NORD
National Organization for Rare Disorders

Rare Disease Scientific Symposium

Innovative Clinical Trial Designs

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(Moderator)

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Rare Disease Scientific Symposium

Innovative Clinical Trials: Platform Trials for Diverse *NF1* and *NF2* Driven Tumor Manifestations

Jaishri Blakeley, MD

Johns Hopkins University

Director, The Johns Hopkins Comprehensive Neurofibromatosis Program

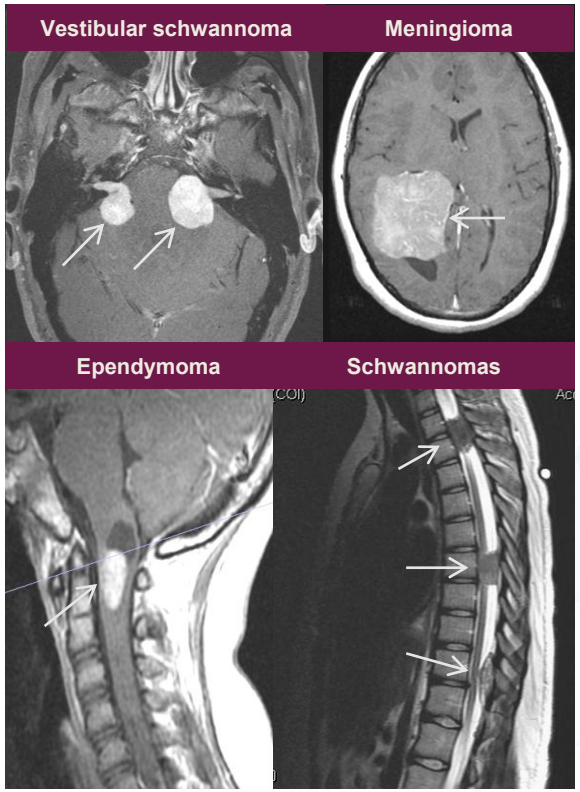
Executive Director, The Neurofibromatosis Acceleration Program

The Neurofibromatoses

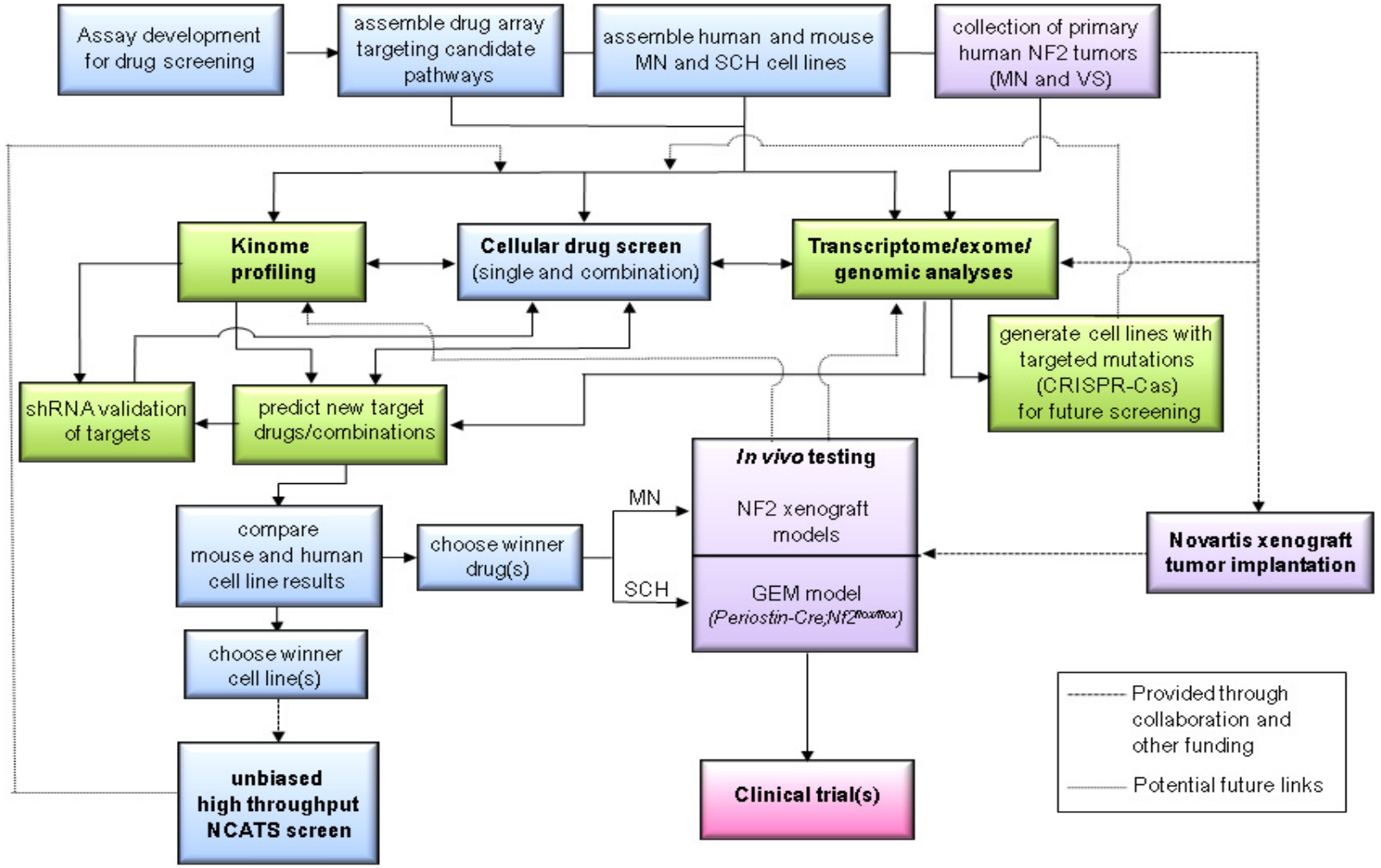
Manifestation	NF1 (1/2600)	NF2-Schwannomatosis (~1/30,000)	Non-NF2 Schwannomatosis (SMARCB1, LZTR1) (>1/500,000)
Café-au-lait spots	X	X	
Freckling	X		
Dermal NF	X		
Plexiform NF	X		
Schwannoma		X	X (not bilateral vestibular, LZTR1)
Glioma	X (optic pathway)	X (ependymoma)	
Meningioma		X	X (SMARCB1)

NF2-Schwannomatosis and INTUITT

NF2-related schwannomatosis: CTF Synodos



1/30,000 prevalence



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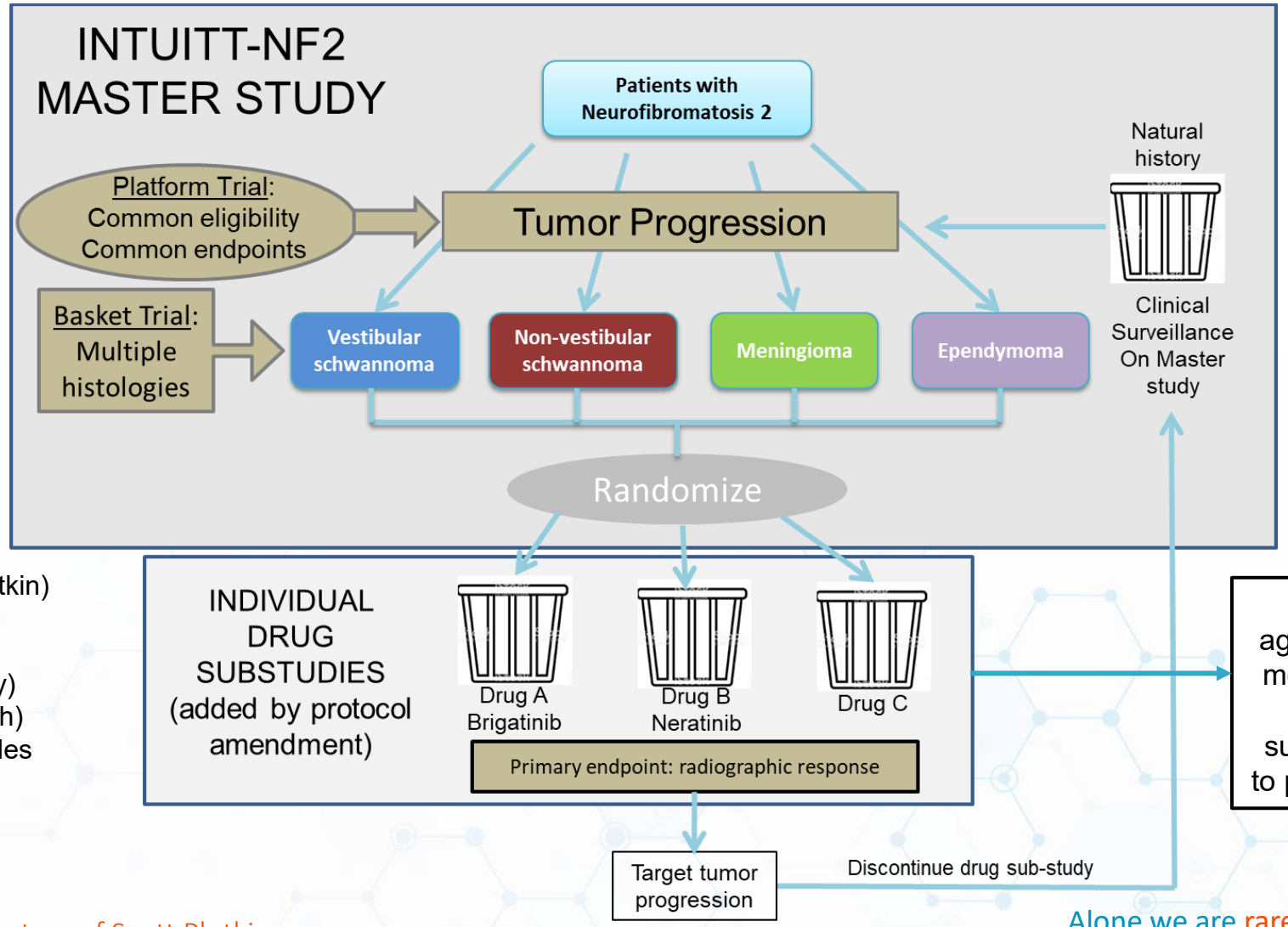
Colla

INTUITT-NF2: Perpetual Platform-Basket Trial for *NF2*-SWN



Participating sites

- Johns Hopkins (Jaishri Blakeley)
- Mass General Hospital (Scott Plotkin)
- Mayo Clinic (Dusica Babovic-Vuksanovic)
- New York University (Kaleb Yohay)
- University of Miami (Christine Dinh)
- University of California, Los Angeles (Leia Nghiemphu)

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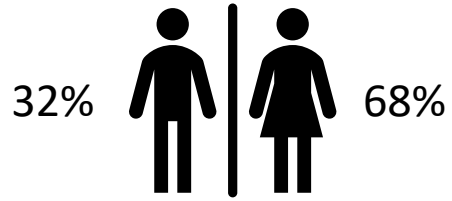
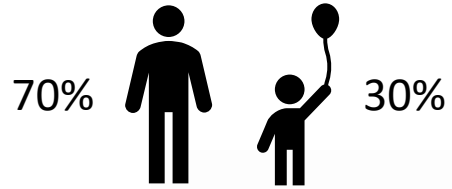
Slide Courtesy of Scott Plotkin

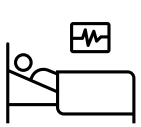
Brigatinib Sub-study: Key Participant and Tumor Characteristics





KPS/
LPS

100: 2
90:16
80: 17
70: 4

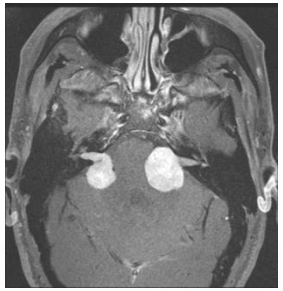


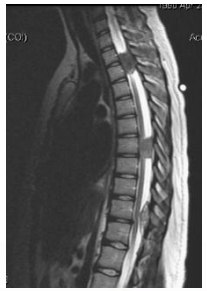
93%

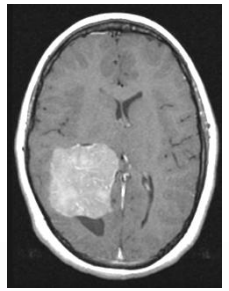
23%

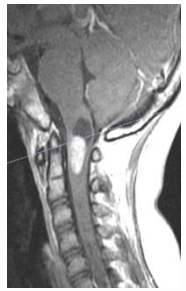
58%

40 participants, median age 26 (12-54)
165 tumors (40 target, 125 non-target)









	VS	Non-VS	Meningioma	Ependymoma
Target	10	8	20	2
Non-target	37	48	37	3
Total	**47 (28%)**	**56 (37%)**	**57 (38%)**	**5 (3%)**

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Plotkin et al, NEJM, 2024

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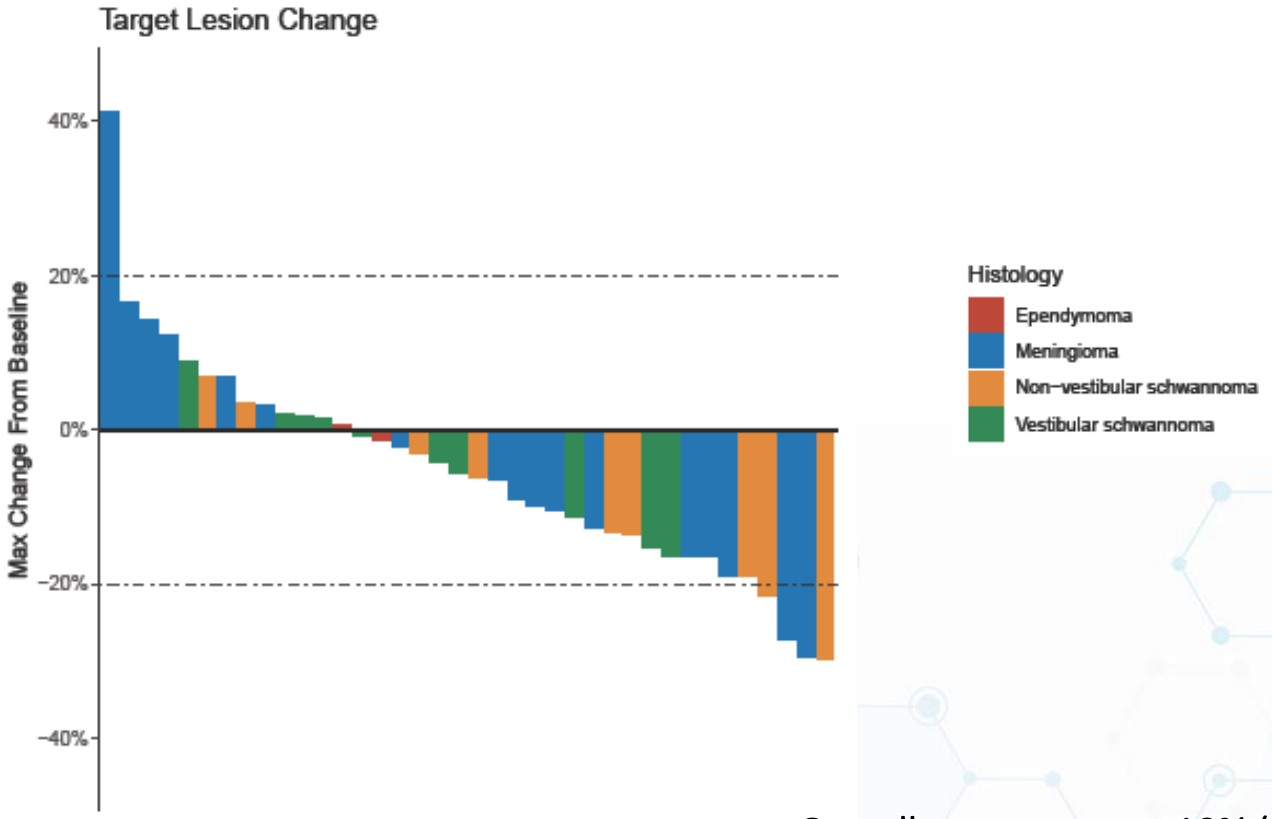
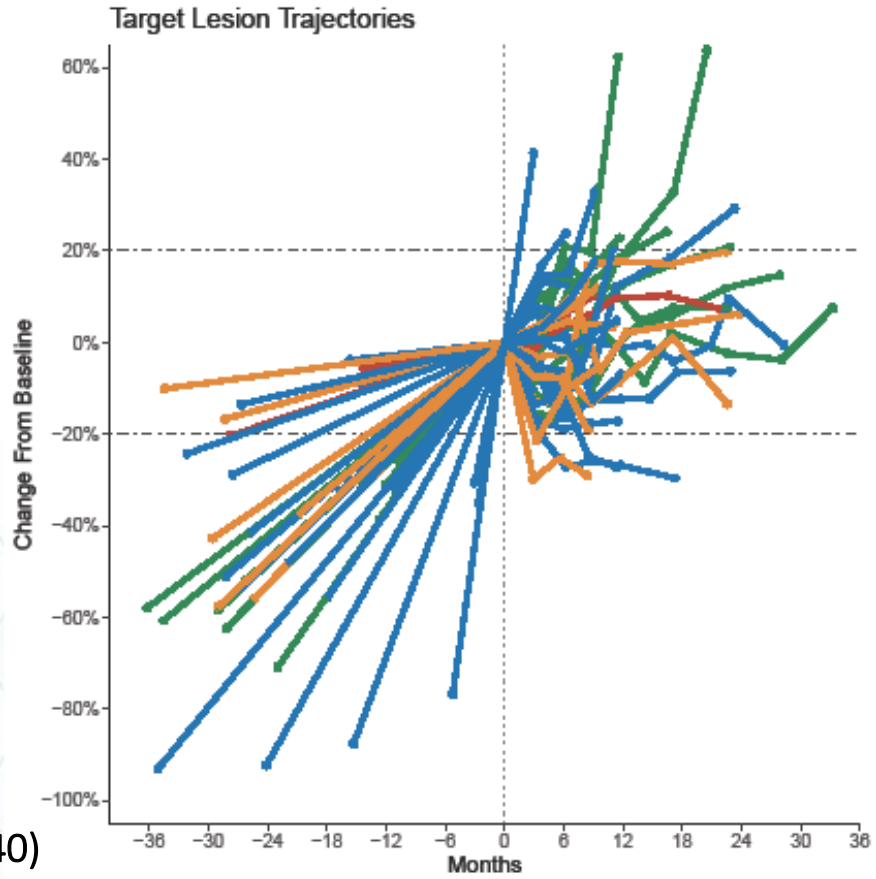
Clinical Activity of Brigatinib in a Range of NF2-related Tumors Based on MRI Tumor Volume Reduction





Overall response rate: 10% (4/40)

- Non-vestibular schwannoma: 22% (2/9)
- Meningioma: 11% (2/19)
- Vestibular schwannoma: 0% (0/10)
- Ependymoma: 0% (0/2)

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Plotkin et al, NEJM, 2024

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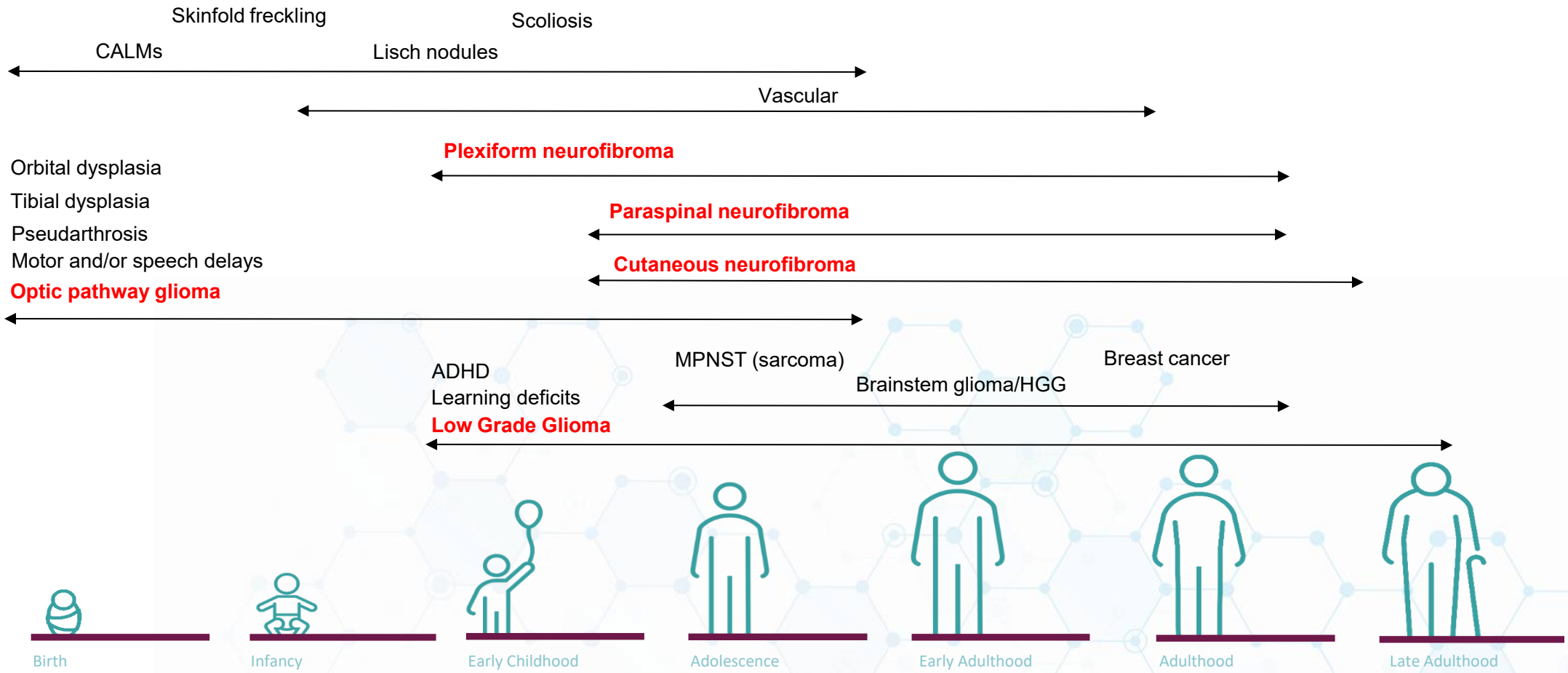
Neurofibromatosis Type 1 and EU PEARL

Manifestations of NF1 Over a Lifetime



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EU PEARL: NF1

- A multicentre, open-label, Phase 1 / Phase 2 proof-of-concept, platform basket study to investigate single-arm study interventions against historical response rates in participants with manifestations of neurofibromatosis type 1 (NF1) including **cutaneous or plexiform neurofibroma; optic pathway glioma or low-grade glioma.**
- Across EU NF specialty care centers; in collaboration with US CDMRP NF Clinical Trials Consortium
- Master protocol + Arm Specific Appendices design EMA approved:
  - Two potential purposes: signal finding versus registration enabling via uniform endpoints and definition of response independent of intervention, specific to manifestation.
  - **Master protocol defines**: Shared design, endpoints, schedules and governance.
  - **Arm-Specific Appendices:** Therapeutic specific details re: dosing, timeline and correlative endpoints.

EU-PEARL
EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

imi innovative medicines initiative

CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH | EUROPE

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Thank You

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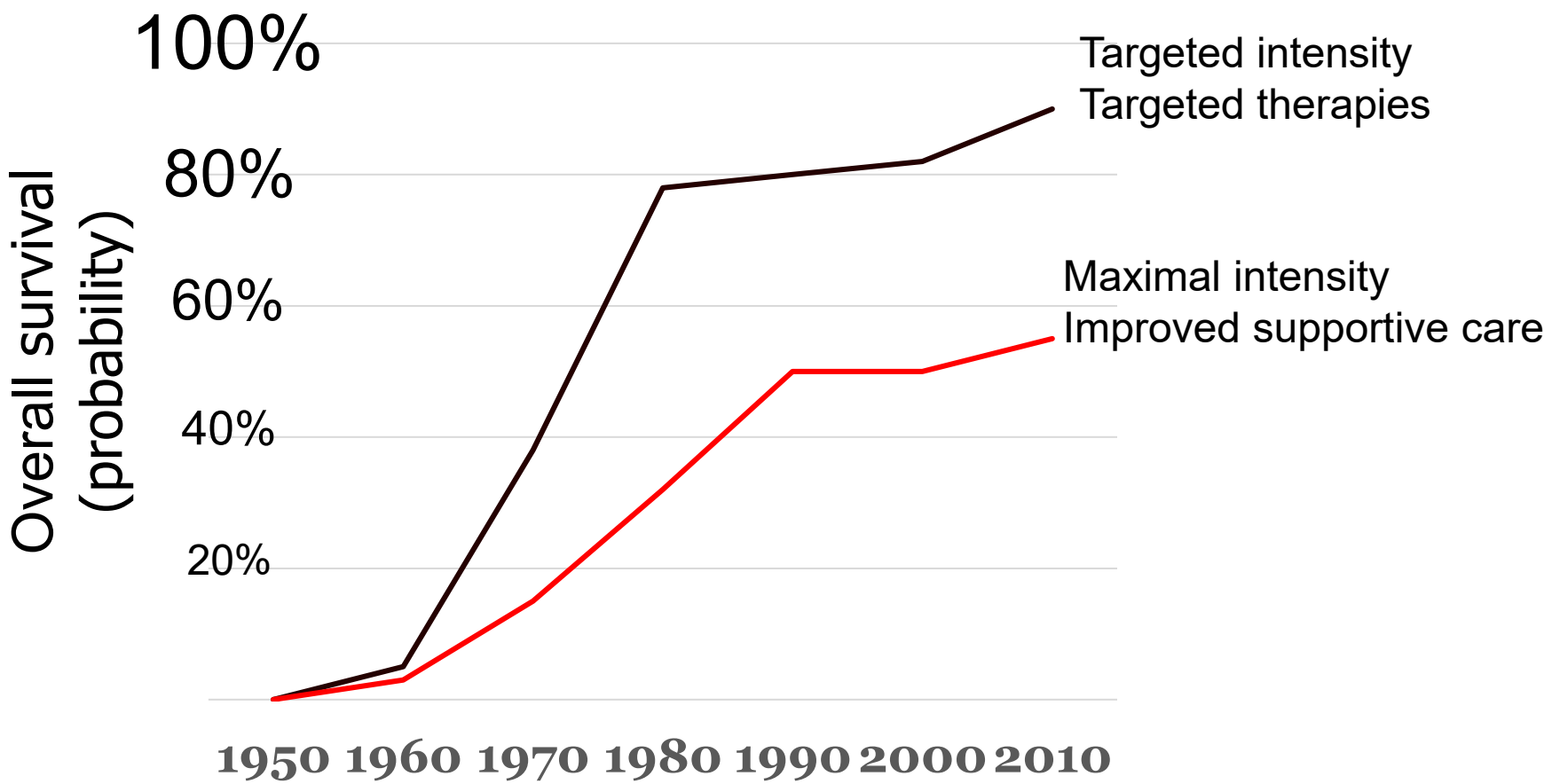
PedAL Global Master Clinical Trial

Gwen Nichols, MD
Chief Medical Officer
Blood Cancer United

We Must Do Better

Outcomes for newly diagnosed leukemia in children



—Acute Lymphoblastic Leukemia

—Acute Myeloid Leukemia

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Childhood AML

Most aggressive leukemia in children

- Leading cause of death from leukemia
- Extremely high short- and long-term toxicity/mortality

Distinct Biology – Different from adult

- Most drugs developed in adults – many with limited utility in children
- Targets seen in older adults not always seen in children, and vice versa

Novel Targets

- Chemotherapy hasn't changed since the '70s and causes severe long-term toxicity
- Targetable mutations are rare in children
- Targeted therapies DO WORK in children
- Discovery of actionable targets a must for developing curative therapies

The Challenge We Faced

- Pediatric leukemia is rare and there are many biologic subsets and targets
- The biology of pediatric leukemia is distinct from leukemia in adults, yet new drugs are mostly developed in adults
- A comprehensive, global effort for trials is necessary to be successful
- Despite regulatory incentives, only seven drugs were approved for pediatric cancers (US) in the past 10 years, while more than 100 new drugs were approved for adults
- Essential data existed within individual international consortia and pediatric hospitals; data sharing was a challenge

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A solution: PedAL

- **SCREEN** – Via the PedAL screening trial, screen all children with relapsed leukemia for precision-medicine trial eligibility based on clinical data, leukemia cell surface markers and next-generation genomic sequencing
- **DISCOVERY** – sample acquisition for correlative biology, target discovery, and biobanking
- **ACCESS** – Partner with pharma, NCI and FDA/EMA, and European study groups to support drug development platform that achieves regulatory objectives to ensure that children have early access to effective therapies
- **DATA** - Improve data collection to inform changes in primary outcome measures and toxicity definitions that are essential for approval of new therapies for children with leukemia
- **Blood Cancer United is the trial sponsor and works collaboratively with academia and pharma partners to collect regulatory quality data**

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PedAL Progress

screening trial

182 sites

611 patients

4 countries

venetoclax subtrial

88 sites

102 patients

20 countries

ziftomenib subtrial

20 sites

24 patients

7 countries

3rd trial in contract

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abbvie

KURA ONCOLOGY

Where we go next: Real World Evidence Project

- Time and cost for trials remains high.
- Large randomized trials are not feasible in targeted subsets of patients
- Having evidence for regulators of target efficacy and outcomes with standard of care could decrease the time and cost of trials in rare diseases

Blood Cancer United is partnering with Tempus AI to create a RWD repository in pediatric AML using parental/patient consent.

RWE can be generated from this database for proposed trials. This will be freely available for investigators and available at cost to pharma.

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Thank you

FOR CHILDHOOD CANCER RESEARCH
Rally!
FOUNDATION

LEUKEMIA & LYMPHOMA SOCIETY® is now
Blood Cancer United