

Nuovi outcomes di trattamento per i neurofibromi plessiformi nei pazienti affetti da NF1

Antonella Cacchione

**Ospedale Pediatrico Bambino Gesù Roma
Area Clinica di Onco-Ematologia, Terapia Cellulare,
Terapie Geniche e
Trapianto Emopoietico e Genica**

Direttore Prof F.Locatelli

ALEXION®
AstraZeneca Rare Disease

M/IT/UNB-NF1/0075



XLIX
CONGRESSO
NAZIONALE
AIEOP

BOLOGNA
30 settembre
2 ottobre

2024

Disclosure

- Speaker for Alexion
- Advisory boards for Astra Zeneca

Disclaimer

- Clinical Cases based on personal experience
- Parents' informed consent obtained
- No pictures or reproductions are allowed

Neurofibromatosis type 1 (NF1)

- ❖ Autosomal dominant (gene NF1: 17q11.2)
- ❖ Incidence: 1/3000 newborns

- ❖ Two or more of the following manifestations (new Legius criteria, 2021):
 - Six or more café-au-lait spots
 - Freckling in the armpits or groin
 - Two or more neurofibromas of any type or one plexiform neurofibroma
 - Optic pathway glioma
 - Two or more Lisch nodules or two or more choroidal abnormalities
 - Skeletal problems (sphenoid dysplasia, bowing of the tibia, long bone pseudoarthrosis)
 - A faulty NF1 gene detected through genetic test



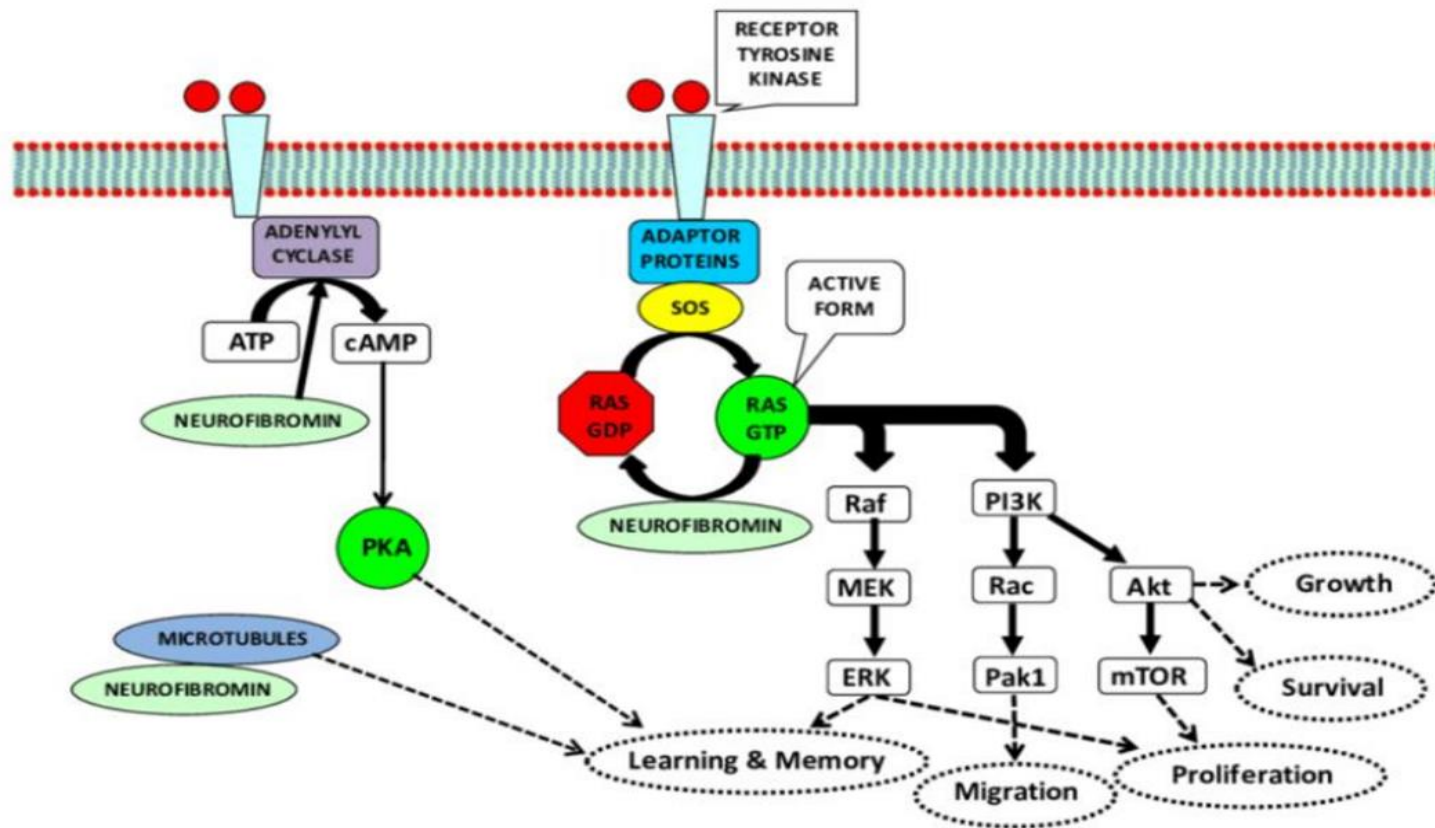
Legius, Eric et al.

*Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation
Genetics in Medicine, Volume 23, Issue 8, 1506 - 1513*

Susceptibility to neoplasms development

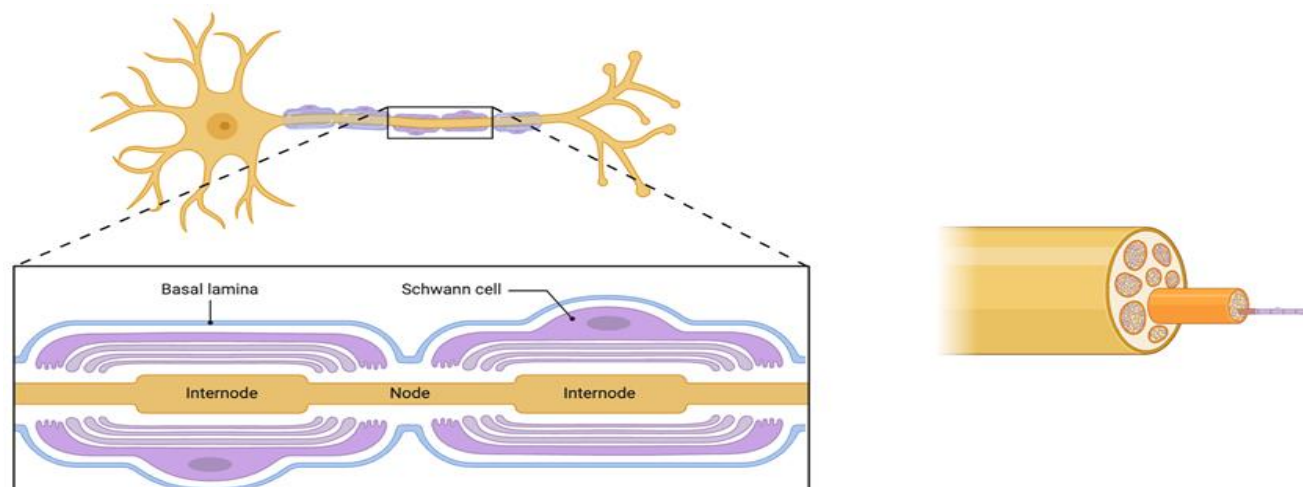
- ❖ Loss of neurofibromin = RAS pathway overactivation

Nf1-mediated signaling pathways



Plexiform neurofibromas (PNs)

- ❖ Serious complication of NF1
- ❖ Histologically benign nerve sheath tumors
- ❖ Tumors most frequently associated with NF1, **50% of cases**
- ❖ Large nerve trunks affected
- ❖ Frequent sites: paraspinal nerves, brachial or sacral plexuses, trunk and neck wall



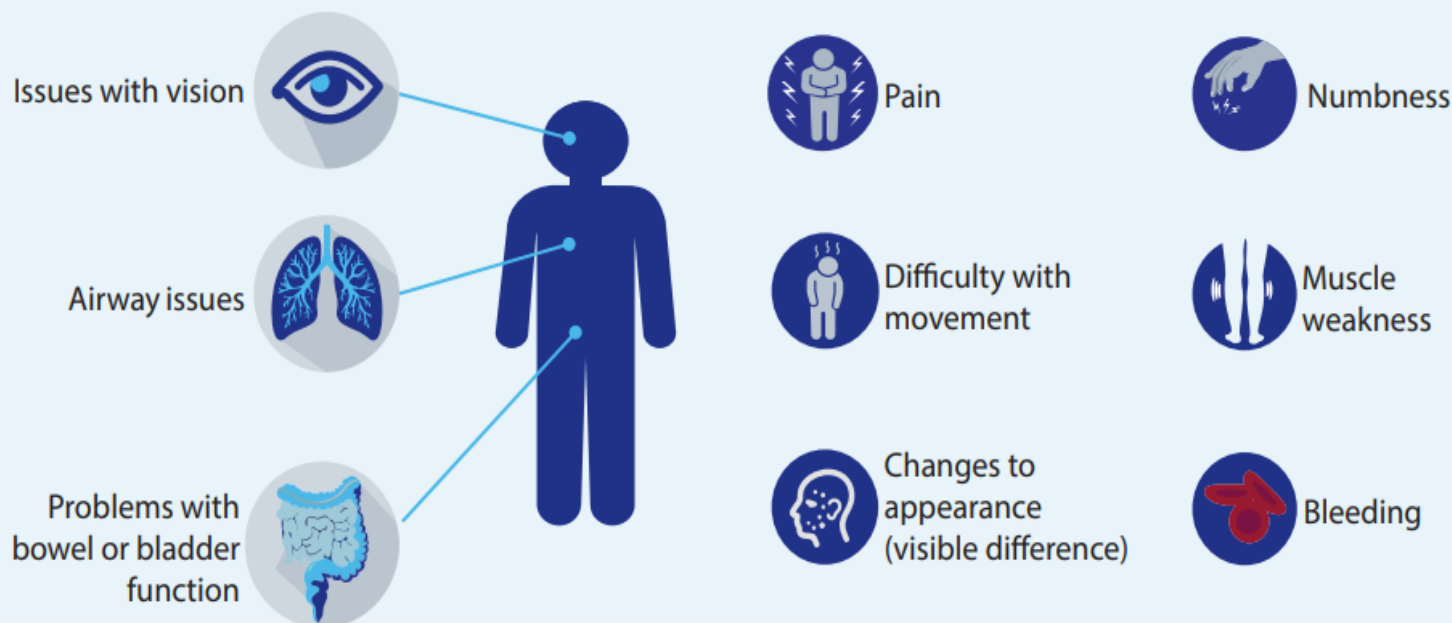
Fisher MJ et al. Management of neurofibromatosis type 1-associated plexiform neurofibromas. *Neuro Oncol.* 2022 Nov 2;24(11):1827-1844

Problems caused by NF1-related PN

A PN can cause issues for patients.

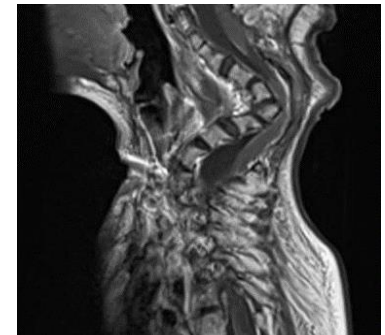
The type of issue depends on where the PN grows in the body.

A PN can cause more than one problem for patients.



Gross AM et al. Selumetinib for children with neurofibromatosis type 1 and plexiform neurofibromas: A plain language summary of SPRINT. *Future Oncol.* 2024 May;20(14):877-890

Clinical impact





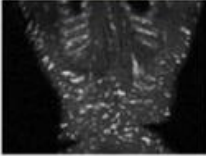
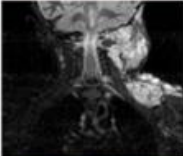
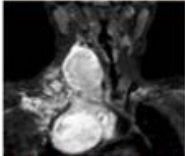
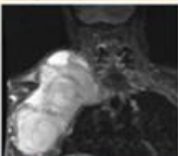

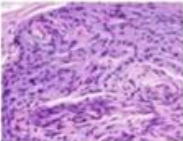
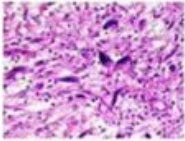
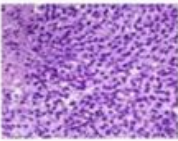


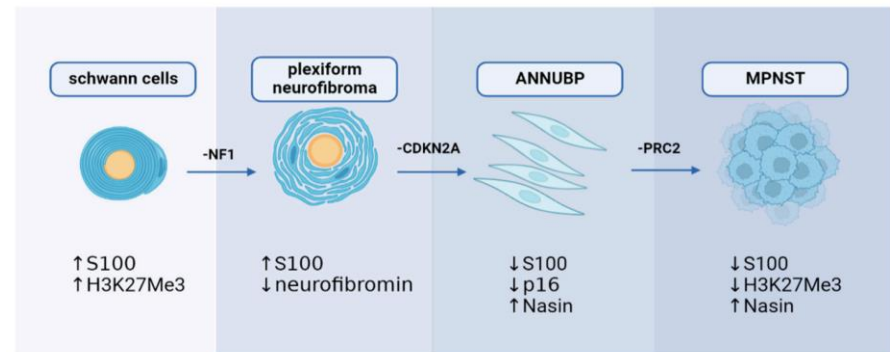
*Based on the speaker's personal experience
Images obtained with patient/family/tutor permission*

**Nuovi outcomes di trattamento per i neurofibromi plessiformi nei pazienti affetti da NF1, AIEOP
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Natural history

- ❖ Typically congenital or most important peak of volumetric increase in early childhood
- ❖ Associated with at least one morbidity
- ❖ Risk of malignant transformation (malignant peripheral nerve sheath tumors, MPNST) of **8-15 %**

| Dermal ≥ 95% | Plexiform 25% to 50% | Atypical Unknown | MPNST 15.8% |
|--|---|---|---|
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
| Disfigurement, pruritus, pain Loss of <i>NF1</i> | Appearance, pain, function loss → Malignant transformation Loss of <i>NF1</i> | + <i>CDKN2A</i> mutations | + <i>PRC2</i> , <i>P53</i> , others |



Malignant Peripheral Nerve Sheath Tumors: Latest Concepts in Disease Pathogenesis and Clinical Management. Chengjun Yao et al. Cancer February 2023

Nuovi outcomes di trattamento per i neurofibromi plessiformi nei pazienti affetti da NF1, AIEOP

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- ❖ Size of PN affects directly the severity of symptoms. These functional impairments have a negative impact on the overall quality of life (QoL), notably affecting pain and discomfort, anxiety and depression and caregiver productivity
- ❖ 1/3 of children and adolescents with PN present social-emotional difficulties (anxiety, depression, social withdrawal)

Yoo et al. *BMC Neurology* (2023) 23:419
<https://doi.org/10.1186/s12883-023-03429-7>

BMC Neurology

RESEARCH

Open Access

Impact of neurofibromatosis type 1 with plexiform neurofibromas on the health-related quality of life and work productivity of adult patients and caregivers in the UK: a cross-sectional survey

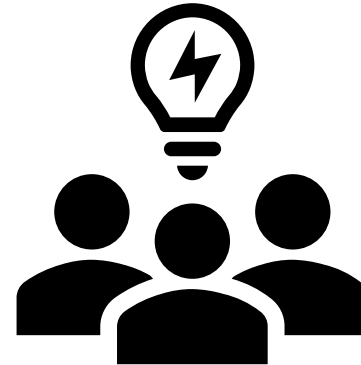
Hyun Kyoo Yoo^{1*}, Alex Porteous², Alvin Ng³, Keval Haria², Annabel Griffiths⁴, Andrew Lloyd⁵, Xiaoqin Yang⁶, Gbenga Kazeem⁷ and Volkan Barut⁷



Wolters PL Substantial Pain and reduced quality of life in adolescents and young adults with neurofibromatosis type 1 and plexiform neurofibromas enrolled in NF Consortium PN Clinical Trials. In: CTF Global Joint NF Conference, Paris, France; 2018.

Nuovi outcomes di trattamento per i neurofibromi plessiformi nei pazienti affetti da NF1, AIEOP Bologna 2024

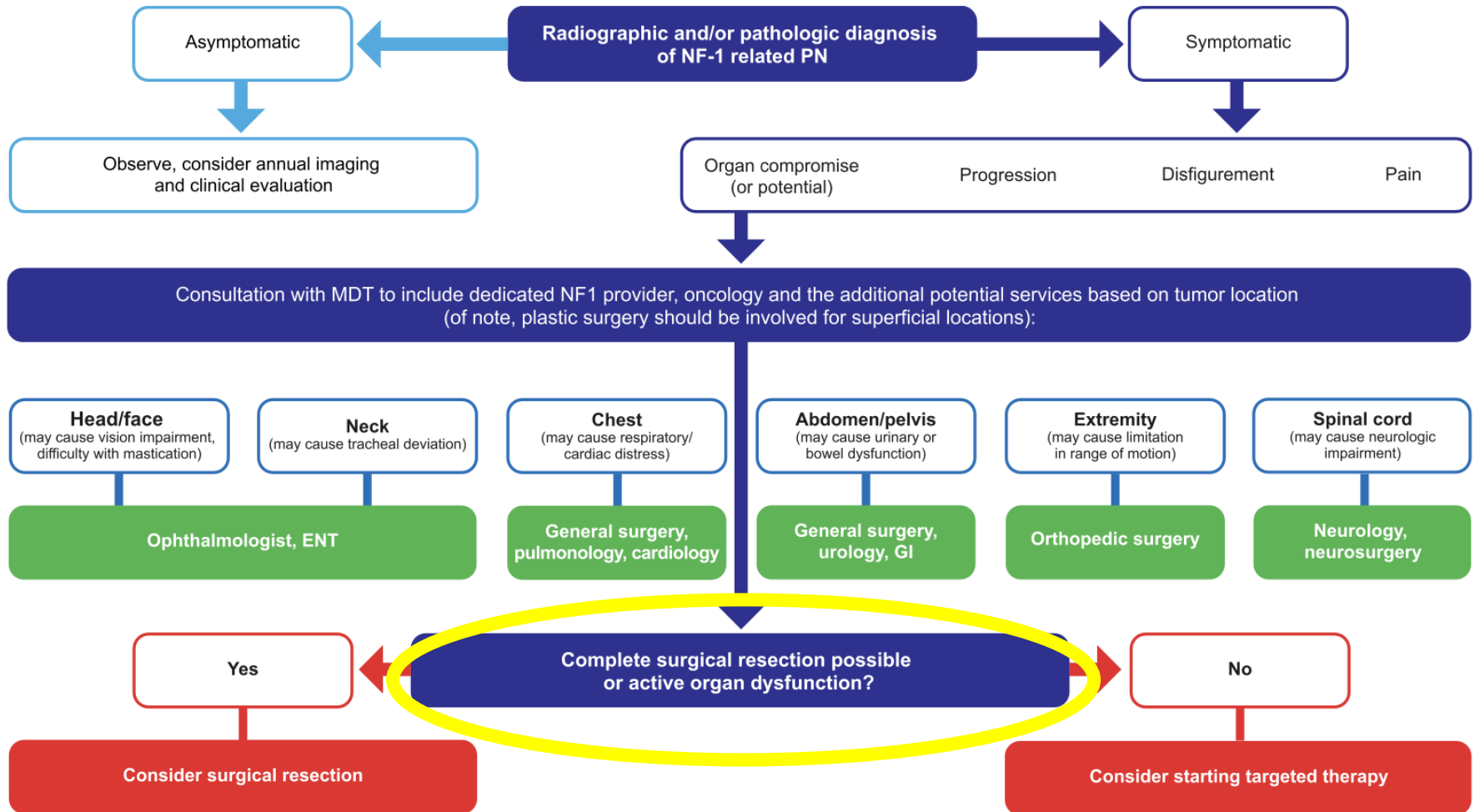
- ❖ Size and location of the PN
- ❖ Age of the patient
- ❖ Growth trajectory
- ❖ Symptomatology
- ❖ Impact on quality of life
- ❖ Multidisciplinary team
- ❖ Patient and Family Preferences



Treatment decisions and the use of MEK inhibitors for children with neurofibromatosis type 1-related plexiform neurofibromas. Amy E. et al. BMC Cancer 2023

**Nuovi outcomes di trattamento per i neurofibromi plessiformi nei pazienti affetti da NF1, AIEOP
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Therapy decision flow chart

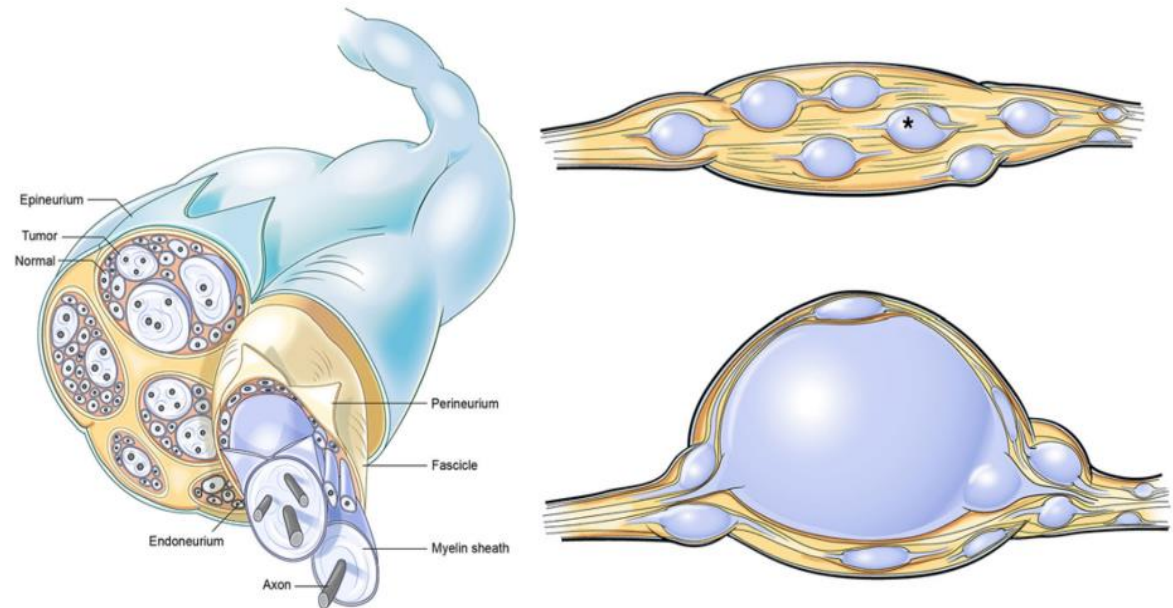


Treatment decisions and the use of MEK inhibitors for children with neurofibromatosis type 1-related plexiform neurofibromas. Amy E. et al. BMC Cancer 2023

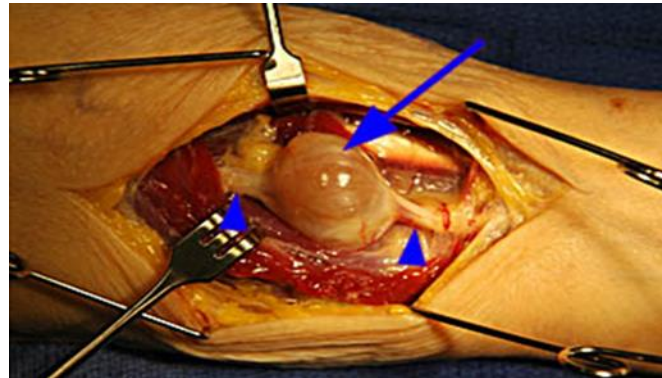
Nuovi outcomes di trattamento per i neurofibromi plessiformi nei pazienti affetti da NF1, AIEOP

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- ❖ Surgical resection has been (historically) the only potentially effective treatment for PNs
- ❖ Infiltrative nature
- ❖ Incomplete resection
- ❖ Risk of regrowth



Nelson CN et al. Safe marginal resection of atypical neurofibromas in neurofibromatosis type 1. *J Neurosurg.* 2019 Oct 25;133(5):1516-1526.



> J Pediatr. 1997 Nov;131(5):678-82. doi: 10.1016/s0022-3476(97)70092-1.

Prognostic signs in the surgical management of plexiform neurofibroma: the Children's Hospital of Philadelphia experience, 1974-1994

M N Needle¹, A Cnaan, J Dattilo, J Chatten, P C Phillips, S Shochat, L N Sutton, S N Vaughan, E H Zackai, H Zhao, P T Molloy

Neurological Sciences (2022) 43:1281–1293
<https://doi.org/10.1007/s10072-021-05361-5>

ORIGINAL ARTICLE



Epidemiological and clinical burden associated with plexiform neurofibromas in pediatric neurofibromatosis type-1 (NF-1): a systematic literature review

Ike Iheanacho¹ · Hyun Kyoo Yoo² · Xiaoqin Yang³ · Sophie Dodman¹ · Rachel Hughes¹ · Suvina Amin²

121 pts

- Complete resection: 15%
- Neurological permanent sequelae: 18%
- Regrowth: 43%

220 pts

- Subtotal resection(< 50%): regrowth 68%
- Partial resection (50-90%): regrowth 45%
- «Complete resection»: regrowth 40%

The past

| NF-Related PN Study | n | Median TTP, mo (Experimental vs Control) | ORR, % |
|---|----|---|--------|
| Tipifarnib vs placebo (2014) ^[a] | 62 | 19.2 vs 10.6 | 0 |
| Pirfenidone vs historical control (2014) ^[b] | 36 | 13.2 vs 10.6 | 0 |
| Sirolimus vs historical control (2015) ^[c] | 29 | 15.4 vs 11.9 | 0 |
| Pegylated IFN-α vs historical control (2017) ^[d] | 29 | 29.4 vs 11.8 | 5 |
| Imatinib (2017) ^[e] | 36 | NA | 17 |

a. Widemann BC, et al. *Neuro Oncol.* 2014;16:707-718; b. Widemann BC, et al. *Pediatr Blood Cancer.* 2014;61:1598-1602; c. Weiss B, et al. *Neuro Oncol.* 2015;17:596-603; d. Jakaacki RI, et al. *Neuro Oncol.* 2017;19:289-297; e. Robertson KA, et al. *Lancet Oncol.* 2012; 13:1218-1224.

The present

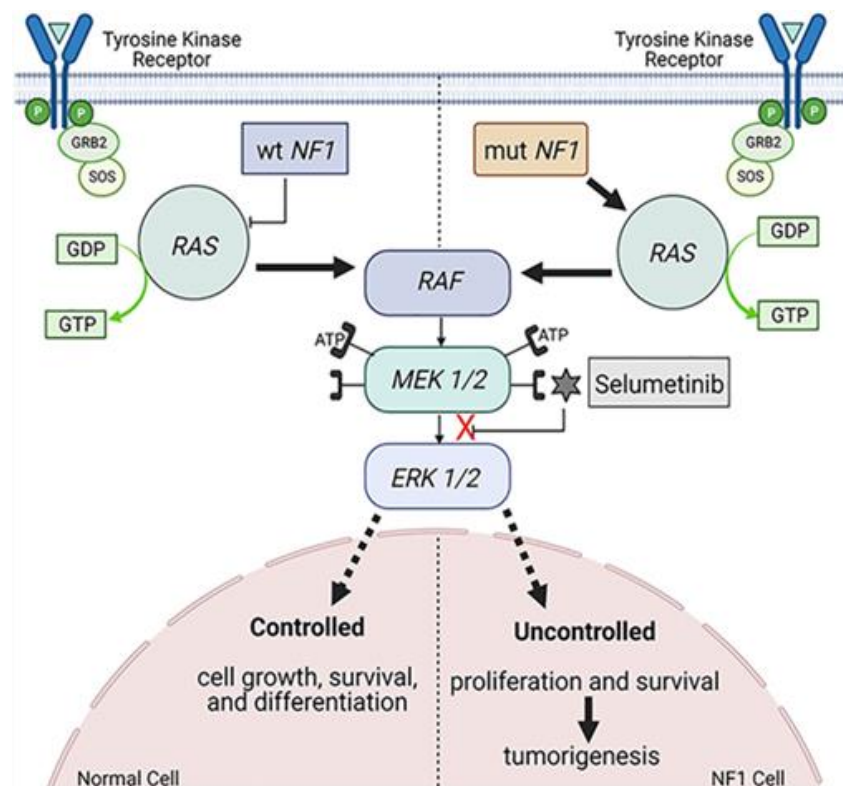
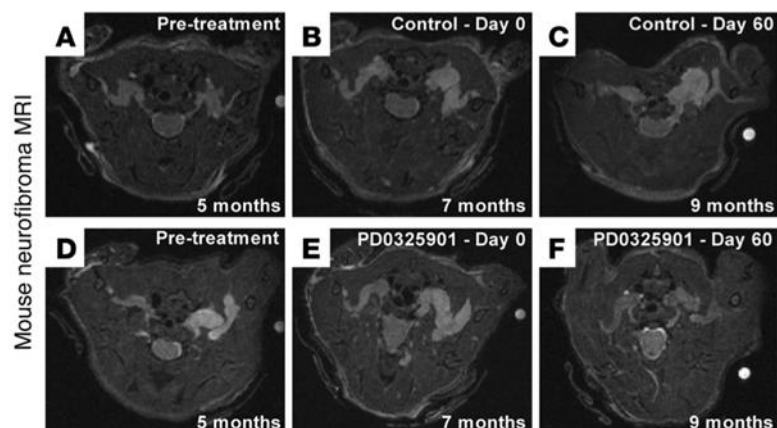
| Drug | Trial name and/or identifier (N) | Phase | Age, median (range), years | Baseline tumor volume, median (range), mL | Tumor shrinkage, median decrease from baseline (range), % | Patients with PR (≥ 20% decrease from baseline in PN volume by MRI) |
|--------------|--|-------|----------------------------|---|---|---|
| Selumetinib | SPRINT NCT01362803 ^a (24) ^[49] | I | 10.9 (3.0, 18.5) | 1205 (29, 8744) | -31 (-47.0, -5.8) | 17/24 (71%) |
| | SPRINT NCT01362803 ^b (50) ^[50] | II | 10.2 (3.5, 17.4) | 487 (5, 3820) | -27.9 (-55.1, 2.2) | 34/50 (68%) |
| Mirdametinib | NCT02096471 (19) ^[51] | II | 24 (16, 39) | 364 (3.9, 5161) | -17.1 (-28.0, 48.7) | 8/19 (42%) |
| | NCT03962543 ^c (20) ^[52] | II | 33.5 | Not reported | Not reported | 7/20 (35%) |
| Cabozantinib | NCT02101736 (19) ^[53] | II | 23 (16, 34) | 557 (57, 2954) | -15.7 (-38.0, 2.8) | 8/19 (42%) |
| Trametinib | NCT02124772 (26) ^[54] | I/IIa | 5.5 (1, 16) | Not reported | Not reported | 12/26 (46%) |
| Binimetinib | NCT03231306 ^d (25) ^[55] | II | 23 (18, 55) | 410 (7, 3128) | -26.5 (-21.1, -35.2) | 13/20 (65%) |

Research article

MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors

Walter J. Jessen,¹ Shyra J. Miller,¹ Edwin Jousma,¹ Jianqiang Wu,¹ Tilat A. Rizvi,¹ Meghan E. Brundage,¹ David Eaves,¹ Brigitte Widemann,² Mi-Ok Kim,³ Eva Dombi,² Jessica Sabo,² Atira Hardiman Dudley,¹ Michiko Niwa-Kawakita,⁴ Grier P. Page,⁵ Marco Giovannini,⁶ Bruce J. Aronow,⁷ Timothy P. Cripe,¹ and Nancy Ratner¹

¹Division of Experimental Hematology and Cancer Biology, Children's Hospital Medical Center, Cincinnati, Ohio, USA. ²Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland, USA. ³Biostatistics and Epidemiology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA. ⁴Institut National de la Santé et de la Recherche Médicale, Paris, France. ⁵Statistics and Epidemiology Unit, RTI International, South Chamblee, Georgia, USA. ⁶Department of Neural Tumor Research, House Ear Institute, Los Angeles, California, USA. ⁷Biomedical Informatics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

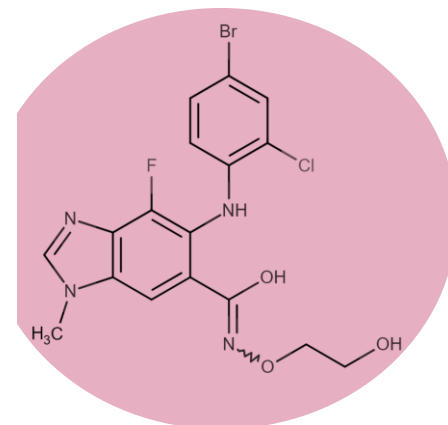
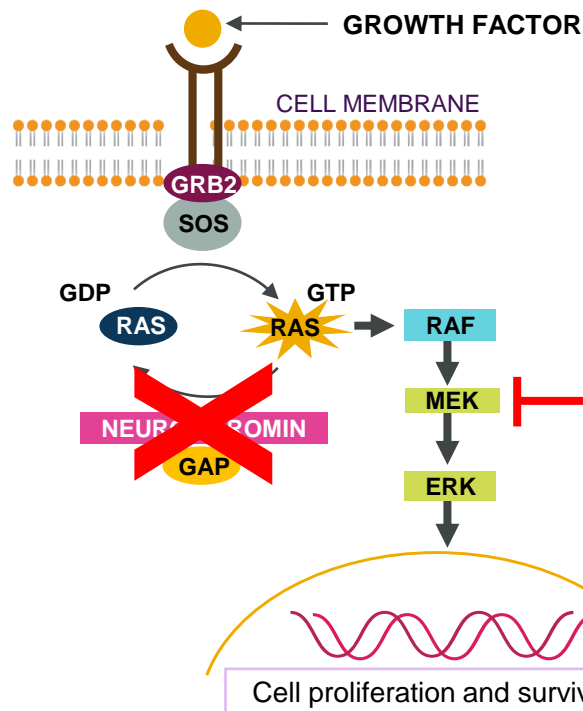


Pediatr Clin N Am 70 (2023) 937–950

Selumetinib: mechanism of action

- ❖ Oral, second-generation, highly selective MEK1/2 inhibitor

Dysregulated growth due to *NF1* pathogenic variant



SELUMETINIB

Inhibits MEK to suppress growth signalling downstream of RAS⁴

Blakeley JO and Plotkin SR. *Neuro Oncol* 2016;18:624–638; 2. Dombi E et al. *N Engl J Med* 2016;375:2550–2560; 3. Ciombor KK et al. *Exp Opin Invest Drugs* 2015;24:111–123;

Leijen S et al. *Cancer Chemother Pharmacol* 2011;68:1619–1628; 5. Yap YS et al. *Oncotarget* 2014;5:5873–5892.

Nuovi outcomes di trattamento per i neurofibromi plessiformi nei pazienti affetti da NF1, AIEOP

Bologna 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Selumetinib in Children with Inoperable Plexiform Neurofibromas

A.M. Gross, P.L. Wolters, E. Dombi, A. Baldwin, P. Whitcomb, M.J. Fisher, B. Weiss, A.R. Kim, M. Bornhorst, A.C. Shah, S. Martin, M.C. Roderick, D.C. Pichard, A. Carbonell, S.M. Paul, J. Therrien, O. Kapustina, K. Heisey, D.W. Clapp, C. Zhang, C.J. Peer, W.D. Figg, M. Smith, J. Glod, J.O. Blakeley, S.M. Steinberg, D.J. Venzon, L.A. Doyle, and B.C. Widemann

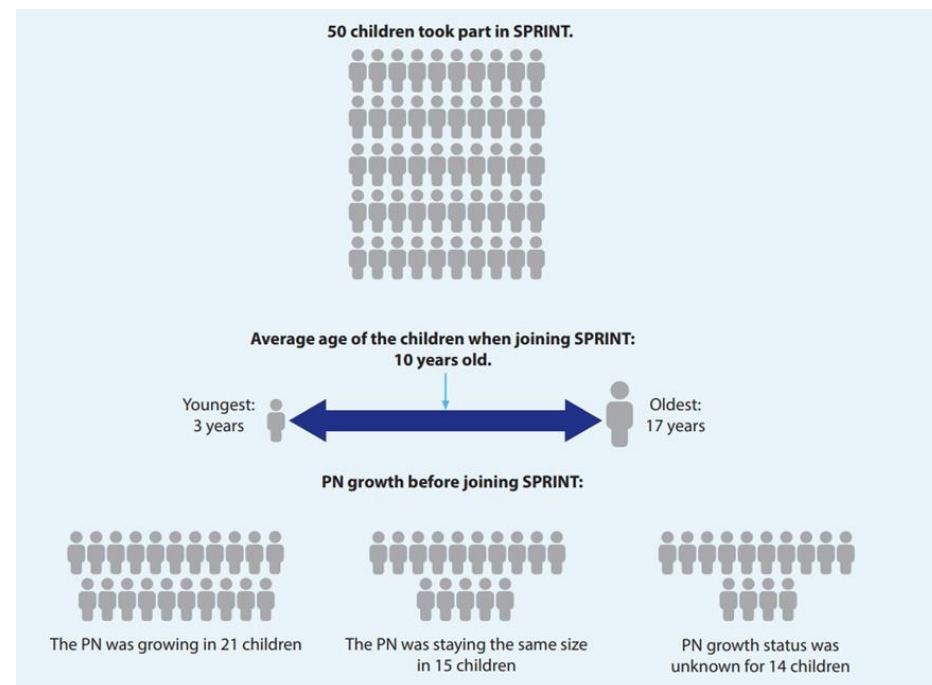
ABSTRACT

BACKGROUND

No approved therapies exist for inoperable plexiform neurofibromas in patients with neurofibromatosis type 1.

METHODS

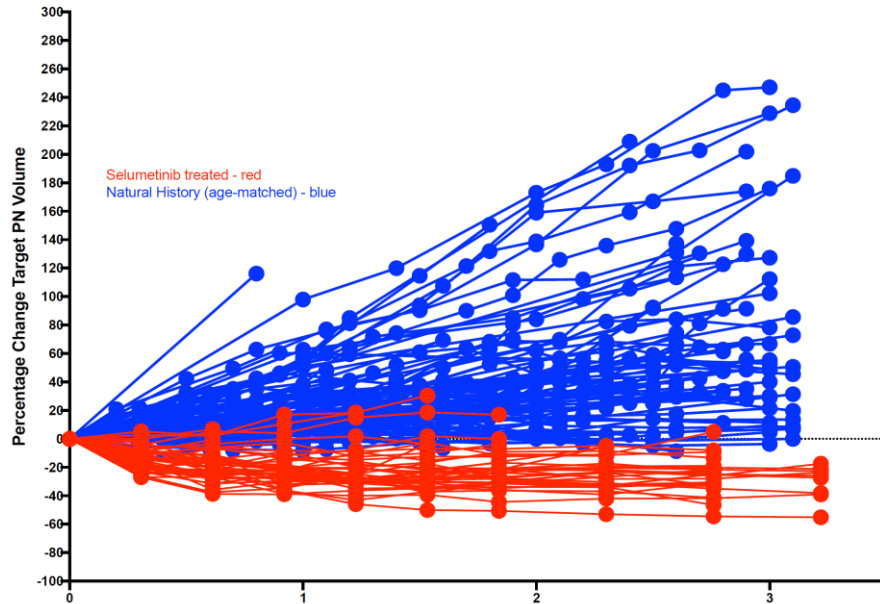
We conducted an open-label, phase 2 trial of selumetinib to determine the objective response rate among patients with plexiform neurofibromas and to assess clinical benefit. Children with neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas received oral selumetinib twice daily at a dose of 25 mg per square meter of body-surface area on a continuous dosing schedule (28-day cycles). Volumetric magnetic resonance imaging and clinical outcome assessments (pain, quality of life, disfigurement, and function) were performed at least every four cycles. Children rated tumor pain intensity on a scale from 0 (no pain) to 10 (worst pain imaginable).



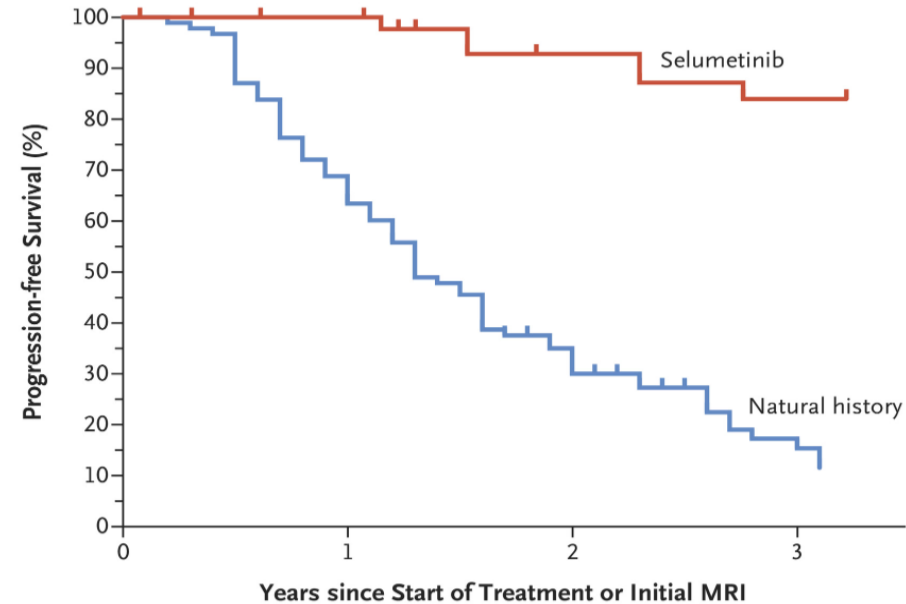
Gross AM et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas.
N Engl J Med. 2020 Apr 9;382(15):1430-1442

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SPRINT phase II



Spider plot: difference in PN growth between patients treated with selumetinib (red, n = 48) and age-matched controls from the NCI NF1 natural history (blue, n = 93)



SPRINT ➡ PFS 3Y 84% in selumetinib group (N=50) VS 15% in natural history group (N=92)

Gross AM et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas.
N Engl J Med. 2020 Apr 9;382(15):1430-1442

Shrinkage of PN in SPRINT compared with the NF1 Natural History study

Before SPRINT (2015–2019), doctors measured the growth of PN in 93 patients in the NF1 Natural History study (2008–2013).

Patients were not treated with selumetinib at the time.

The results of SPRINT (selumetinib treatment) were compared with the results of the NF1 Natural History study (no selumetinib treatment).

Children in SPRINT

The PN shrinkage lasted for more than a year in 28 patients



In 34 out of 50 children

(68%), the PN shrank

(decreased by more than one-fifth in volume at any point during selumetinib treatment)



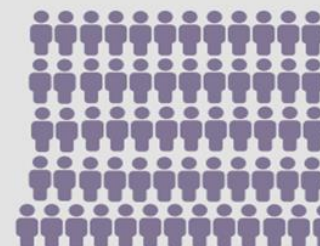
In 6 out of 50 children (12%), the PN increased by more than one-fifth in volume at any point during selumetinib treatment (worsened)

Children in the NF1 Natural History study



The PN did not shrink in any children (0%)

(decreased by more than one-fifth in volume at any point during the study)



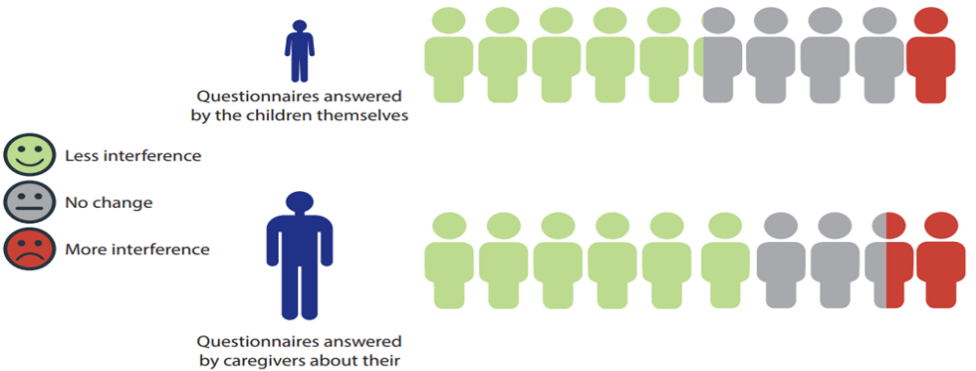
In 73 out of 93 children (78%) the PN increased by more than one-fifth in volume at any point during the study (worsened)

Gross AM et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas.
N Engl J Med. 2020 Apr 9;382(15):1430-1442

How much pain was caused by PN compared with before selumetinib treatment? (based on questionnaires from 29 children)

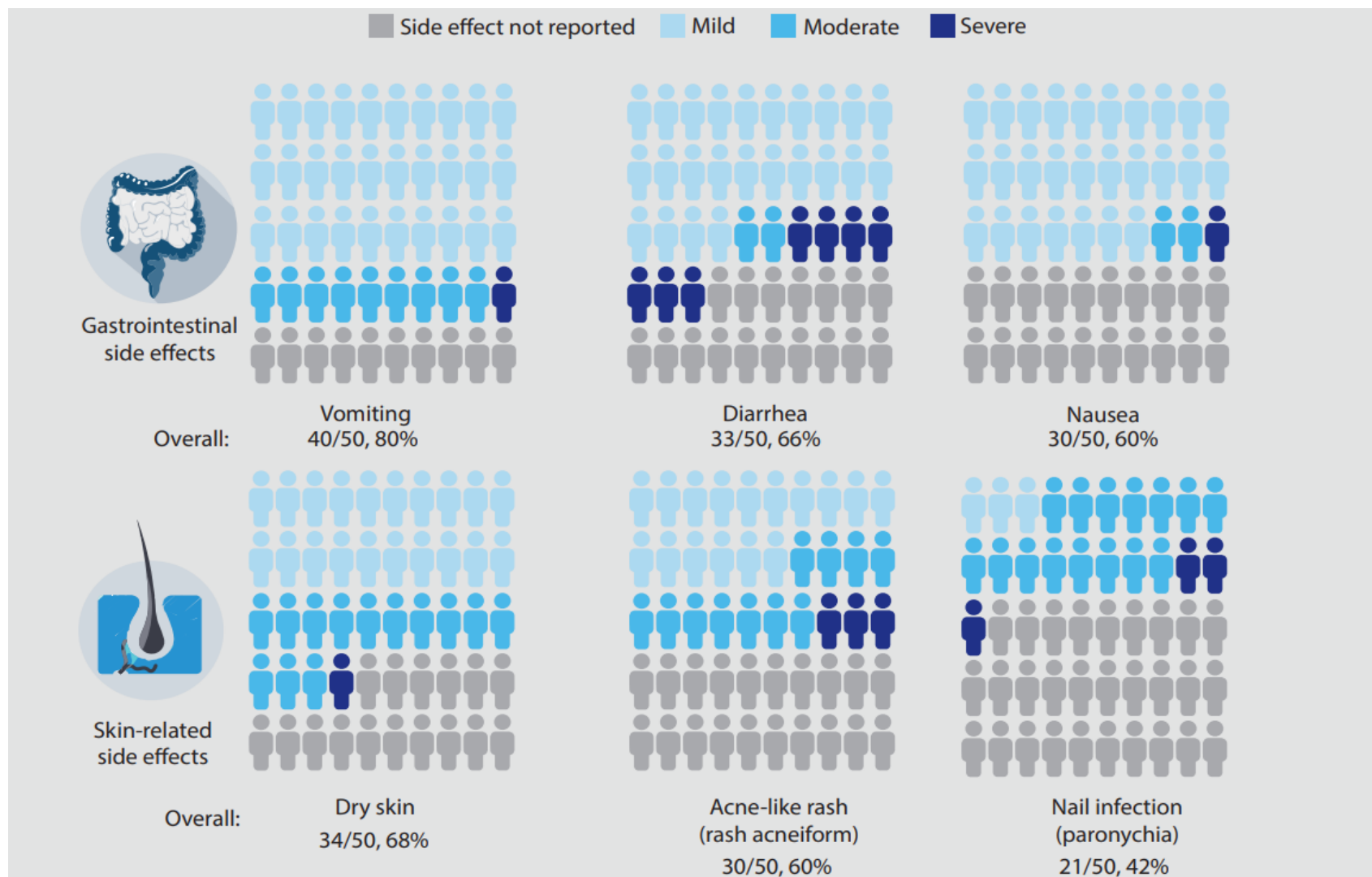


How much did pain interfere with daily living compared with before selumetinib treatment? (based on questionnaires from 29 children and 42 caregivers)



Gross AM, Selumetinib for children with neurofibromatosis type 1 and plexiform neurofibromas: A plain language summary of SPRINT. Future Oncol. 2024 May;20(14):877-890

SPRINT toxicity



Gross AM, Selumetinib for children with neurofibromatosis type 1 and plexiform neurofibromas: A plain language summary of SPRINT. *Future Oncol.* 2024 May;20(14):877-890

Nuovi outcomes di trattamento per i neurofibromi plessiformi nei pazienti affetti da NF1, AIEOP

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Pediatric Precision Oncology: Target Therapy/New Drugs in Pediatric Brain Tumors-Original Research Article

Safety and Efficacy of Mek Inhibitors in the Treatment of Plexiform Neurofibromas: A Retrospective Study

Cancer Control
Volume 30: 1-13
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DOI: 10.1177/10732748231144930
pmc.ncbi.nlm.nih.gov/articles/PMC10114493/
SAGE

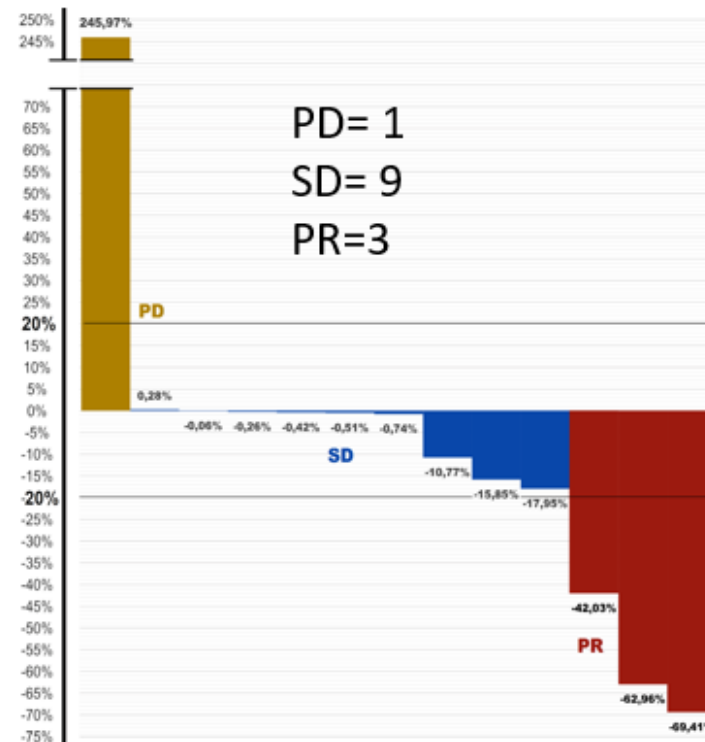
Antonella Cacchione, MD¹, Francesco Fabozzi, MD^{1,2}, Andrea Carai, MD, PhD³, Giovanna Stefania Colafati, MD⁴, Giada del Baldo, MD¹, Sabrina Rossi, MD⁵, Martino Diana, MD¹, Giacomina Megaro, MD¹, Giuseppe Maria Milano, MD, PhD¹, Marina Macchiaiolo, MD⁶, Alessandro Crocoli, MD⁷, Maria Antonietta De Ioris, MD¹, Luigi Boccuto, MD⁸, Domitilla Elena Secco, MD⁹, Mario Zama, MD⁷, Emanuele Agolini, MD¹⁰, Paolo Tomà⁴, and Angela Mastronuzzi, MD, PhD^{1,11}

Primary goals

- Evaluation of radiological and clinical response to the use of medical therapy with MEK inhibitors (selumetinib and trametinib) in pediatric NF1 patients affected by inoperable and symptomatic PN

Secondary goals

- Evaluation of treatment toxicity
- Evaluation of the impact of therapy on quality of life



These results have led to FDA and European Medicines Agency approval of selumetinib (Koselugo) in treating patients between the ages of 2 and 18 with NF1- NF1-associated PN that are inoperative and symptomatic. This was the first FDA approval of a drug for NF1.



25 mg/m²



12 hours apart



25 mg/m²



❖ April 2020

Gross AM, Selumetinib for children with neurofibromatosis type 1 and plexiform neurofibromas: A plain language summary of SPRINT. Future Oncol. 2024 May;20(14):877-890

**Nuovi outcomes di trattamento per i neurofibromi plessiformi nei pazienti affetti da NF1, AIEOP
Bologna 2024**

❖ March 2024



Neurofibromatosi di tipo 1, selumetinib rimborsabile in Italia

Autore: Redazione, 07 Marzo 2024

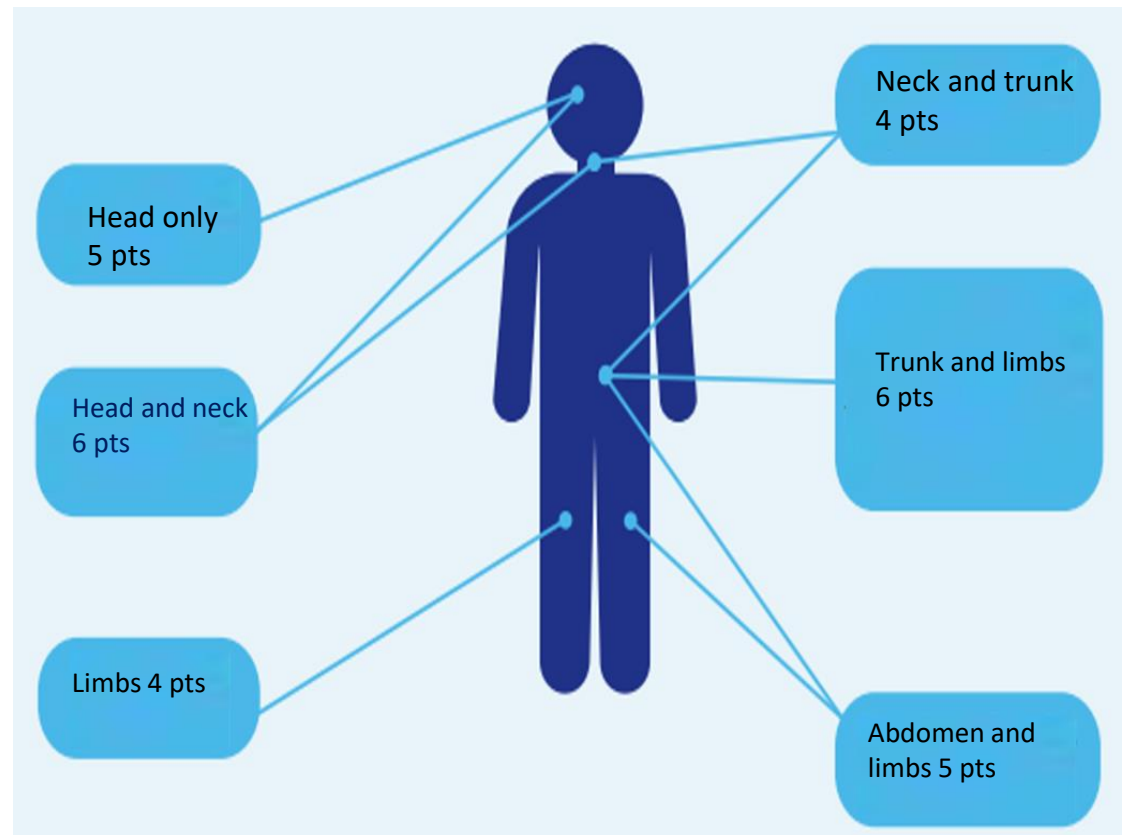


Il farmaco è indicato per il trattamento dei neurofibromi plessiformi associati alla patologia in bambini di almeno 3 anni

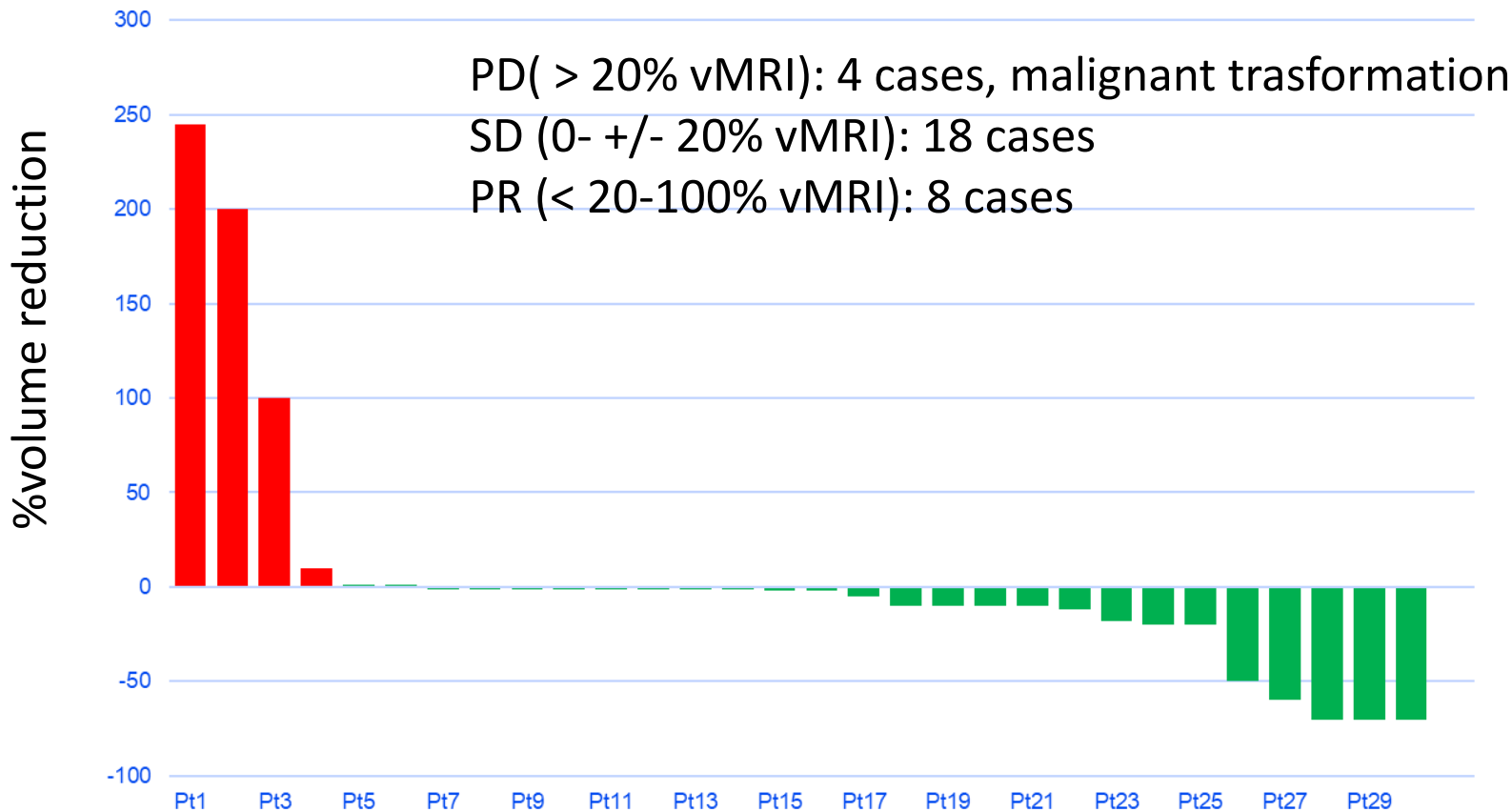
L'Agenzia Italiana del Farmaco (AIFA) ha autorizzato la rimborsabilità di selumetinib, prima terapia approvata in Italia per il trattamento dei neurofibromi plessiformi (PN) sintomatici e non operabili in pazienti pediatrici affetti da neurofibromatosi di tipo 1 (NF1) di età pari o superiore a tre anni. La NF1 è una condizione genetica debilitante che in tutto il mondo colpisce una persona su 3.000 e che in Italia si stima coinvolga circa 20.000 pazienti. **In circa il 30-50% delle persone affette da NF1 si sviluppano tumori sulle guaine nervose, denominati neurofibromi plessiformi**, che causano potenziali problemi clinici come dolore, deturpazioni, disturbi visivi e disfunzioni motorie, vescicali, intestinali o respiratorie.

Our experience – Bambino Gesù Children's Hospital (commercial and expanded access)

- ❖ 30 patients (24 ongoing)
- ❖ 2019-2024
- ❖ Age: 3-26 (median 10.5)
- ❖ Inoperable and symptomatic PNs



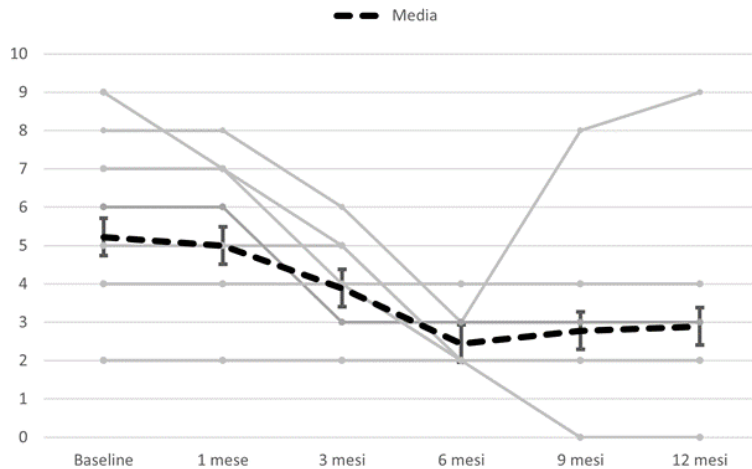
❖ Radiological response (volumetric MRI, criteri Reins)



Our experience – Clinical improvement

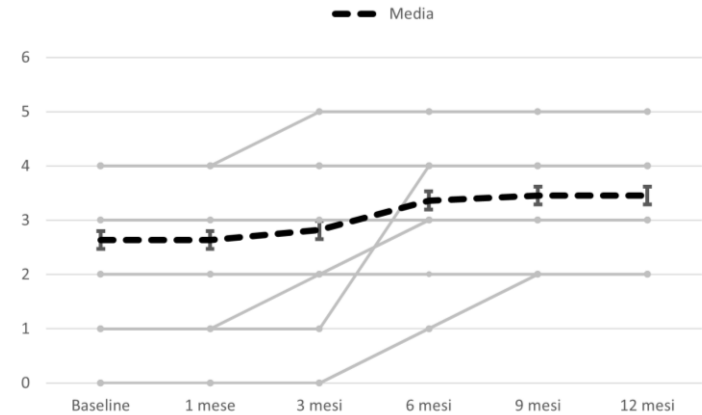
❖ Pain (Visual Analog Scale)

18/30 pts (60%) decrease in symptoms (16/18 possibility of discontinuing analgesic therapy)

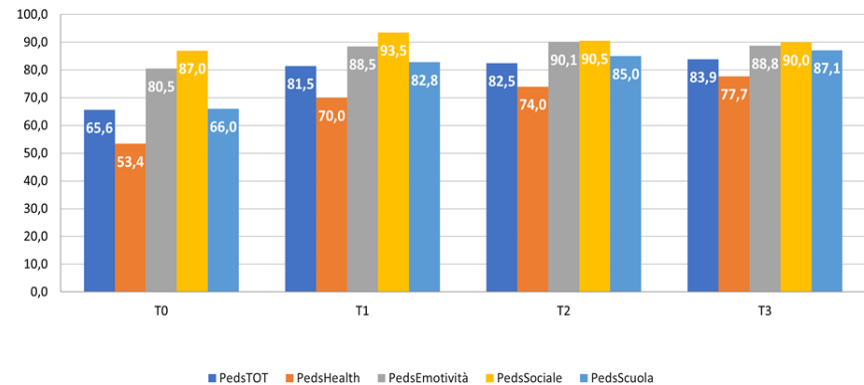


❖ Neurological deficits (Medical Research Council muscle power scale)

12/30 pts (40%) improvement in limbs function



❖ Questionario PedsQL TM 4.0 Generic Core Scale



- ❖ No grade 4 toxicity
- ❖ 100 % cutaneous toxicity (G1-G3)
- ❖ 100% change hair color (G1)
- ❖ 70% paronychia (G1-G3)
- ❖ 30% Diarrhoea (G2)
- ❖ Ordinary management except in 2 cases of paronychia (surgery)



Based on the speaker's personal experience

Images obtained with patient/family/tutor permission

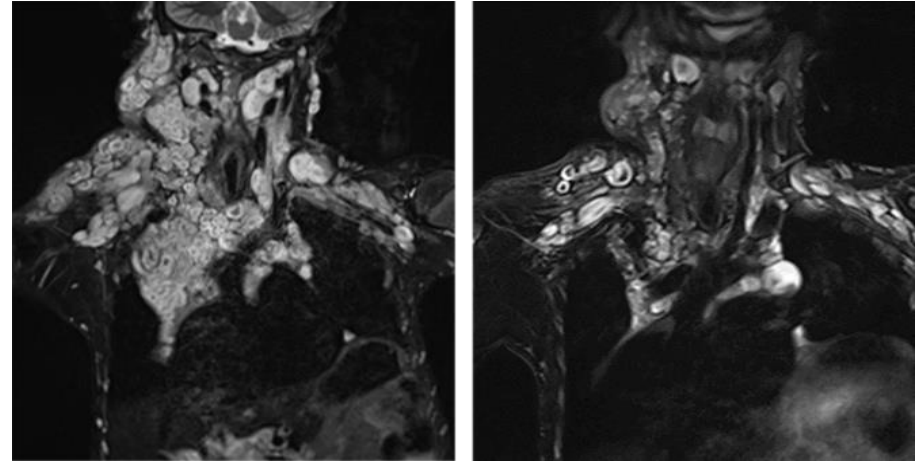
Clinical case #1

- ❖ 8 yo (02/2015) diagnosis of craniofacial/mediastinal
- ❖ Right arm pain/hypostenia
- ❖ Treatment with pegylated interferon (2 years) with no evidence of clinical/radiological benefits
- ❖ 12 yo (08/2019) (radiological progression, VAS score 7, Muscle power scale score 1, impaired QoL)



Start therapy with iMEK selumetinib

August 2019 vs August 2024



2019-2024: five years of treatment, still ongoing (G2 skin toxicity)

vMRI: PR

VAS: score from 7 to 2

British muscle power scale: score from 1 to 3

Quality of life: improvement in all fields

*Based on the speaker's personal experience
Images obtained with patient/family/tutor permission*

Clinical case #2

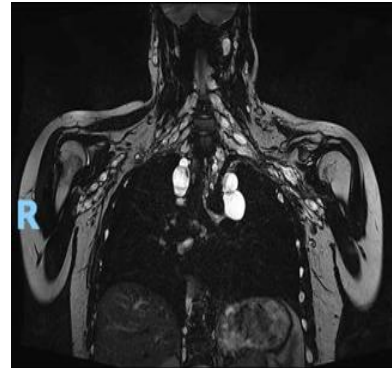
- ❖ 18 yo (09/2017) diagnosis of PN involving bilateral brachial plexus and intercostal nerves
- ❖ Uncontrollable pain, lower limbs hypoesthesia
- ❖ 07/2019 VAS score 9, British medical research council muscle power scale: score 1, impaired quality of life



Start therapy with iMEK selumetinib

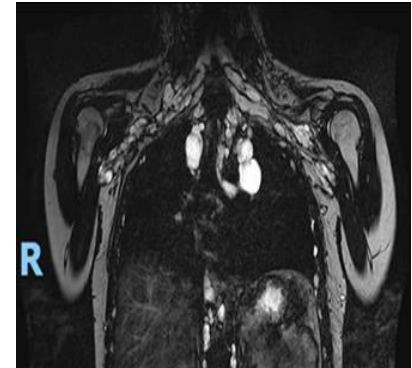
*Based on the speaker's personal experience
Images obtained with patient/family/tutor permission*

August 2019



Vs

May 2024



2019-2024: five years of treatment, still ongoing (G2 skin toxicity, paronychia)

vMRI: stable

VAS: score from 9 to 3

British muscle power scale: score from 1 to 4

Quality of life: improvement in all fields

**Stop of all pain
medicaments**

Clinical case #3

October 2022 vs August 2024



*Based on the speaker's personal experience
Images obtained with patient/family/tutor permission*

**Nuovi outcomes di trattamento per i neurofibromi plessiformi nei pazienti affetti da NF1, AIEOP
Bologna 2024**

Take home message

- ✓ Plexiform neurofibromas are **the most frequent tumors** associated with NF1, in 50% of cases
- ✓ **High morbidity and risk of malignant transformation**
- ✓ **Surgery**: not always feasible and usually not conclusive
- ✓ **Selumetinib**, an oral selective MEK ½ inhibitor, **approved for inoperable, symptomatic PN in children > 3 years**
- ✓ **Efficacy: volumetric MRI but overall clinical improvements also with stable vMRI**
- ✓ **Skin, mucosa, and gastrointestinal** the major toxicities



Prof. Franco Locatelli
Dr.ssa Angela Mastronuzzi
Dr.ssa Federica D'Antonio
Dr.ssa Tiziana Corsetti
Dr Arturo Greco
Dr.ssa Federica Tangari
Dr.ssa Stefania Giovanna Colafati
Dr.ssa Marina Macchiaiolo
Dr Emanuele Agolini
Dr.ssa Selene Cipri
Dr.ssa Maya El Hachem
Dr Antonino Romanzo



Bambino Gesù
OSPEDALE PEDIATRICO

Vite che aiutano la Vita

