Selumetinib trial targeting cutaneous neurofibromas: preliminary findings and lessons learned

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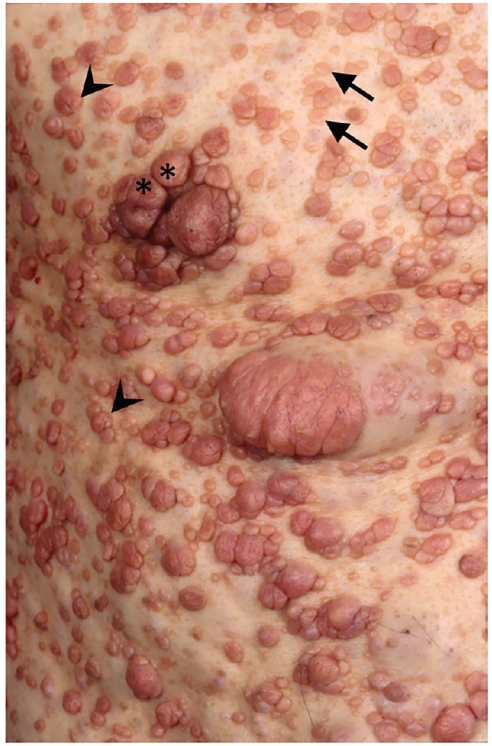
Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Cutaneous neurofibromas

- Cutaneous neurofibromas affect more than 99% of adults with NF1
- Although these tumors do not have malignant potential, they have significant negative effects on quality of life
- Current treatment of cutaneous neurofibromas are limited, treat only a subset of cutaneous neurofibromas, and can result in scarring and future tumor recurrence
- There is a strong unmet need for the development of effective medical therapies

Figure 1 Polymorphism of cutaneous neurofibromas (cNF) in a single patient



Many different aspects of cNF can be seen in this patient, including sessile cNF (arrows), globular cNF (arrowheads), and pedunculated cNF (asterisks). NF = neurofibromas.

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

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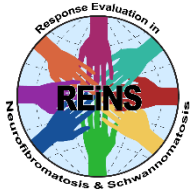
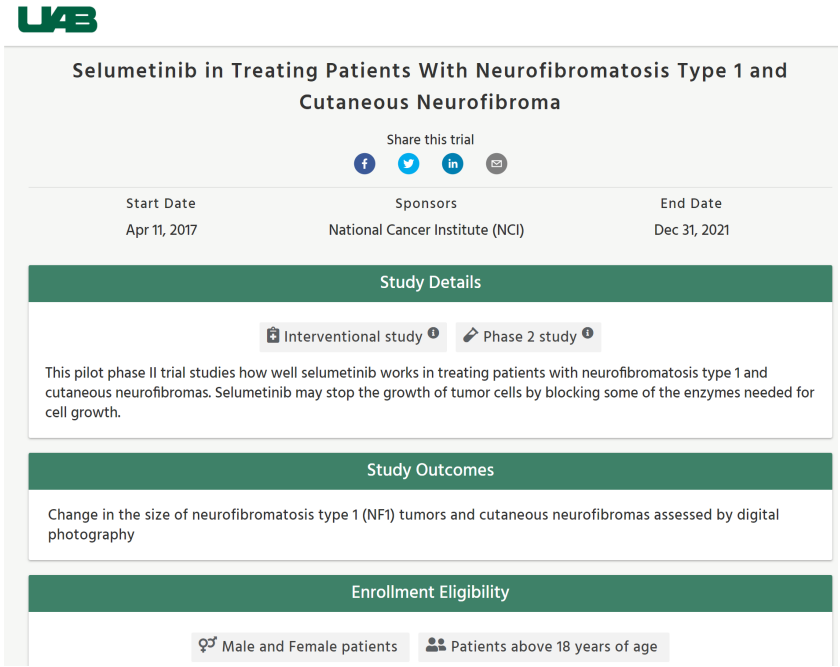
Experimental cNF drug trials

	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 progression (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



Selumetinib trial targeting cNFs

- Sites: UAB and NCI
- Participants: Adults with NF1 and cNFs
- 24 cycles (1 cycle=28 days)
- Primary outcome measure: cNF volume
- Exploratory aims: cNF counts, Skindex, genomic + methylation + transcriptomic studies



UAB

Selumetinib in Treating Patients With Neurofibromatosis Type 1 and Cutaneous Neurofibroma

Share this trial

Start Date	Sponsors	End Date
Apr 11, 2017	National Cancer Institute (NCI)	Dec 31, 2021

Study Details

Interventional study | Phase 2 study

This pilot phase II trial studies how well selumetinib works in treating patients with neurofibromatosis type 1 and cutaneous neurofibromas. Selumetinib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth.

Study Outcomes

Change in the size of neurofibromatosis type 1 (NF1) tumors and cutaneous neurofibromas assessed by digital photography

Enrollment Eligibility

Male and Female patients | Patients above 18 years of age

Response Evaluation in REiNS Neurofibromatosis & Schwannomatosis

Selumetinib Trial Schema and Key Evaluations

Day 0	Prior to cycle 2, or 5	Prior to cycles 5, 9, 13, 17, 21, 25	Disease progression Dose reduction
Measure cNF Biopsy cNF Skindex NRS-11	Biopsy cNF Skindex NRS-11 GIC	Measure cNF Skindex NRS-11 GIC	Measure cNF Biopsy cNF Skindex NRS-11 GIC

- Selumetinib at 50 mg every 12 hours continuous dosing schedule (1 cycle -28 days)
- Selumetinib dose may be escalated to 75 mg every 12 hours after cycle 1, if tolerated (no toxicities of grade 2 or greater).
- Dose determined by pediatric phase I study in NF1 PN
- Regular safety evaluations including physical exam, laboratory evaluations, ophthalmology evaluation, echocardiogram, EKG

cNF= cutaneous neurofibroma

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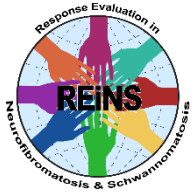
Trial Enrollment as of 12/8/2019

	UAB	NCI
Screened	12	3
Enrolled	8	1
Off Study (adverse event)	2	0
On study (active)	6	1

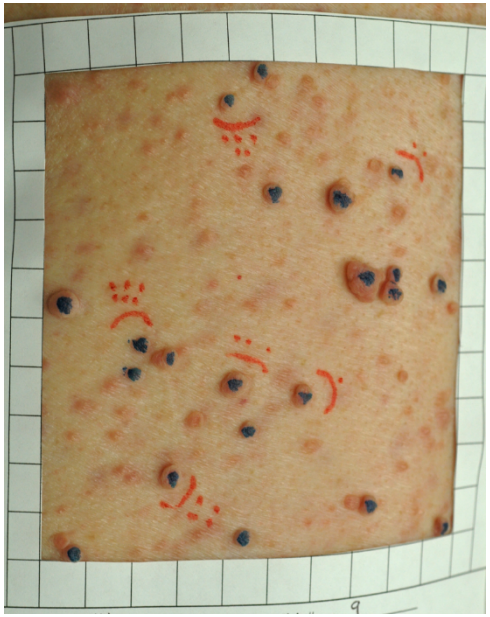
Adverse Events

Adverse event	Grade	Attribution	Participants Experienced (#)
Rash acneiform	2	5	4
Rash acneiform	1	5	4
Dry skin	1	4	4
Dry skin	2	4	1
Constipation	1	4	2
Onchomycosis	1	3	2
Nausea	2	4	1
Nausea	1	4	1
Vomiting	2	4	1
Fatigue	1	4	1
Hypertension	4	3	1
Hypertension	2	3	1
Edema face	1	3	1
Edema limbs	1	3	1
Diarrhea	1	3	1
Dry mouth	1	3	1
Dysgeusia	1	3	1



cNF Outcome Measurements

- 100cm^2 paper frames are applied to 3 body locations (e.g. back, abdomen, arm/leg)
- Each location must have:
  - 3-5 “small” cNFs (4-7mm)
  - 3-5 “large” cNF (>8mm)
- All cNFs larger than 4mm within the frame are counted
- cNFs are manually measured with calipers



Counted / **Measured**

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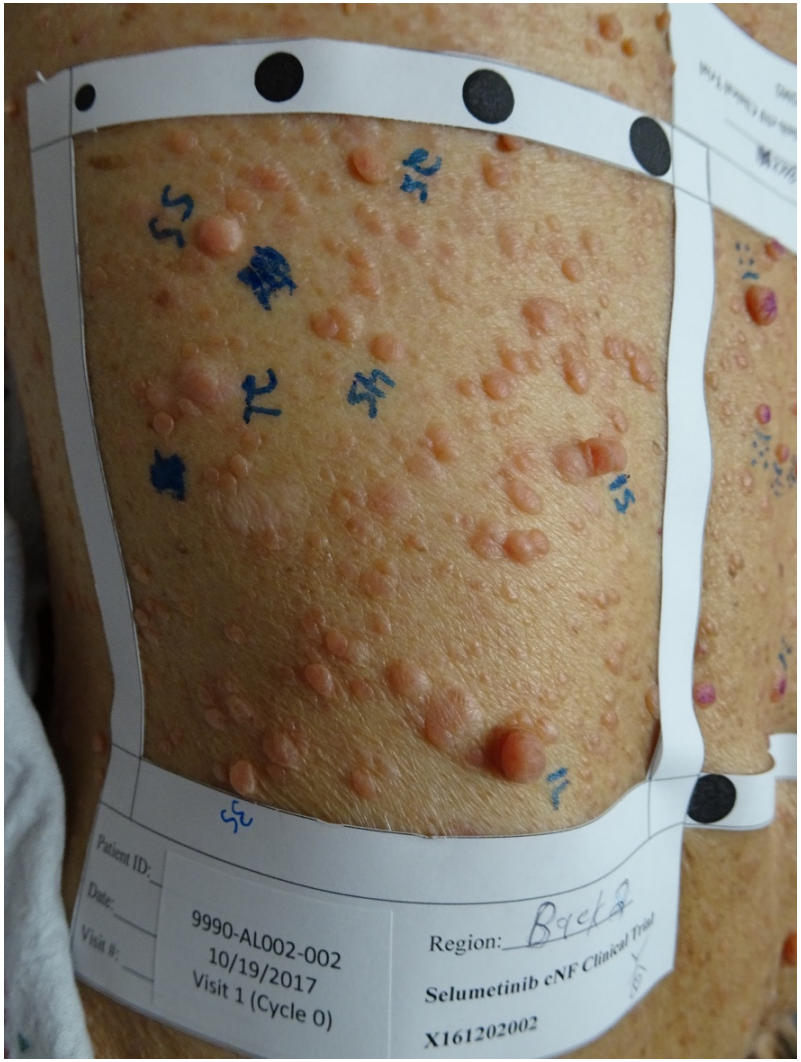
Response Criteria

- Change in (sum of lesion volumes)
- Responsive disease= ≥ 20% decrease in the average volume of the smaller or larger cutaneous neurofibromas compared to the baseline volume
- Progressive disease= ≥ 20% increase in the average volume of smaller or larger cutaneous neurofibromas compared to the baseline volume
- Stable disease= measurements not meeting criteria for responsive or progressive disease

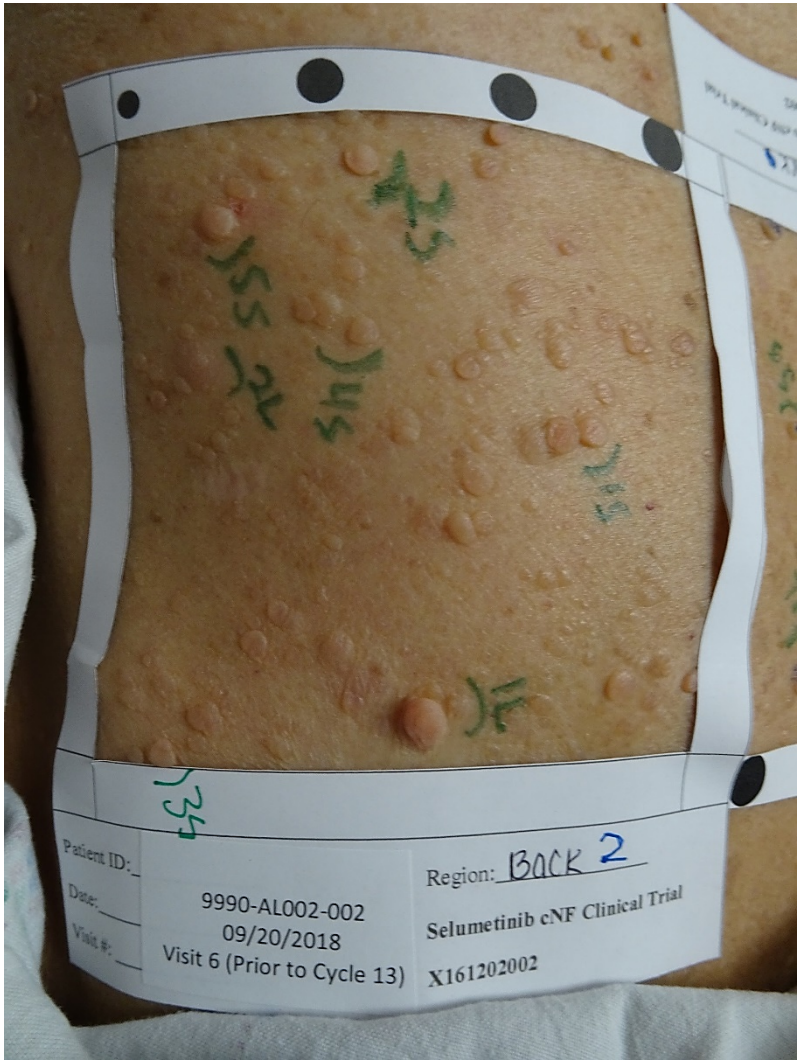
cNF Volume Response

Maximum % cNF volume change (per participant analysis)

Maximum % cNF volume change (per cNF analysis)



Baseline



Post cycle 12

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cNF Number Response

Skindex Scores

Selumetinib cNF trial summary

- Manual caliper measurement of cNF volume is feasible for clinical trials but does have limitations
- Selumetinib decreases cNF volume
  - All participants had responsive disease (≥20% decrease)
  - Slow regrowth has been observed in cases where selumetinib was held
  - No disease progression observed (≥20% increase)
- To date, selumetinib has not significantly changed cNF number
- The Skindex-29 quality-of-life tool may lack the specificity and sensitivity needed to detect cNF treatment responses
- Additional study participant data are needed!

Response Evaluation in REiNS Neurofibromatosis & Schwannomatosis

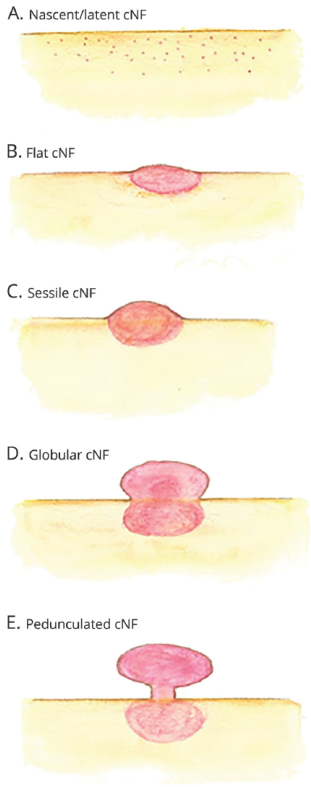
Lessons learned

- Limitations of manual cNF measurement
- Older patients have more comorbidities (HTN, obesity, diabetes)
- Skindex-29 quality-of-life tool may lack the specificity and sensitivity needed to detect cNF treatment responses
  - "skin condition" changed to "cutaneous neurofibromas" in each line item
  - Analyze each line item to see which ones correlate with toxicities, volume response, and other NF-related issues
- Global impression of change may be a better PRO measure
- A lot of interest in cNF treatment but enrollment was hindered due to:
  - Participant financial/travel/time burden
  - Staff turnover

Manual cNF measurement limitations

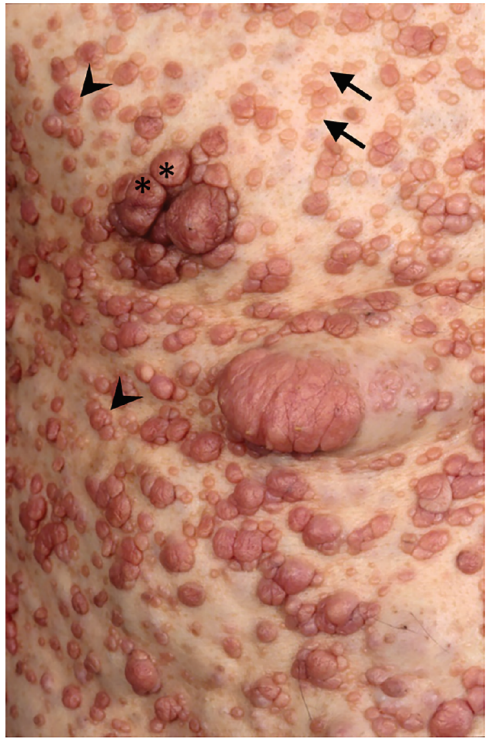
- **TIME FOR MANUAL MEASUREMENTS**
  - Identify frame boundaries
  - Higher cNF burden = >>>time
  - Requires 2 people
  - Takes 1-2 hours
- Measurement variability
- Measure/count fused cNFs?
- Hair visually impairs measurement
- Body positioning makes a difference
- How do you measure peduncular and globular cNFs?
- cNF shrinkage and skin inelasticity leads to cNF boundary issues

Figure 2 Proposed categories of clinically observed cutaneous neurofibromas (cNF) to be considered in the prospective validation study



(A) Nascent/latent cNF. (B) Flat cNF. (C) Sessile cNF. (D) Globular cNF. (E) Pedunculated cNF.

Figure 1 Polymorphism of cutaneous neurofibromas (cNF) in a single patient



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Recommendations for future cNF trials

- Identification of, or development of, a quality of life index that captures the burden of disease and will be sensitive to change of cNFs
- Topical vs. oral formulation of medication
- When measuring response to therapy, the goal should not be 100% clearance of a cNF
- Reduce barriers to participating in cNF clinical trials

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