REVIEW

Past, Present, and Future Therapeutic Strategies for NF-1-Associated Tumors

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Abstract

Purpose of Review Neurofibromatosis type 1 (NF-1) is a cancer predisposition syndrome caused by mutations in the *NF1* tumor suppressor gene that encodes the neurofibromin protein, which functions as a negative regulator of Ras signaling. We review the past, current, and future state of therapeutic strategies for tumors associated with NF-1.

Recent Findings Therapeutic efforts for NF-1-associated tumors have centered around inhibiting Ras output, leading to the clinical success of downstream MEK inhibition for plexiform neurofibromas and low-grade gliomas. However, MEK inhibition and similar molecular monotherapy approaches that block Ras signaling do not work for all patients and show limited efficacy for more aggressive cancers such as malignant peripheral nerve sheath tumors and high-grade gliomas, motivating novel treatment approaches.

Summary We highlight the current therapeutic landscape for NF-1-associated tumors, broadly categorizing treatment into past strategies for serial Ras pathway blockade, current approaches targeting parallel oncogenic and tumor suppressor pathways, and future avenues of investigation leveraging biologic and technical innovations in immunotherapy, pharmacology, and gene delivery.

Keywords Neurofibromatosis type 1 · Targeted therapy · Cell signaling · MEK inhibition

Introduction

Neurofibromatosis type 1 (NF-1) is an autosomal dominant genetic disorder affecting 1 in 3000 individuals caused by germline mutation of the *NF1* gene. The *NF1* gene product neurofibromin is a Ras GTPase-activating protein (RAS-GAP) that converts active GTP-bound Ras into inactive GDP-bound Ras [1–4]. Thus, *NF1* loss leads to constitutive Ras activation and many clinical manifestations of NF-1 such as café-au-lait macules, seizures, chronic pain, vascular issues, bone defects, central and peripheral nervous system tumors, breast cancer, and other malignancies [5, 6]. Of note, tumorigenesis typically requires a second somatic hit and consequent loss of function in the remaining wildtype *NF1* allele [7].

Patients with NF-1 are at significantly increased risk for plexiform neurofibromas (PNs), a benign peripheral nervous system tumor that can transform into malignant peripheral nerve sheath tumors (MPNSTs), and low-grade gliomas (LGGs), a benign central nervous system tumor that can transform into malignant high-grade gliomas (HGGs) [8–10]. In addition, atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP) comprise an intermediate tumor entity that reflect the transition from plexiform neurofibromas to MPNSTs [11]. ANNUBPs are associated with *CDKN2AB* loss, and their diagnosis and classification remain an area of active investigation [12•, 13, 14].

Here, we summarize past, present, and future treatment approaches for NF1-associated tumors. Given neurofibromin's function as a Ras-GAP and resulting Ras pathway misactivation, therapies to date have primarily focused on

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inhibiting Ras signaling output at the level of RAF, MEK, ERK, and mTOR [15]. Leveraging our improved understanding of additional genetic hits required for NF1-associated tumorigenesis, more recent work leverages novel pharmacologic approaches to block parallel pathways such as PRC2 or *CDKN2A/B* loss. We conclude with an eye toward the future of NF1 therapeutics currently in preclinical development and early clinical trials including oncolytic viruses, cellular therapy, immune checkpoint inhibitors, gene therapy, and direct Ras inhibition.

Past Approaches: Serial Inhibition Along the Ras Signaling Axis

Ras signaling begins at the cell membrane with receptor tyrosine kinase (RTK) activation, setting off a signaling cascade to activate Ras through G-protein exchange factors (GEFs) such as SOS, a process that requires SHP2 and adapter proteins such as GRB2 to promote the formation of active GTP bound Ras (Fig. 1A) [16]. GTP-bound Ras subsequently activates RAF-MEK-ERK while mTOR is classically activated by PI3K signaling, classically through RTK activation with a potential contribution directly by active GTP-bound Ras. Accordingly, upstream RTKs and downstream RAF-MEK-ERK and mTOR have been the primary area of therapeutic investigation to date.

Mitogen-Activated Protein Kinase Kinase (MEK) Inhibitors (MEKi)

MEK inhibitors (MEKi) have shown significant efficacy for NF1-associated PNs. In particular, the MEKi selumetinib has received FDA approval for symptomatic and inoperable PNs in patients aged 2–18, with ongoing Phase 2 trials in adults displaying similar positive responses [17, 18•, 19].
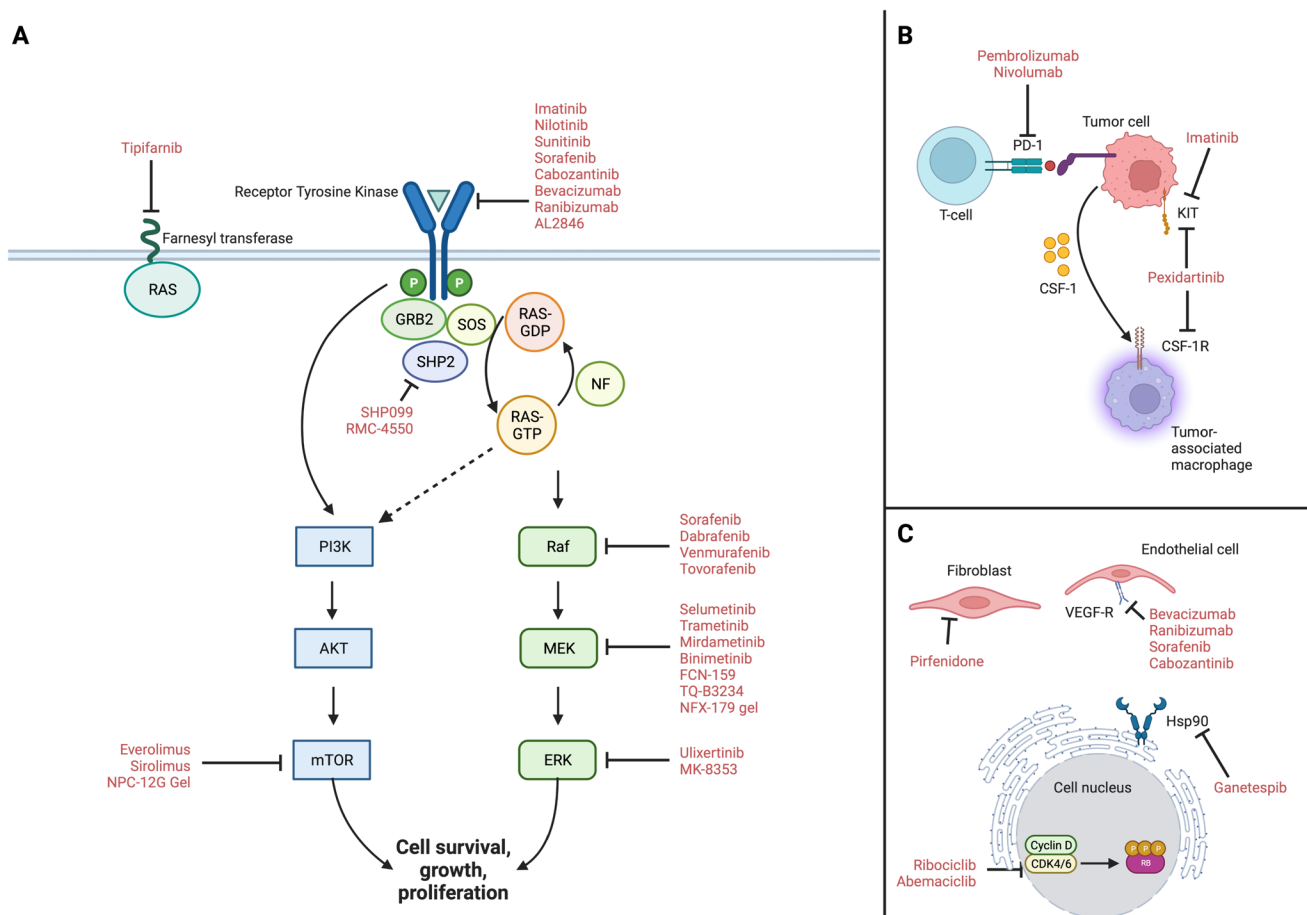

Fig. 1 Pathways involved in NF1-associated tumorigenesis. **A** RAF/MEK/ERK inhibitors act on the MAPK pathway; mTOR inhibitors act on the PI3K/AKT/mTOR pathway; receptor tyrosine kinase (RTK) inhibitors and SHP2 inhibitors act on both pathways. Farnesyl transferase inhibitors inhibit RAS signaling. **B** Immunotherapeutic approaches and strategies targeting the tumor microenvironment have been explored, utilizing immune checkpoint, CSF1-R, and KIT inhibitors. **C** Other approaches include targeting other cells within the tumor microenvironment, including fibroblasts and endothelial cells. Cell cycle inhibition utilizing CDK4/6 inhibitors has also been tested

The success has spurred the investigation of other MEKi such as binimetinib, cobimetinib, and mirdametinib to enhance clinical efficacy and impact on the tumor microenvironment [20].

Beyond PNs, MEKi is under investigation for additional NF1 manifestations, including atypical neurofibromas, MPNSTs, cutaneous neurofibromas, LGGs, and juvenile myelomonocytic leukemia. In particular, MEKi for cutaneous neurofibromas and LGGs is currently being tested in Phase 2 and 3 trials (NCT03871257, NCT03363217, NCT02285439, NCT03326388, NCT04201457) [21]. Beyond tumor-associated manifestations, MEKi may also have utility for non-tumor manifestations such as pain, bone issues, and neurocognition [17, 18•, 22, 23]. Clinical trials indicate reduced pain in PNs, hinting at the MEK pathway's role in NF1-related pain and suggesting that the tumor microenvironment plays an instrumental function in NF1-PN pathogenesis [17, 18•, 23–25]. Despite MEKi's promise, many challenges remain including dosing strategies, heterogenous responses, treatment resistance, and long-term safety persist, underscoring the need for additional research.

RAF Inhibition

RAF inhibition, the most proximal downstream signaling protein from RAS, has been studied extensively in *NF1*-mutant tumors. First-generation RAF inhibitors selectively targeting the BRAFV600E mutation show minimal efficacy, with resistance occurring within 6 to 7 months [26, 27]. Accordingly, pan-RAF inhibitors have been developed to address these challenges. Tovorafenib, which inhibits both monomeric and dimeric BRAF, has demonstrated efficacy in pre-clinical *NF1* mutant glioma models, and building on these promising results, a Phase 2 trial FIREFLY-1 (NCT04775485) investigated tovorafenib for recurrent pediatric LGGs and demonstrated a meaningful radiographic response, albeit not exclusively in *NF1*-mutant LGG [28•].

ERK Inhibition

The ERK inhibitor ulixertinib, a novel first-in-class drug exhibiting highly selective, reversible ATP-competitive inhibition of ERK1/2, has demonstrated an antitumor profile for MAPK-activated LGGs [29], and multiple clinical trials testing ulixertinib in the context of *NF1*-deficient cancers are currently underway (NCT05804227, NCT03454035). In addition, preclinical work in mice suggests ERK inhibition may be effective as combination therapy for plexiform neurofibromas [30]. MK-8353 is another ERK1/2 inhibitor that targets both the active and inactive form of ERK [31], but an open-label phase 1b clinical trial investigating the combination therapy of MK-8353 with MEKi selumetinib for advanced solid tumors found unacceptable levels of toxicity

at dose levels required for clinical response (NCT03745989) [32]. Additionally, concern has been raised over the long-term effects of both MEK and ERK inhibition on abnormal skeletal manifestations inherent to NF-1 patients. In that regard, the tyrosine kinase inhibitor ponatinib with activity against MEKK2 rescues skeletal defects in vivo, perhaps offering an additional combinatorial strategy to optimize the therapeutic window of ERK inhibitors [33].

Tyrosine Kinase Inhibitors (TKIs) and SHP2 Inhibition

TKIs disrupt upstream RTK input into Ras signaling, and initial studies with the multi-TKI sunitinib showed reduced tumor burden in a mouse model of NF1-related PNs [34, 35]. However, a subsequent clinical trial was terminated following an adverse event [36]. Furthermore, trials for TKIs imatinib and sorafenib exhibited only modest efficacy in PNs [37, 38]. A more recent Phase 2 trial with the TKI cabozantinib showed promise, with 42% of participants achieving a partial response in progressive PNs [39]. It remains unclear if this effect is mediated directly through RTKs or via alternate pathways, as preclinical work indicates that cabozantinib activity against MAPK interacting kinases (MNKs), when combined with the MEKi mirdametinib, induces regression in a genetically engineered mouse malignant peripheral nerve sheath tumor (MPNST) model [40].

Another approach to modulate upstream inputs is through SHP2, which potentiates Ras GTP loading, and thus, SHP2 inhibitors (SHP2i) may offer a promising approach for NF-1-associated tumors [41]. Indeed, *NF1*-mutant neuroblastomas are sensitive to the SHP2 inhibitor SHP099, and the combination of MEKi/SHP2i demonstrated improved efficacy across multiple preclinical models [42, 43]. By targeting signaling proteins upstream within the RAS-MAPK pathway, SHP2 inhibition may potentiate other targeted therapies in NF-1-associated tumors.

Mammalian Target of Rapamycin (mTOR) Inhibitors

The mTOR pathway is hyperactivated in *NF1*-deficient tumors [8, 44, 45]. Sirolimus, an FDA-approved mTOR inhibitor, was tested for PNs in a Phase 2 clinical trial, leading to increased time to progression but no significant difference in tumor volume [46, 47]. Similarly, everolimus was studied in a Phase 2 trial and showed no efficacy for NF1-related PNs but exhibited a significant radiographic reduction in recurrent NF1-LGGs, perhaps underscoring heterogeneity between different NF1 tumor entities [48, 49]. A recently completed Phase 2 trial investigated a combination therapy of sirolimus plus MEKi for unresectable or metastatic MPNSTs, and final trial results are eagerly anticipated [50].

Present Approaches: Parallel Inhibition of Co-mutated Tumor Suppressors

Following *NF1* loss, additional genetic hits are required for malignant transformation of benign nervous system tumors into their malignant entities [51, 52]. Of these, *CDKN2A/B* loss and PRC2 loss are well-appreciated steps in the transition from PN to MPNST [53, 54]. Loss of the tumor suppressor *CDKN2A/B*, which is associated with transition from PN to ANNUBP, leads to cyclin-dependent kinase (CDK) activation, motivating the application of CDK4/6 inhibitors (CDK4/6i) in NF1-associated tumors [55]. With respect to PRC2, *SUZ12* and *EED*, obligate members of the PRC2 epigenetic complex, are recurrently mutated in MPNSTs but not PNs [54].

CDK4/6 Inhibition (CDK4/6i)

The CDK4/6i abemaciclib demonstrated synergistic antitumor effects when combined with the ERKi LY3214996 for PN treatment in vivo [30]. A clinical trial (NCT04000529) is ongoing to evaluate the safety and efficacy of ribociclib combined with the SHP2 inhibitor TNO155 for advanced solid tumors. In *NF1*-mutant breast cancer, the CDK4/6i palbociclib reduced growth and enhanced sensitivity to the antiestrogenic medication fulvestrant, indicating a synergistic relationship [56, 57]. These findings suggest that CDK4/6 inhibition combined with targeted therapies may offer an improved treatment strategy.

Targeting Polycomb Repressive Complex 2 (PRC2)

PRC2 loss through mutation of its obligate members *SUZ12* or *EED* is common and provides a rationale for targeted combination therapies of NF1-associated tumors with bromodomain inhibitors [54, 58, 59]. The bromodomain protein BRD4 plays a crucial role in NF1-associated MPNST development and comprises a therapeutic target to potentially overcome MEKi resistance [60]. Interestingly, MPNSTs depleted of BRD4 protein exhibit a strong cytotoxic response to the pan-BET bromodomain inhibitor JQ1 [61]. Additionally, suppressing *SUZ12* enhances the impact of PD-901/JQ1 administration in NF1-deficient cells [62]. In a study on *NF1*-mutated ovarian cancer, co-administration of JQ1 and MEKi trametinib proved effective in overcoming the common rapid drug resistance associated with single-agent MEKi [63]. A second bromodomain inhibitor, bromosporine, demonstrated a superior therapeutic index when combined with MEKi cobimetinib for treating immunotherapy-resistant *NF1*-mutant melanoma, compared to MEKi treatment alone [64•]. More recent work suggests DNMT1

inhibition may be a druggable dependency upon PRC2 loss, providing yet another targeted approach [65]. Overall, targeting PRC2 loss holds significant promise for enhancing existing strategies for *NF1*-deficient tumors by increasing cytotoxicity and limiting the development of drug resistance.

Future Therapeutic Approaches: Beyond Targeted Therapeutics

Decades of work understanding the genetic and signaling mechanisms underlying *NF1*-associated tumorigenesis have nominated numerous targets, yet there remains an urgent, unmet clinical need for new therapies with improved therapeutic windows and more durable responses. Promising preclinical approaches leveraging pharmacologic advances to investigate gene therapy, directly targeting Ras, or reestablishing immune system function with cellular CAR-T therapies, checkpoint inhibitors, or oncolytic viral therapy (Fig. 1B) are areas of active investigation that offer potential for the next generation of therapeutics.

Gene Therapy

Gene therapy through adeno-associated viral (AAV) vectors offers a potentially curative approach aimed at *NF1* gene reconstitution. Although full-length reconstitution has been historically limited by the size of the *NF1* gene, the neurofibromin GTPase-activating protein-related domain (GRD) alone, fused with an H-Ras C10 sequence, demonstrates potent ERK1/2 suppression, reduced cell growth, and exhibiting specificity for *NF1*-mutant MPNST cells compared to *NF1*-intact cells [66, 67]. However, numerous open questions remain regarding gene targeting specificity, efficient delivery, and maximum therapeutic payload size that require further research to harness the potential of neurofibromin reconstitution.

Direct Ras Inhibition

Although Ras was historically considered to be undruggable as a direct pharmacologic target, multiple covalent inhibitors targeting oncogenic Ras variants now exist. In NF-1-associated tumors lacking an oncogenic Ras variant, multiple levels of evidence support a critical role for KRAS in mediating the effects of *NF1* loss [68, 69]. Accordingly, recently described pan KRAS inhibitors that inhibit wildtype KRAS yet spare NRAS and HRAS may show therapeutic efficacy for *NF1* mutant tumors [70•]. However, whether KRAS is the critical Ras effector for all NF-1 manifestations remains unclear. Moreover, blocking Ras alone may be insufficient, and thus, combination approaches with existing therapies may be required to overcome resistance. Indeed,

treatment resistance is a recognized problem for KRAS G12C inhibitors [71]. SHP2 inhibition has shown synergy with KRAS^{G12C} inhibitors [72, 73]. SHP2 inhibition prevents the action of SOS1/2, increasing the amount of the GDP-bound state of KRAS^{G12C} which is the target of KRAS inhibitors [74]. This is supported by the findings of KRAS-amplified cancer cell lines exhibiting increased sensitivity to SHP2 inhibition [72, 75].

CAR-T Cell Therapy

CAR-T cell therapy engineers T-cells with the ability to target overexpressed antigens specific to cancer cells and has revolutionized the treatment of cancer types, primarily hematologic malignancies such as leukemia and lymphoma [76]. Ongoing clinical trials (NCT03618381) are investigating EGFR-targeting CAR-T cell therapy for MPNSTs, and CAR-T therapy for *NF1*-mutated high-grade gliomas using tumor-specific internal peptides is being tested to address the challenge of non-unique expression on the surface of solid tumors. While many questions remain, including the competency of T cells derived from patients harboring a germline *NF1* mutation, [77] CAR-T cell therapy is a promising area of investigation for *NF1*-mutant tumors.

Immune Checkpoint Inhibitors (ICI)

ICIs have revolutionized cancer care for multiple solid tumor types, and case reports suggest potential ICI efficacy in patients with MPNSTs [78]. The PD-1 inhibitor pembrolizumab was investigated in an MPMS clinical trial but was closed due to limited accrual (NCT02691026). Ongoing clinical trials are evaluating the efficacy of adjuvant nivolumab along with CTLA-4 checkpoint inhibitor ipilimumab for newly diagnosed MPNSTs (NCT04465643, NCT02834013).

Beyond PD-1 axis blockade, colony-stimulating factor-1 receptor (CSF-1R) is often upregulated in various cancer phenotypes and plays a critical role in macrophage polarization, converting tumor-associated macrophages from the tumoricidal M0 or M1 phenotype to the tumorigenic M2 phenotype [79]. Pexidartinib, a novel small molecule CSF-1R inhibitor, showed promising results in a Phase 1 study for MPNSTs when combined with sirolimus, and a Phase 2 trial is now underway (NCT02584647) [80]. MK-1775, another novel ICI, is being investigated for combating MPNSTs by inhibiting *WEE1*, a key regulator of cell cycle progression [81].

Oncolytic Viral (OV) Therapy

OV therapy is another promising approach for *NF1*-associated tumors. A measles virus-based OV approach shows efficacy in MPNST cells [82], leading to a Phase 1 trial underway to investigate the clinical efficacy of this technique (NCT02700230).

Other trials leverage alternate viral agents such as Herpes Simplex Virus (HSV) HSV1716 to preferentially target actively dividing nervous system tumor cells (NCT00931931).

Conclusion

Patients with NF-1 can exhibit a diverse array of clinical manifestations. Building on classic NF1/Ras biology, MEK inhibitors are an effective therapy for a number of NF1-related manifestations, yet the heterogeneity and durability of their response motivate the development of additional approaches. Ongoing research into biologic mechanisms and signal transduction pathways dysregulated in *NF1*-associated tumors holds the potential to reveal additional therapeutic vulnerabilities. Moreover, targeting the tumor microenvironment and employing combination molecular therapies show promise. Continuous investigation through mechanistic investigation, preclinical modeling, clinical trials, the accumulation of long-term safety data, and collaboration between basic scientists and clinicians will be pivotal in advancing therapeutic interventions for NF1-associated tumors.

Declarations

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