MEKi bij plexiforme neurofibromen in NF1

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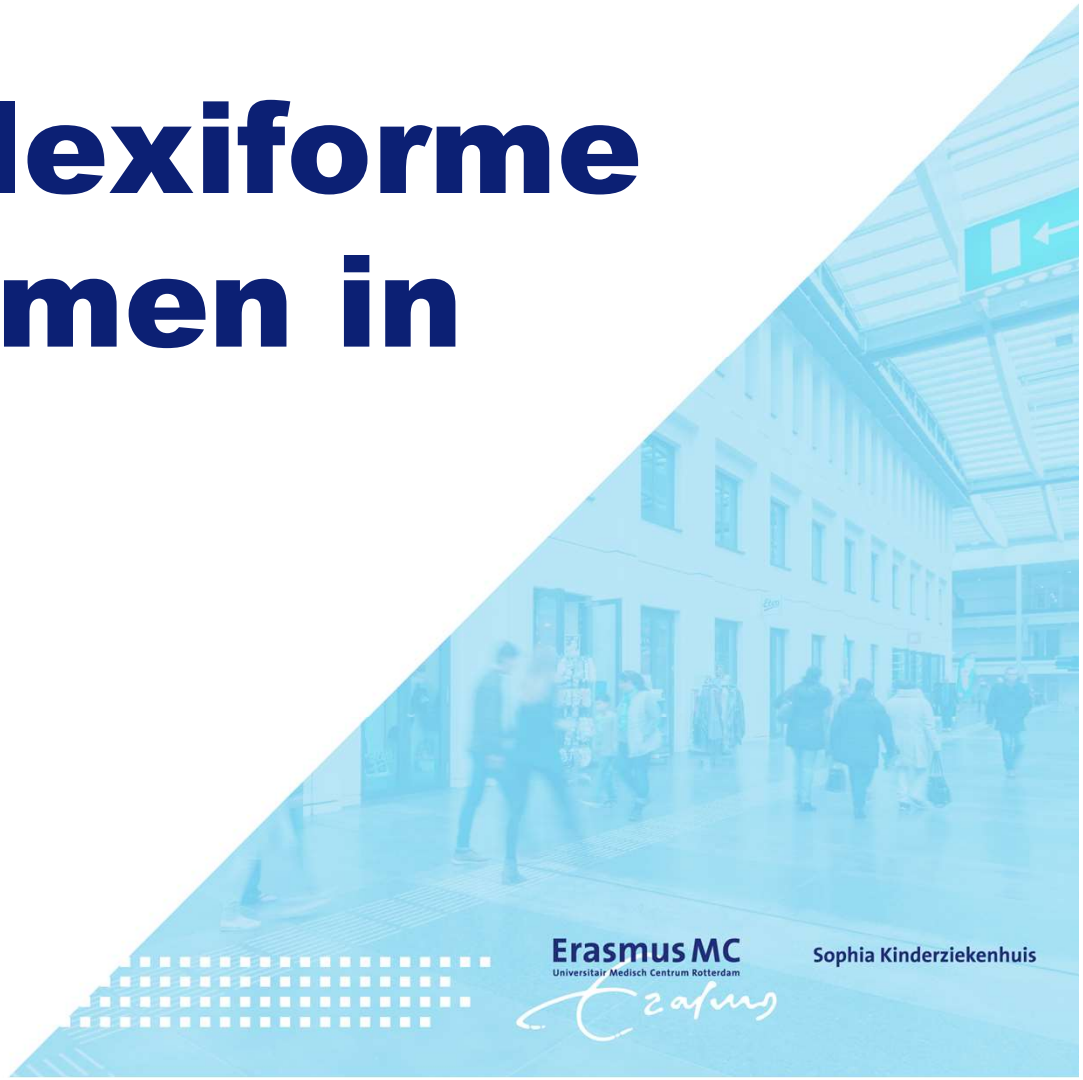


SPRINT trial
Selumetinib in children with NF1 plexiform neurofibromas

Design: Open label Phase II study

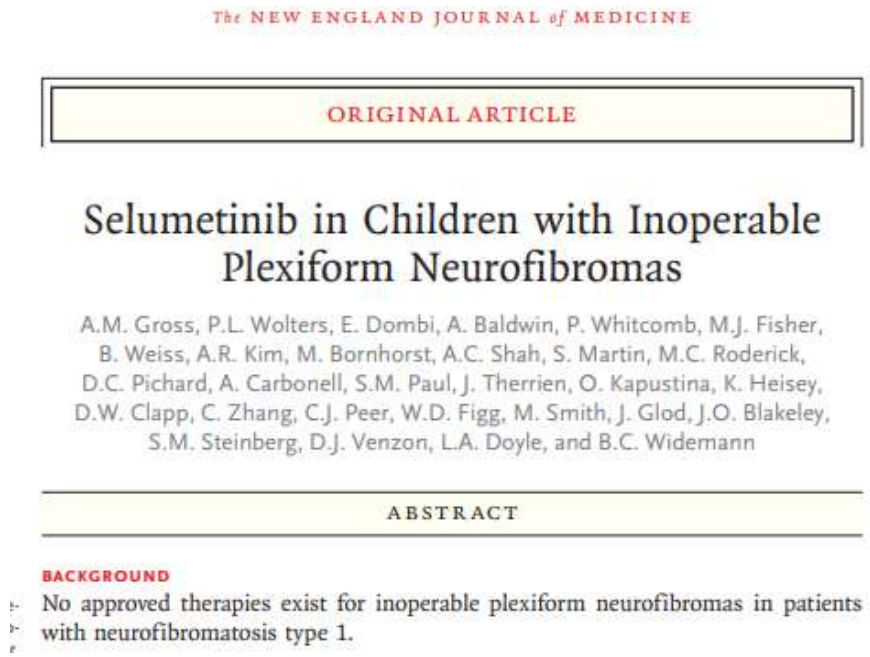
Age 2-28 yrs with NF1

Inoperable PN or 1+ PN with morbidity

Selumetinib 25 mg/m2 continuous (cycli 28d)

Outcome after 4 cycli

- *Growth*
- *Pain*
- *Disfigurement*
- *Functional morbidity*



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

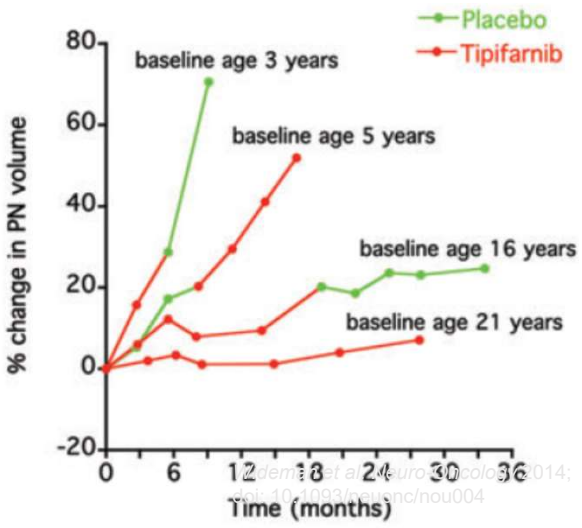
ABSTRACT

BACKGROUND

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

Erasmus MC Sophia Kinderziekenhuis

Plexiform neurofibromas grow age dependent



dem et al. Neuro-Oncology 2014; doi: 10.1093/neuonc/nou004

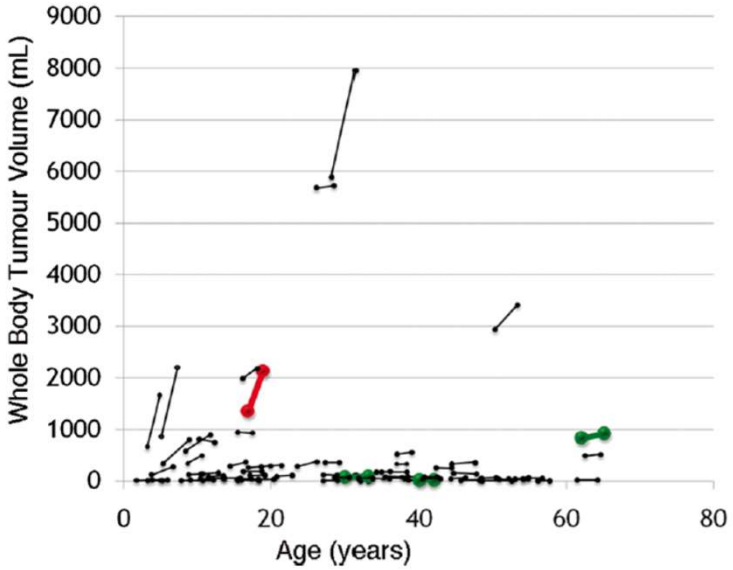


Figure 1 Whole body tumour volume by person and age; whole body tumour volume by person and age in 71 patients with NF1. Patient 1890, who developed MPNST during the course of the study, is shown in red. Patients 1140, 1730, and 2490, who were treated for MPNSTs prior to their entry into the study, are shown in green.

Nguyen *et al. Orphanet Journal of Rare Diseases* 2012, **7**:75
http://www.ojrd.com/content/7/1/75

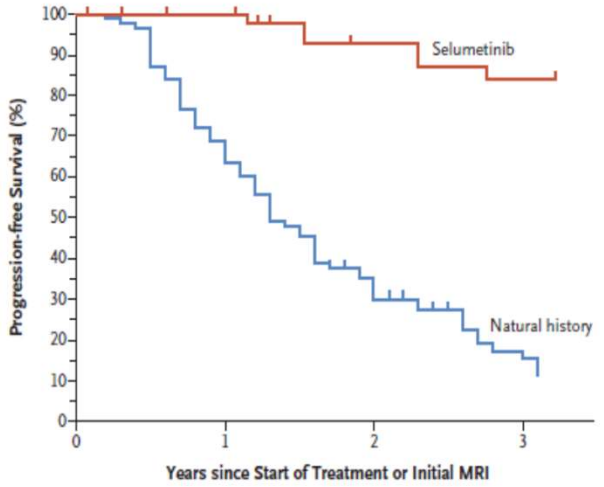


Figure 1. Target Plexiform Neurofibroma Progression–free Survival during Selumetinib Treatment as Compared with Natural History of Neurofibromatosis Type 1.

At 3 years of follow-up, the progression-free survival was 15% in the natural-history group and 84% in the selumetinib group.

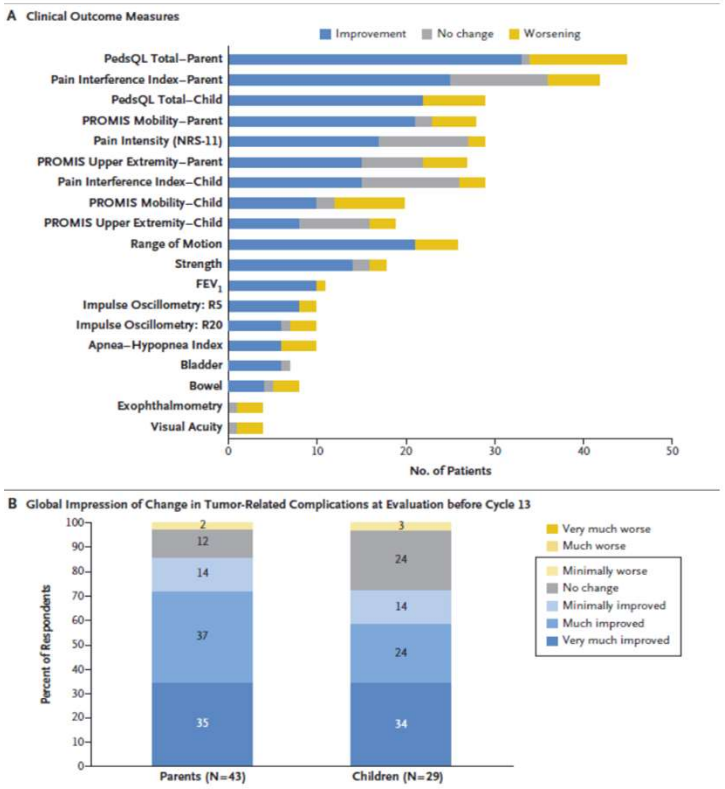


Figure 2. Change in Plexiform Neurofibroma–Related Complications between Baseline and the Evaluation before Cycle 13 of Treatment with Selumetinib.

Most patients had some degree of improvement or no change and few had any worsening in functional, patient-reported, and observer-reported outcome measures of plexiform neurofibroma–related symptoms (Panel A). FEV_1 denotes forced expiratory volume in 1 second, NRS-11 the 11-item Numerical Rating Scale, PedsQL the Pediatric Quality of Life Inventory, PROMIS Patient-Reported Outcomes Measurement Information System, R5 airway resistance at 5 Hz, and R20 airway resistance at 20 Hz. On the Global Impression of Change scale (Panel B), 86% of parents (37 of 43) and 72% of children (21 of 29) (blue shaded areas) who completed the form reported some level of improvement with respect to the child's plexiform neurofibroma–related complications (other than pain) at the evaluation before cycle 13. Percentages may not total 100 because of rounding.

Tijspad of MEKinhibitors in PN

FDA approval 2020

EMA approval mei 2021

Children 2-16 yrs, inoperable PN

Symptomatic / Growing 20% geen criteria per se

Situatie NL voor MEKi bij PN in NF1

Organisatorisch

in sluis voor weesgeneesmiddelen

Klinisch

Beperkte ervaring tav specifieke indicatie

Plexiform neurofibromas affect young children, so life long treatment

- *Side effects*
- *Shared expertise*

Dosing schedules

- *Intermittent*
- *Maintainance dosis*
- *Prophylaxis*

Voorstel tav implementatie MEKi in NL bij PN in NF1

Managed access protocol for the Netherlands

Guiding principles (inclusion, stopping criteria, interim regular controles)

Indication committee (partners from NF1 network?)

Registry (all PN patients or treated only?)

Annual report

Implementatie klinische aspecten

Screening: Cardioloog, dermatoloog, oogarts, algemeen
Target tumor: MRI volumetrie, functionele uitkomsten

Fup

- dermatoloog frequent
- a 3m interval cardioloog, oogarts, algemeen
- a 6m MRI

Voorstel start in ErasmusMC

- interim controles ook in BCs?
- bij meer expertise ook bredere implementatie

Voorbereidende acties

Contacten ZiN, VSOP weesgeneesmiddelen, zorgverzekeraars

DBC?

Uitwerken protocol

Patientenzorg

- beeldvorming
- registratie

Treatment of other NF1 related manifestations

(low grade) Glioma

MPNST

Cutaneous neurofibromas

Skeletal lesions

Neurobehavioural disorders