THANK YOU SCOTT

Proposed design for activity-finding trial using systemic therapy for cNF

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Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Background comments

- In 2019, our community is not (yet) prepared for clinical trials with registration purpose for cNF
- However, we have reasonable drug candidates (e.g., MEKi) that can be assessed for activity
- Multiple pharmaceutical companies have shown interest in this space
- Our goal is to create trial design templates 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

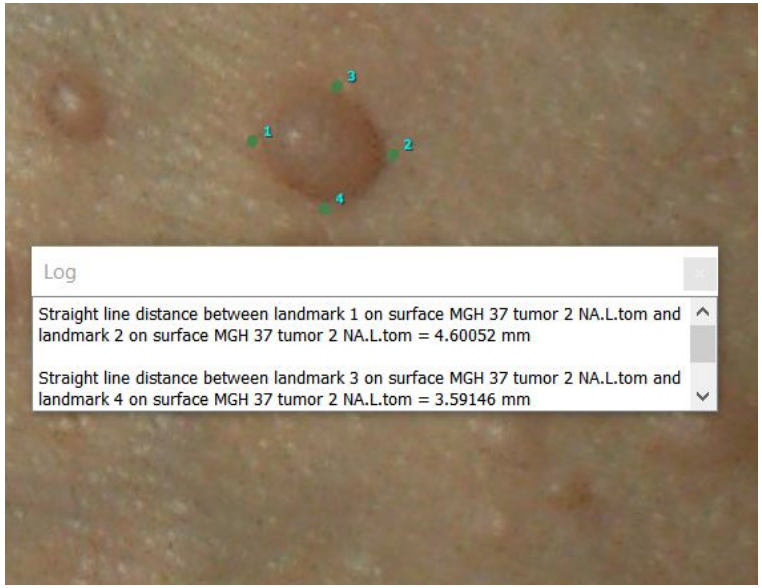
Objectives

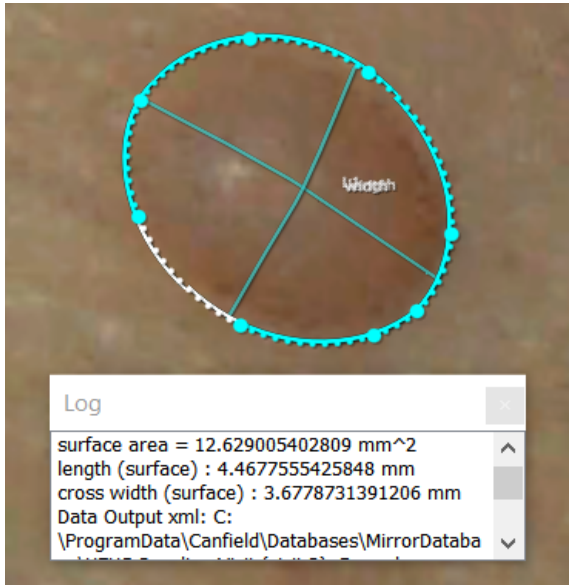
- Primary objective:
  - to evaluate safety/tolerability of the systemic AGENT during treatment of cNF
  - to determine the activity (decrease in size of cNFs) of the systemic AGENT for treatment of NF1-related cNF
- Secondary objective:
  - to determine the effect of the systemic AGENT on number of NF1-related cNF
  - to evaluate effect on cNF-related quality of life (QOL)
  - To evaluate plasma pharmacokinetics (PK)
- Exploratory objectives:
  - to evaluate tumor PK and pharmacodynamic effect of AGENT on cNF
  - To explore activity in different 'types' of cNF
  - To explore relationship between change in size and QoL

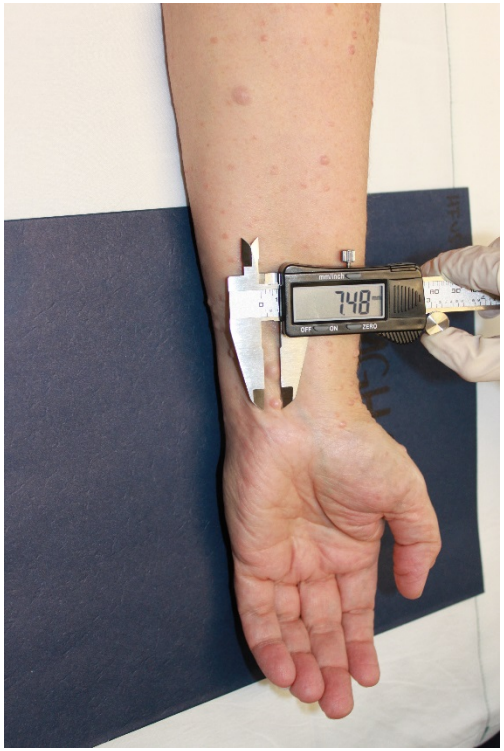
Study design

- 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 or investigator select 10 x 10 cm area of skin as target area; investigator ensures there are adequate number of evaluable lesions. Three 10 x 10 cm areas will be selected
  - 3-5 small lesions (3-5 mm) and 3-5 larger lesions (> 5 mm) in each region
- Treatment: Administration of the agent per protocol (PO, IV, SC)
  - Treatment duration: up to 2 years or until evidence of tumor progression:
    - worsening on GAC for both investigator and participant or
    - increase in average volume of small and large cNF by ≥ 20%)
- cNF biopsies:
  - Recommend collection of treated cNF for PK/PD analysis
  - Systemic plasma PK analysis

Canfield Scientific, Vectra H1







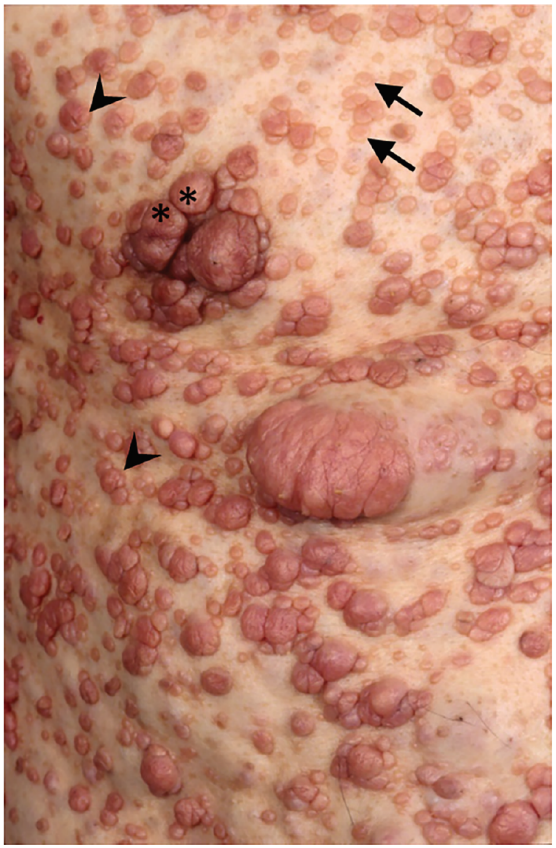
Key tumor inclusion criteria

- Diagnosis of NF1
- Raised cNF (exact number determined by protocol)
- Size 3 mm or larger
- cNF burden has to be associated with clinical burden experienced by patient

Key tumor exclusion criteria

- Tumors that 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 safety

- Safety:
  - Hold agent for related AE ≥ grade 3 and for intolerable ≥ grade 2 events (CTCAEv5)
  - Specific criteria depending on profile of agent
  - Cutaneous criteria developed by Plotkin et al.
- Tolerability/feasibility
  - Including medication adherence

Primary endpoint activity

- 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)

Secondary and exploratory endpoints

Secondary endpoint:

- 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

- Analysis per tumor (not per participant)
  - Assess heterogeneity of response
- Need to resolve best way to analyze given that cNF in a single participant are not true independent events

Questions