Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

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Regulatory Approval of Selumetinib for NF1 Plexiform Neurofibromas:

How Did We Get There & Lessons Learned

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REINS Winter Meeting

December 5, 2022

Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

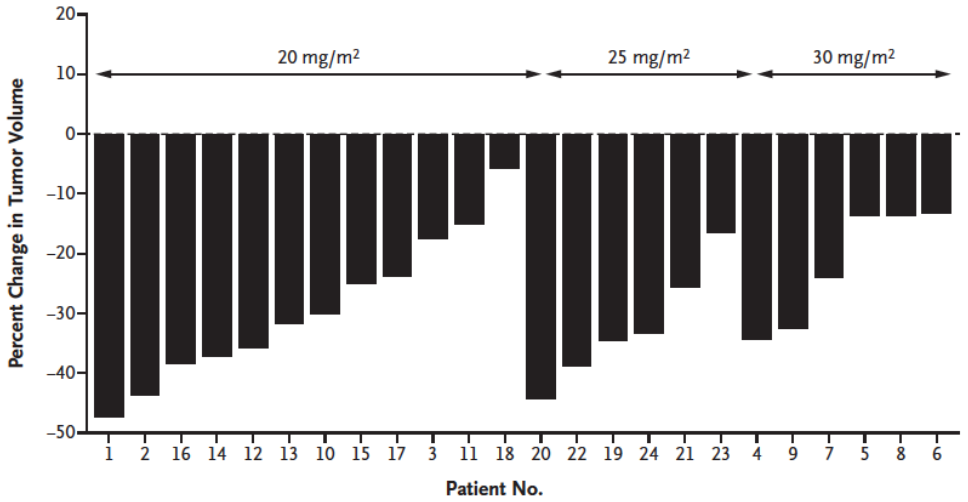
Disclosures

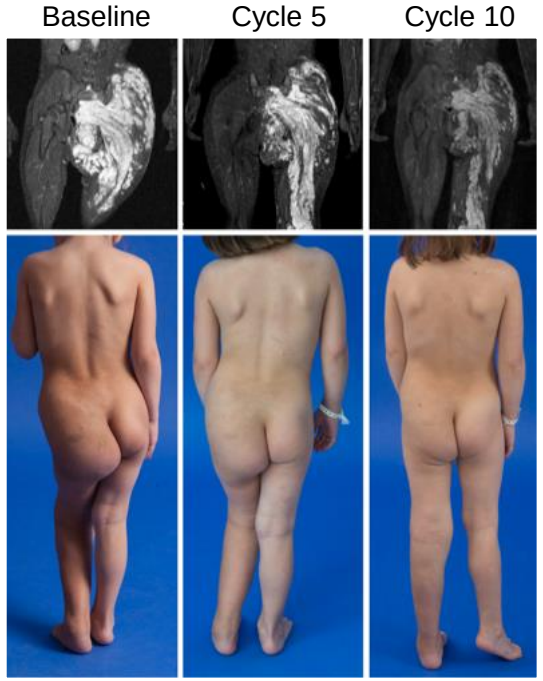
- **Advisory Role**: Unpaid and part of official duty activities as a federal employee
  - Alexion/AstraZeneca
  - Springworks Therapeutics
- **Research Support:**
  - NCI Intramural Research Program
  - Alexion/AstraZeneca
  - Department of Defense NF Research Program
  - Neurofibromatosis Therapeutics Acceleration Program
  - Children's Tumor Foundation

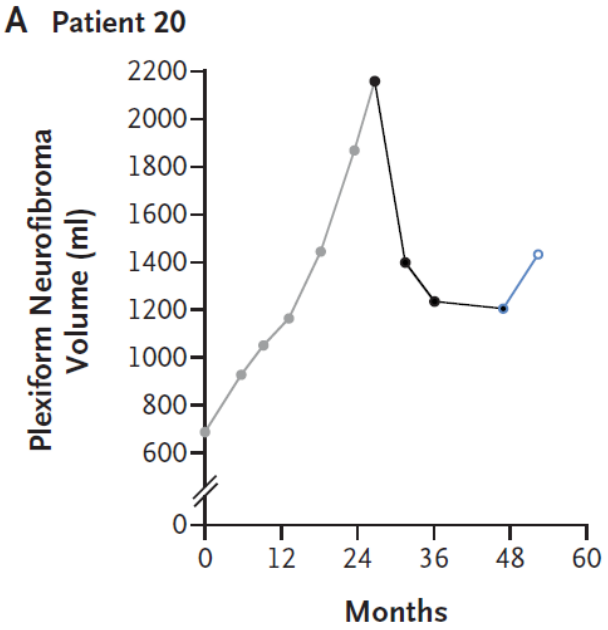
Phase I Trial of Selumetinib for Plexiform Neurofibromas in Children with NF1

- Taken twice daily on a continuous dosing schedule (1 cycle = 28 days)
- Primary Objective: Define the maximum tolerated dose (MTD) of selumetinib for pediatric patients with inoperable PN
- First treatment to show shrinkage in majority of plexiform neurofibromas (PN) in NF1
  - Partial response in 17/24 patients

Responses at ~60% of adult recommended dose







Dombi E, et al. *N Engl J Med.* 2016.

Meeting with FDA in 2015

- Phase I study with anecdotal clinical benefit but no prospective patient reported or functional measures in this study
- Approval strategy:
  - Collaboration with CTEP, academic institutions (CHOP, CNMC, Cincinnati), AstraZeneca, NTAP, FDA
- FDA approval depends on clinical benefit:
  - Show PN volume reduction AND clinically meaningful improvement in pain, function, disfigurement
- Challenges:
  - No validated patient reported and functional outcomes for NF1 and PN
  - Limited natural history data for PRO/Functional Measures

Considerations for Use of External Control Groups

- ❑ Not possible or ethical to run placebo control
- ❑ No available therapy for comparison
  - ❑ Absence of a standard therapy
- ❑ Disease progression is well understood or predictable
- ❑ The outcome measure is objective
- ❑ The effect of the treatment is:
  - ❑ Large/dramatic
  - ❑ Not affected by investigator motivation or choice of subject
  - ❑ Strong temporal association with drug/administration/intervention
  - ❑ Consistent with effect in animal models
- ❑ Control group: well documented, access to individual patient data
- ❑ Results provide compelling evidence of change in established progression of disease

Jahanshahi M et al.: Therapeutic Innovation & Regulatory Science, 202

Phase II Trial of Selumetinib for Symptomatic, Inoperable Plexiform Neurofibromas in Children with NF1

Red = 2013 REiNS Supplement
Blue = 2016 REiNS Supplement
Orange = 2021 REiNS Supplement

First patient enrolled August ***2015***

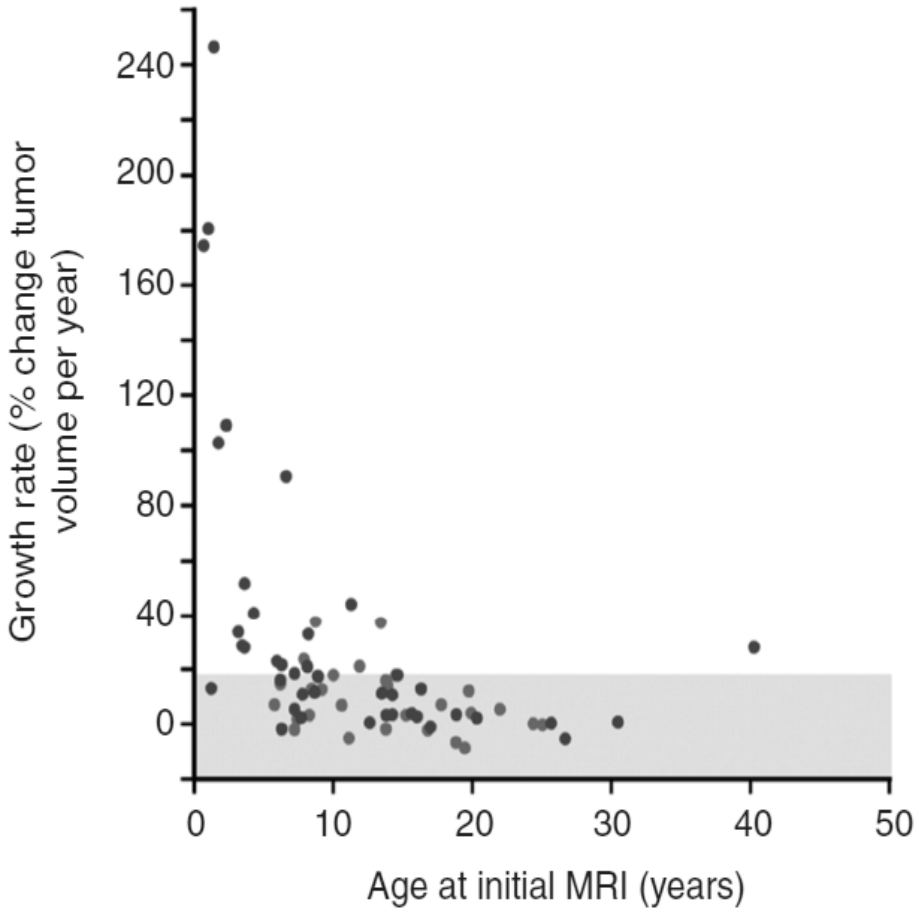
Table 1. Trial Evaluations.*

Evaluation	Category of Plexiform Neurofibroma–Related Complications	Baseline	Time Point after Baseline†
Safety and disease evaluations			
History taking and physical examination, safety laboratory studies	All	Yes	Before cycles 2, 3, 4, 5, 7, 9, 11, 13, 17, 21, and 25, then every 6 cycles
Echocardiography, plexiform neurofibroma disease evaluation (MRI)‡	All	Yes	Before cycles 5, 9, 13, 17, 21, and 25, then every 6 cycles
Ophthalmologic examination	All	Yes	Before cycles 5 and 13, then every 12 cycles
Patient diary and capsule count	All	No	Before cycles 3, 5, 9, 13, 17, 21, and 25, then every 6 cycles
Pharmacokinetics and pharmacodynamics			
Selumetinib and N-desmethyl selumetinib	All	Yes	Before cycle 2 or 3
Cytokines and bone marrow–derived precursor cells	All	Yes	Before cycles 3, 5, 9, and 13 and at the time of progression
Patient-reported outcome measures			Before cycles 3, 5, 9, and 13, then every 12 cycles
Pain intensity (NRS-11)‡	All ≥8 yr of age	Yes	
Pain Interference Index‡	All ≥5 yr of age§	Yes	
PedsQL quality-of-life scales‡	All§	Yes	
Global Impression of Change scale‡	All ≥5 yr of age§	No	
PROMIS Mobility and Upper Extremity scales	Motor§	Yes	
Functional measures			Before cycles 5, 9, and 13, then every 12 cycles
Photography and videography	All visible plexiform neurofibromas	Yes	
Strength evaluation (manual muscle testing using the MRC scale)‡	Motor	Yes	
Range of motion‡	Motor	Yes	
Leg length evaluation, grooved pegboard test	Motor	Yes	
6-Min walk test	Motor, airway¶	Yes	
Polysomnography‡	Airway¶	Yes	
Pulmonary-function tests (spirometry, impulse oscillometry)‡	Airway¶	Yes	
Exophthalmometry‡	Orbital	Yes	
Visual acuity‡	Orbital	Yes	
Bowel and bladder questionnaire‡	Bowel and bladder	Yes	
Audiologic and otolaryngology examination	Other	Yes	
Speech evaluation, swallow study	Other	Yes	

NCI NF Natural History Study for NF1 PN Growth

- Established PN Growth Rate:
  - PN grow most rapidly in young children
  - Spontaneous PN shrinkage occurs BUT no patients with >20% shrinkage per year
- Collected an age-matched control cohort using identical methodology to the SPRINT cohort

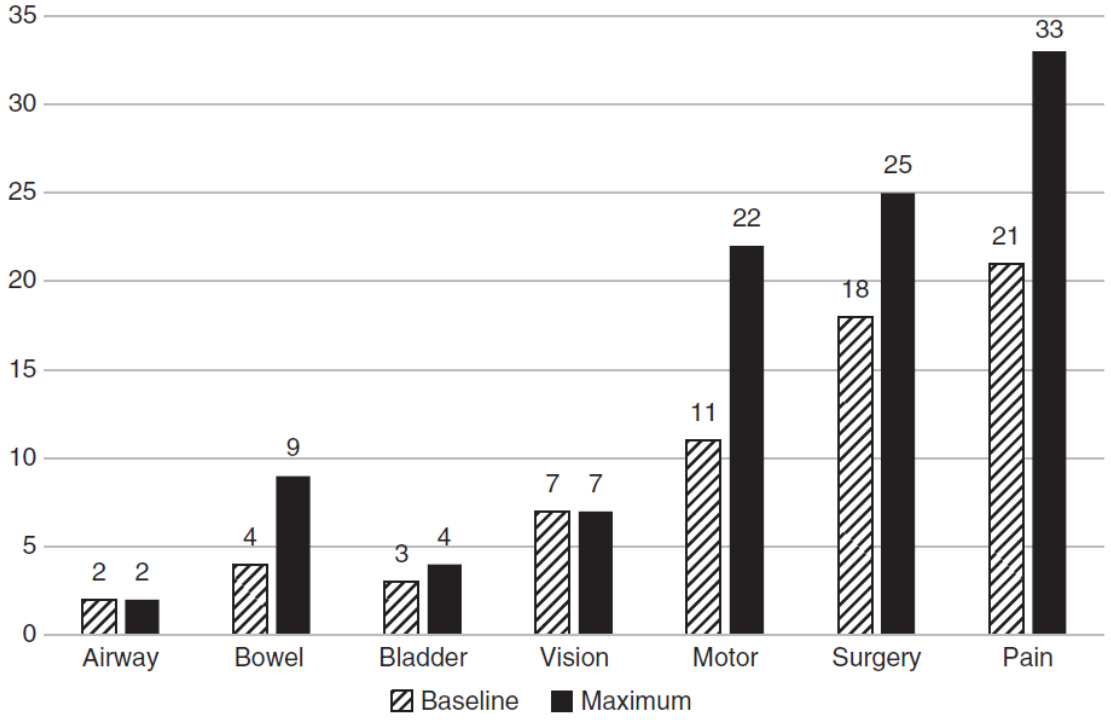
Plexiform Neurofibromas
(N=70)

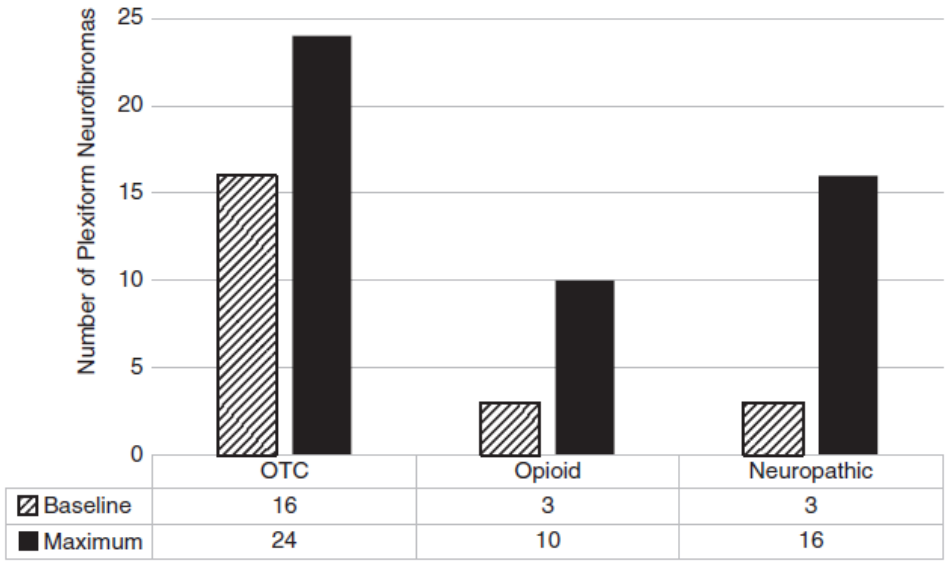


(Akshintala, 2020; Gross 2020)

NCI NF Natural History Study for PN Morbidity

- Majority of patients in NCI cohort had PN related morbidity even at baseline assessment
- Once a morbidity develops, does not generally resolve in patients with growing tumors





- Higher PN percent growth per year associated with increased need for pain medication

(Gross 2018)

When is Use of Use of External Control Design Most Meaningful?

- ☑ Not possible or ethical to run placebo control
- ☑ No available therapy for comparison
  - ☑ Absence of a standard therapy

No other agent with similar activity in NF1 PN

- ☑ Disease progression is well understood or predictable

NF1 NHx study characterized growth & morbidity

- ☑ The outcome measure is objective

Volumetric MRI analysis

- ☑ The effect of the treatment is:
  - ☑ Large/dramatic
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Response Evaluation in Neurofibromatosis & Schwannomatosis
REiNS

Jahanshahi M et al.: Therapeutic Innovation & Regulatory Science, 2021

Phase 2 Trial: Selumetinib in Children with NF1 PN

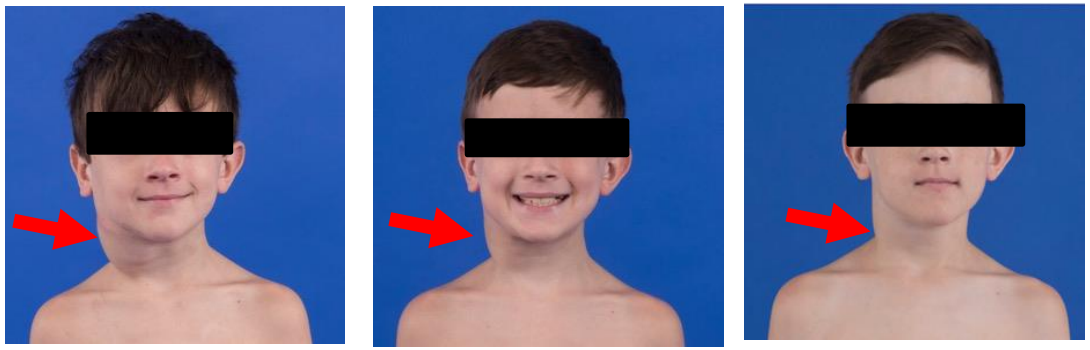
Primary objective: Overall Response Rate

Key Secondary Objectives:

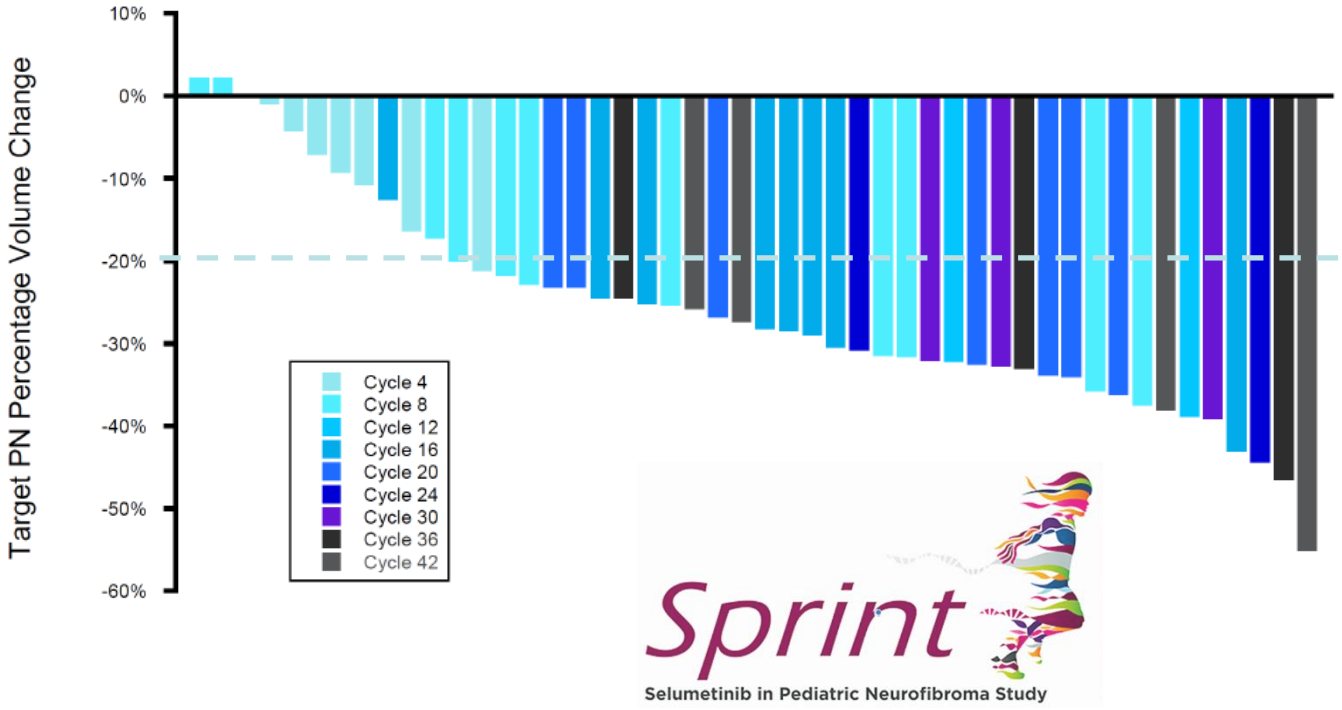
Functional and Patient Reported Outcomes

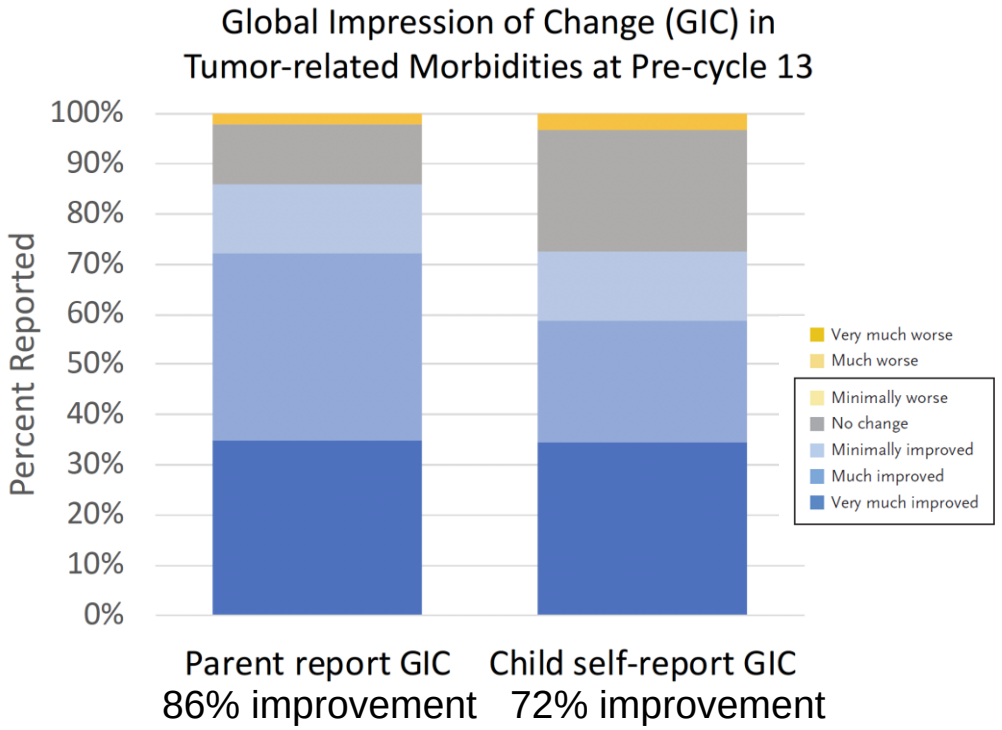
Results:

Confirmed Partial response 34/50 (68%) patients



Baseline | Pre-Cycle 13 | Pre-Cycle 37

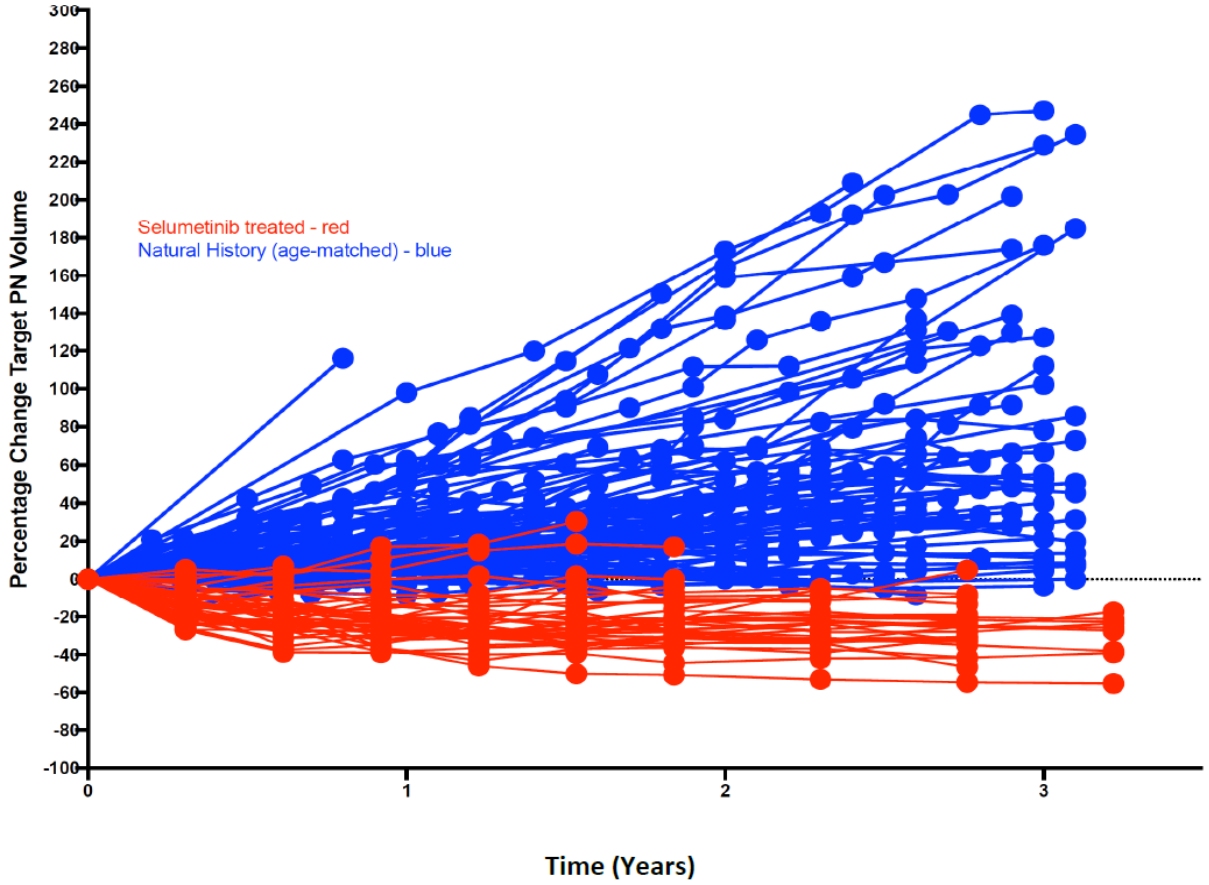


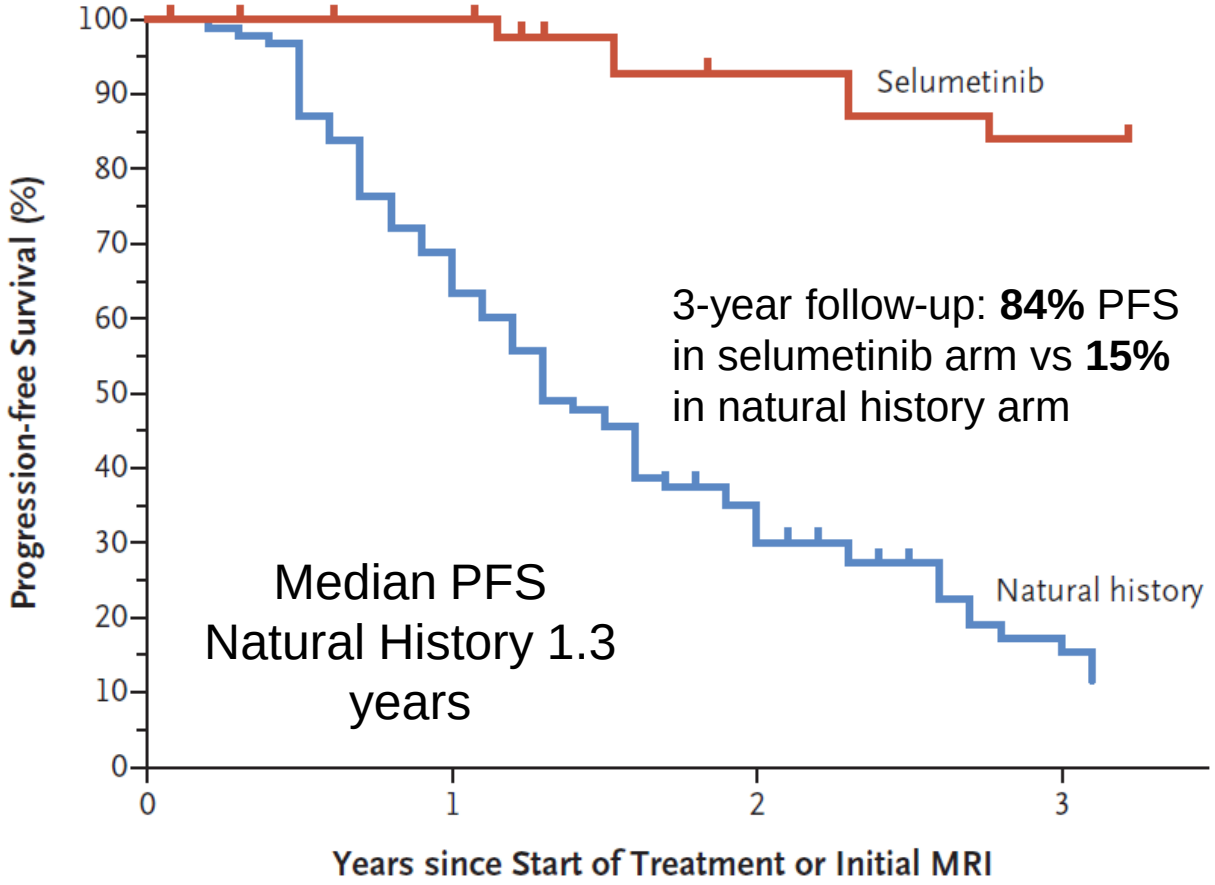


Gross AM, et al. *N Engl J Med.* 2020.

PN on Selumetinib vs Natural History

Age matched control: NCI Natural history and selumetinib





Gross AM, et al. *N Engl J Med.* 2020.

Defining Clinical Benefit in SPRINT

- Group Level Analyses:
  - Advantages:
    - Can assess for change across multiple individuals
  - Challenges:
    - Small # of patients in each subgroup (e.g. motor, airway, etc)
    - No external control cohort
- Individual Level Analyses:
  - Advantages: Allows for assessment of TOTALITY of the data
  - Challenges: Is this any better than anecdotal evidence?

SPRINT Functional Evaluations Feasibility & Interpretation

- No accepted methodologies for assessing change relative to PN-specific location
- Normative data for NF1 not available
- REiNS Recommendations for NF1 Available

	Characteristics of Eligible Subjects	# of Eligible* Subjects at Baseline, n	# completed at Baseline n (%)	# completed at preC13 n (%)
Photography/Videography	All visible PN	44	44 (100)	41 (93)
Strength Evaluation (Manual Muscle Test (MMT) using MRC scale)	Motor	33	30 (91)	27 (82)**
Range of Motion	Motor	33	31 (94)	28 (85)**
Leg Length Evaluation	Motor – Lower extremity	13	13 (100)	12 (92)
Grooved Pegboard	Motor – Upper extremity	20	18 (90)	16 (80)
6-Minute Walk Test	Motor (lower extremity), Airway	29	27 (93)	23 (79)
Polysomnography	Airway (without tracheostomy)	11	11 (100)	11 (100)
Spirometry	Airway (without tracheostomy)	11	11 (100)	11 (100)
Impulse Oscillometry	Airway (without tracheostomy)	11	10 (91)	10 (91)
Exophthalmometry	Orbital	10	6 (60)	4 (40)
Visual Acuity	Orbital	10	9 (90)	7 (70)
Bowel/Bladder Questionnaire	Bowel/Bladder	10	10 (100)	9 (90)

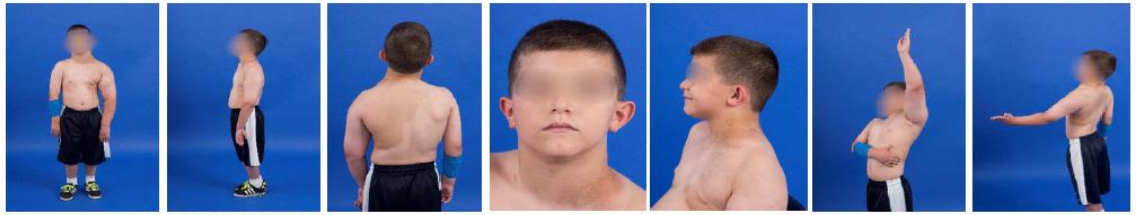
Patient Narratives & Individual Patient Reviews

- Patient Narratives:
  - 15-30 pages per patient describing:
    - Patients baseline tumor status & morbidity assessment
    - Safety assessments and adverse event reports
    - Results of all functional and patient reported outcome measures including photographs
- Individualized Patient Reviews
- Individualized Patient Reviews
  - Prepared by AZ and reviewed at each site by study team
  - Site study team made assessment about whether patient received clinical benefit from treatment

Individual Patient Review Example

DISFIGUREMENT

Baseline



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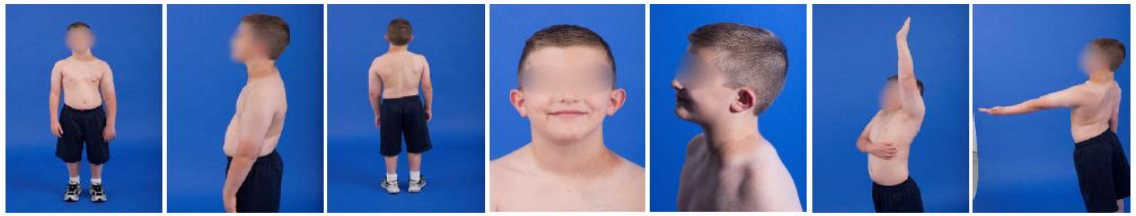
Pre-cycle 13



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MOTOR

Parameter	Range of motion in degrees (sum in affected quadrant)					
	Baseline	Pre-cycle 5	Pre-cycle 9	Pre-cycle 13	Pre-cycle 25	Pre-cycle 37
Assessment date (study day)	17AUG2015 (-7)	16DEC2015 (115)	05APR2016 (226)	20JUL2016 (332)	12JUL2017 (689)	27JUN2018 (1039)
Left Upper	649	958	985	977	1000	969
*number of joints assessed differs from baseline; HIGHER values represent BETTER status						

Parameter	Strength evaluation (average in affected quadrant)					
	Baseline	Pre-cycle 5	Pre-cycle 9	Pre-cycle 13	Pre-cycle 25	Pre-cycle 37
Assessment date (study day)	17AUG2015 (-7)	16DEC2015 (115)	05APR2016 (226)	20JUL2016 (332)	12JUL2017 (689)	27JUN2018 (1039)
Left Upper	4.7	4.88	4.91	5	5	5
HIGHER values represent BETTER status						

Pain domain	Pain Interference Index - self-report (total mean score)						
	Baseline	Pre-cycle 3	Pre-cycle 5	Pre-cycle 9	Pre-cycle 13	Pre-cycle 25	Pre-cycle 37
Pain interference - total mean score	2	3	2.17	0.33	1	0	0
Lower mean scores represent BETTER status; 0 = not at all; 6 = completely							

Pain domain	Pain Interference Index - parent report (total mean score)						
	Baseline	Pre-cycle 3	Pre-cycle 5	Pre-cycle 9	Pre-cycle 13	Pre-cycle 25	Pre-cycle 37
Assessment date (study day)	18AUG2015 (-6)	19OCT2015 (57)	16DEC2015 (115)	01APR2016 (222)	19JUL2016 (331)	10JUL2017 (687)	25JUN2018 (1037)
Pain interference - total mean score	3.67	1.83	1.33	0.33	0.83	0.67	0.33
Lower mean scores represent BETTER status; 0 = not at all; 6 = completely							

Start day[a]/ Stop day[a] (date)	Preferred term / CTCAE term / AE description[b]	CTC grade	Dose at time of AE	Outcome	Reporter Causality[c]	Action
5/50 28AUG2015/ 12OCT2015	Stomatitis/ Mucositis oral/ Lt lower lip	1	25 mg/m² BID	RECOVERED/ RESOLVED	Yes	DOSE NOT CHANGED
8/8 31AUG2015/ 31AUG2015	Abdominal pain/ Abdominal pain	1	25 mg/m² BID	RECOVERED/ RESOLVED	Yes	DOSE NOT CHANGED
8/8 31AUG2015/ 31AUG2015	Constipation/ Constipation	1	25 mg/m² BID	RECOVERED/ RESOLVED	Yes	DOSE NOT CHANGED
8/8 31AUG2015/ 31AUG2015	Diarrhoea/ Diarrhea	1	25 mg/m² BID	RECOVERED/ RESOLVED	Yes	DOSE NOT CHANGED
20 12SEP2015/	Nausea/ Nausea	1	25 mg/m² BID	UNKNOWN	Yes	DRUG INTERRUPTED

When is Use of Use of External Control Design Most Meaningful?

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Phase 2 study showed change in natural history of tumor growth AND clinical outcome measures

Response Evaluation in Neurofibromatosis & Schwannomatosis: REiNS

Jahanshahi M et al.: Therapeutic Innovation & Regulatory Science, 2021

Regulatory Agency Approval of Selumetinib (Koselugo™)

April 10, 2020

"The Food and Drug Administration (FDA) approved selumetinib for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)."

April 22, 2021:

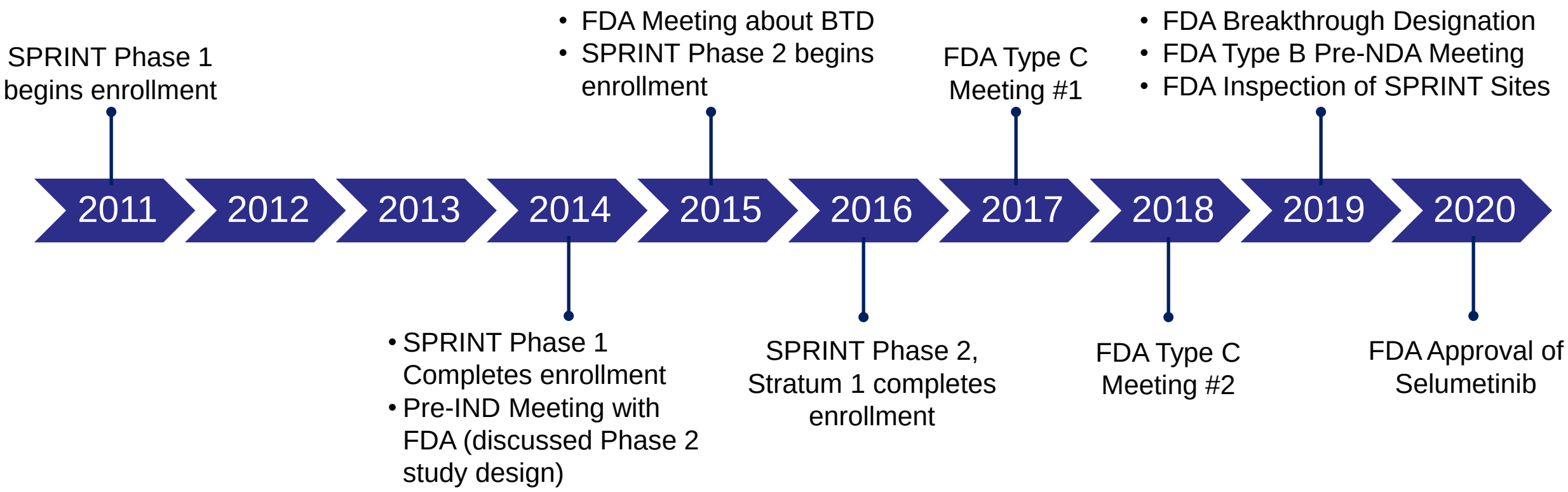
"Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional1 marketing authorisation for the medicinal product Koselugo2, intended for the treatment of paediatric patients with neurofibromatosis type 1 (NF1) plexiform neurofibromas (PN)."

FDA Prescribing Information; FDA Press Release, April 10, 2020.
https://www.ema.europa.eu/en/medicines/human/summaries-opinion/koselugo (April 22, 2021)

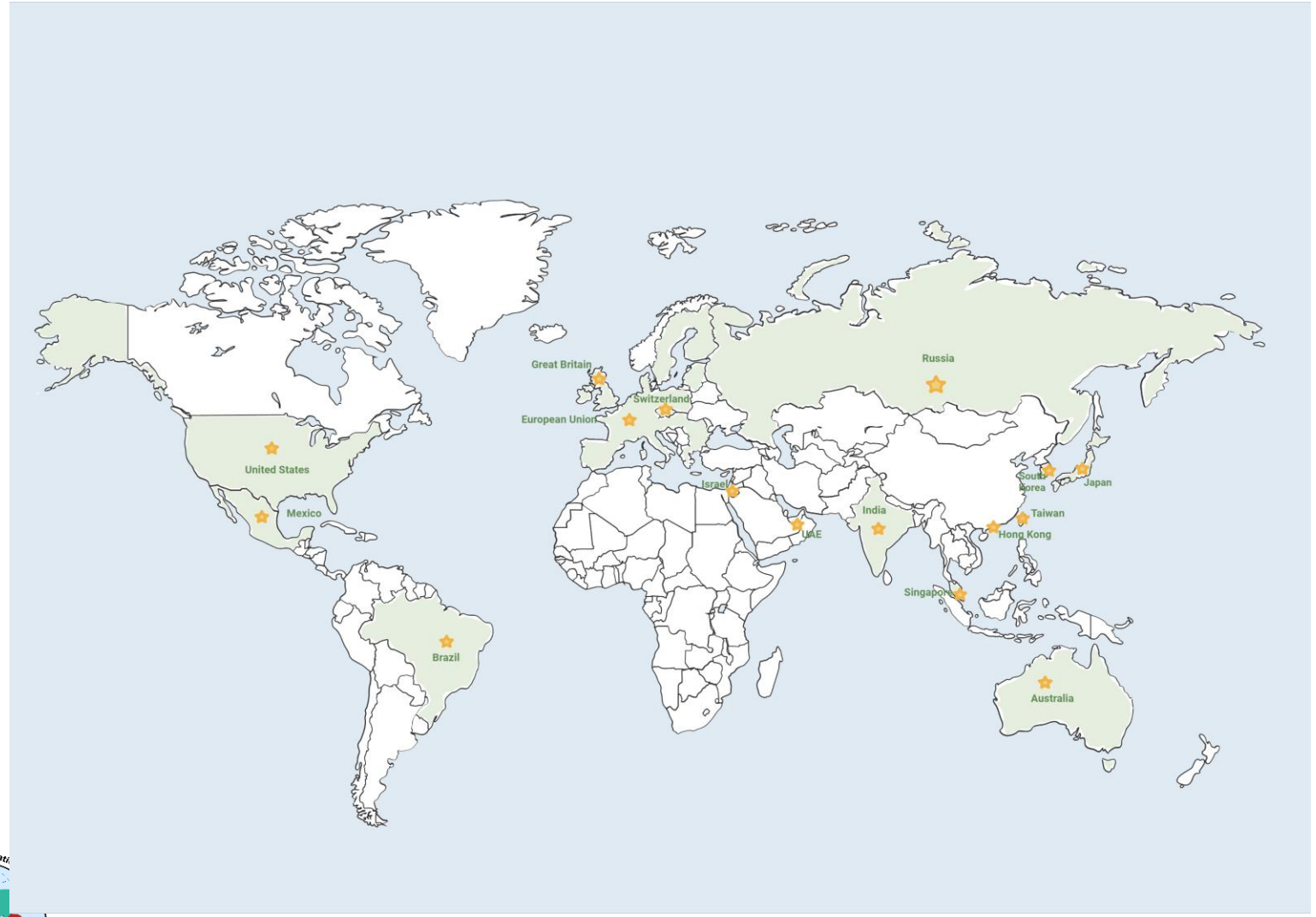
Logistical Challenges with FDA Submission

- NCI internal databases not configured for registration studies
  - Unable to lock the study database
  - Used 2 separate databases (one for safety data, one for efficacy/functional/PRO data)
- Monitoring/auditing happened after many patients were already enrolled on trial
- Study sponsor was not a pharmaceutical company – not used to registration trials

Timeline of SPRINT and FDA Interactions



Regulatory Agency Approval of Selumetinib (Koselugo™) - October 2022



1. USA
2. Brazil
3. United Arab Emirates
4. South Korea
5. European Union (27 member countries)
6. Israel
7. Singapore
8. Great Britain
9. India
10. Mexico
11. Russia
12. Australia
13. Taiwan
14. Hong Kong
15. Switzerland
16. Japan

Key Conclusions & Lessons Learned

- Importance of consistency of methodologies between the trial and the natural history cohort
- Databases matter! (and so does early monitoring)
- “Totality of the Data”
- Feasibility depends on the impact of the treatment
  - Similarity of eligibility criteria
  - Temporal association of effect
  - Degree of effect