

Oltre la riduzione del volume: il beneficio clinico esteso di selumetinib nella pratica clinica

13/10/26

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ALEXION®
AstraZeneca Rare Disease

DISCLOSURES

Advisory boards

- Alexion
- Oncoscience
- Merck
- Astra Zeneca

NF1 is a genetic disorder of the nervous system, often disabling for patients[1]

- Multisystem disorder[2]
- NF1 worldwide: 1/3000; it means 120 people are born each day[3]
- Primarily involves the skin and peripheral nervous system as well as cardiovascular, musculoskeletal and gastrointestinal systems[2]
- Predisposes patients to tumour onset[4]
- Wide spectrum of health implications[2]
- NF1 significantly impact patient Quality of life (social, mental, physical, awareness)[5,6,7]

Life expectancy reduced by ~20 years[8]



Copyright © University of Washington: Neurofibromatosis 1. 1993–2017.

NF1, neurofibromatosis type 1.

1. Blakeley JO and Plotkin SR. Neuro Oncol 2016;18:624–638; 2. Miller DT et al. Pediatrics 2019;143:e20190660; 3. United Nations Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022: Summary of Results.4 Stewart DR et al. Genet Med 2018;20:671–682;. 5. Rietman AB et al. Am J Med Genet A 2018;176(5):1150-60; 6. Kjaer TK et al. Eur J Hum Genet 2020;28:1028–33; 7. Cohen JS et al. Clin Genet 2015;88(5):425–30; 49 Kongkriangkai AM et al. Am J Med Genet A 2019;179(4):602–7. 8. Masocco M et al. Orphanet J Rare Dis 2011;6:11

DIAGNOSTIC CRITERIA FOR NF1

≥2 specific criteria
(child of a parent with NF1 requires at least one of the criteria to establish the diagnosis of NF1).[1]

≥6 café-au-lait macules[1,2,a]



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Image used from (Just for teens: Living with NF1. Children's Tumor Foundation. https://ctfchildrenstumourfound.blob.core.windows.net/assets/pages/NF-Just-For-Teens_Living-with-NF.pdf (Accessed June 7, 2024) – copyright permissions to be obtained.

≥2 Lisch nodules[1,2]

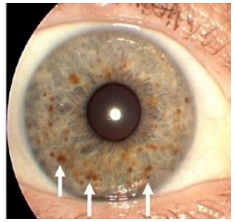


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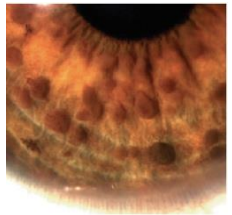


Image used from (Just for teens: Living with NF1. Children's Tumor Foundation. https://ctfchildrenstumourfound.blob.core.windows.net/assets/pages/NF-Just-For-Teens_Living-with-NF.pdf (Accessed June 7, 2024) – copyright permissions to be obtained.

Optic pathway glioma[1]



White arrow, glioma of right optic nerve; black arrow, glioma of chiasm

Image used from (Legius E, et al. *Genet Med.* 2021;23(8):1506–13). Published by Elsevier under CC BY 4.0 License.

Heterozygous pathogenic *NF1* variant with a variant allele fraction of 50%[1]



in apparently normal tissue such as WBCs

≥2 neurofibromas of any type or ≥1 PN[1,3,4]



Cutaneous neurofibromas

Image used from (Allaway RJ et al. *Br J Cancer.* 2018;118(12):1539–48). Published by Springer Nature under CC BY 4.0 License.



PN

Image used from (Dagalakis U, et al. *J Pediatr.* 2014;164(3):620–24). With permission from Elsevier.

Distinctive osseous lesion[1,5,b]



Pseudoarthrosis of the tibia



Bowing of tibia and fibula



Sphenoid dysplasia

Image used from (Xu J, et al. *Front Genet.* 2022;3:991314) - copyright permissions to be obtained.

Images used from (Legius E, et al. *Genet Med.* 2021;23(8):1506–13). With permission from Elsevier.

Freckling in axillary or inguinal regions[1,2]





Image used from (Just for teens: Living with NF1. Children's Tumor Foundation. https://ctfchildrenstumourfound.blob.core.windows.net/assets/pages/NF-Just-For-Teens_Living-with-NF.pdf (Accessed June 7, 2024) – copyright permissions to be obtained

Image used from (Legius E, et al. *Genet Med.* 2021;23(8):1506–13). With permission from Elsevier.

aOver 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals. b Such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone.
NF1, neurofibromatosis type 1; PN, plexiform neurofibroma; WBC, white blood cell

1. Legius E, et al. Genet Med 2021;23(8):1506-13; 2. Just for teens: Living with NF1. Children's Tumor Foundation. Available from: https://ctfchildrenstumourfound.blob.core.windows.net/assets/pages/NF-Just-For-Teens_Living-with-NF.pdf (Accessed June 7, 2024); 3. Allaway RJ, et al. Br J Cancer 2018;118(12):1539–48; 4. Dagalakis U, et al. J Pediatr. 2014;164(3):620–24; 5. Xu J, et al. Front Genet 2022;3:991314.

Some symptoms are congenital while some present during teenage years or in adulthood, which adds to the complexity of diagnosing and managing NF1[1,2]



Osseous lesions[2]



Diffuse PNs of the face and neck rarely develop after 1 year; and on other parts of the body, rarely after adolescence[2]



Optic pathway gliomas are present in the first 6 years of life[2]



Cutaneous neurofibromas appear (Or develop significantly) between the ages of 10 and 20 years[1]



MPNSTs usually occur in adolescence or adulthood[2,3,a]

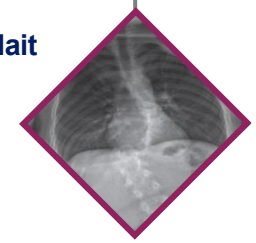
Birth | **1 year** | **6 year** | **10 year** | **20 year**



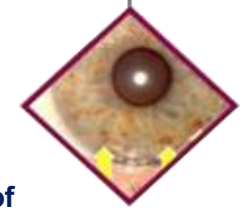
Café-au-lait macules, which tend to increase in number throughout early childhood years[2]



Freckling, mostly seen after café-au-lait macules form[1]



Scoliosis, a rapidly progressive form typically develops between 6–10 years of age; milder forms tend to occur during adolescence[2,4]



Lisch nodules often not present in childhood but develop with age; majority of adults with NF1 have them[1]

aImage used from (Kim A, et al. Sarcoma. 2017;2017:7429697). With permission from Hindawi Publishing Corporation OA.
MPNST, malignant peripheral nerve sheath tumor; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma

1. Rasmussen SA, et al. Am J Epidemiol 2000;151(1):33–40; 2. Friedman JM. Gene Reviews 1998 Oct 2 [updated 2022 Apr 21]; 1993–2025; 3. Kim A, et al. Sarcoma. 2017;2017:7429697; 4. TonsgardJH. Semin PediatrNeurol 2006;13:2–7.

NEUROFIBROMAS ARE BENIGN TUMORS THAT FORM ALONG THE NERVE SHEATH[1]

- **Cutaneous neurofibromas** tend to develop on or just under the skin surface and range from only a few to hundreds or thousands[1,2]
  - **Usually present in adults with NF1**; rare before late childhood[2]
- **Plexiform neurofibromas (PNs)** may involve superficial skin layers or form in deeper skin layers below the surface[1]
  - Occur in up to 50% of patients with NF1[3,a]
  - May be progressive (ie, continue to increase in size and scope) or non-progressive[3]
  - **Mostly congenital; usually grows most rapidly during the first decade of life[5]**



Diagnostic Criterion
Two or more neurofibromas of any type or one plexiform neurofibroma[4]

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Image 2 used from (sciencephoto.com: M220/0023) – copyright permissions to be obtained.

aWhole body MRI had been administered to patients with NF1 since it is preferable for assessment of large tumors that cross traditional body regions and provides more accurate longitudinal evaluation of complex tumors.3
MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1

1. Tonsgard JH. Semin Pediatr Neurol 2006;13:2–7; 2. Friedman JM. Gene Reviews 1998 Oct 2 [updated 2022 Apr 21]; 1993–2025; 3. Blakeley J, et al. Neuro-Oncology 2016;18:624–38; 4. Legius E, et al. Genet Med 2021;23:1506–13; 5 Anderson JL et al. Handb Clin Neurol 2015;132:75–86.

THE LOCATION, NUMBER, SIZE, AND SEVERITY OF PNs CAN VARY GREATLY[1,2]



MRI of large PN in neck, chest and arm
Images used from (Dagalakis U, et al. *J Pediatr*. 2014;164(3):620–24). With permission from Elsevier.

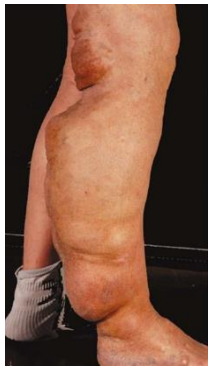


Image used from (Ferner RE. *Eur J Hum Genet*. 2007;15:131–38). Published by Springer Nature – copyright permissions to be obtained.

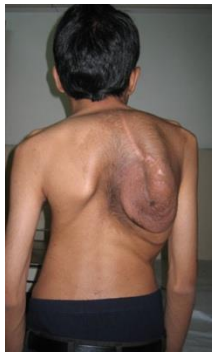


Image used from (Shahcheraghi GH, Tavakoli AR. *J Child Orthop*. 2010;4:203–10). Published by SAGE Publications under CC BY 4.0 License.



Image used from (Wise JB, et al. *Head and Neck*. 2002;24:207–11). Published by John Wiley and Sons – copyright permissions to be obtained.



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Image used from (Hirbe AC, Gutmann DH. *Lancet Neurol*. 2014;13:834–43). With permission from Elsevier.



Image used from (Abdelmoughit E, et al. *J Pioneer Med Sci*. 2015;5:103–106)). Published by iARCON International LLP under CC BY 4.0 License.



Image used from (Kluwe L et al. Nervous system: neurofibroma. Atlas Genet Cytogenet Oncol Haematol. 2007. https://atlasgeneticsoncology.org/solid-tumor/5098/nervous-system-neurofibroma [Accessed June 8, 2022]) – copyright permissions to be obtained.



Image used from (Flaherty M. Neurofibromatosis type 1: reviewing the diagnostic criteria. Mivision Education. https://www.mieducation.com/pages/neurofibromatosis-type-1-reviewing-the-diagnostic-criteria [Accessed June 8, 2022]) – copyright permissions to be obtained.

- An estimated 30% of people with NF1 have "***visible"*** PN and approximately 20% have "***internal"*** PN [3]
- PNs occur most commonly in the trunk including the paraspinal region (31%), head and neck (31%), and the extremities (25%)[4]
- Common morbidities include pain, disfigurement, motor dysfunction, airway dysfunction, visual impairment, and bladder/bowel dysfunction[1-5]
- NF1-PN may significantly impact QoL and activities of daily living[6,7]

PN, plexiform neurofibromas

1. Friedrich RE, et al. World J Surg Oncol 2005;3(1):6; 2. NHS. Symptoms: neurofibromatosis type 1. Available from: https://www.nhs.uk/conditions/neurofibromatosis-type-1/symptoms/ (Accessed March 3, 2023); 3. Bergqvist C et al. Orphanet J Rare Dis 2020;15:37; 4. Blakeley JO, et al. Neuro Oncol 2016;18(5):624–638; 5. Ferner RE, et al. J Med Genet. 2007 Feb;44(2):81-8. Bergqvist C, et al. Orphanet J Rare Dis 2020;15:37; 6. Hamoy-Jimenez G, et al. Neuro-Oncol Adv 2020;1:i141–i149; 7. Copley-Merriman C, et al. Adolesc Health Med Ther 2021;12:55–66; 9. Wolters PL, et al. Am J Med Genet A 2015;167A:2103–113.

DEVELOPMENT OF NEW PAIN, OR CHANGES IN PAIN INTENSITY IN A PN SHOULD RAISE CLINICAL SUSPICION FOR MALIGNANT TRANSFORMATION[1,3]

Patients with NF1 carry an **8–16%** lifetime risk of developing **MPNST**[1]

Lifetime risk of cancer in patients with NF1: 59.6% versus general population 30.8% [6]

- MPNST typically develops during or after young adulthood[2] but rarely develops in childhood[1] and typically arise from **malignant transformation of PN**[1]
- It is usually **diagnosed between the ages of 20 and 40 years**[1]

PN are also at increased risk for malignant transformation to ANNUBPs, an intermediate (premalignant) stage between PN and MPNST[1]

- ANNUBPs are characterized by at least two of the following features: cytological atypia, hypercellularity, loss of neurofibroma architecture, and an increased mitotic index[3]
- Almost half of the ANNUBPs are palpable lesions and **~80% cause clinical symptoms**[1]

Malignant transformation of NF1-PN to MPNST is the leading cause of NF1-related death, with 5-year overall survival rate of approximately 50%, in both children and adults [4-5]

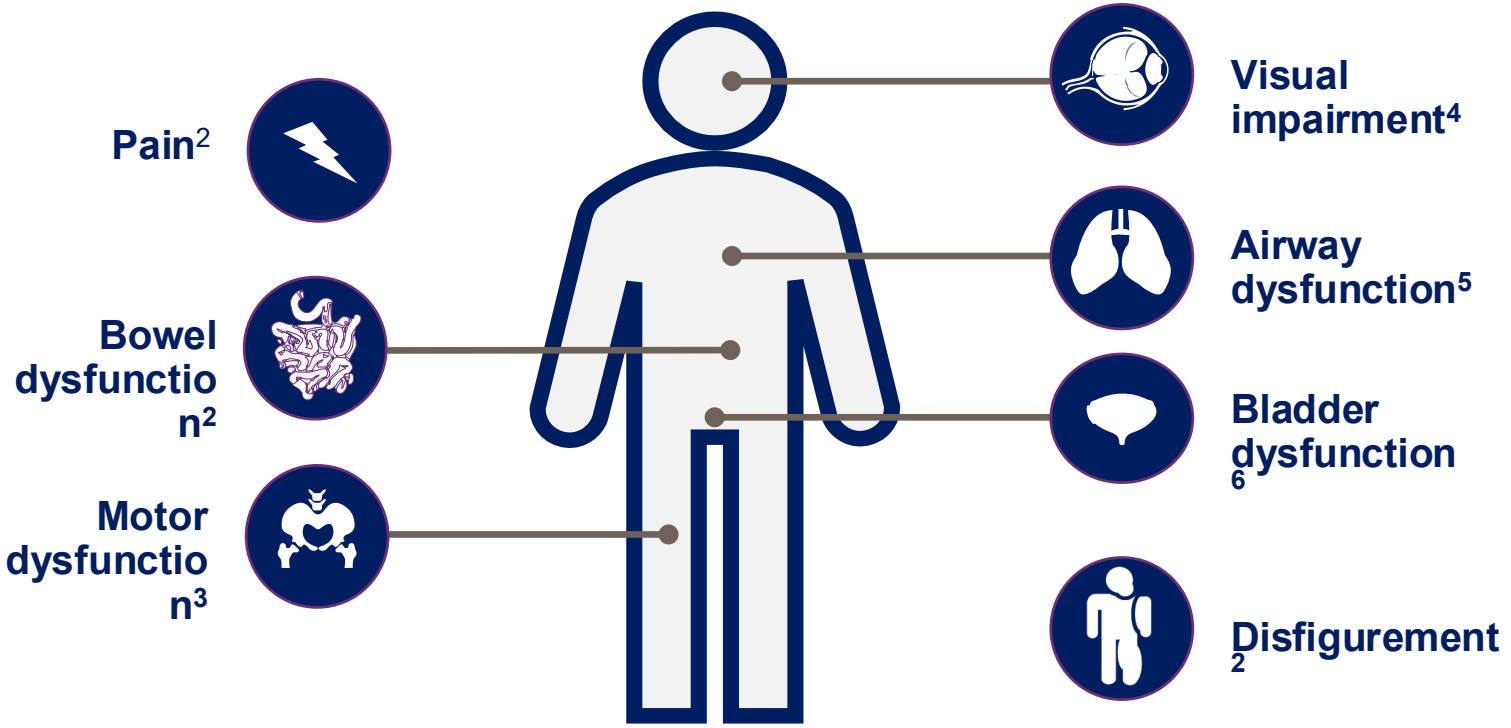
The median age of cancer diagnosis in patients with NF1 is 39 years. However, the standardized incidence ratio for cancer in children and women <30 years of age with NF1 is especially high[1]

ANNUBP, Atypical neurofibromateous neoplasm of uncertain biologic potential; MPNST, malignant peripheral nerve sheath tumour; PN, plexiform neurofibromas.

1. Carton C, et al. EClinicalMedicine. 2023 Jan 13;56:101818; 2. Miller DT, et al. Pediatrics 2019;143(5):e20190660; 3. Fisher MJ, et al. Neuro Oncol 2022;24:1827–44. 4. Martin E et al. Pediatr Blood Cancer 2020;67:e28138; 5. Cai Z et al. World J Surg Oncol 2020;18:257. 6. Uusitalo E, et al. J Clin Oncol 2016;34:1978–86;

SYMPTOMATIC PN:SIGNIFICANT MORBIDITY AND LIFE-THREATENING COMPLICATIONS

The term '**symptomatic**' is used to describe PN that are **associated with pain, disfigurement and difficulties with physical functioning**[1]



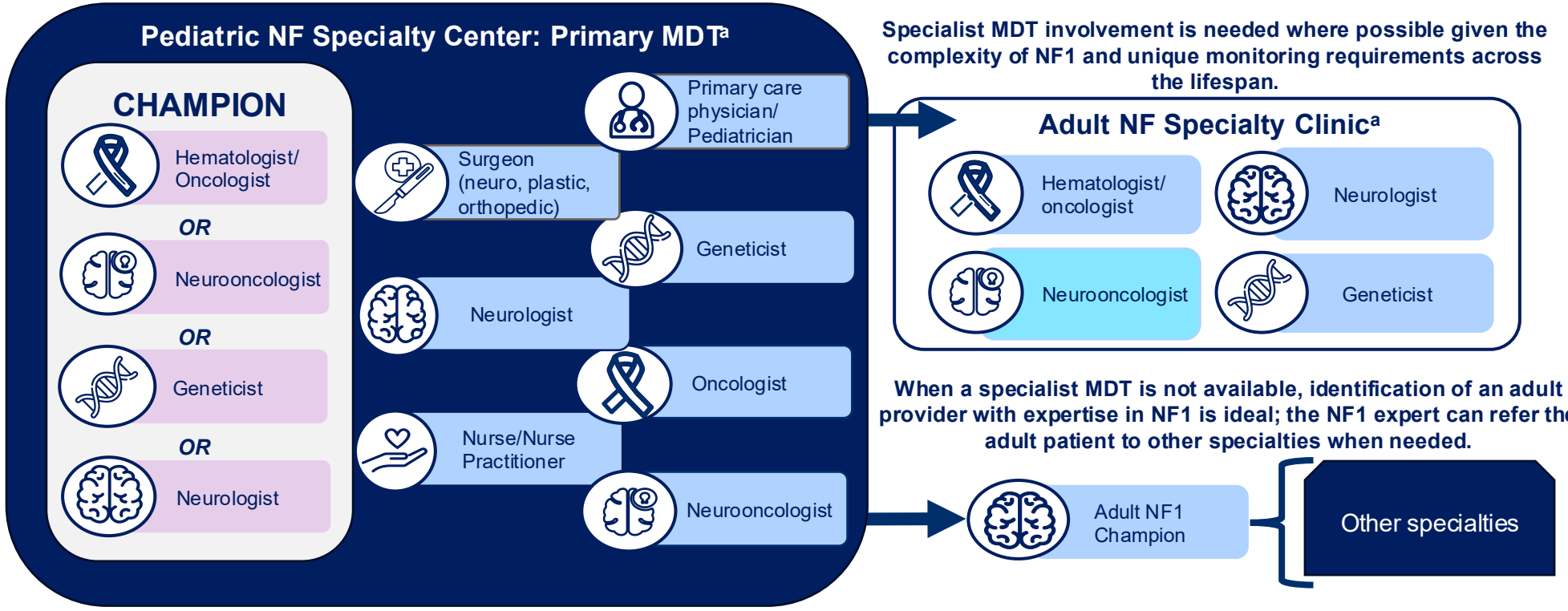
Factors contributing to the **severity of PN-associated morbidities**: **areas** where PN occur, tumors number, tumors size/volume, **tumor growth**[3,7-9]

Once PN-associated morbidities arise, they are extremely unlikely to resolve spontaneously and can have lifelong impact[3, 10]

NF1, neurofibromatosis type 1; PN, plexiform neurofibromas

1. Fisher MJ, et al. Neuro Oncol 2022;24:1827–44; 2.Korf BR. Neurofibromas and malignant peripheral nerve sheath tumours (MPNST) in neurofibromatosis 1. In: Korf BR and Rubenstein AE, eds. Neurofibromatosis: A Handbook for Patients, Families, and Health Care Professionals. Stuttgart, Germany: Thieme Verlagsgruppe, 2005; 3. Gross AM, et al. Neuro Oncol 2018;20:1643–1651; 4. Avery RA, et al. Ophthalmology 2017;124:123–132; 5. Wise JB, et al. Arch Otolaryngol Head Neck Surg 2005;131:712–718; 6. Üre I, et al. Case Rep Urol 2013;2013:145076; 7. Friedman JM. Gene Reviews 1998 Oct 2 [updated 2022 Apr 21]; 1993–2025; 8. Nguyen R, et al. J Pediatr. 2011;159(4):652–655.e2; 9. Ejerskov C, et al. Oncol Ther. 2023 Mar;11(1):97-110. 10

Patients with NF1 experience difficulties with the transition of care into adulthood, including a lack of:[6,7,a]



Many AYAs are referred back to their general practitioner for care, despite their care needs often increasing after the age of 18 years.[6]

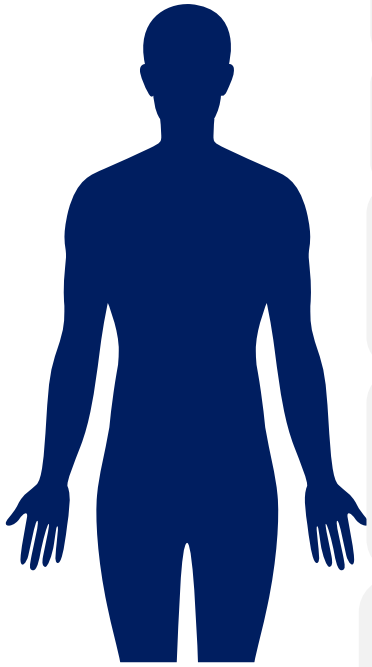
aThe list is not exhaustive.
MDT, multidisciplinary team; NF1, neurofibromatosis type 1
Lalvani S, Brown RM. J Multidiscip Healthc 2024;17:1803–17

1. Van Lierde A et al. Am J Med Genet A 2013;161A(7):1666–74; 2. Crawford HA et al. Clin Genet 2016;89:385–91; 3. Camfield P, Camfield C. Ann Neurol 2011;69(3):437–44; 4. Goetsch Weisman A et al. Compr Child Adolesc Nurs 2023;46(3):223-39; 5. Gregory TA et al. Neurooncol Pract 2022;9(3):229–35; 6. Rietman AB et al. Am J Med Genet A 2018;176A:1150–60; 7. Radtke HB et al. Pediatric Health Med Ther 2023;14:19–32.

UNMET NEEDS OF AYAs WITH NF1-PN

PN that are causing morbidity, or associated with impending morbidity, should be considered for treatment.[1]

Treating the PN before it leads to morbidity could potentially improve outcomes for patients with PN.[1]



AYAs reported experiencing more chronic pain, with a perceived worsening of this pain over time, leading to **mobility difficulties and necessitating pain management** interventions[2]

Invasive PN in the **face, head and neck** region can lead to functional deficits and **disfigurement**.[4]

While both adults and adolescents noted persistent external stigma with age, adults developed a more **internalized stigma related to body image,** feeling more "self-conscious" about their appearance. [2]

Limitations of numerical scales: both patients and doctors consider standard scales (NRS 11) inadequate for capturing the complexity of NF1 pain in AYAs. Patients develop a high tolerance, eventually coming to regard constant pain as ‘their normal’.

Adults reported limited social participation and intentional **avoidance of activities, leading to fewer social interactions**. They faced challenges in forming and maintaining relationships, particularly emphasizing the adverse effects of PNs on romantic relationships and family planning. Additionally, adults experienced lower educational achievement and higher unemployment rates, which further impacted their social roles.[2,4]

NF1, neurofibromatosis type 1; PN, plexiform neurofibroma

1. Fisher MJ et al. Neuro Oncol 2022;24(11):1827–44; 2. Jensen SE, et al. J Clin Psychol Med Settings. 2019 Sep;26(3):259-270 ; 3. Zacharia TT et al. Pediatr Radiol 2005;35(3):317–22; 4. Mautner VF et al. Neuroradiology 2006;48(3):160–5; 5. Hummelvoll G, et al. J Genet Couns. 2013 Apr;22(2):188-99.

KEY TAKEAWAYS IN NF1 PN AYAS

CHARACTERISTICS OF PN

NF1-PNs can **continue to develop and grow into adulthood**, but at a **slower rate** than that observed during childhood[1,2,3]



PAIN

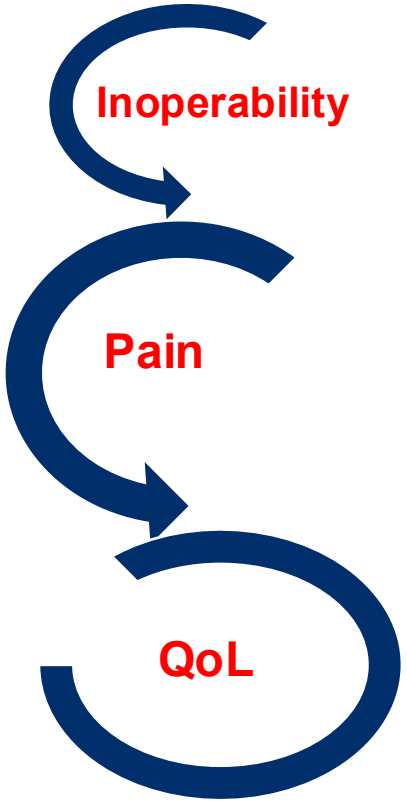
In adults, **pain** is the most commonly reported symptom: it **affects 80% of patients** and worsens over time[4,5]

QoL

The wide range of complications associated with PN has a significant impact on patients' quality of life, affecting their social and physical functioning, as well as stigma and emotional distress[5]



PN that are causing morbidity, or associated with impending morbidity, should be considered for treatment.[4] Spontaneous resolution of these morbidities, once developed, has been shown to be extremely unlikely[5]



The severe burden of this disease on the QOL of patients demonstrates **the high unmet need for an effective treatment option** that can reduce tumor burden and improve QOL[6]

1. Nguyen R et al. Orphanet J Rare Dis 2012;7:75; 2. Fisher MJ et al. Neuro Oncol 2022;24:1827–44; 3. Ly IK et al. Neurology 2023;100:e661–e670; 4. Yang X, et al. Neurology and Therapy. 2026;15(2):597–616. doi:10.1007/s40120-025-00855-2; 5. Jensen SE, et al. J Clin Psychol Med Settings. 2019 Sep;26(3):259-270; 6. Copley-Merriman C, et al. Adolesc Health Med Ther. 2021 May 19;12:55-66.

THE GOAL OF TREATMENT IS IMPROVEMENT OR PREVENTION OF PN-ASSOCIATED MORBIDITY[1]

In PN in NF1, treatment options have been **limited historically to surgery**[1]



Surgery may improve:

- QoL[2]
- Pain[3]
- Functional deficits[3]
- Disfigurement[3]
- Spinal cord compression or airway obstruction[3,4]

- NF1-associated PN are **inoperable** when they cannot be completely removed without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity of the PN[5]

NF1, neurofibromatosis type 1; PN, plexiform neurofibromas; QoL, quality of life

1.Fisher MJ, et al. Neuro Oncol 2022;24:1827–44; 2. Taylor LA, et al. Plast Reconstr Surg Glob Open 2019;7:e1982; 3. Nguyen R, et al. Genet Med 2013;15:691–97; 4. Mersal AY, et al. J Clin Neonatol 2012;1:214–16; 5. RCP selumetinib 09 Gennaio 2026

SELUMETINIB IS A TARGETED MEK 1/2 INHIBITOR[1,2]

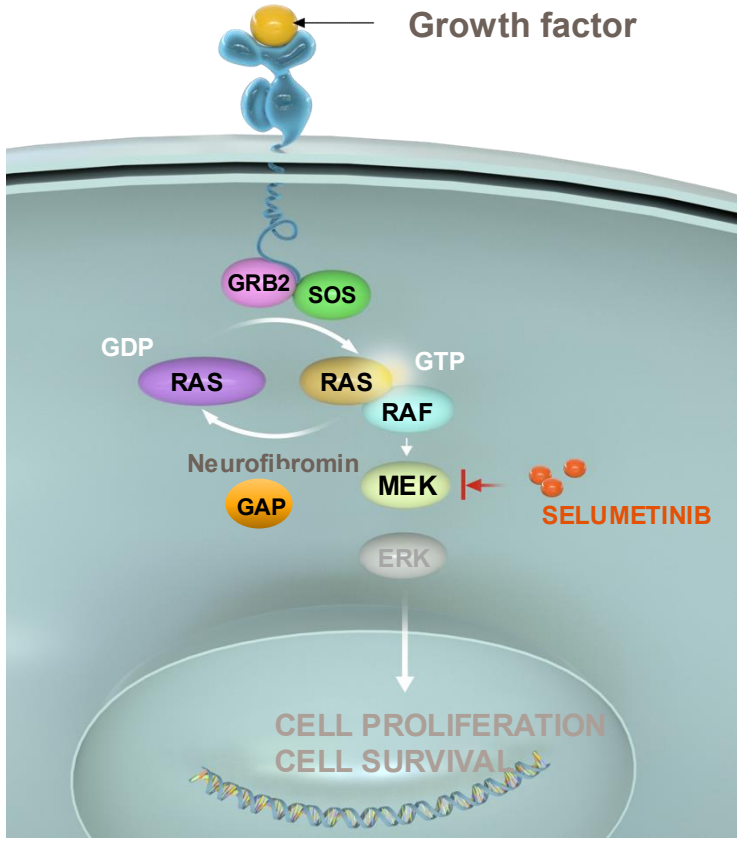


Figure adapted from (Yap YS, et al. *Oncotarget*. 2014;5(15):5873-92). Published by Impact Journals under CC BY 4.0 License.

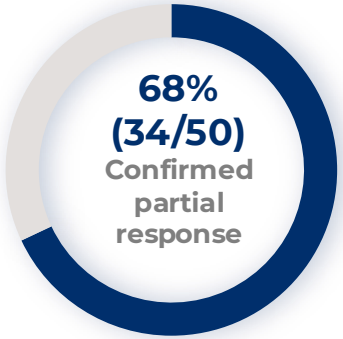
- Selumetinib is an orally active, selective, small-molecule inhibitor of MEK 1 and 2[1,2]
- The **MEK1/2 kinases are essential mediators** in the activation of the **RAS/RAF/MEK/ERK pathway**[1,2]
- **Selumetinib** inhibition of MEK1/2 **prevents the overactivation of this pathway** (arising from neurofibromin dysfunction), leading to inhibition of tumor cell proliferation and survival[3,4]

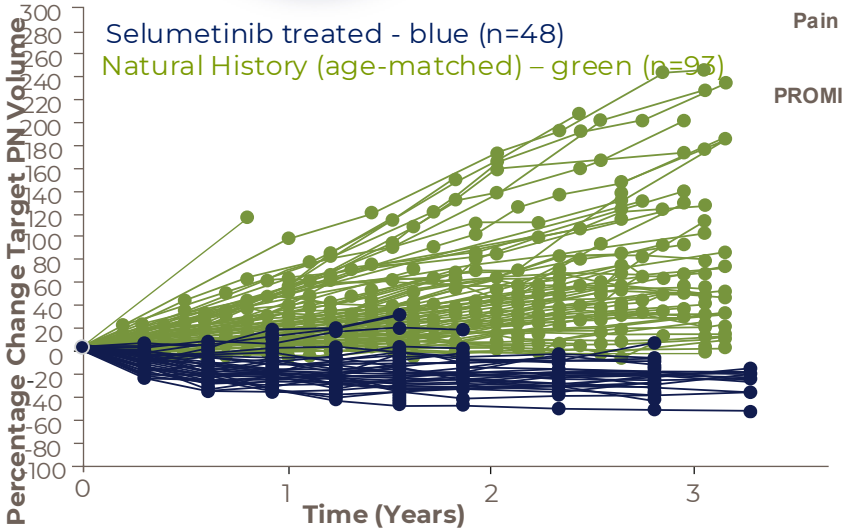
ERK, extracellular signal-regulated kinase; GAP, guanosine triphosphatase activating protein; GDP, guanosine diphosphate; GRB2, growth factor receptor bound 2; GTP, guanosine triphosphate; MEK, mitogen-activated protein kinase; RAF, murine sarcoma viral oncogene homologue; RAS, rat sarcoma viral oncogene homolog; SOS, mammalian homolog of the Drosophila son of sevenless

1. Blakeley J et al. Neuro Oncol 2016;18:624–38; 2. Dombi E et al. N Engl J Med 2016;375:2550–60; 3. Yap YS et al. Oncotarget. 2014;5:5873–92; 4. Wu PK, Park JI. Semin Oncol. 2015;42(6):849–62.

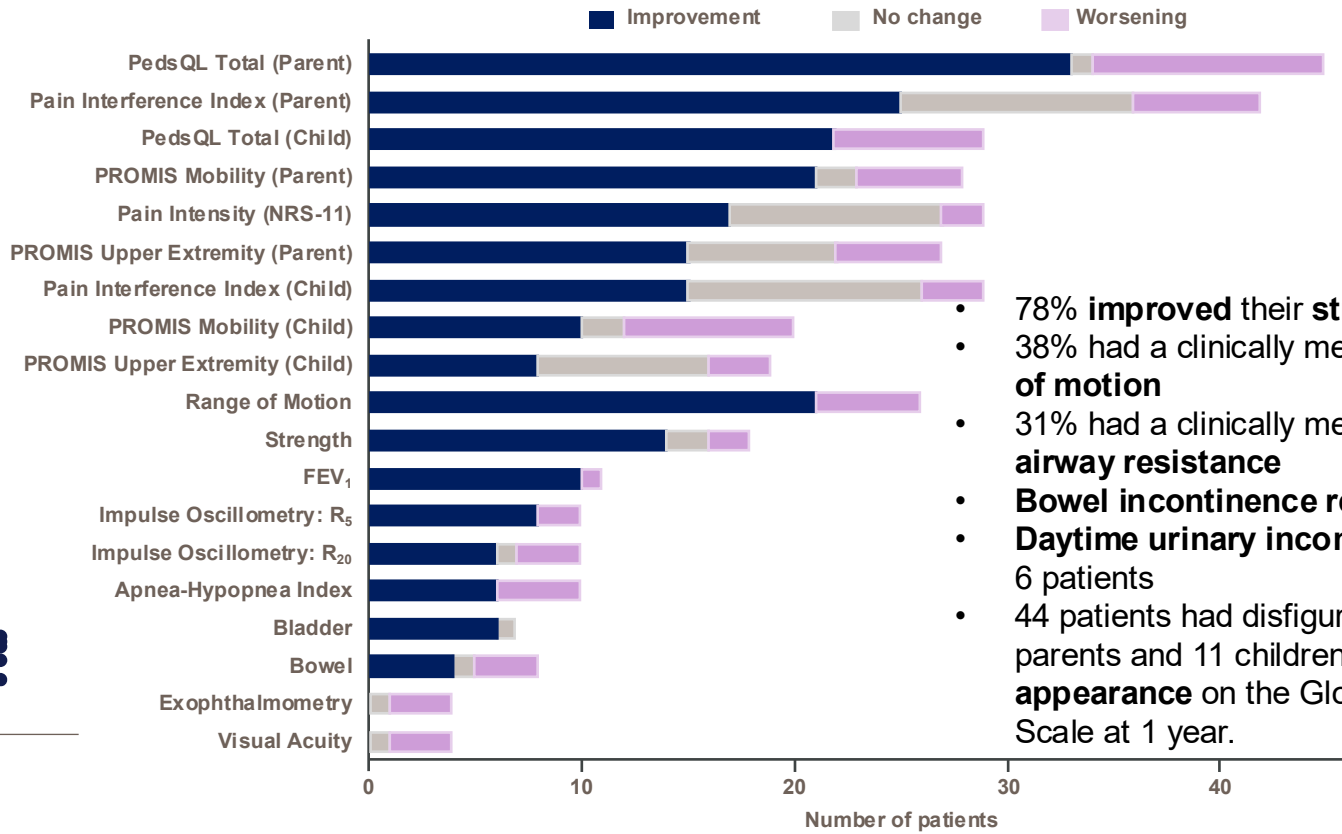
Radiological Response & Clinical Benefit

ORR[a]





Changes in PN-related clinical outcome measures between baseline and the evaluation before Cycle 13 with Selumetinib



- 78% **improved** their **strength**
- 38% had a clinically meaningful **increase in range of motion**
- 31% had a clinically meaningful improvement in **airway resistance**
- **Bowel incontinence resolved** in 3 out of 5 patients
- **Daytime urinary incontinence** resolved in 2 out of 6 patients
- 44 patients had disfigurement at baseline: with 24 parents and 11 children describing **improved appearance** on the Global Impression of Change Scale at 1 year.

a ORR is defined as the percentage of patients with complete response (defined as disappearance of the target PN) or confirmed partial response (defined as ≥20% reduction in PN volume, confirmed at a subsequent tumor assessment within 3–6 months), based on NCI centralized review

FEV1, forced expiratory volume in 1 second; Hz, hertz; NRS-11, Numeric Rating Scale 11; NF1, neurofibromatosis type 1; ORR, objective response rate; PedsQL, pediatric quality of life inventory; PN, plexiform neurofibroma; PROMIS, patient-reported outcomes measurement information system; R5, airway resistance at 5 Hz; R20, airway resistance at 20 Hz.

1. Gross AM et al. N Engl J Med 2020;382(15):1430–42; 2. Gross AM et al. N Engl J Med 2020;382(15)(Suppl 1):S1–76.

Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-025-05197-5

RESEARCH

Real-world experience with selumetinib in children with neurofibromatosis type 1: a multicentric retrospective study

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70 patients treated with selumetinib in **11 Italian centers** from 2018 to 2024

Table 1 Baseline patient demographic and clinical characteristics of the study population

Characteristic	All patients (*N*=70)
Sex, *n* (%)	
Male	39 (55.7)
Female	31 (44.3)
Age at NF1 diagnosis, median (range), years	1 (0–12)
Age at PN diagnosis, median (range), years	6 (0–15)
Age at therapy start, median (range), years	7.9 (2.6–12.6)
Age at the closing date of the study, median (range), years	15.4 (5.6–22.7)
PN volume at baseline, median (range), mL	126.8 (5–3820)
Number of treatment cycles, median (range)	49 (7.5–79)

Objectives

- **Radiological Response**
  - **CBR**=PR/MR/SD after ≥24 cycles
  - PR: reduction in tumor volume ≥20% compared to baseline; MR: reduction in tumor volume ≥50% compared to baseline;
  - SD: a change in tumor volume <20% compared to baseline
- **Clinical Benefit**
  - **VAS**
  - **ECOG PS**
  - **PedsQL**

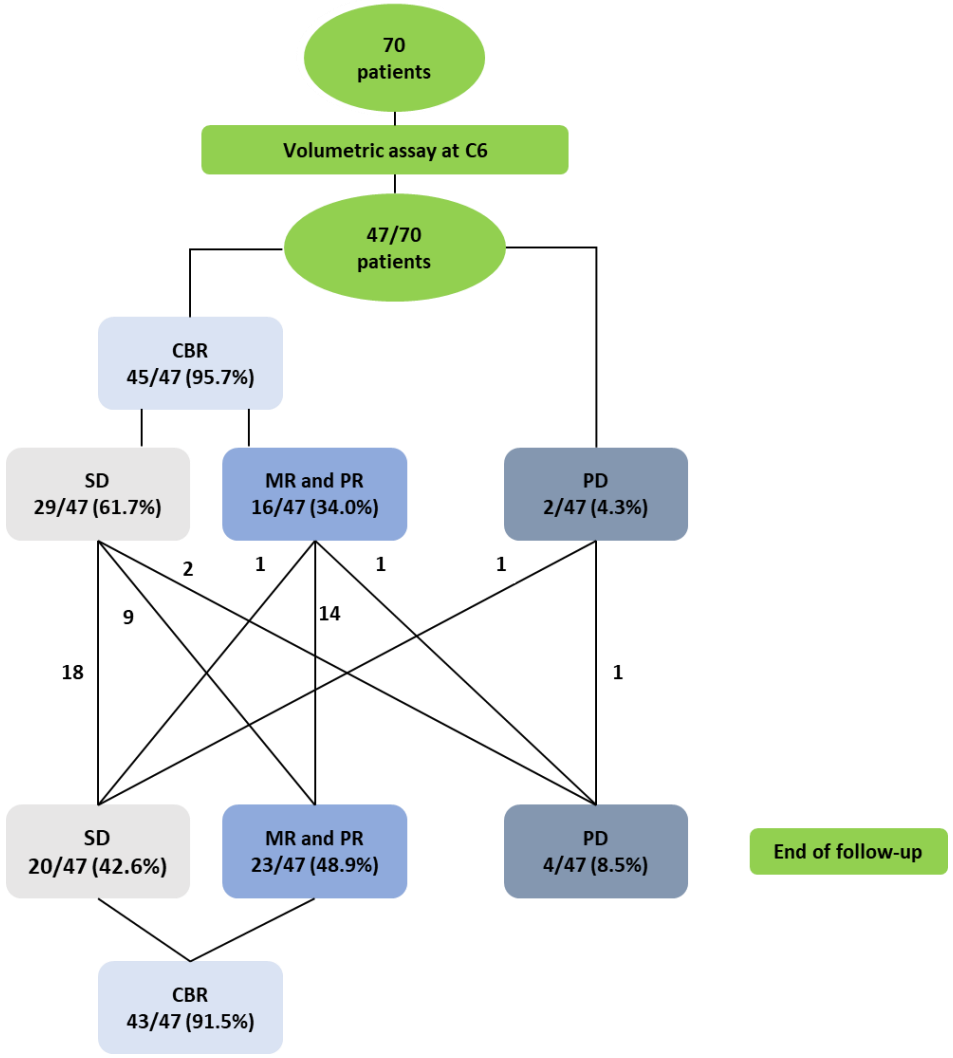
- **PNs** were primarily located in the **head** (27.14%), **neck** (17.14%), upper and lower **abdomen** (21.42%)
- **24.3%** (17/70) had **two clinical symptoms** or signs at baseline.
- The most frequent symptoms were **pain (51.4%),** deformity (35.7%), and motor dysfunction (15.7%)

CBR, clinical benefit rate; ECOG PS, eastern cooperative oncology group performance status; MR, major response; NF1, neurofibromatosis type 1; PD, progressive disease; PN, plexiform neurofibroma; PR, partial response; SD, stable disease; VAS, visual analog scale.

Santoro C, et al. J Neurooncol. 2025 Aug 13.

SELUMETINIB EFFECTIVELY SHRINK OR STABILIZE THE GROWTH OF PNS IN NF1 PATIENTS

- Data on the natural history of the target PN prior to therapy was available in 45 of the 70 enrolled patients:
  - **73%** (33/45) had **confirmed disease progression at the beginning of treatment**
  - An early radiological evaluation at **C6** was available in 17 of the 33 patients, and **94.1%** (16/17) **had a SD or PR**
- **Independently by the natural history of the target PN** prior to therapy, an MRI assessment was available at C6 for 47/70 patients:
  - **At C6, the CBR rate was 95.7%**
  - **At the last radiologic follow-up, the CBR rate was 91.5%**
- **The best PR/MR** was observed at C24 and corresponded to a **94% reduction from the baseline volume**



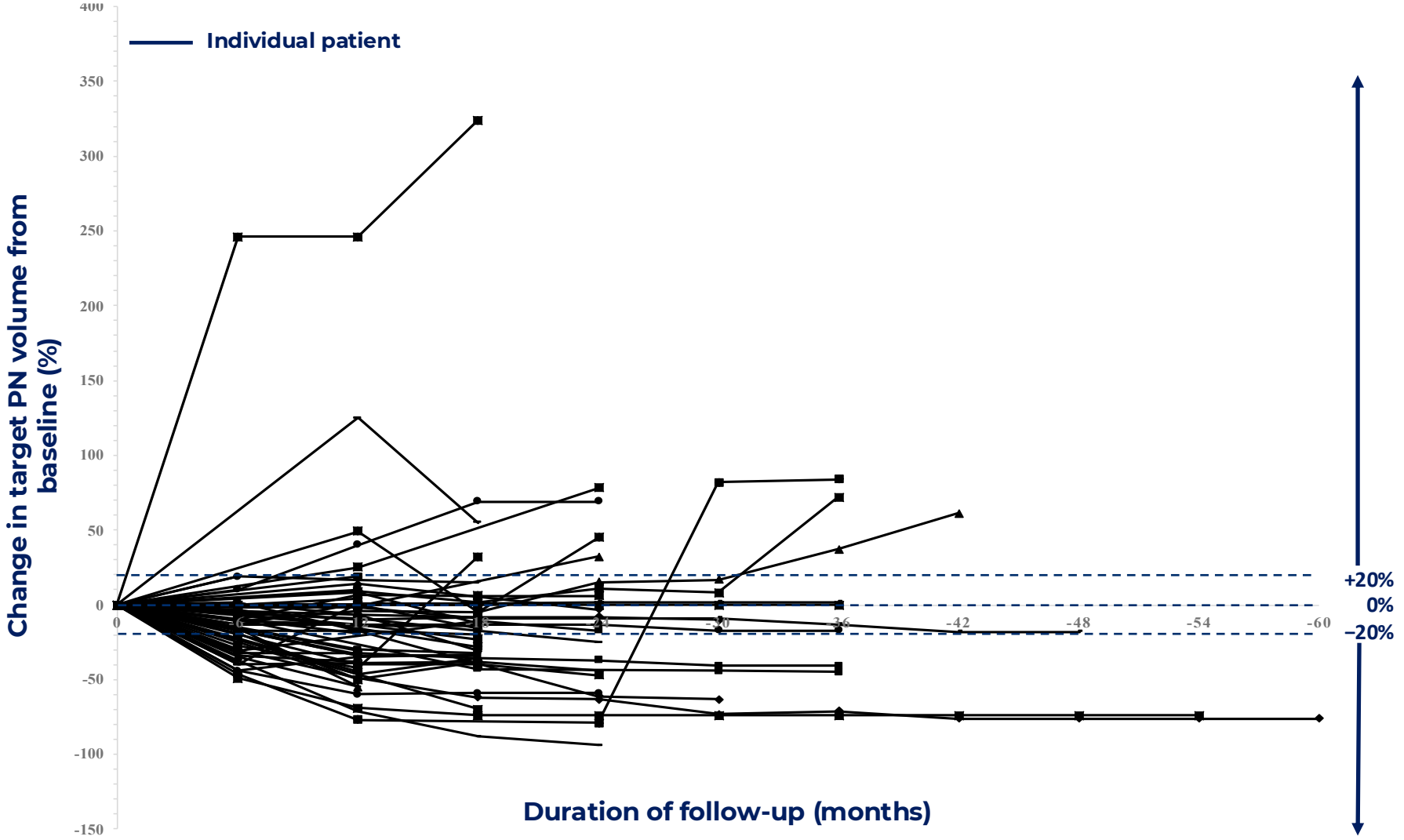
Definitions: PR: reduction in tumor volume ≥20% compared to baseline; MR: reduction in tumor volume ≥50% compared to baseline; SD: a change in tumor volume <20% compared to baseline; PD: an increase in tumor volume ≥20% compared to baseline.
CBR = PR/MR/SD after ≥24 cycles.
C, cycle; CBR, clinical benefit rate; MR, major response; NF1, neurofibromatosis type 1; PD, progressive disease; PN, plexiform neurofibroma; PR, partial response; SD, stable disease
1.Santoro C, et al. J Neurooncol. 2025 Aug 13; 2. Santoro C, et al. J Neurooncol. Suppl. 2025 Aug 13.

SELUMETINIB EFFECTIVELY SHRINK OR STABILIZE THE GROWTH OF PNS IN NF1 PATIENTS

M/IT/UNB-NF1/0084

At the end of follow-up :

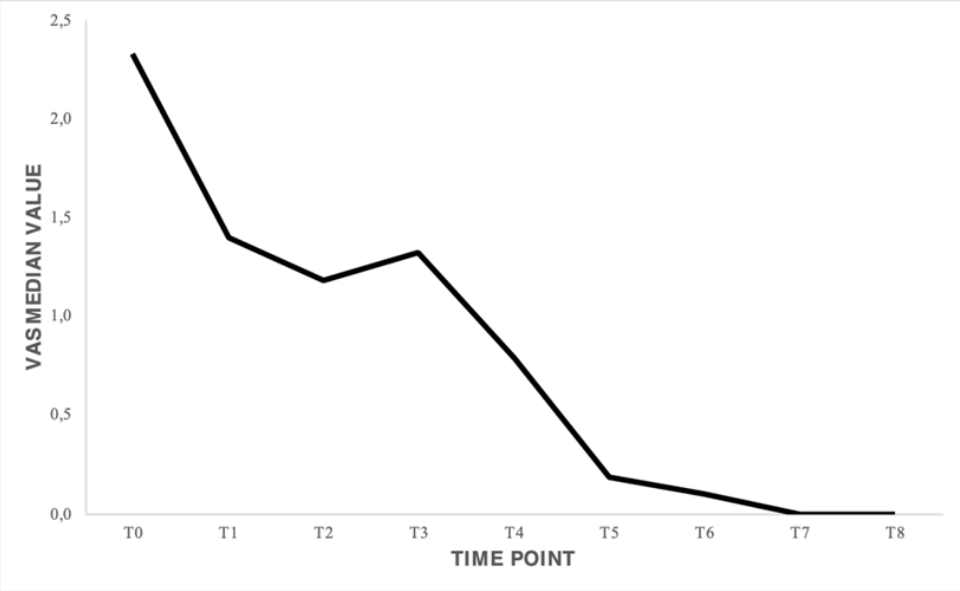
- **PR:**
  - **30.0%** (21/70) patients
  - **Median tumor volume variation: –33.2%** (range: –20.8 to –47.6)
- **MR:**
  - **15.7%** (11/70) patients
  - **Median tumor volume variation: –63.3%** (range: –50.3 to –94.0)
- SD: 41.4% (29/70) patients
- PD: 12.9% (9/70) patients



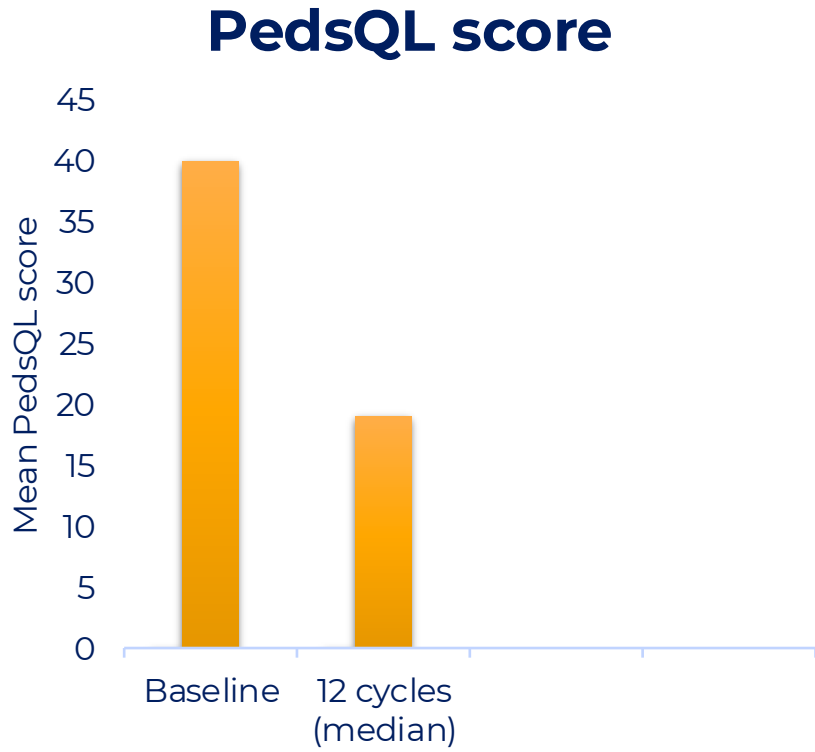
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CLINICAL BENEFIT BESIDE AND BEYOND THE RADIOLOGICAL TUMOR RESPONSE

Pain perception decreased significantly compared to baseline at all timepoints (C6 − C48; $p < 0.05$ for all comparisons), **regardless of radiologic response**



- Among the 57 patients (81.4%) with baseline ECOG available, **ECOG PS** was found to be **significantly improved** compared to baseline with selumetinib treatment ($p < 0.05$), **regardless of radiologic response**
- A total of 25.7% completed the PedsQL questionnaire : At baseline, **the mean PedsQL score** in these patients was 40 which **decreased** to 19 (on a scale 0-100 with higher scores indicating poorer qol) after a median of 12 cycles (range: 6–48), **regardless of radiologic response**



C, cycle; VAS, visual analog scale.

1. Santoro C, et al. J Neurooncol. 2025 Aug 13; 2 . Santoro C, et al. J Neurooncol. Suppl. 2025 Aug 13

Materiale ad esclusivo utilizzo da parte della Direzione Medica per il solo uso reattivo

MOST AEs WERE OF GRADE 1 OR 2 AND MANAGEABLE

- As with previous studies, most of AEs (**78%**) were of **grade 1 or 2 and manageable**
- The majority of AEs (76.9%) **occurred within the first 6 months** of therapy
- **Only 3 patients discontinued treatment due to AEs**

Table 4 Number, type, and grade of adverse events reported for 61 patients during selumetinib treatment

	Grade 1 and 2 (n=71)	Grade 3 (n=18)	Grade 4 (n=2)	Total AEs (n=91)
Number of events, (%)				
Dermatitis	28 (39.4)	6 (33.3)		34 (37.4)
Paronychia	18 (25.4)	8 (44.4)	2 (100.0)	28 (30.8)
Xerosis ± itching	13 (18.3)			13 (14.3)
CPK level increase	4 (5.6)	3 (16.7)		7 (7.7)
Hair depigmentation	4 (5.6)			4 (4.4)
Abdominal pain	1 (1.4)			1 (1.1)
Nausea and vomiting	1 (1.4)			1 (1.1)
Diarrhea	1 (1.4)			1 (1.1)
Eyelid edema	1 (1.4)			1 (1.1)
ALT/AST transaminase ratio increase		1 (5.6)		1 (1.1)
CPK level increase, rhabdomyolysis and regression			1 (50.0)	1 (1.1)

AEs were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

AEs, adverse events.
Santoro C, et al. J Neurooncol. 2025 Aug 13.

KEY TAKEAWAYS



Largest real-world observational **cohort** of Pediatric NF1 patients with symptomatic, inoperable PNs

N=70 across 11 Italian centers



Extended clinical benefit independent by radiological response

CBR: 91.5% at last follow-up
Pain and QoL: significant improvements, independently by radiological reduction



Confirmed safety and tolerability in real-world

Mostly AEs grade ≤2
Manageable events
Median treatment exposure: 49 cycles (range 7.5–79)

AEs, adverse events; CBR, clinical benefit rate; NF1, neurofibromatosis type 1; QoL, quality of life.
Santoro C, et al. J Neurooncol. 2025 Aug 13.

For years, the success of selumetinib in NF1-associated plexiform neurofibromas has been measured by a single metric: tumour volume reduction.

The landmark SPRINT trial (Widemann et al., *NEJM* 2020) reported a **68–70% partial radiological response** rate — an unprecedented result in this condition.

But Is Shrinkage Enough?

Patients and families ask fundamentally different questions:

- Will my child have less pain?
- Will he or she move better?
- Will quality of life improve?
- Could cognition be affected?



Pain reduction is among the most clinically meaningful outcomes reported in the **SPRINT trial** and one of the most compelling reasons to reframe our view of selumetinib.

74% of patients presented basal tumor pain

74% achieved clinically significant relief with ≥2 point reduction the accepted threshold for clinical significance

94% Stable/reduced analgesic use : among pain responders, analgesic burden remained stable or decreased

Pain Interference With Daily Life

Beyond the Numeric Score

The SPRINT trial assessed not only pain intensity but also **pain interference with daily activities:** a patient-centred measure that captures how pain limits functioning, participation, and independence.

Significant reductions in pain interference were observed at 12 months, reflecting a **meaningful improvement in how children experience and navigate everyday life.**



Widemann et al., NEJM 2020

MOTOR FUNCTION: FROM SHRINKAGE TO MOBILITY

The SPRINT trial evaluated functional outcomes alongside volumetric response, revealing that tumour shrinkage translates into meaningful improvements in physical capability.

56% of children showed a **clinically significant improvement in muscle strength** after 12 months

38% demonstrated a **clinically significant improvement in range of motion**

68% improved in **at least one functional or patient-reported outcome**

Old Paradigm

"The tumour became smaller."

Radiological response as the primary (and often sole) measure of treatment success.

New Paradigm

"The patient became more functional."

Treatment benefit is now understood in terms of **reduced disability** and **greater participation in everyday activities.**

Functional assessments should be embedded in clinical follow-up, not treated as secondary endpoints.

Widemann et al., NEJM 2020

HEALTH-RELATED QUALITY OF LIFE

Using the validated **PedsQL instrument**, the SPRINT trial captured quality of life from two perspectives: the child's own experience and the parent's assessment.

Child-Reported

Mean QoL increase: **+6.7 points**

Clinically significant improvement in **48%** of children

Parent-Reported

Mean QoL increase: **+13 points**

Clinically significant improvement according to **58%** of parents

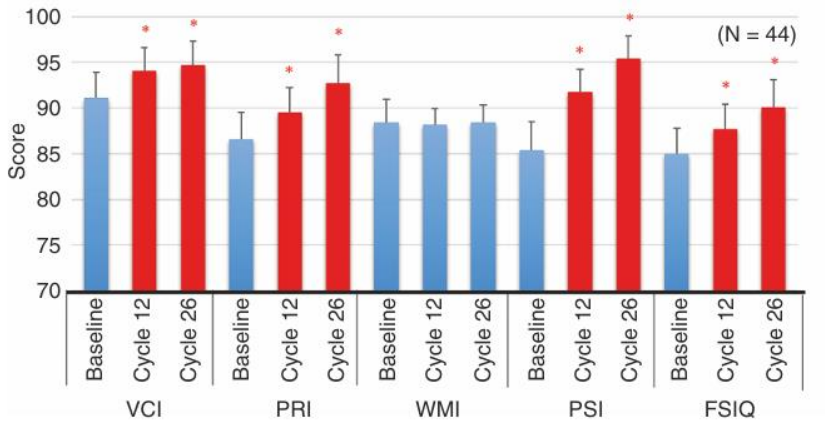
Multidimensional Gains

Improvements spanned physical, emotional, and social functioning extending well beyond tumour related symptoms

1. Gross AM et al. N Engl J Med 2020;382(15):1430–42; 2. Gross AM et al. N Engl J Med 2020;382(15)(Suppl 1):S1–76

NEUROCOGNITIVE EFFECTS: EMERGING EVIDENCE

A Korean multicenter study evaluated cognitive outcomes in **89 patients with NF1-PN** (pediatric and adult), using standardized neuropsychological batteries (K-WISC / K-WPPSI / K-WAIS).



Important caveat!!!!

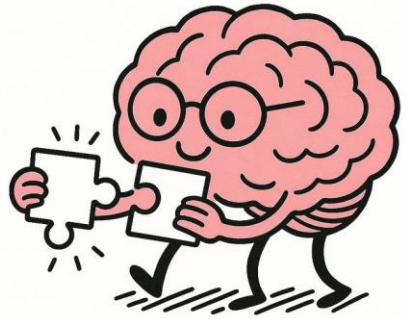
Open-label, non-randomised, no control group. Cognitive gains may reflect reduced pain, improved functioning, and reduced tumour burden — not solely a direct pharmacological effect.

After 12 Cycles

- VCI improved in children
- PSI improved in children and adults
- FSIQ improved in children and adults

After 26 Cycles

- Significant improvements in VCI, PRI, PSI, FSIQ
- Reduction in proportion of patients in borderline intellectual functioning / intellectual disability categories



Kim H, et al. Safety and efficacy of selumetinib in pediatric and adult patients with neurofibromatosis type 1 and plexiform neurofibroma. Neuro Oncol. 2024 Dec 5;26(12):2352-2363.

SUMMARY OF KEY STUDIES REFERENCED

Study	Population	Design	Key Outcome
Widemann et al. *NEJM* 2020 (SPRINT)	50 paediatric NF1-PN	Phase II RCT	Pain, function, QoL, volumetric response
Korean multicentre, *Neuro-Oncology* 2024	86 NF1-PN (paed + adult)	Open-label, non-randomised	Neurocognitive outcomes, growth, pigmentation
EPNS Congress 2025	86 NF1-PN patients	Longitudinal fMRI study	Brain connectivity, cognitive trajectory
Italian multicentric study 2025	70 paediatric NF1-PN, 11 centres	Real-world observational	Pain, QoL, ECOG performance status
Phase II, *Nature Medicine* 2025	Adults with NF1-PN	Phase II single-arm	ORR, pain, function
KOMET Phase III	Adults with NF1-PN	Randomised Phase III	PlexiQoL, pain — mixed results

Gross AM, Selumetinib in Children with Inoperable Plexiform Neurofibromas. N Engl J Med. 2020

Kim et al. Safety and efficacy of selumetinib in pediatric and adult patients with neurofibromatosis type 1 and plexiform neurofibroma, Neuro-Oncology, Volume 26,December 2024

Kwon O, et al. Selumetinib Improves Cognitive Function and Modulates Brain Connectivity in NF1 Patients: A Longitudinal Study. EPNS 2025, Abstract EPNS25_250.

Santoro C, et al. J Neurooncol. 2025 Aug 13; 2

Gross AM, et al. Selumetinib in adults with NF1 and inoperable plexiform neurofibroma: a phase 2 trial. Nat Med. 2025 Jan;31(1):105-115.

Chen AP, et al. KOMET study investigators. Efficacy and safety of selumetinib in adults with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas (KOMET): a multicentre, international, randomised, placebo-controlled, parallel, double-blind, phase 3 study. Lancet. 2025 Jun 21;405(10496):2217-2230.

“WHAT TO TELL PATIENTS AND FAMILIES?”

"Will my child have less pain?"

The evidence is strong: **74% of children with baseline pain achieved clinically significant relief**. Pain interference with daily activities also decreased significantly. (SPRINT, NEJM 2020)

"Will he move better?"

Likely yes: **56% showed improved muscle strength**, 38% improved range of motion, and 68% improved in at least one functional outcome. (SPRINT, NEJM 2020)

"Will quality of life improve?"

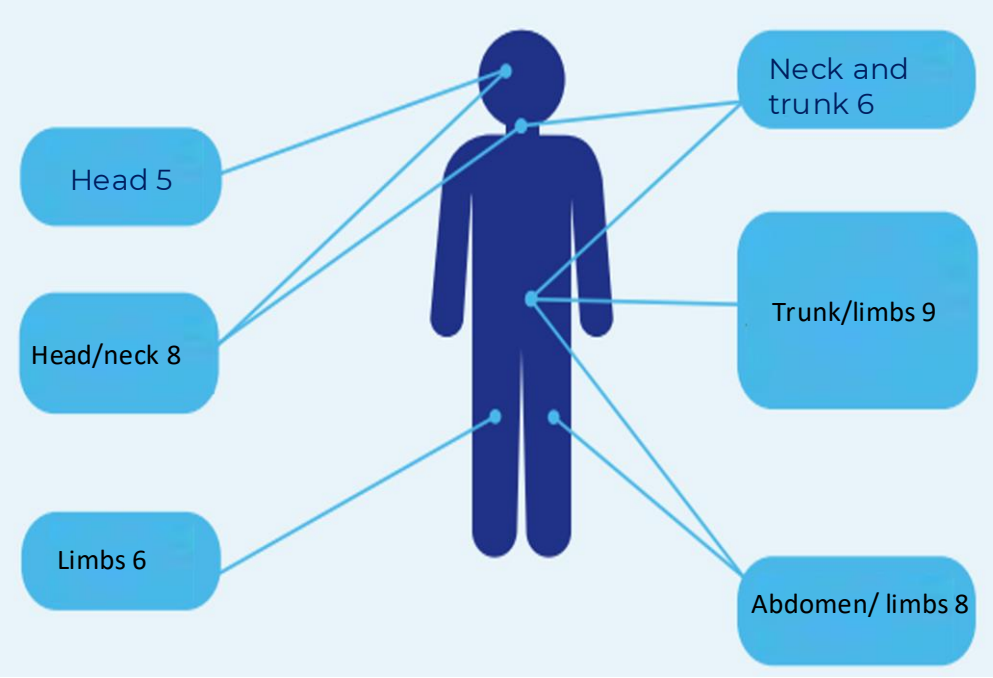
Yes, with meaningful effect sizes: parents reported a mean QoL increase of **+13 points** and 58% reported clinically significant improvement. (SPRINT, NEJM 2020)

"Could cognition improve?"

Possibly — but this is **emerging evidence**, not yet definitive. We are watching this closely with great scientific interest. (Neuro-Oncology 2024; EPNS 2025)

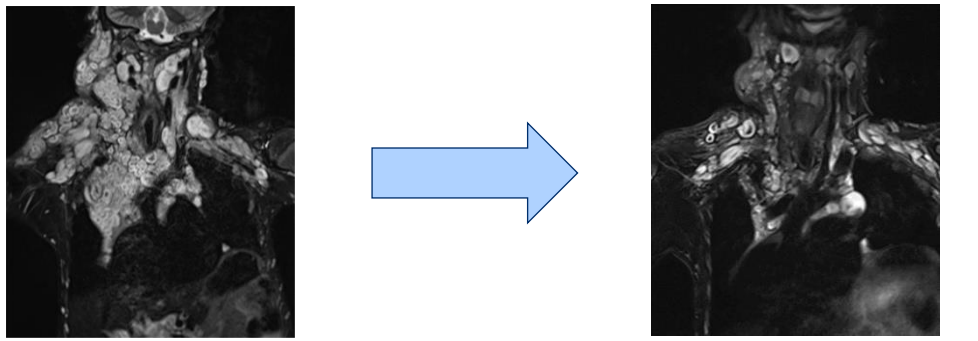
Experience with selumetinib treatment in compassionate-use and commercial settings

- 42 patients
- 2019-2025
- Age: 3-26 (median 10.5 yo)
- Inoperable and symptomatic PNs

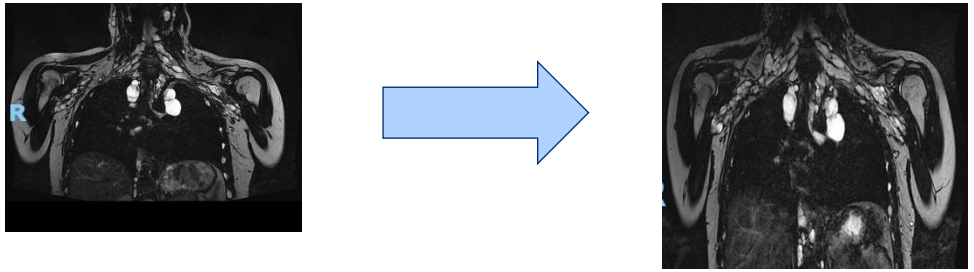


Clinical Cases at the Bambino Gesù Children's Hospital.

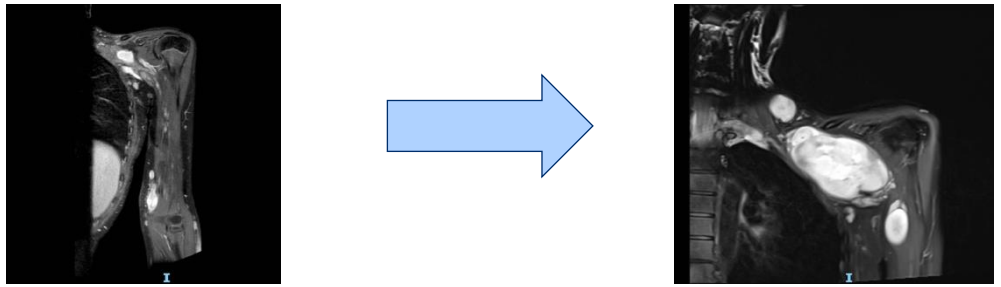
Volumetric MRI: radiological response, after 12 cycles of treatment with Selumetinib



Partial response: 54%, 23/42 cases



SD: 35%, 15/42 cases

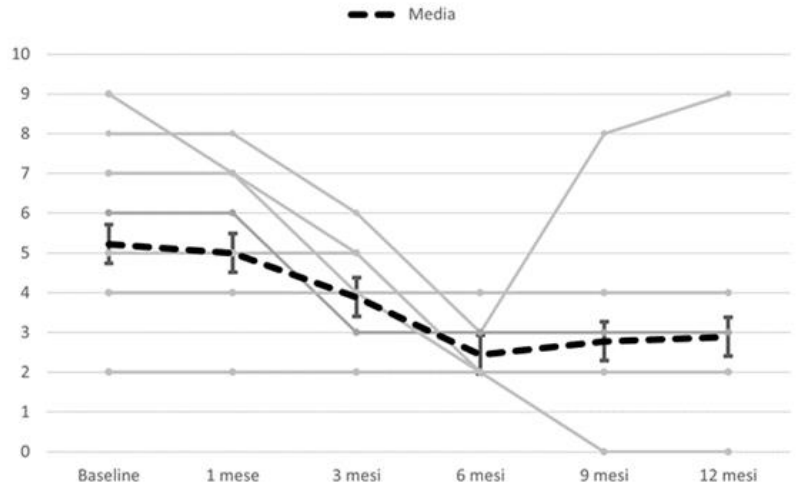


Progression disease :
10%, 4/42 cases, malignant transformation

Clinical Cases at the Bambino Gesù Children's Hospital.
Images obtained with informed consent from the legal guardian.

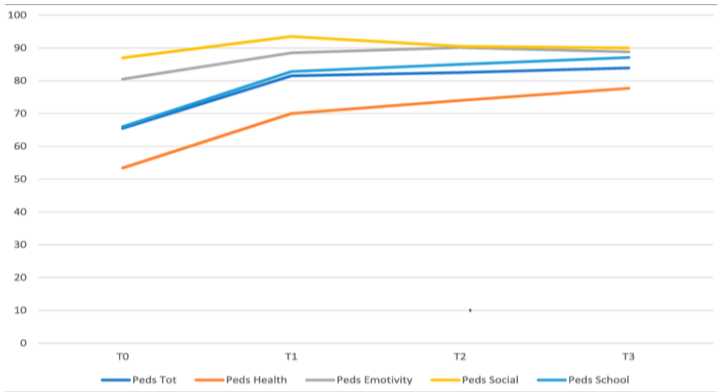
Clinical outcomes, after 12 cycles of treatment with selumetinib

Pain
A clinically relevant reduction in pain was observed, with a mean decrease of 2.33 points on the Visual Analog Scale, from 5.22 at baseline to 2.89 at 12 months (P = .03). Overall, 55% of patients reported a reduction of more than 2 points, and 10 discontinued analgesic therapy.



Muscle strength
limprovement in motor function was observed, with recovery of muscle strength and motor skills in paretic limbs. Overall efficacy was 45%, with mean muscle strength increasing from 2.64 at baseline to 3.45 at 12 months (P = .03).

Quality of life
QoL improved significantly from baseline (65.6 ± 19.8) to 12 months (83.9 ± 17.9), with the greatest improvements observed in health perception, emotionality, and school activities.



Clinical Cases at the Bambino Gesù Children's Hospital.

Cacchione A, et al. Safety and Efficacy of Mek Inhibitors in the Treatment of Plexiform Neurofibromas: A Retrospective Study. Cancer Control. 2023 Jan-Dec;30:10732748221144930.

Safety profile

- No grade 4 toxicity
- 100 % cutaneous toxicity
- 100% change hair color
- 30% dhiarroea G2
- Ordinary management except in 2 cases of paronychia (surgery)







Clinical Cases at the Bambino Gesù Children's Hospital.
Image obtained with informed consent from the legal guardian.

Baldo F. et al Selumetinib side effects in children treated for plexiform neurofibromas: first case reports of peripheral edema and hair color change. BMC Pediatr. 2021 Feb 6;21(1):67

IS SELUMETINIB SIMPLY A TUMOUR-SHRINKING DRUG?

PROBABLY NOT

The available evidence, from randomised trials, real-world studies, and emerging neuroimaging data, suggests that MEK inhibition with selumetininb in NF1-PN translates into multidimensional clinical benefits that extend well beyond the imaging report.

Strong Pain, physical function — robust RCT data confirmed in real-world practice	**Moderate** Health-related QoL — meaningful effect sizes, though mixed in adult trials
Emerging Neurocognition, brain connectivity — compelling hypothesis, needs controlled validation	**Exploratory** Growth velocity, café-au-lait reduction — intriguing secondary observations only

TAKE HOME MESSAGES

Reframe the narrative

Move beyond volumetric response. Pain, function, and QoL are equally, if not more, meaningful to patients and families

Use patient-centred tools

Integrate pain scales, functional assessments, QoL instruments into routine follow-up, not just MRI

Interpret emerging data

Neurocognitive and fMRI findings are exciting but preliminary

Think phenotypically

Selumetinib may be modifying the NF1 phenotype in ways we are only beginning to understand



Think beyond the tumour

THANK YOU!













- Prof Franco Locatelli
- Prof ssa Angela Mastronuzzi
- Dr Giada Del Baldo
- Dr Andrea Carai
- Dr Stefania Colafati
- Dr Federica D'Antonio
- Dr Maria Giuseppina Cefalo
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