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REVIEW ARTICLE

CNS Tumors in Neurofibromatosis

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A B S T R A C T

Neurofibromatosis (NF) encompasses a group of distinct genetic disorders in which affected children and adults are prone to the development of benign and malignant tumors of the nervous system. The purpose of this review is to discuss the spectrum of CNS tumors arising in individuals with NF type 1 (NF1) and NF type 2 (NF2), their pathogenic etiologies, and the rational treatment options for people with these neoplasms. This article is a review of preclinical and clinical data focused on the treatment of the most common CNS tumors encountered in children and adults with NF1 and NF2. Although children with NF1 are at risk for developing low-grade gliomas of the optic pathway and brainstem, individuals with NF2 typically manifest low-grade tumors affecting the cranial nerves (vestibular schwannomas), meninges (meningiomas), and spinal cord (ependymomas). With the identification of the *NF1* and *NF2* genes, molecularly targeted therapies are beginning to emerge, as a result of a deeper understanding of the mechanisms underlying *NF1* and *NF2* protein function. As we enter into an era of precision oncology, a more comprehensive awareness of the factors that increase the risk of developing CNS cancers in affected individuals, coupled with a greater appreciation of the cellular and molecular determinants that maintain tumor growth, will undoubtedly yield more effective therapies for these cancer predisposition syndromes.

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INTRODUCTION

Neurofibromatosis (NF) encompasses at least three distinct medical disorders, including NF type 1 (NF1), NF type 2 (NF2), and schwannomatosis.[1] Each of these conditions has a different genetic etiology.[2] Although all three disorders are characterized by peripheral nerve sheath tumors (neurofibromas or schwannomas), the diagnostic criteria used to render an accurate clinical diagnosis for each are quite specific and readily distinguish one disorder from another.

NF1 is the most common of the three conditions, affecting 1 in 3,000 individuals worldwide.[3] As a tumor predisposition syndrome, individuals with NF1 are prone to the development of a diverse spectrum of benign and malignant cancers. Within the nervous system, the pathognomonic feature of this disorder is the formation of peripheral nerve sheath tumors (neurofibromas); however, children with NF1 manifest brain tumors (optic pathway gliomas [OPGs] and brainstem gliomas [BSGs]). Accurate estimates of the frequency of malignant tumors in NF1 have not been established; however, 5% of individuals will develop a malignant peripheral nerve sheath tumor,[4] with a lifetime risk between 9% and 13%,[5] whereas the prevalence of high-grade gliomas is 10 to 50 times higher than it is in the general population.[6]

NF2 affects 1 in 30,000 individuals worldwide and is predominantly a tumor predisposition disorder.[7] Children and adults with NF2 harbor a spectrum of nervous system tumors, including cranial and peripheral nerve schwannomas, as well as meningiomas and spinal ependymomas.[8] In addition, 60% to 80% of individuals with NF2 may develop early cataracts[9] and retinal abnormalities (hamartomas and epiretinal membranes[10]) that can impair vision.[11] Schwannomatosis is less common than NF2, and adults typically present with spinal and peripheral schwannomas.[12] In this review, we will restrict our discussion to CNS tumors arising in children and adults with NF1 and NF2. Treatises on peripheral nervous system involvement (neurofibromas, malignant peripheral nerve sheath tumors, and schwannomas) in the neurofibromatoses can be found elsewhere.[7,13-17]

NEUROFIBROMATOSIS TYPE 1

Optic Gliomas

The most common brain tumor affecting individuals with NF1 is the OPG, seen in 15% to

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20% of people with this condition.[18] These neoplasms are classified as pilocytic astrocytomas, which do not progress to high-grade malignancies. OPGs can arise anywhere along the optic pathway from the retro-orbital optic nerve to the postchiasmal optic radiations (Figs 1A-1D); however, the majority of these gliomas are restricted to the optic nerves and chiasm. Importantly, OPGs are tumors of childhood, most frequently arising in children younger than 7 years of age (mean age, 4.5 years). Although the majority of these tumors appear in young children, late-onset OPGs have been reported.[19]

OPGs are usually identified on magnetic resonance imaging (MRI), where they typically appear as swollen optic nerves, frequently with robust gadolinium enhancement. Some practitioners use baseline neuroimaging in early childhood; however, a normal brain MRI does not preclude the later development of an OPG.[20] Moreover, initially symptomatic children are more likely to require treatment than are those with incidentally identified tumors.[21] In most centers, children undergo annual age-appropriate visual assessments, beginning in the first year of life, to detect changes in visual acuity,[22,23] with neuroimaging reserved for symptomatic children to track the growth of a known OPG.[24]

Unlike their sporadic counterparts, NF1-associated OPGs do not always exhibit progressive enlargement on neuroimaging studies, and only 30% to 50% of children with NF1-associated OPGs will experience a decline in visual acuity (two-line decrement). Fewer than 50% of initially symptomatic children will have continued visual impairment requiring treatment. The decision to treat should be based on a progressive decline in visual acuity, using age-appropriate vision tests (Teller, HOTV, and Snellen acuity cards).[22]

Risk factors for vision loss related to NF1-associated OPGs include young age, optic tract/radiation involvement, and female sex. In studies, children younger than 2 years of age, as well as those harboring optic tract/radiation gliomas, were more likely to experience declines in visual acuity and require treatment.[25] Although the frequency of OPGs is similar in males and females with NF1, two studies found that girls with NF1-associated OPG required treatment more often than their male counterparts did,[26] especially for OPGs restricted to the optic nerve.[27,28]

A small number of young children with NF1-associated OPGs will present with signs of precocious puberty. Most of these children harbor chiasmal tumors, requiring evaluation of the hypothalamic-pituitary-gonadal endocrine axis.[29] The finding of early secondary sexual characteristics in a child with NF1 should warrant further evaluation for a chiasmal/hypothalamic glioma.

First-line treatment of symptomatic children with NF1-associated OPG is carboplatin/vincristine therapy,[30] resulting in tumor stabilization in 50% to 60% of treated individuals. However, it is not clear whether this therapy results in recovery of vision, which remains a source of lifelong morbidity for children and adults with NF1.[31] For this reason, therapies aimed at inhibiting the growth control pathways hyperactivated as a result of *NF1* loss are currently being pursued in clinical trials (Table 1).

Brainstem Gliomas

The second most frequently encountered brain tumor in individuals with NF1 is the BSG.[32] NF1-associated BSGs have been comparatively understudied relative to NF1-associated OPGs, with a small number of reports describing the clinical features in 20 to 30 children with these tumors.[33] In general, NF1-associated BSGs

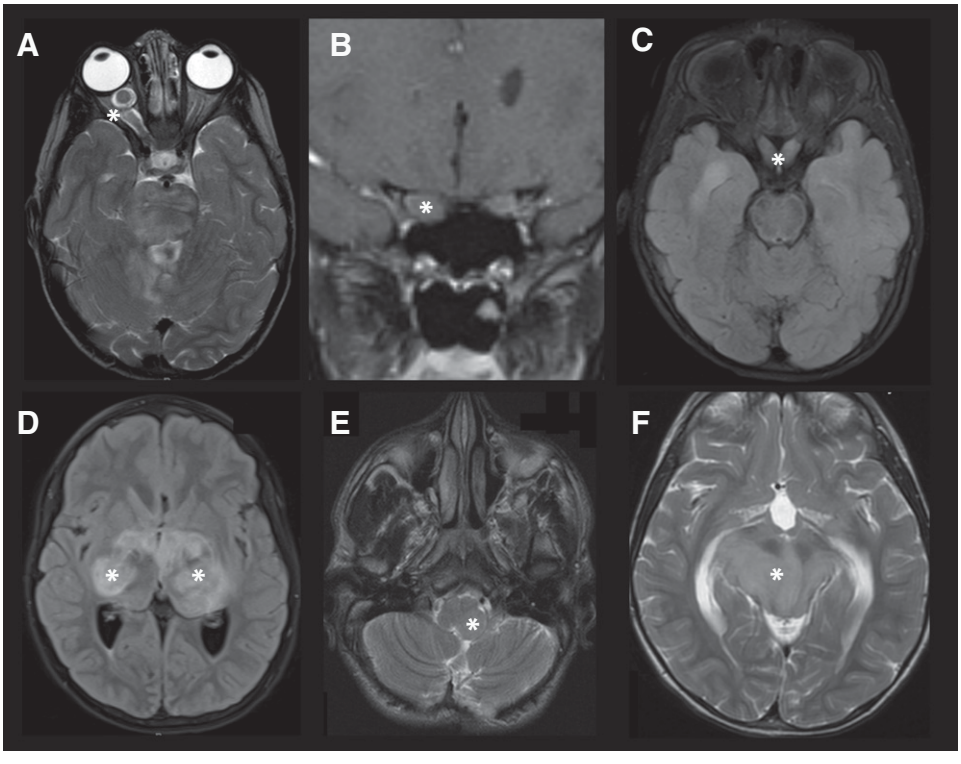

Fig 1. CNS tumors in neurofibromatosis type 1. (A) Right optic nerve glioma with contrast enhancement. (B) Right optic glioma in the coronal plane, revealing asymmetry in the sizes of the optic nerves. (C) Bilateral optic chiasm and tract glioma. (D) Bilateral optic radiation glioma. (E) Left pontine glioma extending into the medulla. (F) Bilateral midbrain glioma with associated obstructive hydrocephalus (note the enlarged posterior horns of the lateral ventricles). Asterisks denote the location of the tumors in all panels.

Table 1. Clinical Trials for Neurofibromatosis Type 1 CNS Tumors

Tumor	Drug	Mechanism of Action	ClinicalTrials.gov
Low-grade glioma	RAD001	mTOR inhibitor	NCT01158651
	Lenalidomide	thalidomide derivative	NCT01553149
	Tarceva/Rapamycin	EGFR/mTOR inhibitor	NCT00901849
	MEK162	MEK inhibitor	NCT02285439
	Selumetinib	MEK inhibitor	NCT01089101

Abbreviation: mTOR, mechanistic target of rapamycin.

are indolent neoplasms, often discovered as incidental findings on neuroimaging studies used to monitor the growth of a known OPG or to discover the etiologic cause of headache (Fig 1E). Similar to NF1-associated OPGs, these tumors are usually pilocytic astrocytomas, arising anywhere within the brainstem (midbrain, pons, and medulla). In contrast to OPGs, children with NF1-associated BSGs tend to be slightly older (average age, 7 to 8 years).[34]

When children with NF1-associated BSGs are symptomatic, they may come to medical attention because of headache with associated nausea and vomiting. These children typically harbor a midbrain tumor that results in obstructive hydrocephalus (Fig 1F) and requires ventriculoperitoneal shunt placement or an endoscopic ventriculostomy. In other cases, children may have less localizing signs or symptoms, such as cranial nerve palsies, ataxia, or hypotonia. Current medical treatment is also carboplatin/vincristine chemotherapy[35]; however, molecularly targeted drug therapies are also being evaluated in clinical trials.

Gliomas in Adults

Most low-grade gliomas are observed in children with NF1, but these tumors can arise, albeit less commonly, in adults with NF1.[36,37] Although NF1-associated OPGs and BSGs do not progress to malignancy, young adults with NF1 are prone to the development of malignant gliomas. These tumors are uncommon, affecting fewer than 1% of all individuals with NF1; however, it should be appreciated that young adults with NF1 harbor a 10-fold to 50-fold increased risk of developing these deadly cancers.[6] For this reason, adults with NF1 who present with signs of increased intracranial pressure, new-onset seizures, or neurologic deficits should be promptly evaluated with neuroimaging studies. Unfortunately, the prognosis for NF1-associated malignant glioma is dismal, and treatments are similar to those administered to adults with malignant gliomas in the general population.

NEUROFIBROMATOSIS TYPE 2

Vestibular Schwannomas

The most common brain tumor affecting individuals with NF2 is the vestibular schwannoma (VS), observed in 90% to 95% of people with NF2.[9,38] Bilateral VSs are pathognomonic for this tumor predisposition condition. VSs are contrast enhancing and are best evaluated by high-resolution, contrast-enhanced T1-weighted MRI with fine continuous cuts through the internal auditory canal (Fig 2A). Given their anatomic location, people with VSs usually present with hearing loss, tinnitus, or imbalance, or a combination of these three symptoms.[39]

The decision to treat with either surgery and/or radiosurgery requires a consideration of the patient's age and his or her general medical condition, hearing status, neurologic symptoms, and the size of the tumor. Many VSs can be safely monitored with serial imaging studies, coupled with assessments of hearing and other neurologic functions.[40] When safely possible, the goal of surgery is complete resection of the tumor; however, when the VS is in close proximity to other cranial nerves or the brainstem, surgery may involve only a partial resection. Some patients, particularly those with larger VSs, may develop hydrocephalus, requiring a diversionary ventriculoperitoneal shunt.

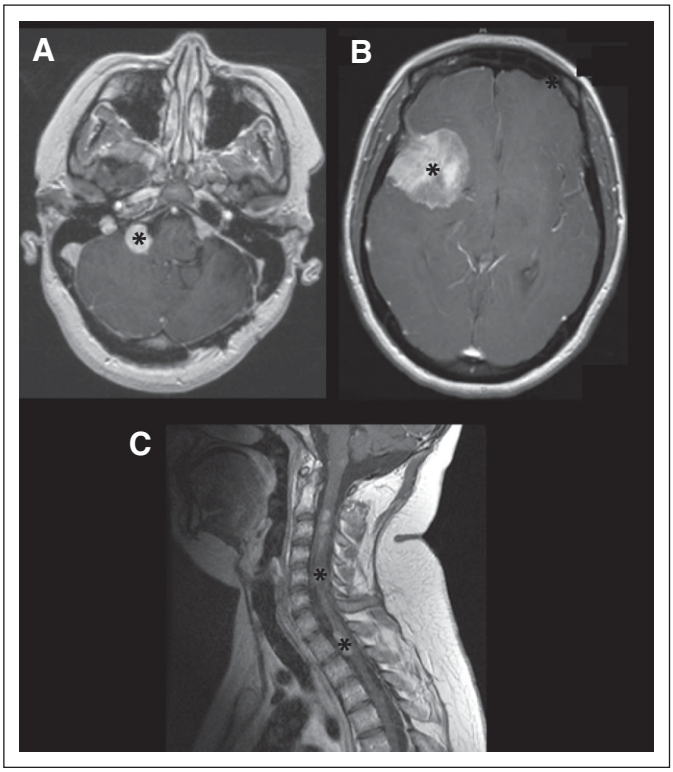

Fig 2. CNS tumors in neurofibromatosis type 2. (A) Bilateral vestibular schwannomas with gadolinium contrast enhancement (asterisk). (B) A large meningioma in the right anterior and middle cranial fossa in the axial plane (asterisk). (C) Multiple spinal cord ependymomas (string of pearls) in the sagittal T1-weighted contrast-enhanced magnetic resonance image of the cervical spine (asterisks).

Stereotactic radiosurgery is a well-tolerated option for individuals harboring smaller tumors. Although far less invasive, this procedure carries some risk of delayed hearing loss and cranial nerve dysfunction. Relative long-term hearing preservation has been reported in 33% to 53% of patients with NF2 treated with stereotactic radiosurgery.[41,42] Subtotal tumor resection followed by stereotactic radiation may be used in some situations, especially for people with large tumors, to preserve the function of the facial nerve and other CNS structures.[42]

Until recently, there were no promising medical therapies for VSs, limiting the management of these tumors to surgery or radiosurgery. Over the past several years, numerous molecularly targeted treatments have emerged (Table 2). Bevacizumab is a humanized immunoglobulin monoclonal antibody specific for vascular endothelial growth factor, expressed by nearly 100% of VSs.[43] Recent studies have shown that bevacizumab treatment resulted in hearing improvement and tumor shrinkage in some, but not all, patients with NF2.[44]

Meningiomas

Meningiomas are the second most common tumor encountered in individuals with NF2. Intracranial meningiomas are observed in 45% to 58% of people with NF2, whereas spinal meningiomas are found in approximately 20% of affected individuals. Intracranial meningiomas tend to be multiple in number and often develop at a younger age than do their sporadic counterparts.[9] Meningiomas homogeneously enhance after contrast administration, and are best evaluated with contrast-enhanced T1-weighted MRI (Fig 2B).

Clinical symptoms from meningiomas are usually related to their size and anatomic location. Although most meningiomas can be safely and fully resected, surgical resection of meningiomas involving the optic nerve sheath and skull base is associated with significant neurologic morbidity.[45] In situations where there is residual tumor from a partial resection, stereotactic radiosurgery has been used for local control.[46] However, to date, there are no established medical treatments for NF2-associated meningiomas, and clinical studies using molecularly targeted drug therapies are currently being investigated.

Ependymomas

Ependymomas are present in 33% to 53% of individuals with NF2, with the cervical cord or cervicomedullary junction being the most common anatomic sites of involvement.[47] On MRI, these tumors appear as hyperintense masses on T2-weighted sequences, which are hypointense to isointense on T1-weighted sequences. The majority of NF2-associated ependymomas are contrast-enhancing tumors (Fig 2C).

Clinical symptoms of spinal cord ependymomas are variable and depend on the size and anatomic location of the tumor. In contrast to sporadic tumors, the majority of NF2-associated spinal tumors are asymptomatic. As such, fewer than 20% of patients with these tumors are symptomatic, and those with intramedullary spinal cord tumors most commonly present with back pain, weakness, or sensory disturbances.[48]

The management of NF2-associated ependymomas has not been firmly established. Although observation is often used to follow asymptomatic tumors, surgical resections are frequently effective and curative in patients with NF2-associated symptomatic spinal cord ependymomas. The timing of the resection is best determined by detailed neurologic surveillance to assess for early onset of symptoms.[49] Because most NF2-associated spinal cord ependymomas are grade II tumors, gross total resection is often the mainstay of treatment, with radiation therapy reserved for recurrent or residual tumors. WHO grade I myxopapillary ependymoma has also been reported in patients with NF2, and these tumors are usually treated with surgery.[50] Given that NF2 is a tumor predisposition syndrome, there are concerns about the additional risks of radiation therapy in this patient population. For this reason, chemotherapeutic options for the treatment of recurrent and unresectable tumors are desirable. The evaluation of molecularly targeted therapies for these tumors is currently ongoing. Bevacizumab treatment improved symptoms related to NF2-associated ependymomas.[51]

FUTURE THERAPIES

Molecular Etiologies

NF1 is caused by a germline mutation in the *NF1* gene located on chromosome 17.[52] Although this mutation alone is sufficient

Table 2. Clinical Trials for Neurofibromatosis Type 2 CNS Tumors

Tumor	Drug	Mechanism of Action	ClinicalTrials.gov
Vestibular schwannoma	Icotinib	EGFR inhibitor	NCT02934256
	Endostatin	Broad spectrum antiangiogenesis inhibitor	NCT02104323
	Lapatinib	EGFR/ErbB2 inhibitor	NCT00973739
	RAD001	mTOR inhibitor	NCT01490476; NCT01419639; NCT01345136
	Bevacizumab	Antiangiogenic agent (VEGF-A monoclonal antibody)	NCT01767792; NCT01207687
	Axitinib	VEGFR/PDGFR/c-KIT inhibitor	NCT02129647
Meningioma	AZD2014	mTOR inhibitor	NCT02831257
	RAD001	mTOR inhibitor	NCT01880749
	Bevacizumab	Antiangiogenic agent (VEGF-A monoclonal antibody)	NCT01125046
	Sunitinib	PDGFR/VEGFR/c-KIT inhibitor	NCT00589784
Ependymoma	RAD001	mTOR inhibitor	NCT02155920
Cutaneous schwannoma	Sorafenib	multiple kinase inhibitor	EudraCT 2011-001789-16

Abbreviation: mTOR, mechanistic target of rapamycin.

for some NF1-associated clinical features (eg, autism symptoms), tumor formation requires that a somatic (acquired) mutation in the remaining normal *NF1* allele occur.[53] In this manner, both copies of the *NF1* gene are inactivated in NF1-associated cancers, resulting in loss of *NF1* protein (neurofibromin) expression. Neurofibromin is a large protein (220-250 kilodaltons), which functions as a GTPase-activating protein to accelerate the conversion of active, GTP-bound RAS to its inactive, GDP-bound form.[54] In this manner, neurofibromin normally suppresses RAS-mediated growth,[55] such that its loss in tumor cells results in elevated RAS activity and increased cell proliferation and survival (Fig 3A). Active RAS transmits its growth-promoting signal through cascades of small proteins whose phosphorylation by kinases (eg, RAF kinase, phosphoinositide-3-kinase) leads to successive activation of RAS downstream effectors (eg, MEK, AKT). In neuroglial cells, neurofibromin loss leads to both MEK and AKT activation, which each can converge on the mechanistic target of rapamycin (mTOR).[56,57] With the elucidation of the key components of the RAS signaling pathway, a number of molecularly targeted therapies have entered clinical trials, including MEK and mTOR inhibitors (Table 1).

The *NF2* tumor suppressor gene is located on chromosome 22q, and its protein (schwannomin or merlin) bears striking sequence similarity to a family of structural linker proteins, termed Protein 4.1 molecules.[58,59] Among these Protein 4.1 family members, the subclass of molecules containing ezrin, radixin, and moesin (ERM proteins) are the most similar to merlin (Fig 3B). Unlike NF1-associated gliomas, tumor development in NF2 may not require coupling of a germline *NF2* mutation with somatic *NF2* loss. While NF2-associated tumors lack merlin expression, the mechanism of merlin growth suppression has not been completely elucidated. In this regard, numerous reports in different tissue types have demonstrated that merlin can control cell growth using a plethora of distinct, nonintersecting, signaling pathways, including MEK, YAP, mTOR, ErbB2, SRC, FAK, and RAC1 effectors.[60-65] Some of these effectors have emerged as viable targets for therapeutic intervention, such as ErbB2 and mTOR, and agents that inhibit these signaling molecules are now in human clinical trials (Table 2).

Preclinical Models for Drug Discovery and Evaluation

Currently, there are two major barriers that limit progress in the field of NF developmental therapeutics. First, some NF-associated brain tumors (eg, optic pathway and BSGs, spinal ependymomas) are rarely biopsied or surgically removed. To circumvent this particular issue for NF1 brain tumors, the Children's Tumor Foundation has initiated a multi-institutional international project to sequence low-grade gliomas from children with NF1. Other genomic landscaping efforts focused on brain tumors in NF2 are also in progress.

Second, unlike high-grade malignancies, it has been challenging to maintain NF-associated tumors as patient-derived xenografts (PDXs). To date, successful orthotopic transplant models have only been developed for NF2-associated meningioma.[66] In the case of NF1-associated OPG, the low clonogenicity and frequent senescence of glioma tumor stem cells has precluded PDX modeling. In the absence of tractable preclinical PDX models, preclinical researchers have turned to the use of genetically engineered mouse strains.

Although there are no preclinical models of NF1-associated BSGs, NF1-associated OPGs and high-grade gliomas have been generated in mice. Several high-grade glioma models have been established by coupling complete *Nf1* gene inactivation with loss of other tumor suppressor genes (eg, p53, PTEN). Each of these high-grade glioma models is distinct with respect to mouse

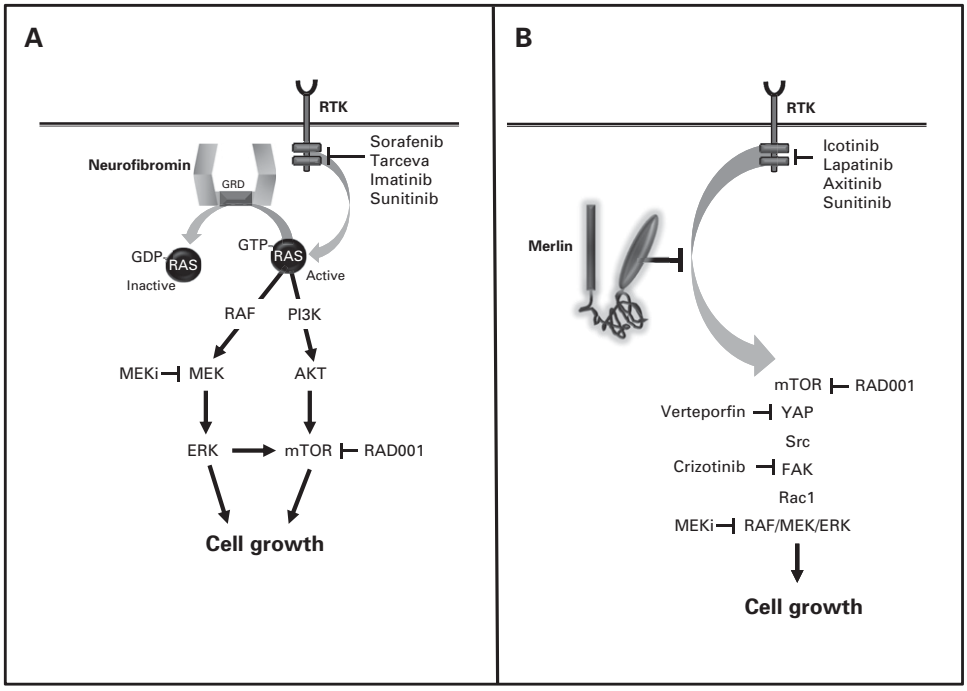

Fig 3. *NF1* and *NF2* genes/proteins. (A) The *NF1* gene encodes a 2818 amino acid protein with a central RAS-GTPase-activating protein domain. Neurofibromin functions to accelerate the conversion of active GTP-bound RAS to its inactive GDP-bound conformation. Active RAS transmits its growth-promoting signal by activating MEK, AKT, and mechanistic target of rapamycin (mTOR). (B) The *NF2* gene encodes a 595 amino acid protein with striking sequence similarity to molecules of the protein 4.1 (ezrin, radixin, and moesin) superfamily. Numerous mechanisms have been proposed for merlin growth regulation, including suppression of RAF/MEK, YAP, mechanistic target of rapamycin (mTOR), ErbB2, Src, FAK, and Rac1 activation. Molecularly targeted therapies that inhibit specific signaling intermediates and receptor tyrosine kinases have been evaluated in preclinical and clinical trials.

engineering and entails a variety of genetic targeting strategies, such as CRISPR/Cas9,[67] standard and conditional knockout mice,[68,69] and viral gene silencing.[70]

Similar to children with NF1, *Nf1* optic gliomagenesis in mice requires a combination of a germline inactivating *Nf1* gene mutation and somatic *Nf1* loss in neuroglial progenitor cells.[71] These preclinical models have been instructive in revealing new insights into disease pathogenesis, risk assessment, and tumor treatment. First, optic gliomagenesis requires a productive interaction between neoplastic tumor cells and non-neoplastic immune system–like cells (microglia) in the glioma microenvironment.[72] These monocytes provide growth-promoting signals (eg, chemokines) for *NF1*-deficient neoplastic cells,[73] such that silencing microglia function or chemokine signaling greatly attenuated optic glioma growth in mice.[74] Second, mice with *Nf1* optic gliomas exhibit reduced visual acuity, which reflects retinal ganglion cell loss.[75] Using these mice, the molecular basis for the sexual dimorphism observed in female children with NF1 (reduced visual acuity) was identified.[76] In addition, defining the temporal course of events in mice has revealed therapeutic windows in which treatments at the time of early retinal ganglion cell death may limit additional vision loss.[77] Third, *Nf1* optic glioma mice have allowed early preclinical evaluations of promising therapies that inhibit RAS downstream signaling effectors, leading to clinical trials with MEK and mTOR inhibitors.[78,79]

Although no models of NF2-associated ependymoma have been generated to date, *Nf2* genetically engineered mouse strains with meningioma and schwannoma have been developed. Somatic *Nf2* loss after subarachnoid or subdural viral injection of Cre recombinase into newborn $Nf2^{flox/flox}$ conditional knockout mice results in meningioma in 20% to 30% of mice by 11 months of age.[80] More aggressive tumors develop when *Nf2* loss is coupled with loss of other tumor suppressor genes (eg, *Ink4a*).[81] In addition, these mice have been instructive in identifying a common cell of origin for these tumors[82] and the value of HSP90 inhibitors as potential treatments for NF2-associated nervous system tumors.[83] Similarly, mice with biallelic *Nf2* inactivation in periostin-expressing cells develop schwannomas histologically identical to their human counterparts,[84] as well as functional impairments in hearing and balance.

With the availability of an efficient Neurofibromatosis Clinical Trials Consortium[85] and numerous authenticated preclinical models of NF-associated brain tumors, it now becomes possible to identify molecular targets and evaluate their efficacy in mice prior to human clinical trials. As we enter an era of precision medicine, we are poised to make outstanding progress for NF1 and NF2 CNS tumors. However, it is important to deploy these preclinical platforms in a way that most closely resembles human clinical trials, both in terms of dosing and outcome measures.[86] This is particularly relevant to NF1-associated OPGs and NF2-associated VSs, where vision and hearing loss, respectively, need to be considered as success metrics in rodent drug trials. Moreover, individuals with NF-associated brain tumors represent a heterogeneous population of individuals in terms of sex,[28] germline *NF* gene mutation,[87,88] and coexisting genetic changes.[89] The use of a diverse collection of mice that fully capture this heterogeneity will be critical to identify populations of persons most likely to respond to any given therapy. Third, we need to better calibrate our expectations with respect to celebrating preclinical outcomes. Setting a higher bar for tumor responses in rodent drug studies may result in greater efficacy in human clinical trials. In summary, we have come a long way since the discovery of the *NF1* and *NF2* genes in the early 1990s and now are uniquely positioned to find effective medical therapies for the CNS tumors arising in this population of at-risk individuals.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Manuscript writing: All authors
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Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

CNS Tumors in Neurofibromatosis

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