation and survival of tumor cells.

ongoing and recruiting participants, including those with CNS involvement (NCT02568267).

Another compound that targets the TRK family is the small molecule inhibitor larotrectinib (LOXO-101, ARRY-470). An ongoing phase I trial is evaluating the safety and efficacy of larotrectinib in patients with solid tumors (NCT02122913). A preliminary analysis of six patients with *NTRK* gene fusions in extracranial tumors found partial responses in five (83%) patients according to RECIST criteria [74]. The efficacy of larotrectinib for treatment of intracranial metastases will be an important endpoint, given that preclinical studies showed that the drug has limited brain penetrance (Table 2) [75, 76]. One patient in this preliminary analysis had brain metastases from NSCLC and exhibited an 18% reduction and stable disease in the primary tumor along with decreases in the size of intracranial lesions during treatment, although the lesions were not measurable by RECIST criteria [74]. A phase II basket trial evaluating larotrectinib in patients with solid tumors harboring *NTRK* gene fusions is ongoing (NCT02576431). Results from an integrated dataset of three studies demonstrated an objective response rate of 76% (38/50); however, only the one patient with NSCLC noted above had CNS metastases, and updated response data were not provided for this patient [77]. Larotrectinib was well tolerated, and the most common treatment-emergent AEs included fatigue (38%), dizziness (27%), nausea (26%), and anemia (26%).

Another promising target in NSCLC is the ROS1 receptor tyrosine kinase, which is encoded by the *ROS1* oncogene [78]. *ROS1* gene fusions are present in approximately 2% of patients with NSCLC (Table 3) [79, 80], 19% of whom may have brain metastases at diagnosis [81]. The ALK TKI crizotinib also inhibits ROS1 and was associated with objective responses in 36 of 50 patients (72%) who had advanced NSCLC harboring a *ROS1* gene fusion [82]. However, no evidence was provided that crizotinib was active against brain metastases in ROS1-positive NSCLC, and, as detailed above, the CNS was a preferential site of disease progression in ALK-positive NSCLC brain metastases treated with crizotinib [83]. Regarding the previously mentioned pooled results of the phase I studies ALKA-372-001 and STARTRK-1, an overall response rate of 86% to treatment with entrectinib was detected in a total of 14 patients, of whom 13 patients had ROS1-positive NSCLC and 1 patient had ROS1-positive melanoma [73]. Interim results in patients with ROS1-positive NSCLC were recently reported from the ongoing STARTRK-2 phase II trial. Among 32 total patients, the objective response rate was 78% ($n = 25$) as assessed by the investigator and 69% ($n = 22$) as assessed by blinded-independent central review (BICR). The median duration of response was 28.6 months (95% CI: 6.8–34.8) and median PFS was 29.6 months (95% CI: 7.7–36.6) with a median follow-up of 12.9 and 8.5 months, respectively. In patients with measurable CNS lesions, there was an 83% intracranial objective response rate (five of six patients), and in those with measurable and nonmeasurable CNS lesions, there was a 71% intracranial objective response rate (five of seven patients) as assessed by BICR [84]. The updated tolerability profile of patients treated with entrectinib at the recommended phase 2 dose was consistent with previous reports [84]. Of note, the more concerning neurologic AEs such as mood swings associated with other inhibitors [85] have not been observed with entrectinib treatment at the recommended phase 2 dose to date [84]. The ALK/ROS1 inhibitor lorlatinib, which is also able to cross the BBB (Table 3), recently demonstrated an overall response rate of 36.2% in 47 patients with ROS1-positive NSCLC [86]. Lorlatinib exhibited clinically meaningful intracranial activity, with an intracranial overall response rate of 56% in 25 patients with brain metastases, but was also associated with neurologic AEs, including cognitive effects (17%) and mood effects (13%) [86]. Of note, many of these targeted therapies for gene fusions have demonstrated clinical efficacy regardless of fusion partner [73, 77, 82].

Breast Cancer

Breast cancer is the second most common primary tumor that leads to brain metastasis. Approximately 10%–30% of all breast cancer patients will develop brain metastases during the course of disease [45]. Among subtypes of breast cancer, advanced triple-negative breast cancer and human epidermal growth factor receptor 2 (HER2)-positive breast cancer have the highest propensity to metastasize to the brain, accounting for 25%–46% and 30%–55%, respectively, of brain metastases in breast cancer [87, 88]. Those same subtypes are also associated with shorter median OS after first diagnosis [89]. In comparison with patients with brain metastases from HER2-positive disease, patients with triple-negative brain metastases are more likely to die from progression of systemic disease than from CNS progression only, underscoring the need for drugs simultaneously targeting intra- and extracranial disease [90].

A number of targeted therapies are approved for the treatment of breast cancer and can be administered to patients with brain metastases. These include lapatinib, a dual HER2 and EGFR TKI, and the antibody-drug conjugate trastuzumab-emtansine (T-DM1), which both have some CNS penetration. The combination of lapatinib and capecitabine was associated

Table 4. Outcomes in the treatment of recurrent primary central nervous system tumors

Drug class/MoA	Drug	*N*	Response, %	6-month PFS, %	Median OS, months
Chemotherapy [160]	Multiple chemotherapies	225	CR/PR: 6	15	25 weeks
Chemotherapy [111–113]	Lomustine 100–130 mg/m^2 q6w	203[a]	Objective response: 4–9	13–25	7.1–10
Anti-VEGF mAb [112, 114, 115]	Bevacizumab 10 mg/kg q2w	166[a]	Objective response: 28.2–43	16–43	8–12
VEGF inhibitor [113]	Cediranib 30 mg daily	131	CR: 1; PR: 14; CR + PR: 15; SD: 64	16	8.0
TKI targeting EGFR [161]	Erlotinib 150→200 mg daily	54	CR: 0; PR: 4; CR + PR: 4; SD: 17	11.4	7.7

[a]Composite of multiple studies.
Abbreviations: CR, complete response; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; MoA, mechanism of action; OS, overall survival; PFS, progression-free survival; PR, partial response; q2w, every 2 weeks; q6w, every 6 weeks; SD, stable disease; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

with an objective CNS response rate of 65.9% (95% CI: 50.1–79.5) and a median time to progression of 5.5 months (95% CI: 4.3–6.0) in previously untreated patients with brain metastases studied in the phase II trial [91]. In a retrospective, exploratory analysis of the phase III trial, T-DM1 was associated with a significant increase in OS among patients with HER2-positive brain metastases (26.8 months) compared with those treated with lapatinib plus capecitabine (12.9 months; $p = .008$); however, there was no significant difference in PFS (5.9 months vs. 5.7 months) [92]. The utility of these therapies, and other promising agents, has been previously reviewed. Furthermore, a number of agents are in development for the treatment of breast cancer, and an important distinction with this new generation of drugs is the ability to cross the BBB [45, 93, 94].

Several gene fusions such as *ESR1-CCDC170*, *SEC16A-NOTCH1*, *SEC22B-NOTCH2*, and *ESR1-YAP1* have recently been identified in breast cancer [95], with multiple reports of a gene fusion involving the TRKC tyrosine kinase (*ETV6-NTRK3*) in secretory breast cancer [16, 96, 97]. However, no data are yet available describing targeted therapy for treatment of brain metastases in patients whose cancers are driven by such gene fusions.

Melanoma

Melanoma is the third most common origin of brain metastases [98], and it has the highest propensity of all solid tumors to cause metastatic brain lesions [99]. In patients with newly diagnosed advanced melanoma, brain metastases are present in approximately 20% of patients [100, 101], and up to 75% of melanoma patients will develop brain metastases during the course of disease [100, 102]. Melanoma brain metastasis is associated with a poor prognosis, with a median survival of approximately 7 months [12]. Inhibitors targeting BRAF, its primary downstream target, mitogen-activated protein kinase (MEK), and immune checkpoint inhibitors have changed the landscape of melanoma treatment in recent years. Although these agents have demonstrated initial responses in the brain, CNS metastases are often the first site of progression [15]. Targeted therapies for the treatment of brain metastases arising from melanoma have previously been reviewed [15, 28, 103].

Emerging targeted therapies for patients with melanoma brain metastases also focus on *NTRK, ROS1, ALK*, or *BRAF* gene fusions. A small percentage of melanoma patients, and particularly those with spitzoid melanomas, have been shown to harbor fusions of *NTRK1* (16%), *ROS1* (17%), *ALK* (10%), or *BRAF* (5%) [18]. There was a report of a patient with an extracranial spitzoid melanoma harboring BRAF fusion responding to the MEK inhibitor trametinib [104]. Furthermore, response to treatment with the TKI entrectinib has been observed in patients with *GOPC-ROS1*-positive melanoma [73, 105], but data on patients with melanoma brain metastasis treated with this agent remain unreported (NCT02568267).

Primary CNS Tumors

Glioblastoma is the most common and aggressive primary malignancy of CNS origin, accounting for 47% of such tumors [106]. Survival remains poor with the current standard of care—maximal debulking followed by radiotherapy and temozolomide—with median OS ranging from 14.6 to 16.7 months [1–3, 107]. Multiple studies of novel therapies for newly diagnosed patients have failed to improve OS [2, 108, 109], with the exception of the NovoTTF device combined with chemoradiation [110]. However, the clinical availability of NovoTTF is limited at this time.

Tumor relapse after primary treatment is nearly universal, and outcomes in recurrent GBM are poor with current treatments (Table 4). Treatment with chemotherapy has generally poor outcomes, with lomustine as the most common drug used after temozolomide failure. The 6-month PFS (PFS-6) rate with lomustine is reported to be 13%–19%, objective response rates 4%–5%, and median OS of 7–8 months (Table 4) [111, 112]. Several recent studies of promising agents have not improved efficacy versus standard of care chemotherapy in the recurrent tumor setting [111, 113]. Bevacizumab treatment was associated with improved response rates (28%–38%) and PFS-6 (16%–43%) compared with other treatments, but this effect was partly due to the radiologic artifact of pseudonormalization of tumor vasculature; bevacizumab did not improve median OS (range 7–8 months) [112, 114, 115]. Small molecule inhibitors against a variety of targets, including EGFR, have also failed in trials for recurrence of GBM. Focusing on EGFR illustrates some of the issues that might explain these failures. Brain penetration of erlotinib is poor (brain tissue-to-plasma ratio of 5%–11% for the active metabolite) and insufficient to reliably reduce EGFR signaling [116, 117]. Furthermore, EGFR alterations can occur concurrently with alterations in

other tyrosine kinases or signaling pathways in GBM, which may provide a pathway for continued tumor growth that is resistant to EGFR TKIs [118–121].

Emerging Gene Fusions in GBM and Other Primary CNS Malignancies

Clearly, effective treatments for relapsed GBMs and other gliomas are required. Similar to CNS metastases, drugs that target gene fusions should explored. Individually, such alterations are of low prevalence, but collectively they are quite common. For example, gene fusions were present in 30%–50% of tumor samples from 185 patients with GBM [6]. In addition to gene fusions involving EGFR [4], other gene fusions reported in patients with GBM have involved the tyrosine kinases ROS1 [122], PDGFRA [122], FGFR [123], TRKA, TRKB, and TRKC [4, 124, 125] (Table 3). EGFR and FGFR3 fusions have been reported in 7% and 3%, respectively, of low-grade, isocitrate dehydrogenase wild-type gliomas [126]. Gene fusions observed for *NTRK* include *NFASC-NTRK1*, *BCAN-NTRK1*, *AGBL4-NTRK2*, *VCL-NTRK2*, *ETV6-NTRK3*, and *EML4-NTRK3* [4, 124, 125]. *NTRK* fusions are present in 1% of tumors from adult patients with GBM [4, 127, 128], and they were found in 40% of nonbrainstem high-grade GBM in children younger than 3 years (Table 3) [124]. In a recent analysis of 404 gliomas, 8 were identified with *NTRK* fusions, and 6 of these fusions involved *NTRK2* [128]. In this series, 5 of the *NTRK* fusions (*GKAP1-NTRK2*, *KCTD8-NTRK2*, *TBC1D2-NTRK2*, *SQSTM1-NTRK2*, *EML4-NTRK3*) were in GBM and the remainder in lower-grade gliomas (*BCAN-NTRK1* in pilocytic astrocytoma; *NOS1AP-NTRK2* in anaplastic astrocytoma; *VCAN-NTRK2* in grade 2 astrocytoma) [128]. Fusions have also been found in pilocytic astrocytomas, the most common childhood brain tumor. The most frequently reported gene fusion in these tumors is *KIAA1549-BRAF*, but fusions involving *NTRK2* (*QKI-NTRK2* and *NACC2-NTRK2*) have also been reported [5]. In a recent genomic study of 26 glioneuronal tumors, fusions were detected in 30% of patients and involved *NTRK*, *FGFR1*, and *BRAF* fusions, among others [7].

Clinically, a 54-year-old patient with an unresectable pontine glioneuronal tumor harboring *BCAN-NTRK1* fusion was treated with entrectinib, and a 60% reduction in tumor volume was observed using 3-dimensional volumetric assessment.

Although early, the data about targeting such gene fusion abnormalities are encouraging. Entrectinib has been reported to have efficient brain penetration in preclinical models (Table 2) [129]. A recent report demonstrated that a *BCAN-NTRK1* fusion was a potent driver of high-grade gliomas, and entrectinib demonstrated effective inhibition of tumor growth and increased survival compared with control treatment in a mouse model of *BCAN-NTRK1*-driven glioma [130]. Clinically, a 54-year-old patient with an unresectable pontine glioneuronal tumor harboring *BCAN-NTRK1* fusion was treated with entrectinib, and a 60% reduction in tumor volume was observed using 3-dimensional volumetric assessment [7]. The radiologic response was associated with resolution of clinical symptoms of diplopia and ataxia, and the response was maintained for the 11 months on treatment [7].

The ALK/ROS1 inhibitor lorlatinib has been shown to inhibit tumor growth in a *FIG-ROS1* mouse model of malignant glioma [131]. The ROS1/TRK inhibitor DS-6051b is currently being evaluated in a phase I study in Japanese patients with advanced solid malignancies harboring either a *ROS1* or *NTRK* gene fusion (NCT02675491). The FGFR inhibitor erdafitinib (JNJ-42756493) has been shown to inhibit growth of glioma cells harboring *FGFR3-TACC3* fusions. Two patients with glioma harboring this genetic alteration exhibited stable disease and minor response when treated with JNJ-42756493 in a phase I trial [132].

Conclusion

Central nervous system malignancies, including primary tumors and metastatic tumors of extracranial origin, continue to be a clinical challenge. The incidence of CNS metastases is increasing as new therapies achieve better systemic control and patients are living longer [133]. Gene fusions are an important class of oncogenic drivers and have been identified in a variety of primary CNS malignancies and CNS metastases originating from extracranial tumors. We recommend that testing for gene fusions be considered in patients with primary CNS tumors and CNS metastases where clinically relevant. A number of targeted therapies are approved or under investigation for the treatment of patients with certain gene fusions, and an ability to penetrate the BBB is an important attribute for many of these agents. Investigational therapies that can cross the BBB may treat both the primary tumor and CNS metastases and have the potential to prevent progression to the CNS. It will be interesting to monitor the development of these agents and their ability to provide intracranial and extracranial disease control.

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Disclosures

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For Further Reading:
Adrienne Johnson, Eric Severson, Laurie Gay et al. Comprehensive Genomic Profiling of 282 Pediatric Low- and High-Grade Gliomas Reveals Genomic Drivers, Tumor Mutational Burden, and Hypermutation Signatures. ***The Oncologist*** 2017;22:1478-1490.

Implications for Practice:
By providing objective data to support diagnostic, prognostic, and therapeutic decision-making, comprehensive genomic profiling is necessary for advancing care for pediatric neuro-oncology patients. This article presents the largest cohort of pediatric low- and high-grade gliomas profiled by next-generation sequencing. Reportable alterations were detected in 95% of patients, including diagnostically relevant lesions as well as novel oncogenic fusions and mutations. Additionally, tumor mutational burden (TMB) is reported, which identifies a subpopulation of hypermutated glioblastomas that harbor deleterious mutations in DNA repair genes. This provides support for TMB as a potential biomarker to identify patients who may preferentially benefit from immune checkpoint inhibitors.