Ongoing studies of cutaneous neurofibromas: trial design and endpoints

Ashley Cannon, PhD, MS, CGC for the
Cutaneous Neurofibroma Working Group

Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Types of cNF Treatment

Procedural

- Surgical
- Electrodessication
- Laser-based (e.g., laser photocoagulation, CO2 laser)
- Radiofrequency ablation
- Photodynamic therapy

Experimental Drugs

- Ketotifen
- Rapamycin (topical)
- Ranibizumab
- Imiquimod 5% cream (topical)
- Selumetinib
- Everolimus
- Diclofenac

cNF Treatment

Procedural

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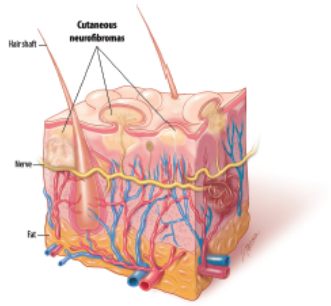

SUPPLEMENT

Translational Discovery for Neurofibromatosis type 1 Cutaneous Neurofibromas: Past, Present and Future

Guest Editors: Sharad K. Verma, PhD, and Jaishri O. Blakeley, MD

ARTICLE OPEN ACCESS

Considerations for development of therapies for cutaneous neurofibroma

Sharad K. Verma, PhD, Vincent M. Riccardi, MD, MBA, Scott R. Plotkin, MD, PhD, Hubert Weinberg, MD, R. Rox Anderson, MD, Jaishri O. Blakeley, MD, Kurt Jarnagin, PhD, and James Lee, MD, PhD

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Abstract

Objective

The only therapies currently available for cutaneous neurofibromas (cNF) are procedural. The goals of the Therapies Development Working Group were to (1) summarize currently available treatment options for cNF, (2) define key considerations for drug discovery and development generally, and specifically for cNF, and (3) outline recommendations for the successful development of medical therapies for cNF.

Methods

The subgroup reviewed published and unpublished data on procedural, drug/device, and medical treatment approaches utilized for cNFs via literature search. The team defined disease- and patient-specific factors to consider for therapies development in a series of consensus meetings.

Results

The team identified 5 approaches entailing procedural and drug/device methods currently under study. There have been 4 clinical studies exploring various interventional therapies, from which outcomes were highly variable. The team identified 4 key factors to prioritize during the development of products for the treatment for cNF: safety, anatomic distribution of cNF, numbers of tumors to be treated, and route of administration.

Conclusions

The number, size, and distribution of cNF is highly variable among patients with NF1 and it is possible that different phenotypes will require different drug development paths. The nonfatal nature of the disease and relatively limited patient numbers suggest that for any product to have a higher likelihood of acceptance, it will have to (1) demonstrate an effect that is clinically meaningful, (2) have a safety profile conducive to long-term dosing, and (3) have a low manufacturing cost.

RELATED ARTICLES

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Clinical trial design for cutaneous neurofibromas
Page S31

From the Department of Neurology (S.K.V., J.O.B.), The Johns Hopkins University School of Medicine, The Neurofibromatosis Therapeutic Acceleration Program, Baltimore, MD; The NF Institute (V.M.R.), La Crescenta, CA; Department of Neurology and Cancer Center (S.R.P.), Massachusetts General Hospital, Boston; Division of Plastic Surgery (H.W.), Mount Sinai Hospital, Icahn School of Medicine at Mount Sinai, New York, NY; Department of Dermatology (R.R.A.), Harvard Medical School, Boston, MA; BioPharm Tech (K.J.), San Mateo, CA; and Dermavant Sciences (J.L.), Durham, NC.

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Electrodessication

Treatment (Ref)	No. of patients	Age (y)	Lesion type treated	Size	Body location treated	Primary end point	Results (study type, average no. lesions removed or intervention, outcome)
Electrodessication for multiple cNFs (8)	97	17–68	Flat and superficial (sessile to pedunculated)	<1–10 cm	Face, neck, anterior trunk, arms, and legs	Patient satisfaction[a]	• Retrospective study
							• An average of 450 lesions removed per session
							• Outcome: minimal scarring; high patient satisfaction as assessed with questionnaires with follow-up out to 6 mo.
Electrodessication in treating cNF (9)	6	27–70	Sessile and globular (but not pedunculated)	Not reported	Face, neck, anterior trunk, arms, and legs	Patient satisfaction[a]	• Retrospective study
							• Several hundreds of lesions removed per session
							• Outcome: minimal scarring and high patient satisfaction as measured by improved cosmetic and functional outcome, and nonrecurrence of lesions in the treated areas out to 6 mo, based on telephone questionnaires.

Laser-based treatment

Treatment (Ref)	No. of patients	Age (y)	Lesion type treated	Size	Body location treated	Primary end point	Results (study type, average no. lesions removed or intervention, outcome)
Laser photocoagulation (surface and interstitial) for the removal of multiple cNFs (11)	12	24–45	Flat and superficial (sessile to pedunculated)	<5 mm to >5 mm	Face, arms, and trunk	Lesion regression and patient satisfaction[a]	• Retrospective study
							• An average of 4 and 10 lesions were removed per session, by surface and interstitial methods, respectively.
							• Outcome: >50% regression in volume from baseline (measurement technique not reported) for the majority of lesions treated with high patient satisfaction based on patient interviews out to a 14-mo follow-up period.
Removal of cNF using CO_2 laser (12)	106	29–55	Sessile to pedunculated	<1 cm	Face, arms, and trunk	Pain, patient satisfaction, and safety	• Retrospective study
							• Average of >50 lesions removed in total, with >5 lesions removed per session.
							• Outcome: assessments for pain and satisfaction conducted by questionnaires asking about pain at each stage (during administration of anesthesia, during laser treatment, and 2 d after treatment). Favorable response for pain with a mean pain score of 4 + 2.7 (numerical rating scale: 0, no pain; 10, severe pain) during local anesthesia, and 2.4 + 2.2 during laser treatment as well as 2 d after treatment. Patient satisfaction (numerical score rating scale: 0, no improvement; 10, major improvement) was 90%, with a mean satisfaction score of 4.6 + 3.4. Safety assessments included evaluation of bleeding, infection rates after the procedure, and scar quality.

Radiofrequency ablation

Treatment (Ref)	No. of patients	Age (y)	Lesion type treated	Size	Body location treated	Primary end point	Results (study type, average no. lesions removed or intervention, outcome)
Radiofrequency ablation (13)	16	16–60	Sessile to pedunculated	4 mm to 10 cm	Trunk, upper extremities, and face	Patient satisfaction[a]	• Retrospective study
							• Average of 80 lesions removed per session.
							• Outcomes: high patient satisfaction reported by all patients as measured by the Vancouver scar scale (VSS) and patient and observer scar scale (PO-SAS), in which the average VSS score was 6 points and POSAS was 12 points, based on outpatient follow-up out to an average period of 11 mo.

Photodynamic therapy

Treatment (Ref)	No. of patients	Age (y)	Lesion type treated	Size	Body location treated	Primary end point	Results (study type, average no. lesions removed or intervention, outcome)
Photodynamic therapy (PhI study) (NCT01682811)	30	≥18	Superficial cNF	<4 mm deep	Trunk, arms, and legs	Photosensitizer uptake, safety, and MTD	• Retrospective study
							• Intervention: microneedle-based delivery of ALA (via Levulan Kerastick) and illumination of the treated area.
							• Outcomes: photosensitizer uptake by microneedling and a 24-h incubation period, and MTD using red light (630 nm) at 100 mW/cm^2 for 1,000 s, assessing up to 8 lesions per patient in a single treatment session.
Photodynamic therapy (Ph2 study) (NCT02728388)	30	14–30	Superficial cNF	<4 mm deep	Trunk, arms, and legs	Time to progression (TTP), defined as 50% growth in size over baseline untreated	• Prospective study
							• Intervention: pairs of similar-size lesions will be treated with a photosensitizer (Levulan Kerastick, via microneedling), or placebo (topically) and after 24 h subjected to illumination with red light (both photosensitizer and placebo) every 4 mo for 3 y.
							• Outcomes: tumors will be measured by calipers to see whether they are growing more slowly than those with the placebo alone.

Procedural Treatment Synopsis

- Target lesion types treated range from flat to pedunculated
- Mainly adults and some adolescents studied
- Outcome measures are mainly satisfaction scales (scar scale, pain scale) within 6mo of tx
  - Generally high patient satisfaction reported
  - Long-term satisfaction in unknown
- Multiple sessions are required, general anesthesia may be necessary

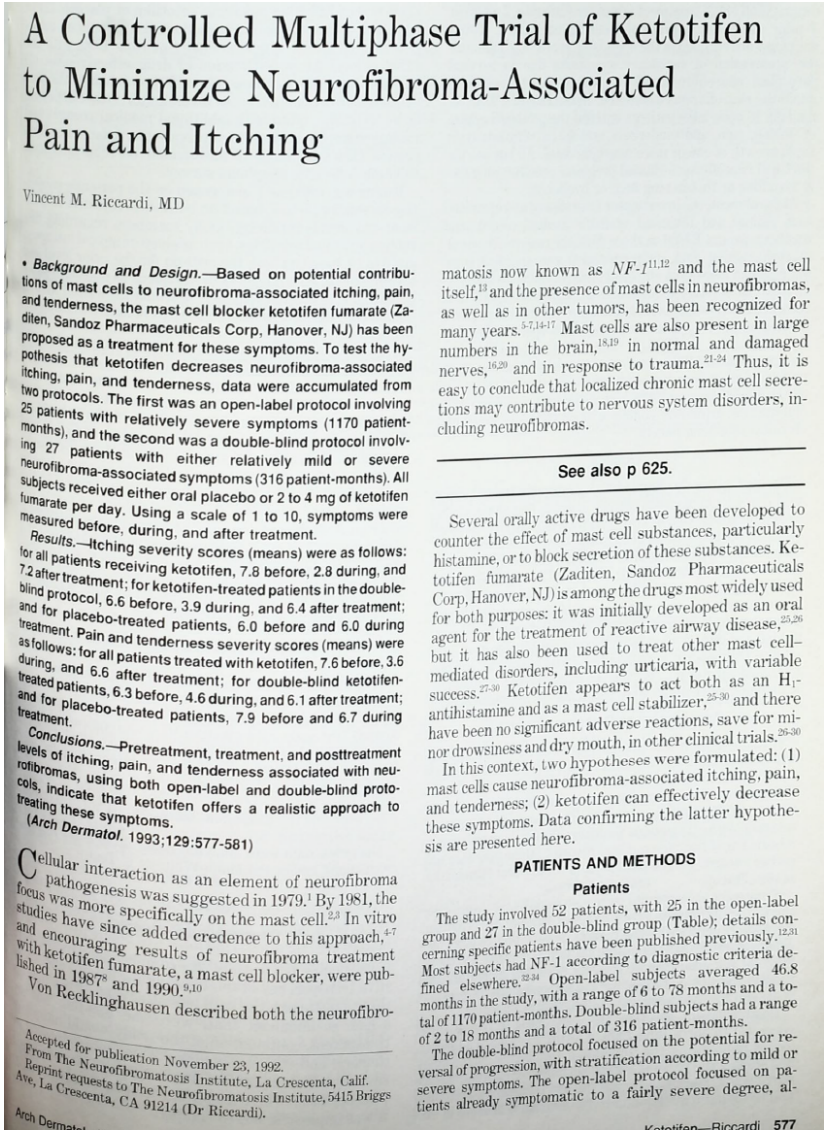
cNF Treatment

Experimental Drugs

“A controlled multiphase trial of ketotifen to minimize neurofibroma-associated pain and itching”

- Drug (target): Ketotifen (Histamine H1 Receptor (mast cells))
- # Participants: 52 total
- Age: ??
- Design: Open-label protocol involving 25 patients with relatively severe symptoms, double-blind protocol involving 27 patients with either relatively mild or severe neurofibroma-associated symptoms
- Outcome Measure: PRO severity scales (1-10) for itching, pain, and tenderness associated with neurofibromas
- Results: …

- Severity was lower during ketotifen treatment compared to pre- and post-treatment
- Would not meet rigorous standards of modern clinical trials



A Controlled Multiphase Trial of Ketotifen to Minimize Neurofibroma-Associated Pain and Itching

Vincent M. Riccardi, MD

• *Background and Design.*—Based on potential contributions of mast cells to neurofibroma-associated itching, pain, and tenderness, the mast cell blocker ketotifen fumarate (Zaditen, Sandoz Pharmaceuticals Corp, Hanover, NJ) has been proposed as a treatment for these symptoms. To test the hypothesis that ketotifen decreases neurofibroma-associated itching, pain, and tenderness, data were accumulated from two protocols. The first was an open-label protocol involving 25 patients with relatively severe symptoms (1170 patient-months), and the second was a double-blind protocol involving 27 patients with either relatively mild or severe neurofibroma-associated symptoms (316 patient-months). All subjects received either oral placebo or 2 to 4 mg of ketotifen fumarate per day. Using a scale of 1 to 10, symptoms were measured before, during, and after treatment.

Results.—Itching severity scores (means) were as follows: for all patients receiving ketotifen, 7.8 before, 2.8 during, and 7.2 after treatment; for ketotifen-treated patients in the double-blind protocol, 6.6 before, 3.9 during, and 6.4 after treatment; and for placebo-treated patients, 6.0 before and 6.0 during treatment. Pain and tenderness severity scores (means) were as follows: for all patients treated with ketotifen, 7.6 before, 3.6 during, and 6.6 after treatment; for double-blind ketotifen-treated patients, 6.3 before, 4.6 during, and 6.1 after treatment; and for placebo-treated patients, 7.9 before and 6.7 during treatment.

Conclusions.—Pretreatment, treatment, and posttreatment levels of itching, pain, and tenderness associated with neurofibromas, using both open-label and double-blind protocols, indicate that ketotifen offers a realistic approach to treating these symptoms.

(*Arch Dermatol.* 1993;129:577-581)

Cellular interaction as an element of neurofibroma pathogenesis was suggested in 1979.[1] By 1981, the focus was more specifically on the mast cell.[2,3] In vitro studies have since added credence to this approach,[4-7] and encouraging results of neurofibroma treatment with ketotifen fumarate, a mast cell blocker, were published in 1987[8] and 1990.[9,10]

Von Recklinghausen described both the neurofibromatosis now known as *NF-1*[11,12] and the mast cell itself,[13] and the presence of mast cells in neurofibromas, as well as in other tumors, has been recognized for many years.[5-7,14-17] Mast cells are also present in large numbers in the brain,[18,19] in normal and damaged nerves,[16,20] and in response to trauma.[21-24] Thus, it is easy to conclude that localized chronic mast cell secretions may contribute to nervous system disorders, including neurofibromas.

See also p 625.

Several orally active drugs have been developed to counter the effect of mast cell substances, particularly histamine, or to block secretion of these substances. Ketotifen fumarate (Zaditen, Sandoz Pharmaceuticals Corp, Hanover, NJ) is among the drugs most widely used for both purposes: it was initially developed as an oral agent for the treatment of reactive airway disease,[25,26] but it has also been used to treat other mast cell–mediated disorders, including urticaria, with variable success.[27-30] Ketotifen appears to act both as an H_1-antihistamine and as a mast cell stabilizer,[25-30] and there have been no significant adverse reactions, save for minor drowsiness and dry mouth, in other clinical trials.[26-30]

In this context, two hypotheses were formulated: (1) mast cells cause neurofibroma-associated itching, pain, and tenderness; (2) ketotifen can effectively decrease these symptoms. Data confirming the latter hypothesis are presented here.

PATIENTS AND METHODS

Patients

The study involved 52 patients, with 25 in the open-label group and 27 in the double-blind group (Table); details concerning specific patients have been published previously.[12,31] Most subjects had NF-1 according to diagnostic criteria defined elsewhere.[32-34] Open-label subjects averaged 46.8 months in the study, with a range of 6 to 78 months and a total of 1170 patient-months. Double-blind subjects had a range of 2 to 18 months and a total of 316 patient-months.

The double-blind protocol focused on the potential for reversal of progression, with stratification according to mild or severe symptoms. The open-label protocol focused on patients already symptomatic to a fairly severe degree, al-

Accepted for publication November 23, 1992.
From The Neurofibromatosis Institute, La Crescenta, Calif.
Reprint requests to The Neurofibromatosis Institute, 5415 Briggs Ave, La Crescenta, CA 91214 (Dr Riccardi).

“Topical Rapamycin Therapy to Alleviate Cutaneous Manifestations of Tuberous Sclerosis Complex (TSC) and Neurofibromatosis I (NF1) (Phase 1)”

- Drug (target): Topical Rapamycin (mTOR)
- # Participants: 28 total
- Age: ≥13y
- Design: Topical treatment of affected area with a placebo, 1% rapamycin, or 5% rapamycin for 6 months
- Outcome Measure:
  - Primary: Rapamycin level, CBC, total cholesterol, dermatologic sensitivity at site of application (pain, erythema, edema, pruritis)
  - Secondary: Reduction in lesion size and appearance (photography and simple PRO: better, no change, worse)
- Results: Study completed but cNF data not published. Dr. Koenig has stated that there is “no obvious difference” like has been the case for rapamycin treatment of TSC

“Ranibizumab for Neurofibromas Associated With Neurofibromatosis 1 (Early phase 1)”

- Drug (target): Ranibizumab (VEGF)
- # Participants: 11 total
- Age: ≥18y
- Design: one injection of ranibizumab into 3 raised cNFs and saline in 1 cNF, monitored over 2 years
- Outcome Measure:
  - Primary: cNF volume measured by caliper and tumor interstitial fluid pressure
  - Secondary: Identify upregulated angiogenic molecules
- Results: Study completed but data not published. Dr. Plotkin has stated that there were “highly variable results”

“Topical Imiquimod 5% Cream for Treatment of Cutaneous Neurofibromas in Adults With Neurofibromatosis 1 (Phase 1)”

- Drug (target): Topical Imiquimod 5% Cream (TLR7)
- # Participants: 11 total
- Age: ≥18y
- Design: topical treatment of 3 raised cNFs 5 times a week for 6 weeks, monitored over 2 years
- Outcome Measure:
  - Primary: cNF volume measured by caliper and tumor interstitial fluid pressure
  - Secondary: Correlate the inflammatory infiltrate adjacent to treated lesions during treatment with tumor response; determine the number of circulating Tregs
- Results: Study completed but data not published. Dr. Plotkin has stated that there were “highly variable results”

"Use of Topical Liquid Diclofenac Following Laser Microporation of Cutaneous Neurofibromas in Patients With NF1 (Phase 2)"

- Drug (target): Topical Liquid Diclofenac (cyclooxygenase (COX; prostaglandin biosynthesis))
- # Participants: 7 total
- Age: ≥18y
- Design: Laser microporation followed by topical diclofenac (25mg/ml) on the surface of 2 cNFs, followed by topical diclofenac twice daily, for three days; 2 control cNFs treated with saline
  Outcome Measure:
  - Primary: Inflammatory process (redness, exculceration)
  - Secondary: Tumor necrosis, size, detachment
- Results: …

- Overall, there was no significant change in neurofibroma size
- Some treated lesions developed signs of necrosis and fell off after a few weeks

A Proof-of-Concept Assessment of the Safety and Efficacy of Intralesional Diclofenac in the Treatment of Cutaneous Neurofibromas

Mauro Geller[1,2,3*], Aguinaldo Bonalumi Filho[4,5], Lisa Oliveira[1], Allan E. Rubenstein[6], Luiz Guilherme Darrigo Jr.[7], David Azulay[8], Allan Bernacchi[9], Marcia Gonçalves Ribeiro[3], Karin Soares Gonçalves Cunha[10]

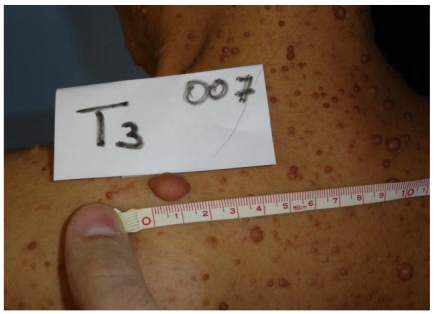


Figure 1. Neurofibroma before starting the treatment.

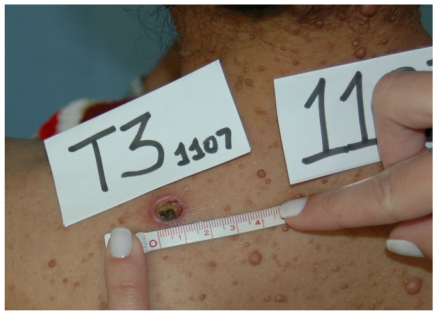


Figure 3. Neurofibroma during week 6 of treatment.

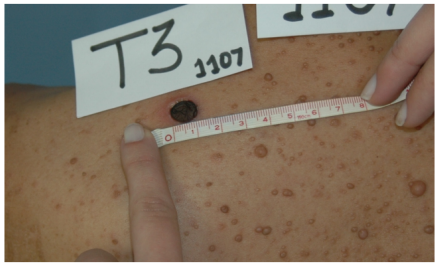


Figure 2. Neurofibroma during week 3 of treatment.

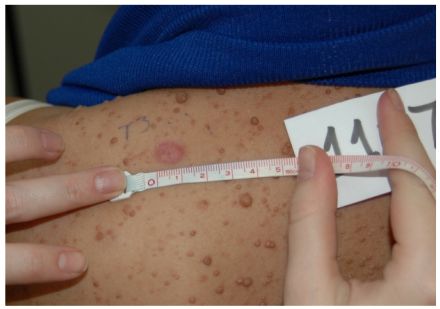


Figure 4. Neurofibroma after three months of the end of the treatment.

"A Single Arm, Multicenter Phase II a Trial of RAD001 as Monotherapy in the Treatment of Neurofibromatosis 1 Related Internal Plexiform Neurofibromas That Cannot be Removed by Surgery"

- Drug (target): Everolimus (mTOR)
- # Participants: 30 total
- Age: ≥18y
- Design: systemic treatment for 1 year
- Outcome Measure:
  - Primary: Volume of internal plexiform neurofibromas
  - Secondary: Number and volume of cutaneous neurofibromas; signaling pathways in cutaneous neurofibromas
- Results: Study completed but data not published

“Everolimus for Treatment of Disfiguring Cutaneous Lesions in Neurofibromatosis1 CRAD001CUS232T (DCLNF1)”

- Drug (target): Everolimus (mTOR)
- # Participants: 22 total (16 had sufficient outcome measures)
- Age: ≥18y
- Design: systemic treatment for 6 months
- Outcome Measure:
  - Primary: 3D photography of surface volume of 4 target lesions
  - Secondary: # Grade 3 and 4 AES
  - Other: IHC
- Results: …

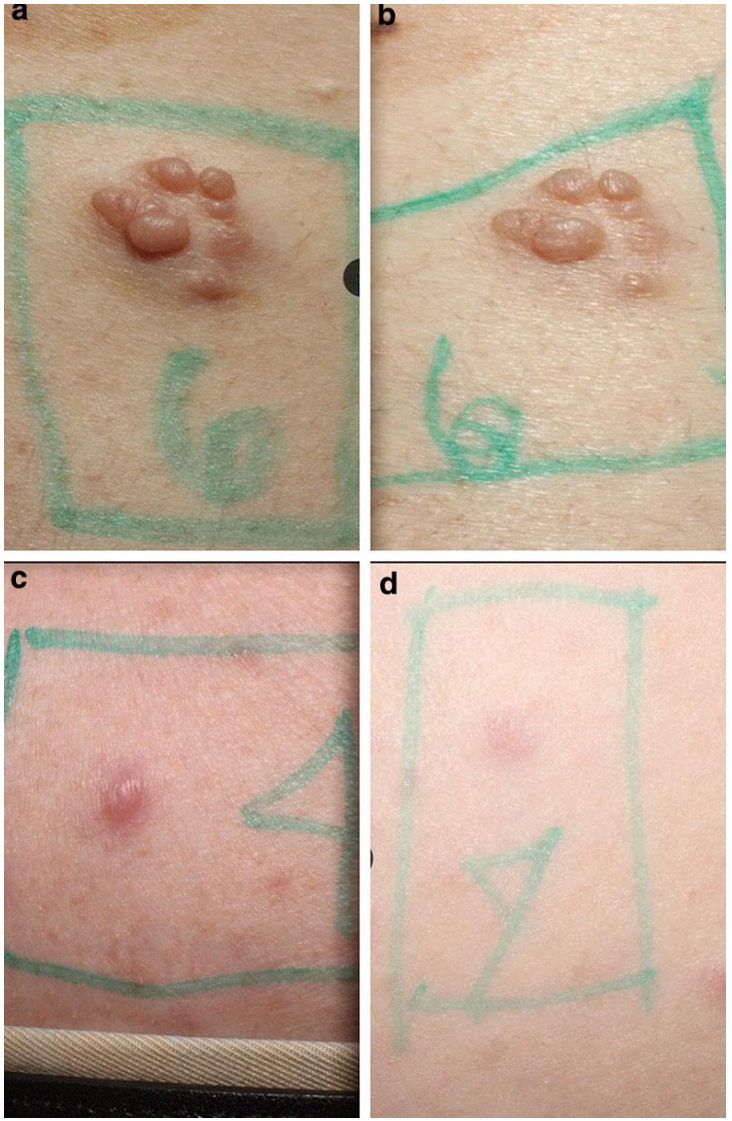
- A significant reduction in lesion surface volume, defined as an end of trial volume > 2 standard errors (SE) less than baseline volume, was observed for 4/31 lesions (13%) from 3/16 patients (19%)
- Limitations: small sample size with limited statistical power and short trial length

Drugs in R&D
https://doi.org/10.1007/s40268-018-0248-6

ORIGINAL RESEARCH ARTICLE

Treatment of Disfiguring Cutaneous Lesions in Neurofibromatosis-1 with Everolimus: A Phase II, Open-Label, Single-Arm Trial

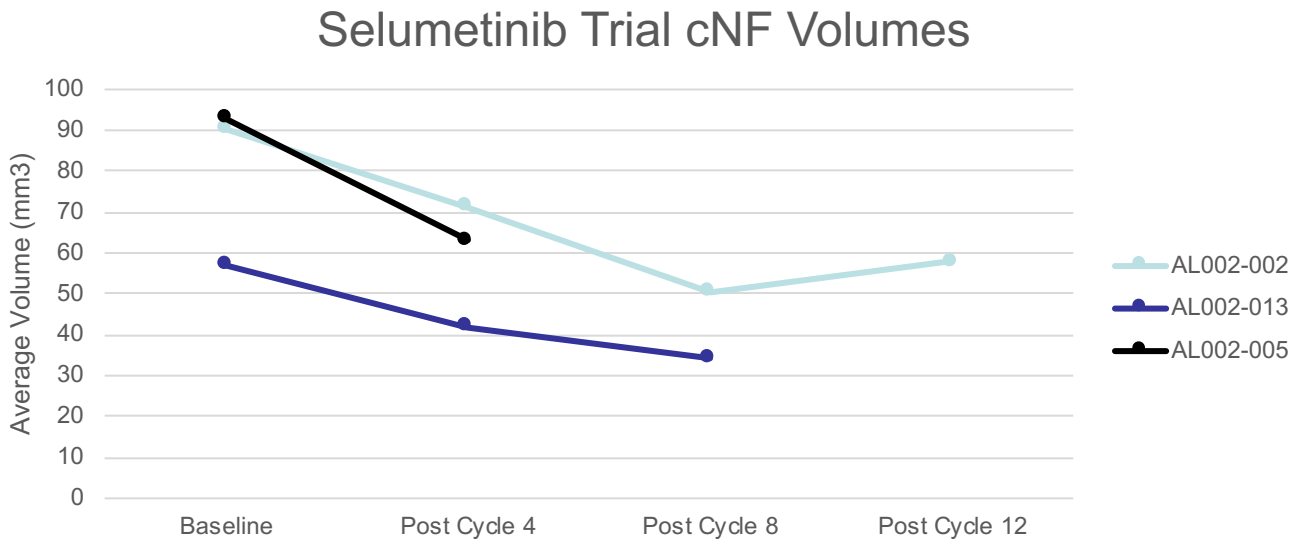
John M. Slopis[1,2] · Octavio Arevalo[3] · Cynthia S. Bell[2] · Adelaide A. Hebert[2,4] · Hope Northrup[2] · Roy F. Riascos[3] · Joshua A. Samuels[2] · Keri C. Smith[5] · Patti Tate[2] · Mary Kay Koenig[2,6]

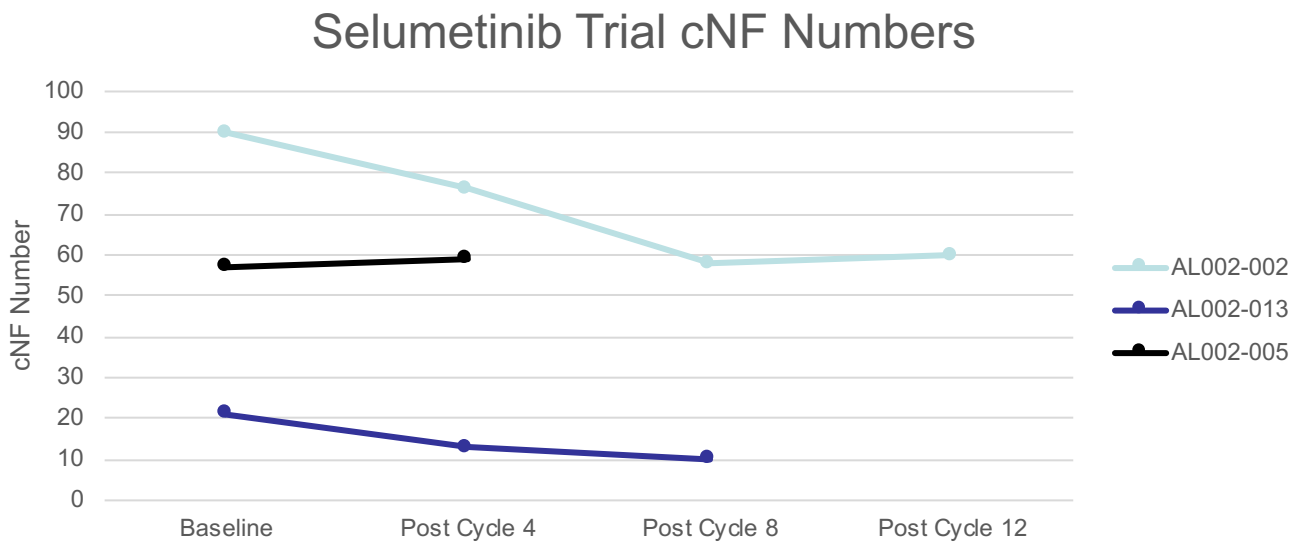


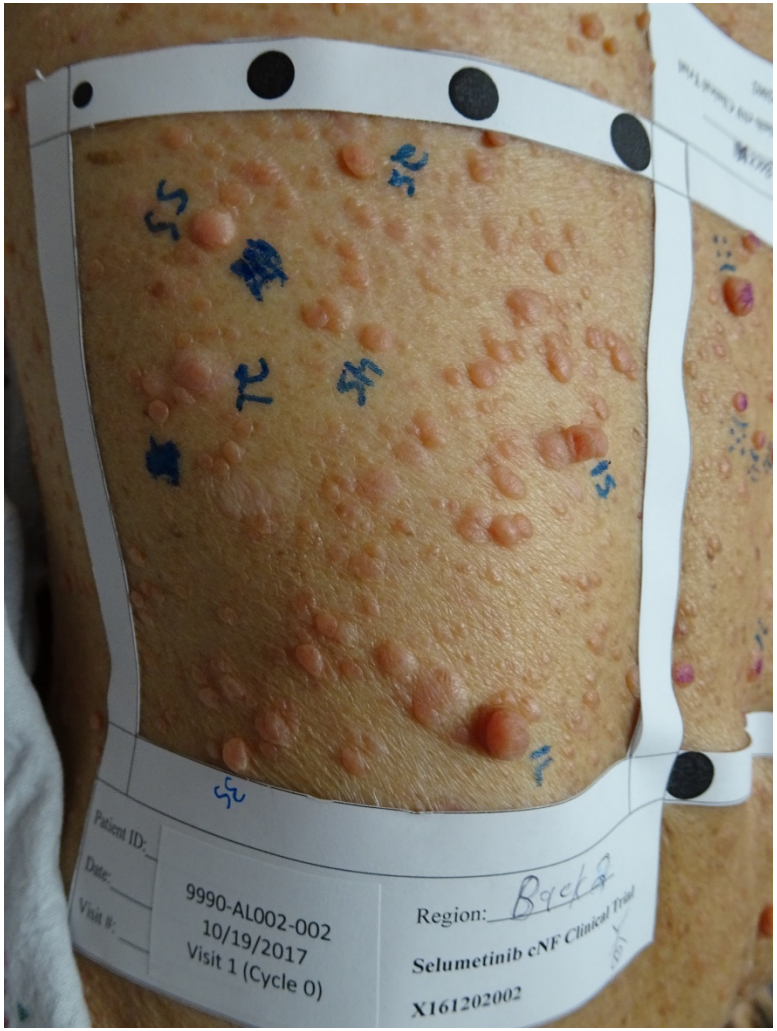
"Selumetinib in Treating Patients With Neurofibromatosis Type 1 and Cutaneous Neurofibroma"

- Drug (target): Selumetinib (MEK1/2)
- # Participants: 24 total Age: ≥18y
- Design: systemic treatment for 2 years
- Outcome Measure:
  - Primary: Volume shrinkage measured by caliper in 3 body regions (100cm^2 each)
  - Secondary: Percent inhibition of phosphorylated ERK (pERK), and changes in phosphorylated AKT (pAKT)
  - Other: Change in cNF number, Skindex PRO, tumor kinome, pilot –omics studies
- Results: …

Preliminary cNF response data



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Visit 1 (Cycle 0)
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Selumetinib cNF Clinical Trial
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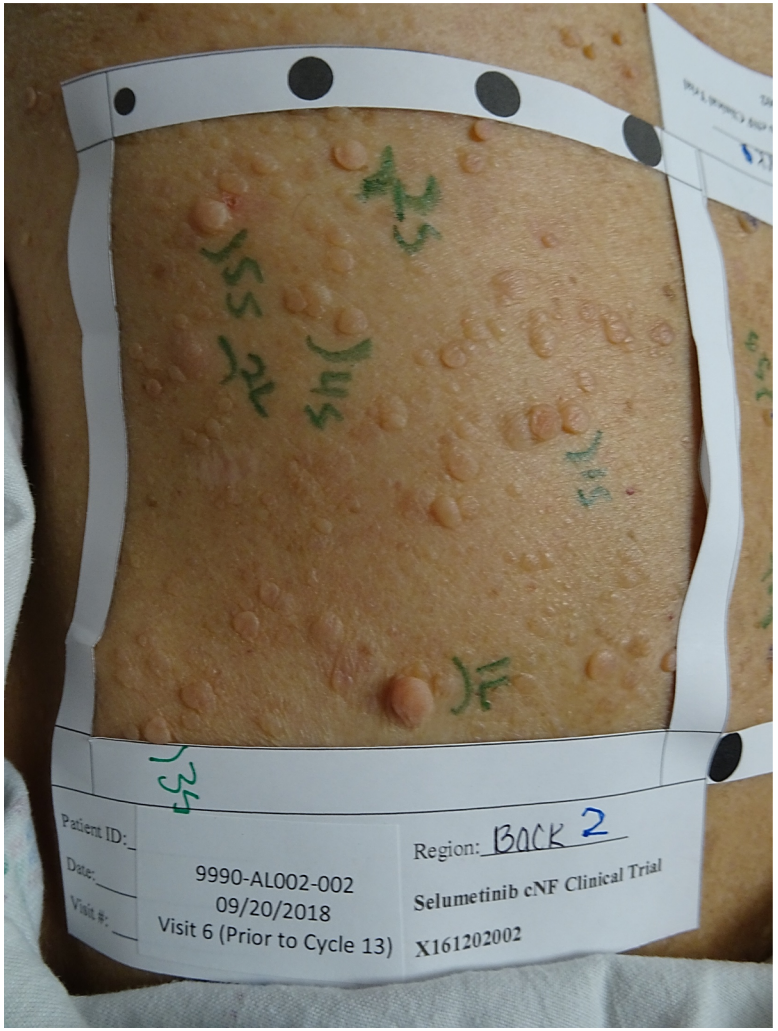
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Selumetinib cNF Clinical Trial
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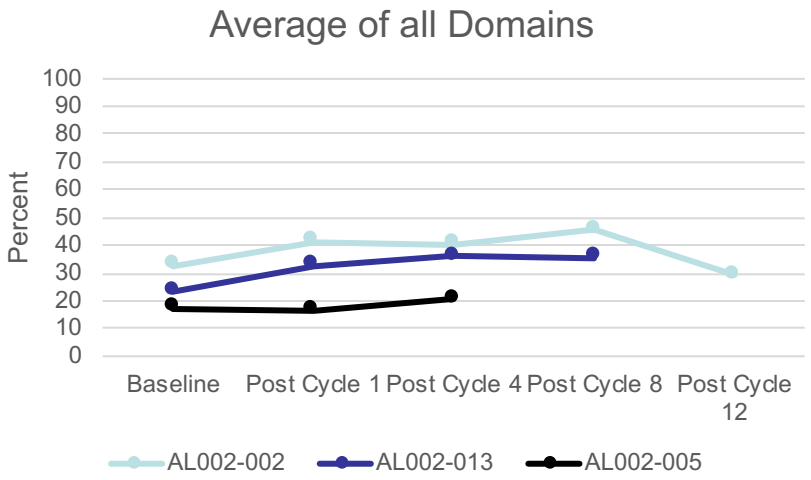
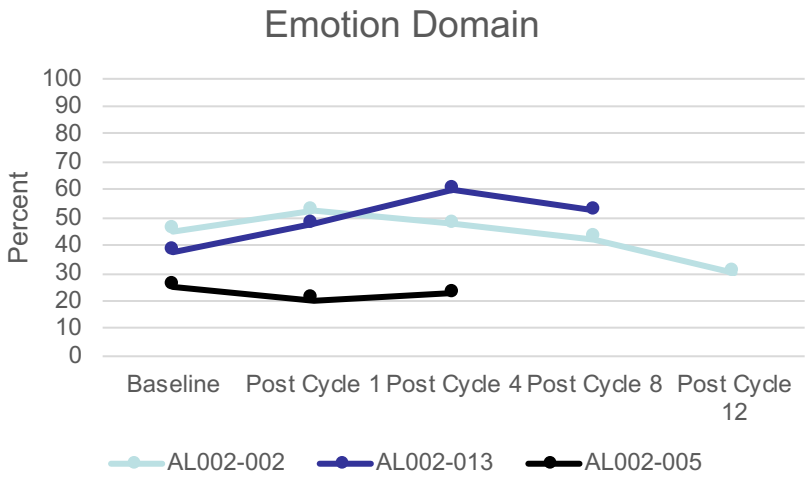
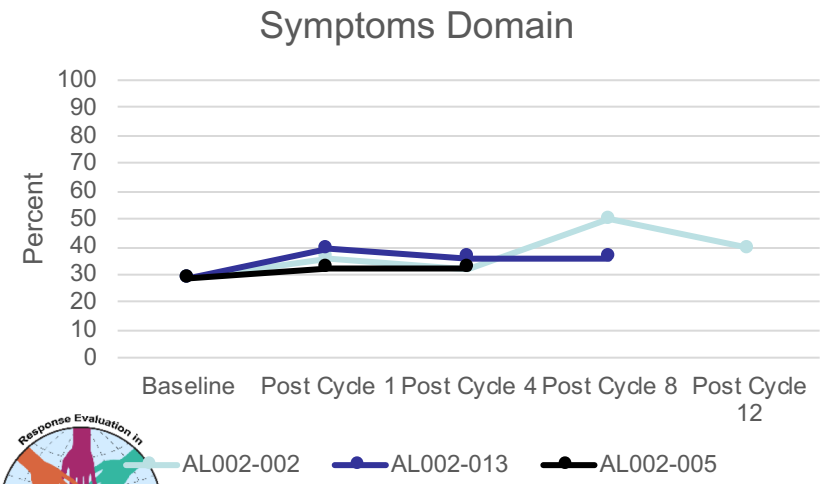
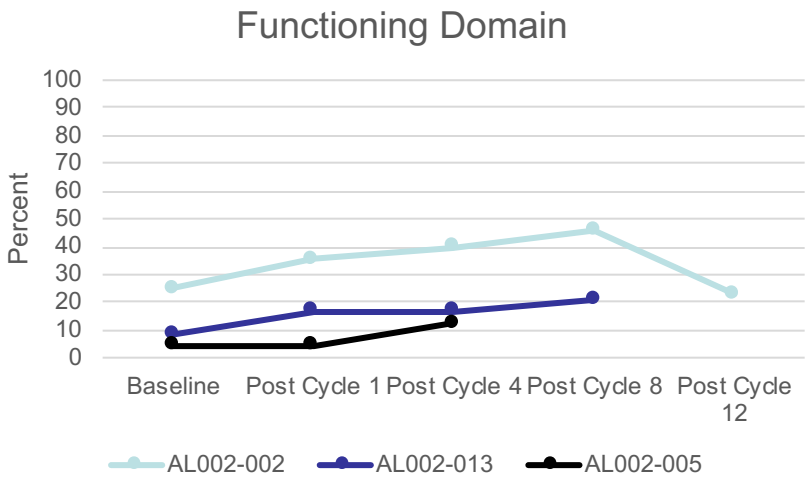
Preliminary Skindex responses









	Size	Number	PRO	IGA	Biomarker	Other
Ketotifen			Primary Outcome: Severity scales (1-10) for itching, pain, and tenderness			
Topical Rapamycin	Secondary: Reduction in lesion size (photography)		Secondary: Simple PRO (better, no change, worse)			Primary: Dermatologic sensitivity at site of application (pain, erythema, edema, pruritis)
Ranibizumab	Primary: cNF volume measured by caliper				Secondary: Angiogenic molecules	
Topical Imiquimod 5% Cream	Primary: cNF volume measured by caliper				Secondary: Inflammatory infiltrate and circulating Tregs	
Topical Liquid Diclofenac	Secondary: Tumor size by photography and measuring tape				Primary: Inflammatory process (redness, exculceration)	
Photodynamic therapy (PDT) / Levulan	Primary: Time to pregression (50% growth in size over baseline); Secondary: Tumor size by caliper					
Selumetinib	Primary: Volume by caliper	Other: Number by manual counts	Other: Skindex		Secondary: pERK/AKT; Other: -omics studies, kinome, pathology	
Everolimus	Primary: Surface volume by 3D photography					Secondary: # Grade 3 and 4 AES; Other: IHC
RAD001 (Everolimus)	Secondary: Volume	Secondary: Number				Primary: Volume of internal plexiform neurofibromas

Experimental Drug Treatment Synopsis

- Target lesion types treated are raised
- Mainly adults and some adolescents studied
- Highly variable, inconsistent, and invalidated outcome measures
  - cNF size is most commonly used as an outcome measure but the methodology is variable
  - PROs are variable, not validated for cNFs
  - No global assessments have been utilized
  - Biomarkers have been dependent on the experimental drug target, not specific to cNF