Proposed design for a activity-finding trial using local therapy

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Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Background comments

- In 2019, our community is not (yet) prepared for a definitive clinical trial for cNF
- However, we have reasonable drug candidates (e.g., MEKi) that can be screened for efficacy
- Multiple pharmaceutical companies have shown interest in this space
- Our goal is to create a template for clinical trials of cNF for use in academia and for companies
- These templates will be modified over time as we learn the optimal way to conduct screening trials.
  - Different phenotypes will require different trial designs

Objectives

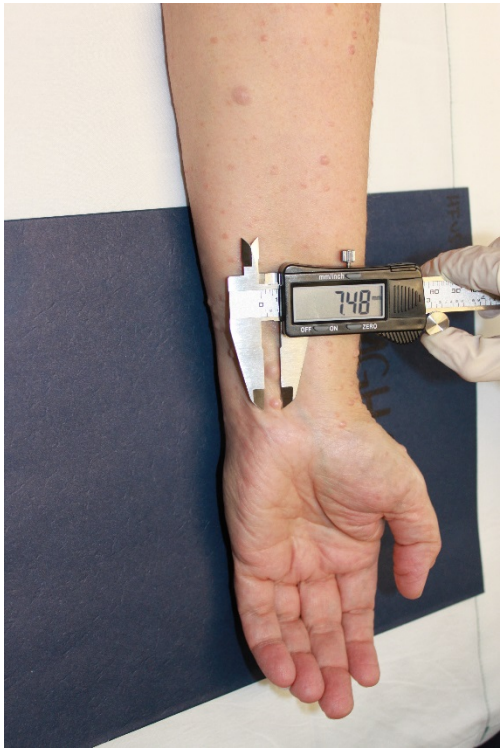
- Primary objective:
  - to evaluate safety/tolerability of topical AGENT during treatment of cNF
  - to determine the activity of topical AGENT on size of NF1-related cNF
- Secondary objective:
  - to determine the effect of topical AGENT on number of NF1-related cNF
  - to evaluate effect on cNF-related quality of life (QOL)
- Exploratory objectives:
  - to evaluate pharmacokinetic (PK) and pharmacodynamic (effect of drug) profile in cNF
  - To explore activity in different ‘types’ of cNF
  - To explore relationship between change in size and QoL

Study design for local therapy

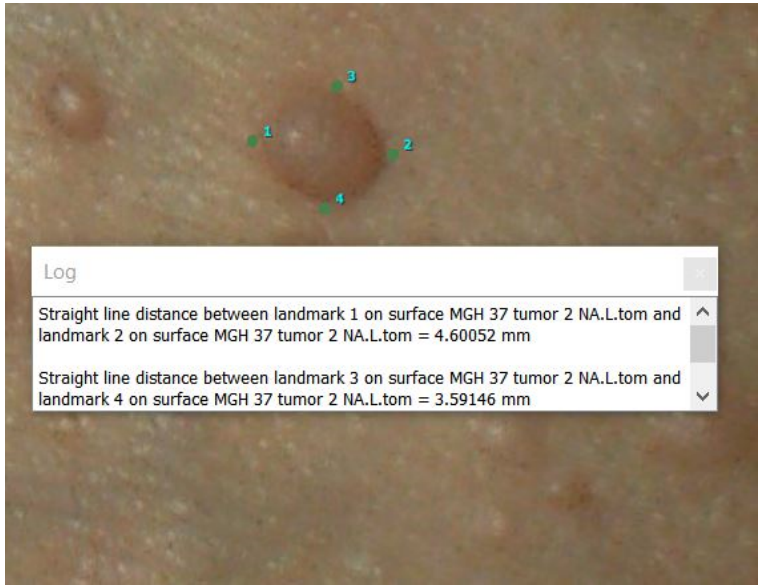
- Evaluable lesions: at least 3 mm in size, able to be photographed
  - Exclude non-assessable/non-evaluable lesions – too small, obscured by hair, near mucus membranes, etc
- Region of interest: Participant selects 10 x 10 cm area of skin as target area; investigator ensures there are adequate number of evaluable lesions
  - 3-5 small lesions (3-5 mm) and 3-5 larger lesions (> 5 mm) in each region
- Control tumors:
  - If there is concern about systemic exposure of topical treatment (e.g., absorption), can enroll patients treated with placebo
  - If there is no concern about systemic exposure of topical treatment, can apply placebo to another 10x10 cm area of akin
- Treatment: application of topical agent for adequate time frame
  - Treatment duration: up to 1 year or until intolerable
- Tissue biopsies:
  - Recommend collection of untreated and treated cNF for PK/PD analysis
  - Systemic plasma PK analysis

Canfield Scientific, Vectra H1

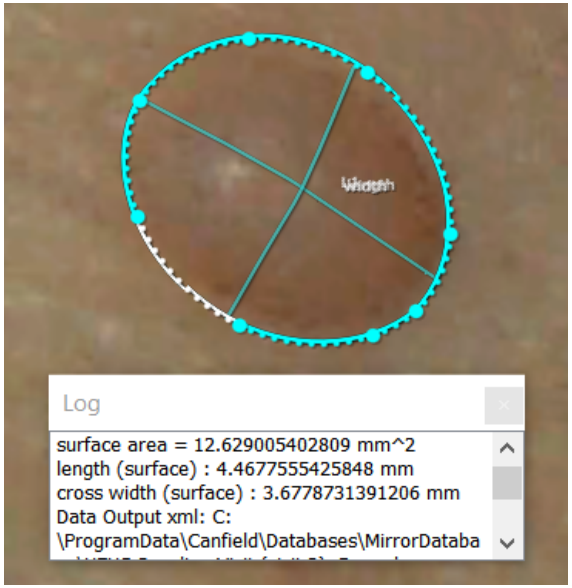
Manual calipers



Semi-automated linear measures



Semi-automated surface area



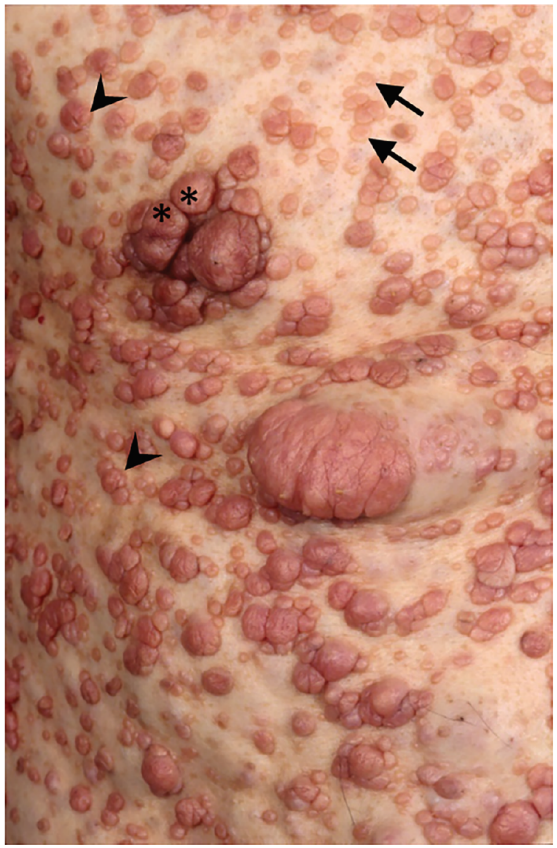
Key tumor inclusion criteria

- Diagnosis of NF1
- Raised cutaneous neurofibromas (exact number determined by protocol) – avoid deep dermal tumors that raise the skin
- Size 3 mm or larger in max linear dimension

Key tumor exclusion criteria

- Tumors who dimensions cannot be evaluated by calipers or 3D photography

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.

Primary endpoint

- Primary endpoint (3D photography)
  - Change in max linear measurement of assessable lesions within region of interest, as calculated by automated script
  - Central review of photographs (can also allow for changes in color in the future)

- Imaging response criteria:
  - Each tumor is evaluated independently
  - In addition, the sum of the longest diameters are evaluated
  - PR: ≥ 20% reduction in max lesion diameter of assessable lesions compared to baseline
  - PD: ≥ 20% increase in max lesion diameter of assessable lesions compared to baseline
  - SD: responses that do not meet criteria for PR or PD
  - NA: not assessable due to toxicity (e.g., treatment-emergent rash, crusting)

Primary endpoint

- Safety
  - Focus on dermatologic side effects
  - Hold drug for grade ¾ cutaneous toxicity
    - Need to use dermatology toxicity criteria (CTCAEv5 will not work)
- Tolerability/feasibility
  - Including medication compliance

Secondary endpoints

- PRO: modified Skindex, DLQI, or others in region of interest
  - Need response criteria for PROs

Exploratory endpoints

- Change in max linear measurement of assessable lesions by calipers within region of interest
- Global assessment of change (GAC) in region of interest
  - To assess change in size and color
  - Major response: +2 or +3
  - Minor response: +1
- Biomarker analysis: paired analysis of baseline and post-treatment
  - PK: does DRUG reach the dermis?
  - PD: does the DRUG engage the predicted target

- +3: significant improvement
- +2: moderate improvement
- +1: minimal improvement

Clinical response

- 0: no change

Stable

- -1: minimal worsening
- -2: moderate worsening
- -3: significant worsening

Clinical worsening

Statistical issues

- Imaging response
  - Change in each tumor (max dimension) → Assess heterogeneity of response
  - Change in sum of tumors (max dimension)
- Need to resolve best way to analyze given that multiple cNF in a single participant are not true independent events

Questions