Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

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REiNS Pre-Meeting Educational Symposium

Summarizing key regulatory issues of interest for REiNS

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Response Evaluation In Neurofibromatosis Schwannomatosis
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CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

What is Required for Drug Approval

<u>To gain FDA approval the intervention must:</u>

- Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
      - Improvement or delay in progression

<u>Evidence of effectiveness:</u> [PHS Act, 505(d)]

- Adequate and well–controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling

<u>Adequate and well controlled: (§314.126)</u>

- Study has been designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation”

Novel drug approvals for 2022 (partial list)

12.	Camzyos	mavacamten	4/28/2022	To treat certain classes of obstructive hypertrophic cardiomyopathy
11.	Vivjoa	oteseconazole	4/26/2022	To reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are not of reproductive potential
10.	Pluvicto	lutetium (177Lu) vipivotide tetraxetan	3/23/2022	To treat prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer following other therapies
9.	Opdualag	nivolumab and relatlimab-rmbw	3/18/2022	To treat unresectable or metastatic melanoma
8.	Ztalmy	ganaxolone	3/18/2022	To treat seizures in cyclin-dependent kinase-like 5 deficiency disorder
7.	Vonjo	pacritinib	2/28/2022	To treat intermediate or high-risk primary or secondary myelofibrosis in adults with low platelets
6.	Pyrukynd	mitapivat	2/17/2022	To treat hemolytic anemia in pyruvate kinase deficiency
5.	Enjaymo	sutimlimab-jome	2/4/2022	To decrease the need for red blood cell transfusion due to hemolysis in cold agglutinin disease
4.	Vabysmo	faricimab-svoa	1/28/2022	To treat neovascular (wet) aged-related macular degeneration and diabetic macular edema
3.	Kimmtrak	tebentafusp-tebn	1/25/2022	To treat unresectable or metastatic uveal melanoma
2.	Cibinqo	abrocitinib	1/14/2022	To treat refractory, moderate-to-severe atopic dermatitis
1.	Quviviq	daridorexant	1/7/2022	To treat insomnia

PYRUKYND® (mitapivat)

- **Patients were included if they had** documented presence of at least 2 variant alleles in the pyruvate kinase liver and red blood cell (PKLR) gene, of which at least 1 was a missense variant, and Hb less than or equal to 10 g/dL. Patients who were homozygous for the c.1436G>A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded because these patients did not achieve Hb response (change from baseline in Hb ≥1.5 g/dL at >50% assessments) in the dose-ranging study.
- **Efficacy was based upon** Hb response, defined as a ≥1.5 g/dL increase in Hb from baseline sustained at 2 or more scheduled assessments (Weeks 16, 20, and 24) during the fixed dose period without transfusions.

OPDUALAG™ (nivolumab and relatlimab-rmbw)

- **Patients were included if they had** previously untreated metastatic or unresectable Stage III or IV melanoma.
- **The major efficacy outcome measure** was progression-free survival (PFS) determined by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

RELYVRIO (sodium phenylbutyrate and taurursodiol)

- **Patients had to have** a definite diagnosis of sporadic or familial ALS with symptom onset within the past 18 months, and a slow vital capacity (SVC) greater than 60% of predicted at screening
- **The prespecified primary efficacy endpoint** was a comparison of the rate of reduction in the ALSFRS-R total scores from baseline to Week 24 in the mITT population.
  - The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). Each item is scored from 0-4, with higher scores representing greater functional ability.

“The impact of treatment on how patient feels, functions or survives”

- What would it look like “to treat neurofibromatosis 1”?
- Neurofibromatosis and schwannomatosis are complex conditions
  - Multiple tumor types
  - Multiple locations
  - Non-tumor manifestations
  - Age range: birth to elderly
  - Multiple effects on quality of life
  - Natural history of when tumors develop and grow not well known
  - High variability of disease manifestations even within a family
- Neurofibromatosis and schwannomatosis are rare condition
  - Challenges with proving “studies must be adequate and well controlled”

Neurofibromatosis 1

Indication ("to treat")	Primary endpoint ("how patient feels, functions or survives")
Cutaneous neurofibroma	Number? Size? Pain? Appearance?
Plexiform neurofibroma	Size? Pain? Disability? Function? Appearance?
MPNST	Survival? Time to tumor growth? Function?
Low grade glioma	Size? Neurological function? Vision?
Learning disability	Which cognitive function to target?
Scoliosis	Preventing worsening? Correcting curve? Pain? Breathing?

"The impact of treatment on how patient feels, functions or survives"

Schwannomatosis

Indication ("to treat")	Primary endpoint ("how patient feels, functions or survives")
Vestibular schwannoma	Size? Hearing? Tinnitus? Balance?
Non-vestibular schwannoma	Size? Pain? Disability? Weakness?
Meningioma	Tumor shrinkage? Time to tumor growth? Function?
Spinal ependymoma	Size? Cyst? Neurological function?
Scoliosis	Preventing worsening? Correcting curve? Pain? Breathing?

"The impact of treatment on how patient feels, functions, or survives"

Organization and Membership of REiNS Collaboration

Working groups:

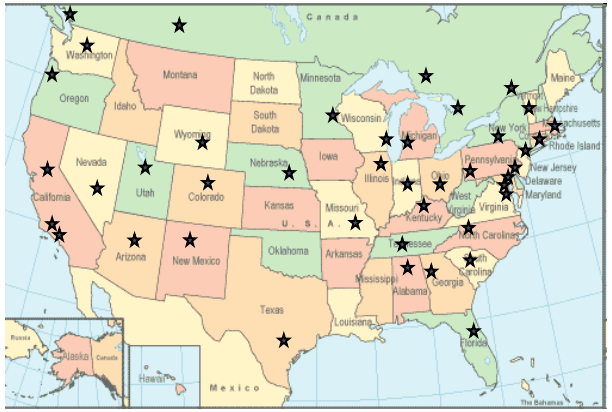
- Cutaneous neurofibromas (Cannon/Sarin)
- Disease biomarkers (Bettegowda)
- Functional outcomes (Gross)
- Gene-directed therapy (Plotkin)
- Neurocognitive outcomes (Janusz)
- Patient reported outcomes (Thompson)
- Patient representation (Merker)
- Tumor imaging/WBMRI (Ahlawat, Dombi)
- Visual outcomes (Avery)

- 9 working groups
- Over 370 active members
- Over 70 institutions and organizations

ACADEMIC MEDICAL CENTERS

PHARMACEUTICAL COMPANIES

The REiNS working groups are open to all participants



REiNS publications (2013-2022)

Functional outcomes

- Functional outcome measures (vision) for NF1-associated optic pathway glioma clinical trials
- Hearing and facial function outcomes for neurofibromatosis 2 clinical trials
- Sleep and pulmonary outcomes for clinical trials of airway plexiform neurofibromas in NF1
- Reliability of strength testing using hand held dynamometry in patients with neurofibromatosis 1 and 2.

Cutaneous neurofibroma

- Use of SkinDex to assess patients with NF1: a report from US and Australian Clinics
- Reliability of digital calipers, photography, and ultrasound to measure cutaneous neurofibromas in patients with neurofibromatosis 1
- Patient Views Regarding Cutaneous Neurofibromas and Treatment

Patient reported outcomes

- Patient-reported outcomes in neurofibromatosis and schwannomatosis clinical trials
- Outcomes of Pain and Physical Functioning in NF Clinical Trials
- Assessing general and disease-specific quality of life in neurofibromatosis clinical trials
- Measures of Quality of Life and function for hearing in patients with neurofibromatosis 2

Imaging

- Current Whole-Body MRI Applications in the Neurofibromatoses: NF1, NF2 and Schwannomatosis
- Recommendations for imaging tumor response in neurofibromatosis clinical trials

Neurocognitive outcomes

- Neurocognitive Outcomes in Neurofibromatosis Clinical Trials: Recommendations for the Domain of Attention
- Social skills outcomes for patients with neurofibromatosis 1
- Measurement of attention as a clinical trials outcome in preschoolers with neurofibromatosis 1

Biomarkers

- Current status and recommendations for biomarkers and biobanking in neurofibromatosis
- Biomarkers for cutaneous neurofibroma
- Genotype-Phenotype correlations in neurofibromatosis and their potential clinical use

Questions?