Advanced pharmacological therapies for neurofibromatosis type 1-related tumors

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Abstract. Neurofibromatosis Type 1 (NF1) is an autosomal dominant tumor-predisposition disorder that is caused by a heterozygous loss of function variant in the NF1 gene, which encodes a protein called neurofibromin. The absence of neurofibromin causes increased activity in the Rat sarcoma protein (RAS) signalling pathway, which results in an increased growth and cell proliferation. As a result, both oncological and non-oncological comorbidities contribute to a high morbidity and mortality in these patients. Optic pathways gliomas, plexiform neurofibromas and malignant peripheral nerve sheath tumor (MPNST) are the most frequent NF1-associated tumors. The treatment of these complications is often challenging, since surgery may not be feasible due to the location, size, and infiltrative nature of these tumors, and standard chemotherapy or radiotherapy are burdened by significant toxicity and risk for secondary malignancies. For these reasons, following the novel discoveries of the pathophysiological mechanisms that lead to cell proliferation and tumorigenesis in NF1 patients, emerging drugs targeting specific signalling pathways (i.e. the MEK/ERK cascade), have been developed with promising results. (www.actabiomedica.it)

Key words: NF1, Malignant Peripheral Nerve Sheath Tumor, MPNST, Optic Pathway Glioma, Plexiform Neurofibroma, Selumetinib, Mtor Inhibitors

Background

Neurofibromatosis Type 1 (NF1) is an autosomal dominant tumor-predisposition disorder that is caused by a heterozygous loss of function variant in the tumor suppressor gene NF1. The average global prevalence is 33/100,000 individuals, varying among different countries from 12.8/100,000 in Russia to 104/100,000 in Israel (1–3).

NF1 was first described as a multisystemic disease by Friedrich Von Recklinghausen, in 1882. Nearly one century later, the National Institution of Health (NIH) Consensus Development Conference identified the diagnostic criteria (1987) (Table 1), which are still in use nowadays (4,5). The clinical hallmarks of NF1 are highly heterogeneous, and encompass non-malignant and malignant features. The former comprise pigmented abnormalities (multiple café-au-lait macules, axillary and inguinial freckling, Lisch nodules), neurofibromas, skeletal deformities, hypertension and neurocognitive deficits. Risk of cancer in NF1 patients is 2 to 5 times higher than in the general population (6,7). Malignancies can develop within or without the nervous system. Nervous system tumours include: op-
tic pathway and brainstem glioma, glioblastoma, and malignant peripheral nerve sheath tumor (MPNST). Patients with NF1 also show an increased risk of tumors developing outside the nervous system, like gastrointestinal stromal tumor (GIST), breast cancer, leukaemia, phaeochromocytoma, duodenal carcinoid and rhabdomyosarcoma (8). Altogether, these clinical manifestations heavily affect life expectancy, which is in average 8-21 years shorter compared to the general population (6,9,10).

Resective surgery is the first line therapeutic option for most of the NF1-associated oncological complications. However, satisfactory results are not always achieved due to local extension and invasion of vital areas, tumor size, and risk of postoperative regrowth. On the other hand, the use of chemotherapy and radiotherapy is limited by high toxicity rates in NF1 patients. Furthermore, chemo- and radiotherapy should be strictly reserved to highly selected patients, when other therapeutic options (including watchful waiting) are not possible, and discussed with both patients and caregivers for the significant risk of developing secondary dysplasias and tumors later in life, due to the intrinsic tumor-predisposition of this syndrome. For these reasons, in the era of precision medicine, novel targeted therapies are highly demanded. In this review, we will briefly summarize the recent advances in the pathophysiological understanding of NF1-associated tumors and the available evidence for new emerging drugs.

**Genetics and pathophysiology of NF1**

The NF1 gene is located on chromosome 17q11.2 and encodes a 250 kDa cytoplasmic protein called neurofibromin. About half of the cases are sporadic and due to de novo mutations. The germline mutation rate of NF1 is some 10-fold higher than that observed for most other inherited disease genes. Currently, over 2600 different inherited mutations in NF1 have been reported in the Human Gene Mutation Database (HGMD®) as a cause of NF1 (11–16).

Neurofibromin is a large multi-domain protein that acts as tumor suppressor. Neurofibromin includes a guanosine triphosphatase (GTPase)–activating protein (GAP) domain. GAP stimulates a GTPase activity intrinsic to RAS to inactivate the signal transduction pathway by converting RAS–guanosine triphosphate (GTP) to RAS–guanosine diphosphate (GDP) (17). This negative regulation of RAS reduces cell prolif-
eration and differentiation by forestalling activation of the downstream signalling pathways phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) and rapidly accelerated fibrosarcoma/mitogen activated protein kinase / extracellular signal regulated kinase (RAF/MEK/ERK) (7,18–21). Neurofibromin also regulates adenylyl cyclase and lowers the levels of intracellular cyclic adenosine monophosphate (cAMP) via RAS-dependent activation of atypical protein kinase C zeta (22). This protein is widely expressed in different organs and tissues, with high levels in the nervous system, and especially in neurons, astrocytes, oligodendrocytes, microglia, and Schwann cells (23,24).

From mutational analysis, the majority of germline NF1 mutations are predicted to be inactivating, resulting in almost complete absence of transcript or protein (25). Pathogenic mutations have been identified in most of its 61 exons, and include complete gene deletions, gene-disrupting chromosome rearrangements, smaller deletion or insertions, nonsense mutations, amino acid substitutions and splicing mutations (26). As a result, loss of neurofibromin expression leads to increased RAS activity and cell growth (27,28).

Some manifestations associated with NF1, such as cognitive problems, result from haploinsufficiency of NF1. Other clinical features require an additional somatic mutation, resulting in biallelic NF1 inactivation, as seen in the development of café-au-lait macules (CALMs), neurofibromas, GIST, glomus tumors, juvenile myelomonocytic leukemia (JMML), bone dysplasia and pheochromocytoma (25). Furthermore, mouse models of MPNST have shown that biallelic inactivation of the NF1 gene may not be sufficient for tumour formation and that additional genetic alterations such as mutation of TP53, CDKN2A or SUZ12, are required for the progression of MPNST (7,29,30).

Clinical evolution of the oncological complications in NF1

Most of the signs and symptoms of NF1 develop progressively from childhood to adulthood, and are rarely seen at birth. About 46% of the patients with sporadic NF1 do not meet the diagnostic criteria by the age of 1-year. When NF1 is suspected, annual monitoring until late childhood is necessary because 97% of the children with at least one feature of NF1 will eventually meet the diagnostic criteria by the age of eight (31). Skeletal deformities are frequently detected during infancy, while CALMs and axillary/inguinal freckling usually appear in childhood, and other typical signs and symptoms, including neurofibromas and lisch nodules, only develop after puberty (Figure 1). Of note, also cognitive impairment and learning, memory, or attention deficits, are diagnosed lately during childhood (32–37). Early diagnosis is thus crucial to appropriately manage the neurocognitive and psycho-social issues and to reduce morbidity and mortality with preventive and therapeutic strategies.

Development and severity of clinical features of NF1 can vary between individuals, but usually follow a common timeline. Café-au-lait spots can be detected early during infancy, while skinfold freckling develops later in childhood. Cognitive dysfunction has a high impact on NF1 children, since school-age children with NF1 have higher rates of developmental delay and cognitive impairment than their pairs, and many of them carry a concurrent diagnosis of attention deficit/hyperactivity disorder. Moreover, one-third of all children with NF1 have a mild to severe autism spectrum disorder. Typical signs and symptoms of NF1 as neurofibromas and Lisch nodules usually develop only after puberty (5). Plexiform neurofibromas are detected on clinical examination in approximately 27% of individuals with NF1. However, these tumors do not always cause symptoms and may be clinically silent, especially when they reside deep within the body (5). About 15-20% of the patients will develop a glioma. Patients with NF1 are also at risk to develop other malignancies in adulthood, like gastrointestinal stromal tumors, pheochromocytoma, duodenal carcinoid, high grade glioma and breast cancer.

Low grade tumors

1. Glioma

About 15-20% of children with NF1 will develop a glioma, with a median age at diagnosis of 4.9 years.
Optic pathways gliomas (OPGs) are pilocytic astrocytomas arising from the optic nerve, they can be unilateral or bilateral, and are the most frequent form (66%) of NF1-related gliomas (38,39).

OPGs can involve every part of the optic nerve from the papilla to the optic radiations, with different symptoms according to the location. NF1-related OPGs are usually asymptomatic, slowly growing and non-aggressive. However, symptoms of tumor progression may include decreased visual acuity, abnormal pupillary function, decreased colour vision, optic nerve atrophy, proptosis or other complications due to compression of the surrounding structures (i.e. between 12 and 40% children with chiasmal OPG develop precocious puberty) (39,40). Postchiasmatic OPGs presenting before the age of 2 years or after the age of 8 years tend to be more aggressive and should therefore be carefully followed up. Although the 5-year overall survival for patients with low grade glioma is 85%, progression-free survival for those with unresectable/residual disease requiring treatment is significantly lower (40%) (41).

The second most frequent CNS tumor in NF1 patients is brainstem glioma, which represent about 17% of all tumors in children with NF1 (42). Other gliomas are rarer, typically develop later in adulthood, and can involve all areas of the brain (37,43–48).

2. Neurofibroma

Neurofibromas are benign peripheral nerve sheath tumors composed of neoplastic Schwann cells, fibroblast, blood vessels and mast cells. According to their location, they can be divided in four types: cutaneous, subcutaneous, spinal and plexiform. Cutaneous and subcutaneous neurofibromas develop during childhood or early adolescence. They are benign tumors, and have no malignant potential (8). Spinal neurofibromas develop from the spinal foramina and can cause nerve roots compression or spinal deformities (i.e. scoliosis, kyphoscoliosis and vertebral body anomalies). When symptomatic, they can cause both motor and sensitive neuropathy and should be surgically treated (8,49). Plexiform neurofibromas (PNF) are
benign nerve sheath tumors that can be found in 30-50% of NF1 patients (50). They are mostly congenital, and arise from the deep peripheral nervous plexuses. As all neurofibromas, they are slowly growing, but can often become large and bulky, developing in complex and infiltrative shapes (51). PNF can occur anywhere throughout the body, but particularly in extremities, thoracic and pelvic region, and tend to surround and invade nearby tissues and structures (i.e. bones) causing pain, disfigurement, neurologic impairment and motor dysfunction (51,52). Furthermore, PNF have an 8-15% lifetime risk of malignant transformation in MPNST (53–55). Therefore, surgery should be considered early and all patients should undergo a careful presurgical evaluations, especially when PNF become symptomatic. Unfortunately surgical outcomes are often dissatisfactory, especially when only partial resection is attainable (56), with post-operative re-growth rates that can reach 44% (57).

Malignancies

1. Malignant peripheral nerve sheath tumor

Malignant peripheral nerve sheath tumors (MPNST) are rare, biologically aggressive soft tissue sarcomas derived from Schwann cells or pluripotent cells of the neural crest. About 22-50% of all cases are associated with NF1. The median age at diagnosis is between 20 and 40 years (10-20 years earlier compared to the sporadic cases). MPNST usually arise from a pre-existing PNF. MPNST most commonly develop in the limbs (45%), the trunk (34%) and the head or neck (19%) (51,58). The clinical presentation is usually characterized by a rapid enlargement causing mass effect and neuropathic symptoms, such as paraesthesia, motor weakness or radicular pain. The prognosis for NF1-related MPNST is poor, with a 50% of early metastatic involvement at diagnosis (mainly...
in the lungs) and a 5-year overall survival of 35–50% (59–61). As for other soft-tissue sarcomas, the best curative option is complete surgical resection, which is often not feasible due to location, size, and presence of metastasis. Furthermore, relapse rate is high and there is a lack of alternative therapeutic options (59). Adjuvant radiotherapy might be used to reduce local recurrence but needs a thorough risk-benefit evaluation for the heightened risk of secondary malignancies (62). Standard chemotherapy remains a treatment option in locally advanced or metastatic MPNST patients. It usually includes a combination of doxorubicin, ifosfamide, and etoposide, but response rate is usually poor compared to sporadic MPNST (17.9% vs 44.4%) (63).

2. Gastrointestinal Stromal tumor

Gastrointestinal stromal tumour (GIST) is a mesenchymal tumour that primarily arises in the gut mucosal wall. Unlike sporadic GISTs, those associated with NF1 usually lack somatic mutations of CD117 (c-KIT) or PDGFR-A (platelet-derived growth factor receptor A) (64,65). Instead, biallelic inactivation of the NF1 gene results in constitutive RAS activation, increasing the downstream mitogenic signalling through the MAP kinase cascade. Interestingly, gain-of-function mutations of c-KIT also activate many downstream signalling pathways including the RAS–MAP kinase cascade, suggesting a common pathogenetic mechanism in both sporadic and NF1-associated GISTs. As other tumors, NF1-associated GISTs have unique clinical features, compared to sporadic forms: they occur in younger patients (mean age at presentation 52.8 years), are multiple (60%) or develop in multiples sites, are smaller in size and with low mitotic activity, and occur mostly in the duodenum or small bowel. They are usually asymptomatic and incidentally detected during routine investigations. Surgery is the only modality that can offer a permanent cure of GIST, and complete surgical resection avoiding tumor rupture and injuries to the pseudocapsule is the initial treatment for primary and localized GISTs when the risk of morbidity and death from surgery is acceptable. The aims of surgery include complete resection with macroscopic and microscopic negative margins and functional preservation by wedge resection, when applicable. Unfortunately NF1 related GISTs show a variable but generally incomplete response to the tyrosine kinase inhibitor Imatinib treatment (64–69).

3. Pheochromocytoma

Pheochromocytomas are neuroendocrine catecholamine-secreting tumors, and occur in 2–2.9% of patients with NF1. Median age at presentation is 43 years (range 14–61 years) (70). This tumor is usually solitary, benign and localized in the adrenal glands, bilateral in 17% of the cases and metastatic or recurrent in 7.3%. Adrenalectomy remains the primary treatment of pheochromocytoma, with the entire gland being surgically removed in order to achieve cure. No differences have been described in the treatment and outcome of NF1-related pheochromocytoma compared to sporadic or other genetically determined forms of phaeochromocytoma (i.e. Multiple Endocrine Neoplasia type 2, Von Hippel Lindau syndrome, Hereditary paraganglioma–pheochromocytoma syndrome, Carney’s triad) (70–75).

4. Breast Cancer

Although rare in patients with NF-1, few studies have shown that women with NF1 are at a higher risk of developing early onset breast cancer with aggressive behaviour and a poorer prognosis, compared to the general population. Cancer management is not well defined in this population, these lesions are usually treated with a combination of surgery, chemotherapy, and radiation in relation to the stage at diagnosis, although risks of secondary fibrosarcomas may be increased by radiotherapy in this vulnerable population group (76–79).

5. Duodenal carcinoid

Carcinoid tumors of the gastrointestinal tract are neuroendocrine tumors (NETs). Most of the cases of carcinoids are sporadic, but approximately 26% of all carcinoid tumors occur in patients with NF1, with the most common site being the peripancreatic region. Mean age at presentation is 47.9 years, with a 59% female preponderance (80). Clinical symptoms
are multiple, and vary depending on the tumor size, compression and dissemination. The most common presenting symptoms are jaundice (65%) and abdominal pain (31%). Biologically, the most common type of peri-ampullary NET in NF1 patients is somatostatinoma (40%). Surgical treatment is recommended: pancreaticoduodenectomy is the first choice approach for well-differentiated ampullary carcinoid >2 cm and for ampullary neuroendocrine carcinomas, while local tumor excision can be considered for carcinoids <2 cm. In patients who are not eligible for surgery, chemotherapy may be considered. Options for management of grade I and II tumors include octreotide, lanreotide, mTOR inhibitors (everolimus), and peptide-receptor radiotherapy (80–84).

6. Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most frequent soft-tissue sarcoma in children, and can be distinguished in alveolar and embryonal subtypes. Less than 1% of patients with NF1 develop RMS, and all have an embryonal histology (due to the known role of RAS activation in the pathogenesis of embryonal-type RMS). The median age at diagnosis is 2.9 years, significantly earlier compared to sporadic RMS (5 years). Frequent locations are pelvic and orbital. These patients tend to develop early non-metastatic RMS, most often in the pelvic sites, that appear to be genetically similar to sporadic cases. Complete resection is the best curative option and treatment does not differ from sporadic cases (85–90).

7. Juvenile myelomonocytic leukaemia

Juvenile myelomonocytic leukaemia (JMML) is a unique, aggressive hematopoietic disorder of infancy/early childhood caused by excessive proliferation of cells of monocytic and granulocytic lineages. Although JMML is an uncommon complication of NF1, it is estimated that patient with NF1 have a 200-350 fold increased risk of developing JMML, compared to the general population. Moreover, this association may be underestimated because patients with JMML may die at an age at which children do not manifest sufficient clinical signs to make the diagnosis of NF1. Allogeneic hematopoietic stem cell transplantation remains the therapy of choice for most patients with JMML, and should be recommended to any child with NF1-mutated JMML (91–93).

Emerging treatments for NF1-related tumors

Standard chemotherapy regimens are weighed by the toll of toxic effect that sometimes may lead to a discontinuation of therapy. Precision medicine is an approach that takes account for the characteristics of NF1 related tumors. Below an analysis of the current standard therapy and new, emerging drug for glioma, plexiform neurofibroma and malignant peripheral nerve sheath tumors. Table 2 illustrates novel target therapies that has been used or are currently under investigation.

1. Glioma

Despite the behaviour of this tumor is usually not aggressive, specific treatment might be necessary in case of tumor progression and clinical symptoms. The mainstay treatment is chemotherapy. Indications for radiation therapy and surgery are less frequent in NF1-associated gliomas. On one hand, radiotherapy it’s not recommended because of the heightened risk of secondary tumors and moyamoya syndrome (94-95). On the other hand, most of the times this tumors are not surgically approachable for a complete resection, although a palliative debulking might be needed under specific circumstances (e.g. vision loss, corneal exposure due to proptosis, or pituitary localization) (95,96). Carboplatin and vincristine are the recommended first line chemotherapy for OPG (97-98), and the treatment protocol should always be handled by a specialist oncologist. Second line drugs include vinblastine, vinorelbine and temozolomide (99-100). Other options combine TPCV (thioguanine, procarbazine, lomustine, and vincristine) and weekly vincristine (98). Recently, a phase II study of bevacizumab plus irinotecan was conducted in children with recurrent low-grade glioma, NF-1 related or not, to measure sustained response and/or stable disease lasting ≥6 months and progression-free survival, the results of
that study show that this therapeutic strategy could be useful (101).

All cited regimens seem to be effective but classic chemotherapy exposes children to toxic effects such as myelosuppression, allergic reactions, peripheral neuropathy, constipation, secondary malignancies, and infertility. Although effective, radiotherapy increases the risk of secondary malignancy, ototoxicity, endocrinopathies, and neurocognitive decline (102,103).

Among new emerging drugs, Selumetinib has shown promising results in the treatment of NF1-associated OPG. Selumetinib is an oral selective inhibitor of MEK 1 and 2. This inhibitor locks MEK1/2 into an inactive conformation that enables the binding of ATP and substrate but disrupts both the molecular interactions required for catalysis and the proper access to the ERK activation loop (104). First evidences of efficacy for selective MEK inhibition came from mouse models of NF1-deficient acute myeloid leukaemia, where it induced tumor regression (105-106). In 2017, the Pediatric Brain Tumor Consortium completed a phase I trial of Selumetinib in 38 children with recurrent, refractory, or progressive paediatric low-grade glioma, establishing the recommended phase II dose as 25 mg/m² twice daily. Five of 25 patients treated at the recommended phase 2 dose achieved a partial response (41). Simultaneously, in a phase I trial, 17/24 (71%) patients with NF1-associated PNF showed partial response after treatment with Selumetinib (107). Both trials showed tolerable toxicities and equal recommended treatment doses. A recent phase II multicentre trial (108) with Selumetinib has shown at least a partial response (≥50% tumour reduction on MRI) in 40% of the patients with NF1-associated low grade glioma. These preliminary results suggest a comparable efficacy to conventional chemotherapy, with a higher tolerability, manageability and safety profile (109).

2. Plexiform neurofibroma

At present, the only curative option for PNF is resective surgery, and it should therefore be considered as soon as possible, whenever applicable. However, due to their infiltrative nature, eventually involving vital structures, and tendency for regrowth, surgery might not always be performed. Unfortunately, as a matter of fact, the medical treatment of PNF hasn’t found its keystone yet. As for many NF1-associated malignancies, radiotherapy is not recommended because of the risk of secondary malignancies (including radiation-induced MPNST, which typically have an even worse prognosis). Similarly, chemotherapeutic agents are not used because of their mutagenic nature and all drugs that have been used until now have shown little evidence of efficacy (56,62,110).

Among alternative treatments, interferon (INF) therapy has been reported in various studies (111,112) as an effective tumor-stabilizer. Jakacki and colleagues (111) eventually reported a 15-20% volume decrease in 29% of the patient. INF is safe and tolerable, and may be useful to reduce neuropathic pain. For this reason, a therapeutic trial of at least 6 months might be recommended, even if it will rarely be resolutive. The efficacy of Thalidomide (113) is less clear, as in a single study on 12 patients it showed a minor response in only 33%.

Since neurofibromin controls cell growth by negatively regulating the mTOR pathway activity, it seems reasonable to use mTOR inhibitors to manage NF1-related tumors (18). Sirolimus is a safe and well tolerated mTOR inhibitor that has been used to lengthen time to progression with fair success (mean increased time to progression: 4 months), but unfortunately failed in achieving a significant response in tumor shrinking or pain relief (114).

Sunitinib malate is a powerful, highly selective Tyrosine Kinase receptor inhibitor with activity against c-Kit, PDGFR, and vascular endothelial growth factor receptor (VEGFR), which are all implicated in the pathogenesis of MPNSTs. Preclinical studies showed that Sunitinib can induce reduction in PNF number and size, decreased mast cell infiltration, diminished fibroblast collagen deposition, and reduced metabolic activity (115). A phase II trial with Sunitinib was prematurely terminated because one patient died for uncertain (but possibly drug-related) causes (NCT01402817).

Meanwhile, other protein kinase inhibitors have undergone clinical trials for the treatment of PNF. A phase I trial (116) with Sorafenib, a protein kinase inhibitor with activity against RAF, PDGFRb, c-KIT and VEGFR-2, showed scarce tolerability at
substantially lower doses than the MTD, in children with refractory PNF. On the contrary, Pirfenidone, an oral anti-fibrotic and anti-inflammatory agent, demonstrated good tolerability in a phase II study (117), although it did not demonstrate clinical effectiveness and was not warranted further evaluation in children with progressive PN. Similarly, Tipirfanib, which selectively inhibits HRAS, did not offer significant efficacy compared to placebo (118,119). Imatinib Mesylate, a tyrosine kinase inhibitor with antineoplastic activity, targets c-KIT ligands secreted by biallelic NF1-inactivated Schwann cells and is able to decrease the volume of PNF in mouse models (120). A phase II trial with Imatinib reported a 17% response with a ≥20% tumor reduction, although a few study limitations (i.e. relatively small sample size and significant heterogeneity of the selected population) may have underestimated its therapeutic effect (120).

Among emerging drugs for NF1, so far Selumetinib seems the most promising for the treatment of PNF. In a recent clinical trial on 24 patients with PNF (107), 71% showed partial tumor regression after a median follow up of 18 months, which is significantly high if compared to the response rates of imatinib (17%) (120) and interferon-alpha-2b (29%) (111). Moreover, all patients showed evidence of some degree of tumor reduction, with a response that remained stable without disease progression in 15/17. The most frequent toxic effects involved mainly the skin and the gastrointestinal tract, with a side-effect profile similar to adults (121), or an asymptomatic increase of the creatin kinase (107). Very recently, a phase II trial with Selumetinib in 50 children with inoperable PNF evidenced a 74% rate of partial response (defined as a ≥20% volume decrease), with a stable response in 56% after approximately one year (12 therapy cycles). In this study only a few children showed disease progression, and most of them (5/6) had experienced a dose reduction before progression. Notably, in addition to tumor shrinkage, 68% experienced improvements in neurofibroma-related complications such as pain or functional limitations. Toxic effects were similar to those evidenced in phase I, and always reversible. Taken together, these results identify Selumetinib as the most promising drug for the treatment of PNF, since its high tolerability and low toxicity profile may allow early prolonged treatments (122).

Finally, there are several ongoing trials with selective tyrosine kinase inhibitors like Nilotinib (NCT01275586), Trametinib (NCT03363217) (123), or Cabozantinib (NCT02101736), and mTOR pathway inhibitors like Everolimus (NCT01365468).

3. MPNST

The recent understandings in the pathogenesis of MPNST have led to the development of preclinical mouse models for the study of targeted agents and precision medicine. Unfortunately, most of these trials have been inconclusive, but several other are still ongoing. In a recent phase I/II study (124) Sirolimus was used in combination with Ganetespib, a novel injectable small molecule inhibitor of Hsp90, to treat MPNST. Despite the promising preclinical rationale and tolerability of the combination therapy, no significant responses were observed. Alike, several other mechanisms of actions are currently under investigation. These include the use of small molecules, like PLX3397 (an inhibitor of CSF1 and KIT) used in combination with mTor pathway inhibitors (NCT02584647) (125), or modified BET inhibitors to overcome resistance in MPNST (126). Knowing that many MPNST arise from previous PNF, however, the best approach would be to prevent malignant degeneration in high risk patients. In the future, the identification of risk factors, early biomarkers and eventually disease modifying drugs (like the promising Selumetinib) may radically change the natural history of these aggressive tumors.

Neurofibromin 1 (NF1) accelerates the conversion from active Guanosine Triphosphate bound RAS to inactive Guanosine Diphosphate bound RAS. RAS signalling transduces extracellular signals from ligand-activated receptors (Receptor Tyrosine Kinase and G-protein coupled receptor). Loss of neurofibromin results in elevated RAS signalling. GTP-RAS activates a multitude of effectors protein, including the RAF and the MEK/ERK signalling cascades, which promote proliferation, and the PI3K/mTOR pathway, which promotes growth and cell survival.
Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: ??????
Accepted: ?????

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