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REVIEW

Novel molecular targeted therapies for patients with neurofibromatosis type 1 with inoperable plexiform neurofibromas: a comprehensive review

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Neurofibromatosis type 1 (NF1) is a genetic disorder that carries a higher risk of tumor development. Plexiform neurofibromas (PNs) are present in 50% of NF1 and cause significant morbidity when surgery is not feasible. Systemic therapies had not succeeded to reduce PN tumor volume until 2016 when the first trial with an MAPK/extracellular-signal-regulated kinase (MEK) inhibitor was published. We performed a systematic research on novel targeted therapies for patients with NF1 and PNs in PubMed, EMBASE, and conference abstracts with the last update in February 2021. Since 2016, seven trials have reported positive results with MEK inhibitors and other molecular targeted therapies (cabozantinib). Selumetinib has shown an overall response rate of 68% in children with NF1 and symptomatic inoperable PNs, and was associated with pain improvement and a manageable adverse events profile. This led to Food and Drug Administration (FDA) approval of selumetinib in May 2020. Recently, cabozantinib and mirdametinib have also proven their efficacy in adult population. Other MEK inhibitors such as trametinib and binimetinib have also communicated promising preliminary results. Ongoing trials in different populations and with intermittent dosing strategies are underway.

Key words: neurofibromatosis type 1, plexiform neurofibromas, neoplasms, molecular targeted therapy

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a common autosomal-dominant hereditary tumor predisposition syndrome with an incidence of ~1 in 3000 people worldwide.[1]

Patients with NF1 typically present at early ages with multiple café au lait spots, axillary and inguinal freckling, choroidal freckling, and iris Lisch nodules.[2] Patients with NF1 frequently develop different types of peripheral nerve sheath tumors. The most common type is cutaneous neurofibroma, which is a benign peripheral nerve tumor that tends to increase in size and number with age but does not carry a risk of malignant transformation.[3] Around 20%-50% of these patients also develop plexiform neurofibromas (PNs), which can cause substantial complications including malignant transformation. Treatment of these tumors is complex. Complete surgical resection is often not feasible due to the extensive growth of the tumor and invasion of surrounding tissues and they are key contributors to reduced life expectancy in patients with NF1.[4]

NF1 is caused by a pathogenic variant in the NF1 tumor suppressor gene, which is located at chromosome 17q11.2.[5] In 90% of the cases, the mutation leads to a loss of function of the NF1 gene product neurofibromin.[6] Although this cytoplasmatic 2818-amino acid protein is ubiquitously expressed, it is mainly found in the neurons of the central nervous system, and in the Schwann cells of the peripheral nervous system.[7] Neurofibromin is a GTPase-activating protein that negatively regulates the RAS pathway promoting the conversion of active guanosine triphosphate (GTP)-bound RAS to its inactive guanosine diphosphate (GDP)-bound conformation.[8] Therefore, loss of NF1 increases RAS activity, and promotes the activation of the downstream cascade of signaling events of the MAPK/extracellular-signal-regulated kinase/mitogenic extracellular signal-regulated kinase (MEK/ERK) pathway, which is a key driver of cancer (Figure 1). Besides, active RAS leads to an increase in the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway activity. Neurofibromin is also a positive regulator of intracellular cyclic adenosine monophosphate

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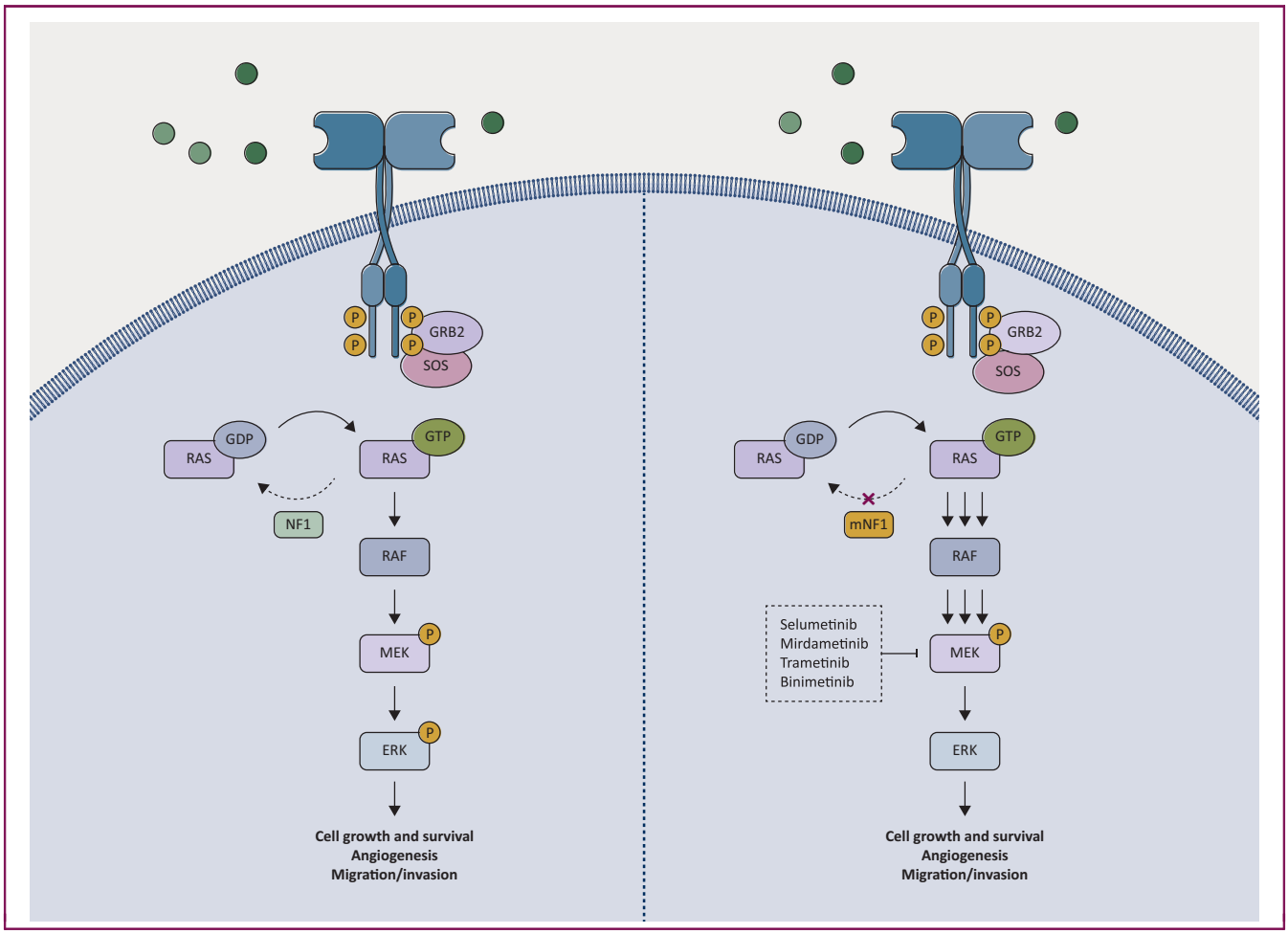

Figure 1. Intracellular tumorigenic signaling pathway of neurofibromin and mechanism of action of MEK inhibitors.
Neurofibromin promotes the conversion of active GTP-bound RAS to the inactive GDP-bound conformation (left). Loss of neurofibromin increases RAS activity and consequently the signaling cascade of the MEK/ERK pathway. MEK inhibitors (selumetinib, mirdametinib, trametinib, and binimetinib) inhibit this protein and block the MAPK signaling cascade (right).
ERK, extracellular signal-regulated kinase; GDP, guanidine diphosphate; GRB2, growth factor receptor-bound protein 2; GTP, guanidine triphosphate; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular-signal-regulated kinase; NF1, neurofibromin; Raf, serine/threonine-protein kinase; SOS, son of sevenless.

generation. This neurofibromin signal transduction is a viable target for potential therapeutic drug development.[9]

During the last decade, the discovery of the molecular pathogenesis and the biological basis of this disorder has made possible the design of targeted therapies against this disease. However, initial studies with imatinib,[10] tipifarnib,[11] pirfenidone,[12] sirolimus,[13,14] and interferon alfa-2b[15] only achieved marginal benefits. The therapeutic revolution came in 2020 with the development of the MEK inhibitor (MEKi) selumetinib as the first effective medical targeted therapy for PN.[16] Since then, other agents that target RAS signaling and other pathways involved in the pathogenesis of PNs are changing the treatment paradigm of these tumors.

This comprehensive review aims to provide detailed information on the novel targeted therapies developed for patients with NF1 with inoperable PNs and ongoing clinical trials in this scenario.

METHODS

To identify relevant published data on novel targeted therapies (MEK inhibitors and cabozantinib, among others) for patients with NF1 and inoperable PNs, we performed a systematic literature search of PubMed using the search term 'plexiform neurofibromas' with the filter 'clinical trial' from 2016 to date, and EMBASE, using the search term 'plexiform neurofibromas' with the filters 'phase II clinical trial' and 'phase I clinical trial' from 2016 to date. We excluded trials with $n \leq 5$, or those that do not report efficacy results. We additionally searched 'NF1 and MEK', 'NF1 and cabozantinib', 'NF1 and selumetinib', 'NF1 and mirdametinib', 'NF1 and trametinib', 'NF1 and binimetinib', 'NF1 and cobimetinib', and 'NF1 and treatment'. We also searched Google Scholar as well as conference abstracts from recent major congresses including the American Society of Clinical Oncology (ASCO) Annual Meeting, the European Society for Medical Oncology (ESMO) Congress, the Society for Neuro-Oncology (SNO) Annual Meeting, and International Symposium on Pediatric Neuro-Oncology (ISPNO). Searches were updated on 28 February 2021.

RESULTS

Within a multistep process, we screened 35 records for duplicates and eligibility, resulting in 15 publications

undergoing screening (Figure 2). Nine reports from eight clinical trials have communicated results on the efficacy of novel targeted therapies in patients with NF1 and PNs (Table 1),[17-25] and eight of them have reported positive results. Nine trials are ongoing (Table 2).[26-34]

Out of the eight reports with positive results[17-24] (seven trials, one of them[18] with two strata reported separately[18,19]), four have been published in peer-reviewed scientific journals[17,18,21,22] and the other four have been communicated as abstracts in international congresses.[19,20,23,24] All the studies included in the final analysis are single-arm phase I/II trials and included between 19 and 50 patients. Four of the trials with positive results were focused on children and adolescents[17-19,23,25] and three on adults with progressive/symptomatic inoperable PNs.[20-22] Two trials also included patients with inoperable PNs that did not necessarily cause symptoms.[17,19] Selumetinib ($n = 3$),[17-20] mirdametinib ($n = 1$),[22] trametinib ($n = 1$),[23] and binimetinib ($n = 1$)[24] were the MEK inhibitors used in the trials. Other targeted therapies include cabozantinib ($n = 1$).[21] The overall response rate (ORR) varies between 42% and 74% (Figure 3). The median time to response was found between cycles 5 and 12, with maximum response achieved between cycles 15 and 20. The median duration of response and progression-free survival have not been reached in studies with longer follow-up.[17,18]

Selumetinib

Selumetinib is an oral, highly potent, and selective inhibitor of MEK1/2[35] that has recently been studied in several malignancies.[36,37]

The first trial to prove the efficacy of selumetinib was published in 2016.[17] In this phase I trial, 24 children and

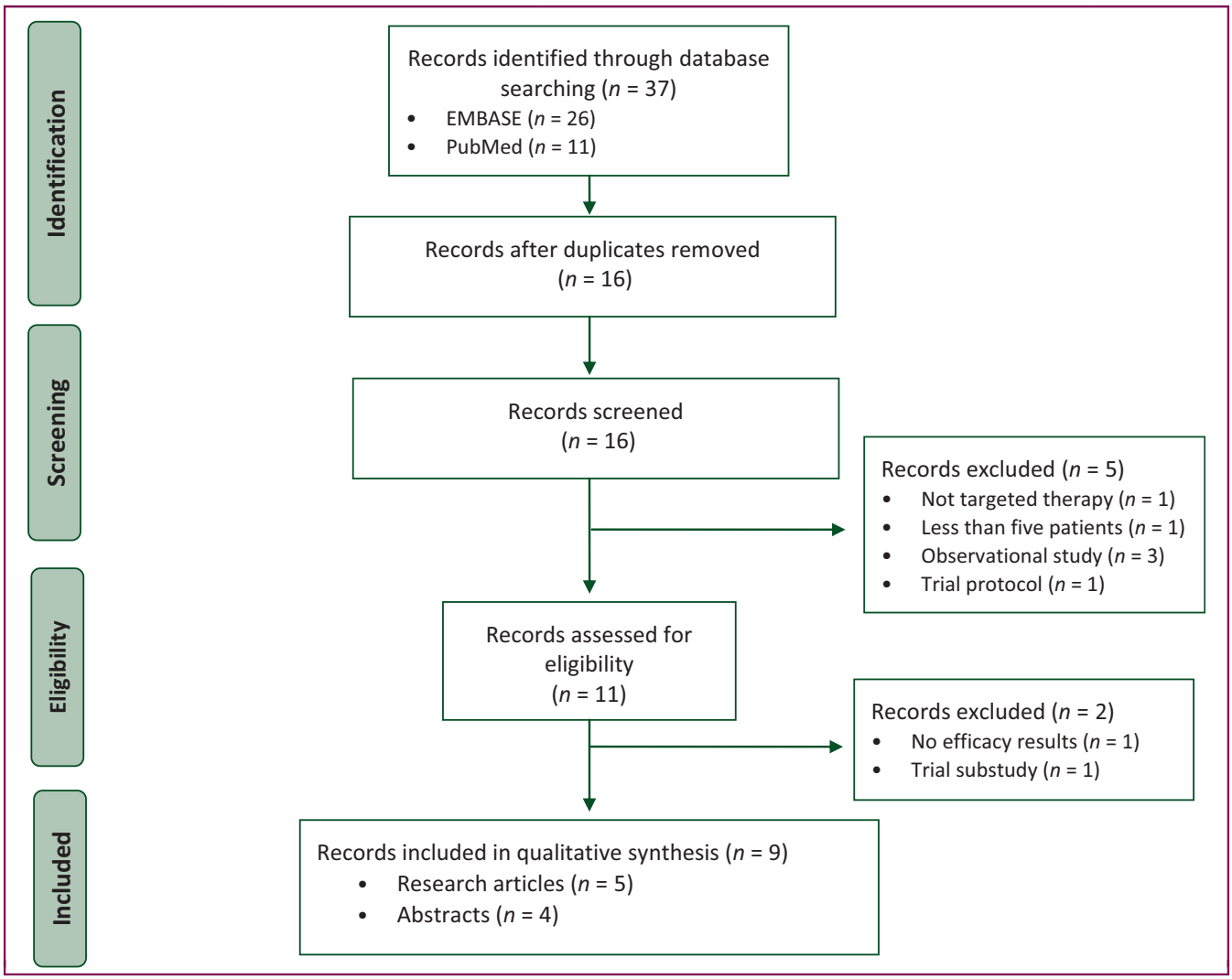

Figure 2. PRISMA flow diagram of the literature search.
Literature search performed in PubMed using the search term 'plexiform neurofibromas' with the filter 'clinical trial' from 2016 to date, and in EMBASE using the search term 'plexiform neurofibromas' with the filters 'phase II clinical trial' and 'phase I clinical trial', from 2016 to date. Trials with $n \leq 5$ and those that do not report efficacy results were excluded.

Table 1. Clinical trials with results of novel targeted therapies for the treatment of NF1-associated PN since 2016

Study and trial number	Type of study	Drug	*N*	Inclusion Criteria	Age (range), years	Initial tumor volume (range), ml	ORR (95% CI), %	Change in volume (range), %	Time to response	Maximum response[a]	Duration of response[a]
Dombi et al.[17] NCT01362803	Phase I trial	Selumetinib Dosing: 20-30 mg/m^2 b.i.d.	24	Children (3-18 years) who had NF1 and inoperable PNs	10.9 (3.0-18.5)	1205 (29-8744)	71 (60-85)	−31 (−5.8 to −47)	—	20 cycles (5-42)	NR
NCT01362803	Phase II trial Stratum 1[18]	Selumetinib Dosing: 25 mg/m^2 b.i.d.	50	Children with NF1 (2-28 years) and symptomatic inoperable PNs	10.2 (3.5-17.4)	487 (5-3820)	68	−27.9 (−55.1 to 2.2)	8 cycles (4-20)	16 cycles (4-36).	NR
	Phase II trial Stratum 2 Abstract[19]		25	Children with NF1 (2-28 years) and inoperable PNs but without clinically significant morbidity	12.3 (4.5-18.1)	381 (12-3159)	72	29 (37.9 to −2.5)	—	—	—
O'Sullivan et al.[20] Abstract NCT02407405	Phase II trial Open label Single group assignment	Selumetinib Dosing: 50 mg b.i.d.	23	NF1 patients ≥18 years old with inoperable/ symptomatic/ progressive PNs	33, (18-60)	—	69	−22 (−41 to +5.5)	11 months (5-25)	—	—
Fisher et al.[21] NCT02101736	Phase II trial Open label Single group assignment	Cabozantinib Dosing: 40 mg daily (escalation to 60 mg). 24 cycles	19	Patients ≥16 years of age with NF1 and progressive or symptomatic, inoperable PNs	23 (16-34)	557 (57-2954)	42	15.7 (+2.8 to −38.0)	10 cycles (4-12)	18 cycles (8-24)	NR
Weiss et al.[22] NCT02096471	Phase II trial Open label Single group assignment	Mirdametinib Dosing: 2 mg/m^2 b.i.d. 3 weeks on/1 week off 24 cycles	19	Patients >16 years with NF1 and a PN that was progressive or causing significant Morbidity	24 (16-39)	363.8 (3.9-5161)	42	17.1 (28.0-48.7)	12 cycles (8-12)	15 cycles (12-24)	NR
McCowage et al.[23] Abstract NCT02124772	Phase I/IIa trial Open label	Trametinib Dosing: 0.025-0.040 mg/kg daily	26	Children and adolescents (1 month to 18 years) with NF1 and PNs that were unresectable and medically significant	5.5 (1-16)	—	46	—	—	—	—
Mueller et al.[24] Abstract NCT03231306	Phase II trial Single group assignment	Binimetinib Dosing: 32 mg/m^2 b.i.d. 24 cycles	20	Children (1-17 years) with NF1 and PNs that were progressive or causing significant morbidity	12 (2-16)	326 (8-6661)	74	25.5 (9 to 54)	5 cycles	—	—
Zehou et al.[25] NCT01412892	Phase IIa trial Open label Single group assignment	Everolimus Dosing: 10 mg daily for 1 year	23	Patients ≥18 years with NF1 and unresectable PNs that were life-threatening or causing significant morbidity	31.6 (8.3)[b]	54.5 (9-453.8)[c]	0	—	—	—	—

b.i.d., *bis in die* (2 days); CI, confidence interval; NF1, neurofibromatosis type 1; NR, not reached; ORR, overall response rate; PN, plexiform neurofibroma.

[a] Values are given as number of cycles (range).

[b] Values are given as mean (SD).

[c] Values are in cm^3.

Table 2. Ongoing clinical trials for the treatment of NF1-associated PNs

NCT	Drug	Title	Trial design	*N*	Inclusion criteria
NCT04590235	Selumetinib	A study of selumetinib in Chinese pediatric and adult patients with NF1 and inoperable PNs	Phase I trial Open label Single group assignment	32	Patients with NF1 and inoperable PNs • Pediatric cohort: Chinese patients ≥3 years and <18 years of age • Adult cohort: Chinese patients ≥18 years of age
NCT03326388	Selumetinib	Intermittent dosing of selumetinib in childhood NF1-associated tumors (INSPECT)	Phase I/II trial Open label Single group assignment	30	Children with NF1 and PNs or progressive/ relapsed optic pathway gliomas
NCT03259633	Selumetinib	An intermediate access protocol for selumetinib for treatment of NF1	Multicenter intermediate access protocol Open label Single group assignment	—	Patients with NF1 and inoperable, progressive, or symptomatic PNs
NCT04495127	Selumetinib	Selumetinib pediatric NF1 Japan study	Phase I trial Open label Single group assignment	12	Patients ≥3-18 years of age with NF1 and inoperable and symptomatic PNs who have PN-related morbidities (symptom and/or complications),
NCT02101736	Cabozantinib	Cabozantinib for PNs in patients (children and adults) with NF1 (NF-105-CABO)	Phase II Open label Single group assignment	24	Cohort B: patients ≥3-15 years of age with NF1 and PNs that are progressive or causing significant morbidity
NCT03962543	Mirdametinib	MEK inhibitor mirdametinib (PD-0325901) in patients with NF1-associated PN (ReNeu)	Phase IIb Open label Single group assignment	100	Patients ≥2 years of age (children and adults) with NF1 and inoperable PNs that are causing significant morbidity
NCT03363217	Trametinib	Trametinib for pediatric neuro-oncology patients with refractory tumor and activation of the MAPK/ERK pathway	Phase II trial Open label	46	Group 2: NF1 patients with progressing/ refractory plexiform neurofibroma
NCT03741101	Trametinib	Treatment of NF1-related plexiform neurofibroma with trametinib (plexifpc)	Phase II trial Open label Single group assignment	15	Patients ≥1-18 years of age with NF1-related PNs with severe or with high suspicion of becoming severe manifestations
NCT02285439	Binimetinib	Phase I/II study of MEK162 for children with Ras/Raf pathway-activated tumors	Phase II trial Open label	—	Stratum 3: patients with NF1 and ≥1-18 years of age with any tumor other than low-grade gliomas

ERK, mitogenic extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

adolescents (3-18 years) with NF1 and inoperable PNs received selumetinib *bis in die* (b.i.d.; 20-30 mg/m^2 continuously) in 28-day cycles. If at the study entry the patient had progressive disease (PD) or a partial response (PR) to selumetinib while on treatment, selumetinib was allowed until disease progression or unacceptable toxicity. If the patient did not have a PD at the trial entry and did not experience a PR to selumetinib, the treatment could be continued for a maximum of 2 years.

The maximum tolerated dose was 25 mg/m^2. ORR was 71% and the median change in volume of PN was −31%. Maximum response was achieved at a median of 20 cycles (range 5-42). As much as 15/17 patients with PR maintained the response after a median of 23 cycles (range 6-42). Interestingly, no PD was observed. Tumor regrowth was observed in some patients with dose reduction or treatment discontinuation due to drug-related toxicities. Although the benefit in quality of life (QoL) was not formally evaluated, an anecdotal improvement in tumor-related pain and a decrease in functional impairment were identified. It was not until 2020 when clinical benefit and QoL assessment with selumetinib were reported. In stratum 1 of the SPRINT phase II study,[18] 50 patients aged 2 to 18 with NF1 and inoperable PNs with associated complications were treated with selumetinib at 25 mg/m^2 in a continuous dosing schedule. Although initial tumor volume was lower than the former study, ORR and median change in tumor volume were similar (68% and −27%, respectively). Best response was reached at a median of 16 cycles (range 4-36 cycles). The median duration of response and median progression-free survival were not reached at the time of data cut-off. A total of 28 patients had tumor response for at least 12 months; 83% of the patients were progression free at 3 years. This contrasts with the 3-year progression-free survival of 15% observed in an age-matched cohort included in the NCI NF1 natural history study. The impressive efficacy of selumetinib was associated with clinically meaningful improvements in child-reported interference of pain in daily functioning and overall health-related QoL (38% and 48%, respectively).

A subanalysis of this study describing the effect of selumetinib on spinal neurofibromas was recently reported. Improvement in spinal canal distortion, disruption of circumferential cerebrospinal fluid, and/or spinal cord deformity was seen in 18 of 24 patients and no worsening was observed during treatment.[38]

Based on these results, the Food and Drug Administration (FDA) approved selumetinib (KOSELUGO) for children aged ≥2 years with NF1 and inoperable and symptomatic PNs in June 2020.

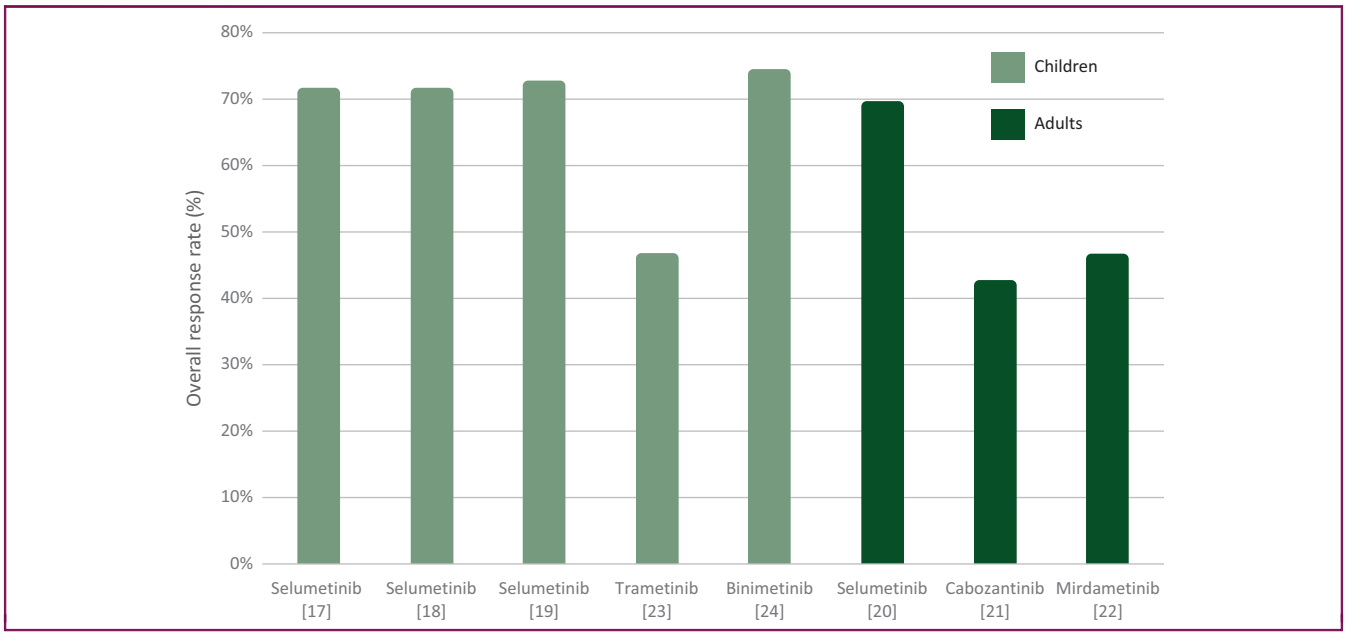

Figure 3. **Overall response rate of MEK inhibitors and cabozantinib in patients with neurofibromatosis type 1 and plexiform neurofibromas.**

The results of stratum 2 of the SPRINT trial were recently communicated at the American Society of Pediatric Hematology/Oncology (ASPHO) 2020 annual meeting.[19] Twenty-five patients aged 2-18 years with NF1-associated unresectable PNs that do not cause significant morbidity were administered 25 mg/m^2 of selumetinib daily. A 72% ORR was observed, with median tumor shrinkage of 25.5% (range 9%-54%). Only three patients experienced DLT. Changes in pain intensity or QoL were not reported.

Selumetinib has also been studied in adults with NF1 and inoperable, symptomatic, and progressive PNs. Preliminary results of an ongoing phase II trial presented at ASCO 2020 Annual Meeting[20] again showed encouraging activity (ORR 69%; 22% tumor volume shrinkage as best response) and decreased pain intensity ($P < 0.03$).

Efficacy of selumetinib outside of a clinical trial has also been reported. In a single-institution case series study, 19 patients with NF and symptomatic PNs were treated with selumetinib, and all but one had a significant clinical benefit.[39]

Regarding toxicity, selumetinib induced mostly mild and reversible adverse events (AEs) in children, including asymptomatic increase in creatine kinase, acneiform or maculopapular rash, paronychia, and gastrointestinal toxicity (diarrhea, nausea, vomiting). In the phase II trial, 28% needed dose reductions and 10% discontinued selumetinib due to dose-limiting toxicity (DLT). No ocular or symptomatic cardiac toxicity was observed.[18] In adults, grade $\geq$3 drug-related toxicities included transaminitis in five patients, rash in one patient, and pancreatic enzyme elevation in one patient. Two patients required dose reduction and six patients discontinued treatment by choice, AEs, or surgical resection.

Cabozantinib

Cabozantinib is an oral multikinase inhibitor with potent activity against vascular endothelial growth factor (VEGFR) 1 and 2, MET, RET, KIT, AXL, and FLT3 among others.[40] Cabozantinib is FDA approved for the treatment of different advanced malignancies, including clear-cell renal carcinoma,[41] medullary thyroid cancer,[42] and hepatocellular carcinoma.[43]

After showing that cabozantinib significantly reduces PN tumor growth in NF1-mutant mice, a phase II trial in adults ($\geq$16 years) with NF1 and progressive or symptomatic inoperable PNs was conducted (NF-105).[21] Patients were administered cabozantinib starting at 40 mg daily in 28-day cycles and reaching 60 mg if tolerated up to 24 cycles. The trial design required to stop cabozantinib if a decrease in tumor volume of $\geq$15% was not observed in cycle 8. Twenty-one patients were evaluable for toxicity and 19 for response. The ORR was 42% and no patient experienced PD. Tumor volume decreased a median of 15% (range +2.8% to −38.0%) and reached the maximum decrease at a median of 18 cycles (range 8-24 cycles). Although there were no unexpected AEs, 38% of the patients experienced grade 3 AEs including palmar-plantar erythrodysesthesia (PPE) and hypertension among others. The most common AEs were diarrhea ($n = 17$), nausea ($n = 14$), hypothyroidism ($n = 15$), fatigue ($n = 13$), and PPE ($n = 10$). Dose reductions were needed in seven patients due to PPE ($n = 7$), skin infection ($n = 1$), and weight loss ($n = 2$). Two patients discontinued treatment due to PPE.

Pain intensity and QoL were also assessed. In patients with PR, pain intensity decreased significantly starting at cycle 4 and worst tumor pain decreased 3 points as per Numeric Rating Scale 11 (NRS-11). No significant change in Pediatric Quality of Life Inventory (PedsQL) NF1 total functioning mean score (validated in adults)[44] was observed over time.

Mirdametinib

Mirdametinib (PD-0325901) is an oral, non-ATP-competitive, highly selective, and potent small-molecule

inhibitor of MEK1 and MEK2[45] that is currently being studied in other solid malignancies.[45,46]

In the NF-106 phase II trial,[22] mirdametinib was administered orally b.i.d. at 2 mg/m^2 for 3 weeks followed by 1 week off therapy for a maximum of 24 cycles to adults (aged ≥16 years) with NF1 and progressive and/or symptomatic PNs. The maximum dose was 4 mg b.i.d. due to the ocular, musculoskeletal, and neurologic toxicity in previous studies. As required in the cabozantinib trial, patients who did not achieve a 15% tumor volume decrease at cycle 8% or 20% at cycle 12 discontinued the treatment. A total of 19 were included (2 patients for progressive PN and 17 patients for PNs that cause significant morbidity). The median initial tumor volume was 363.8 ml (range 3.9-5161 ml). Nearly 42% of the patients obtained a PR. However, a patient with initially progressive PN experienced PD as best response at week 12 and discontinued treatment. Median decrease in tumor volume was 17.1% (range 28.0%-48.7%), and it reached the maximum decreased at a median of 15 cycles (range 12-24 cycles). Interestingly, most responses were seen in patients with an area under the curve 0-12 h exposure to mirdametinib ≥600 ng·h/ml ($P = 0.05$). Patient-reported outcomes also improved with treatment. For instance, the intensity of worst tumor pain decreased in the total sample at course 4 ($P < 0.01$), and patients who achieved PR experienced significant improvement in PedsQL NF1 at cycle 8.

The most frequent AEs reported were acneiform rash (94.7%), fatigue (57.9%), and nausea (52.6%). Only one patient experienced grade 3 treatment-related AEs (back and abdominal pain); 26% of the patients required dose reduction and no patient reached DLT.

Trametinib

Trametinib is a well-known potent, highly specific inhibitor of MEK1/MEK2 that has FDA-approved indication for the treatment of melanoma,[47] advanced non-small-cell lung cancer,[48] and subsets of thyroid cancer.[49]

An interim analysis of a phase I/IIa trial with trametinib (0.025-0.040 mg/kg/day) for the treatment of children and adolescents (1 month to 18 years of age) with NF1 and with medically significant, unresectable PNs was presented at the ASCO 2018 Annual Meeting.[23] A total of 26 patients were included, and 12 of them (46%) achieved a PR. Paronychia (50%) and rash (40%) were the most common AEs. One patient discontinued treatment due to an AE.

Binimetinib

Binimetinib is a potent, selective, non-ATP-competitive allosteric inhibitor of MEK1 and MEK2.[50] It is FDA approved in combination with encorafenib for the treatment of advanced or metastatic BRAF-mutant melanoma.[51] A preliminary report presented at the 19th ISPNO 2020[24] showed that binimetinib at a starting dose of 32 mg/m^2 b.i.d. induced PR in 14 of 19 patients aged 1-17 years with NF1 and PNs that were progressive or causing significant morbidity.

The most common grade 3 AEs reported were dry skin, weight gain, weakness, rash, paronychia, cellulitis, diarrhea, gastric hemorrhage, and creatine kinase increase. Dose reduction was required in 13 patients, and 2 patients discontinued therapy due to toxicity.

Other studies

Other clinical trials have been published in the last years with disappointing results. Everolimus, an mTOR inhibitor, was studied in 25 adults with NF1-associated PN causing significant morbidity.[25] However, none of the patients achieved a PR, which was defined as a 30% reduction in the size of the tumor mass by magnetic resonance imaging. Furthermore, 11 patients experienced severe AEs. Three children with NF1 and PNs received pexidartinib in the context of a phase I trial and had stable disease without DLT.[52]

Ongoing trials

Besides the final results of some of the aforementioned trials, there are several clinical trials still recruiting patients. Ongoing trials are depicted in Table 2. Selumetinib is being tested in other populations (Chinese[26] and Japanese[29]) and in a different dosing schedule (intermittent).[28] Results from cohort B of the NF-105 trial (cabozantinib) are still pending.[30] An ambitious phase IIb trial with mirdametinib has been opened and plans to include 100 patients.[31] Trametinib and binimetinib are also being studied in ongoing trials.[32-34]

DISCUSSION

In this review, we summarize the results obtained with MEK inhibitors and cabozantinib for the treatment of NF1-associated PNs. These novel therapies have remarkable efficacy in decreasing the tumor volume of PNs (ORR ranging from 40% to 74%) and are associated with decreased pain intensity without deterioration in the QoL. Besides, tumor response is probably long lasting. The maximum response usually peaks after >1 year of treatment. However, there are subtle differences between studies that need to be further addressed.

Selumetinib was the first MEK inhibitor to have positive results in this scenario. Globally, it has been tested in more patients and achieves an ORR of ~70%.[17-20] Although the clinical benefit of cabozantinib and mirdametinib is undeniable, ORR is somehow lower (42% in both trials).[21,22] These differences could be partly attributed to the population included in the trials. The growth rate of PN is lower in adults than in children,[53] and thus, PN in adult patients may be less susceptible to tumor shrinkage. Both cabozantinib and mirdametinib were tested in adult population. Only 2 patients out of 19 had progressive PNs at the study entry in the mirdametinib trial in contrast to 42% in the SPRINT trial. Another caveat was the design of the studies. For cabozantinib and mirdametinib, the drug was stopped at cycle 8 if the tumor response was <15% and at cycle 12 if the tumor response did not reach 20%. As we now know

from the results obtained, tumor response may be delayed in time (up to cycle 20 in the SPRINT trial). This strategy may have prevented the authors from identifying late responders and may partially explain the lower ORR. Of note, the pediatric cohort of the cabozantinib trial has removed this criterion from the study design. Finally, due to concerns surrounding toxicity, mirdametinib was administered probably at the minimum effective dose. In the NF-106 trial, a direct association between exposure to mirdametinib and tumor response was observed, suggesting that a higher dose could lead to a greater clinical benefit. Nevertheless, the ORR of selumetinib in adults is 69%, as reported in ASCO 2020.[20] The final analysis of this study may help to better understand these differences.

Another important difference between the drugs relies on their mechanism of action. While selumetinib, mirdametinib, trametinib, and binimetinib are selective MEK inhibitors, the mechanism of action of cabozantinib in this scenario remains to be determined. Cabozantinib is a multikinase inhibitor that does not effectively inhibit MEK.[40] However, preclinical genetically engineered mouse model studies have suggested that neoangiogenesis inhibition and AXL downregulation generated by cabozantinib may have an important role.[21] AXL is a cell receptor and a novel biomarker in cancer research. The growth arrest-specific protein 6 (GAS6)—AXL axis is involved in the Janus kinase/signal transducers and activators of transcription (JAK/STAT), nuclear factor-κB (NF-κB), PI3K/Akt/mTOR, and RAS/RAF/MEK/ERK signaling pathways and plays an important role in tumor cell survival, invasion, angiogenesis, and drug resistance.[54] Inhibition of the mTOR pathway has also been explored in clinical trials with disappointing results. Although in preclinical studies with genetically engineered mouse models mTOR inhibition suppressed the growth of NF1-associated malignancies, everolimus[25] and sirolimus[14] did not produce tumor shrinkage in humans. Subtle differences in the definition of tumor response (30% reduction in target lesion in the everolimus trial versus 20% in other trials) do not seem to account for the divergent results obtained compared with other trials.

Although the response rate to MEK inhibitors and cabozantinib is impressive, continuous treatment during long periods is necessary to achieve a response. It is therefore important to find biomarkers for response to avoid unnecessary toxicities in pediatric and adult patients. In the NF-105 trial[21] a cytokine and biomarker analysis was performed to better characterize the response to cabozantinib. An association that did not reach statistical significance was observed between clinical response and an increase in sAXL ($P = 0.08$), a soluble form of AXL that negatively regulates ALX signaling by binding to GAS6.[55] Some preclinical studies in NF1-deficient malignant peripheral nerve sheath tumors suggest that combination strategies of MEK inhibitors with MET or SHP2 inhibitors may overcome tumor resistance. However, further studies are required in PNs.

A key consideration when treating a patient with these novel therapies is when to discontinue the drug. As mentioned before, the maximum response can be achieved 2 years after starting treatment. In fact, in the trials with long follow-up, there were maximum responses at cycles 36-42.[17,18] The SPRINT trial[18] considered discontinuation of selumetinib after 2 years in patients without disease progression at the study entry and no PR during the trial. The patients with PD at the study entry could continue with the drug as long as no disease progression was observed. For cabozantinib and mirdametinib, treatment was discontinued after 24 cycles. However, tumor regrowth was observed in some patients after selumetinib discontinuation due to drug-related toxicities in the first trial.[17] Thus, some experts reckon that treatment may require to be extended over years.[16] Long-term results are needed to further address this issue.

In this scenario, efficacy should be weighed against toxicity. Appropriate monitoring for toxicity and a thorough assessment of pain and QoL have to be performed. Although the safety profile of MEK inhibitors seems to be acceptable, AEs can decrease treatment compliance and affect the QoL.[58] Skin toxicity, asymptomatic increase in creatine kinase, and gastrointestinal symptoms are the most frequent AEs. In the SPRINT trial, 28% of the patients required dose reduction, and 10% discontinued therapy due to DLT. Nevertheless, pain intensity significantly decreased >2 points after 12 months of therapy and overall QoL improved 6,7 points on the PedsQL score. Twenty-eight percent of adult patients on mirdametinib also required dose reduction, but only one patient experienced grade 3 AEs and no patients discontinued the drug due to DLT. Worst tumor pain decreased almost 2 points at cycle 4, with no significant change in the QoL. Cabozantinib has a different toxicity profile than MEK inhibitors and includes PPE, hypertension, and diarrhea, among others, and reached grade 3 in 38% of the patients. Pain decreased in the eight patients that responded and no significant changes in QoL were reported.

Given the success obtained in the advanced, progressive, and inoperable PN, we should ask whether we should move forward and study these novel therapies as neoadjuvant treatment to enable surgery. Although the landmark trials only include inoperable patients, anecdotal reports suggest that MEK inhibitors could have a role.[59] However, although most of the patients do respond, tumor shrinkage is modest (15%-30%). Combination strategies might overcome resistance to monotherapy[56,57] and offer additional volumetric tumor shrinkage to further optimize surgery, but this is still an underexplored field of research in NF1-related PNs.

In conclusion, novel targeted therapies, including MEK inhibitors and cabozantinib, have revolutionized the treatment of patients with NF1 and inoperable PNs, not only by inducing tumor shrinkage in the majority of patients, but also by improving pain scores and, to some extent, QoL, with manageable toxicity profile. Longer follow-up data and the results from ongoing trials are expected and will increase our knowledge in the field.

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