Pediatric Oncology Drug Development: A Time of and for Change

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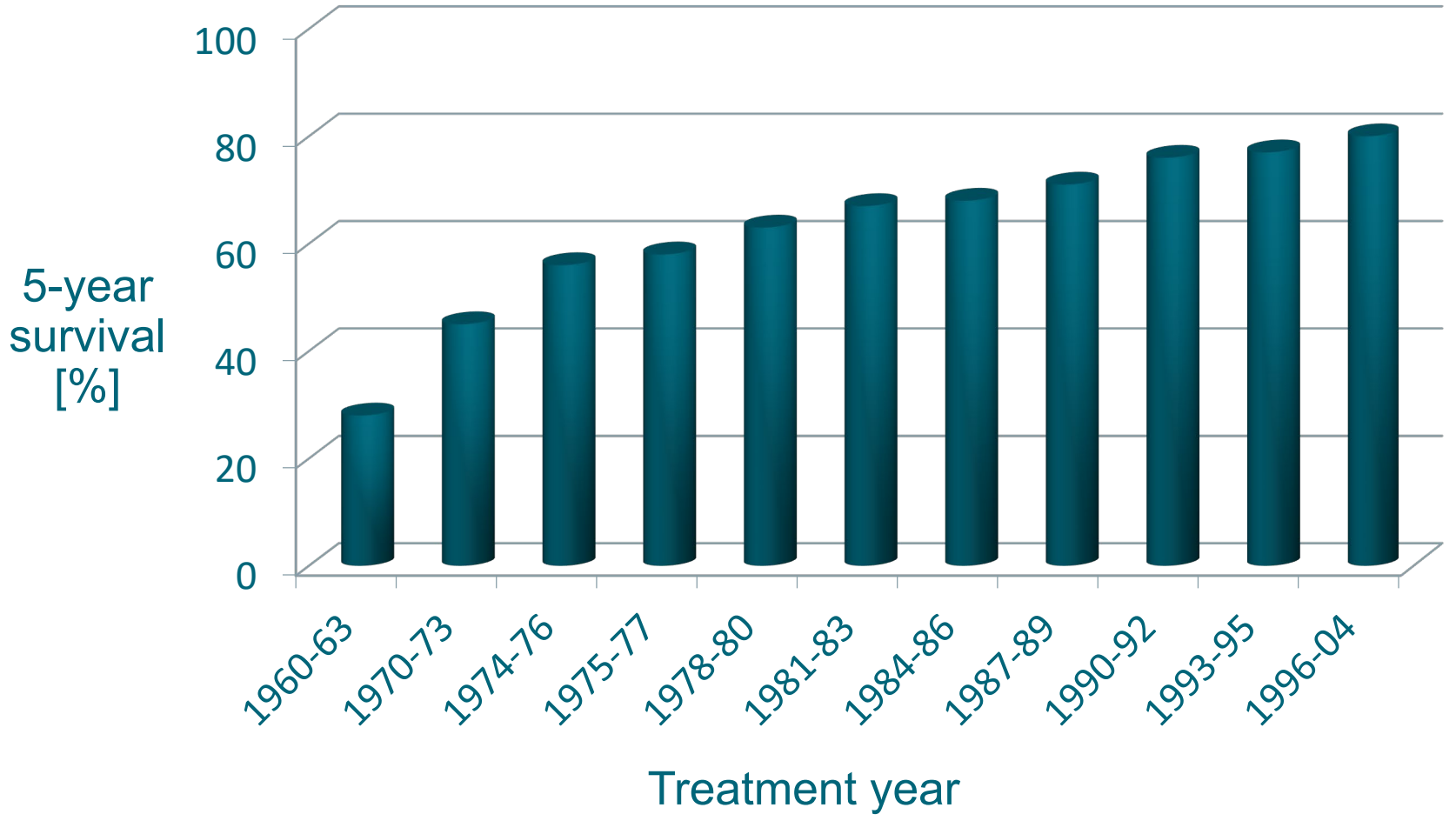
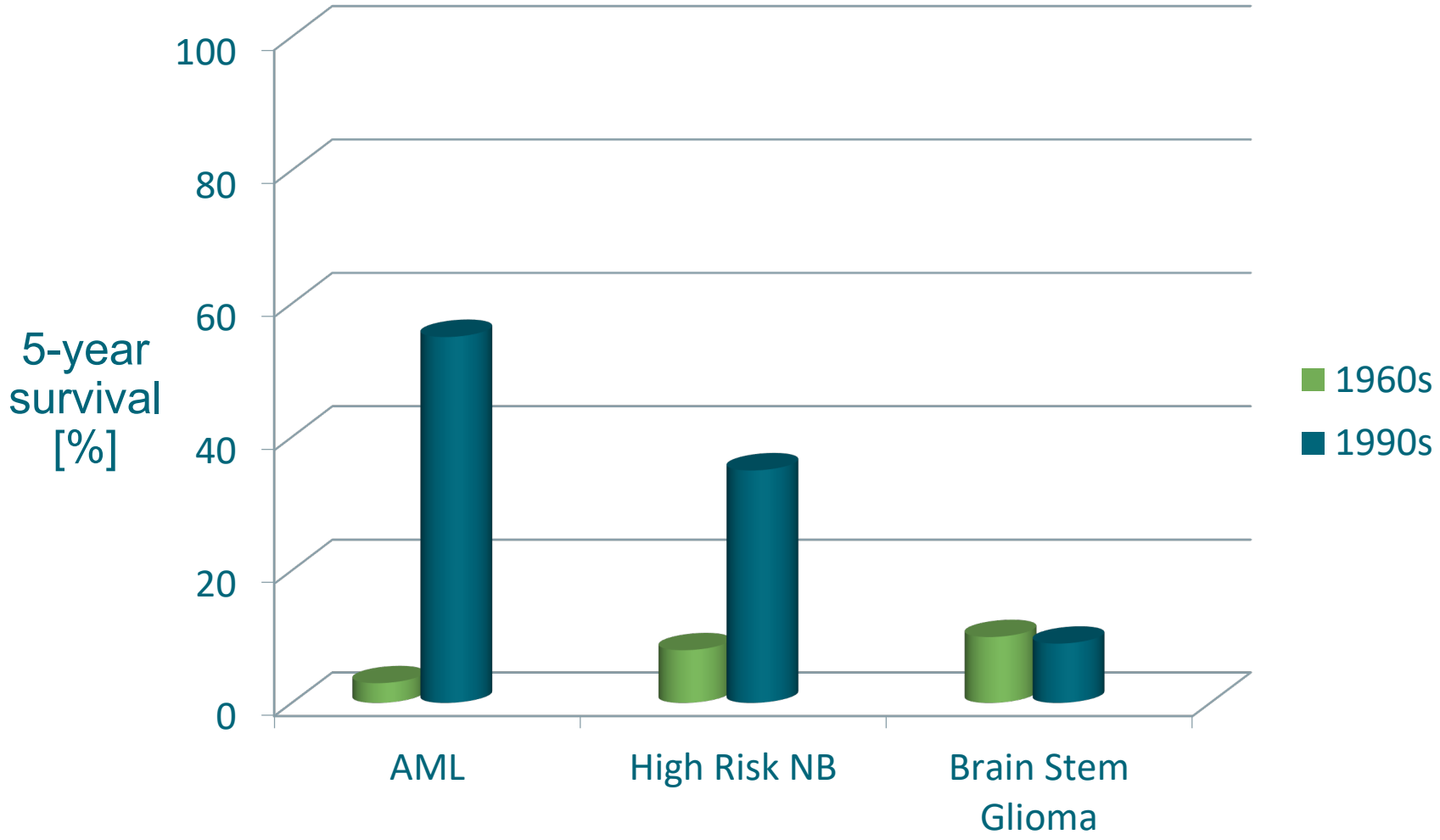
The Challenge

- Improve cure rates
- Diminish acute toxicity
- Minimize risk for late effects

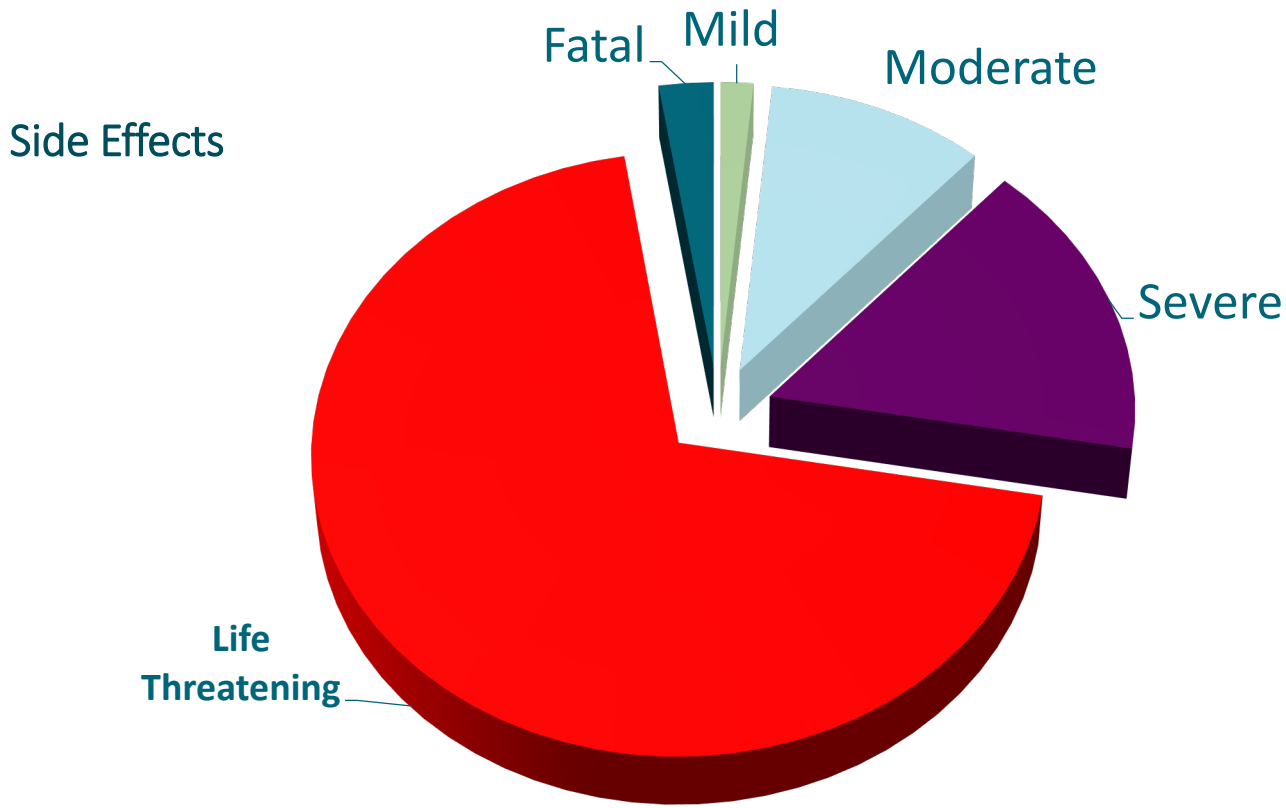
Cure Rates


5-year survival [%]
100
80
60
40
20
0
1960-63
1970-73
1974-76
1975-77
1978-80
1981-83
1984-86
1987-89
1990-92
1993-95
1996-04
Treatment year

Curing Cancer



Curing Cancer



Curing Cancer

Late Effects

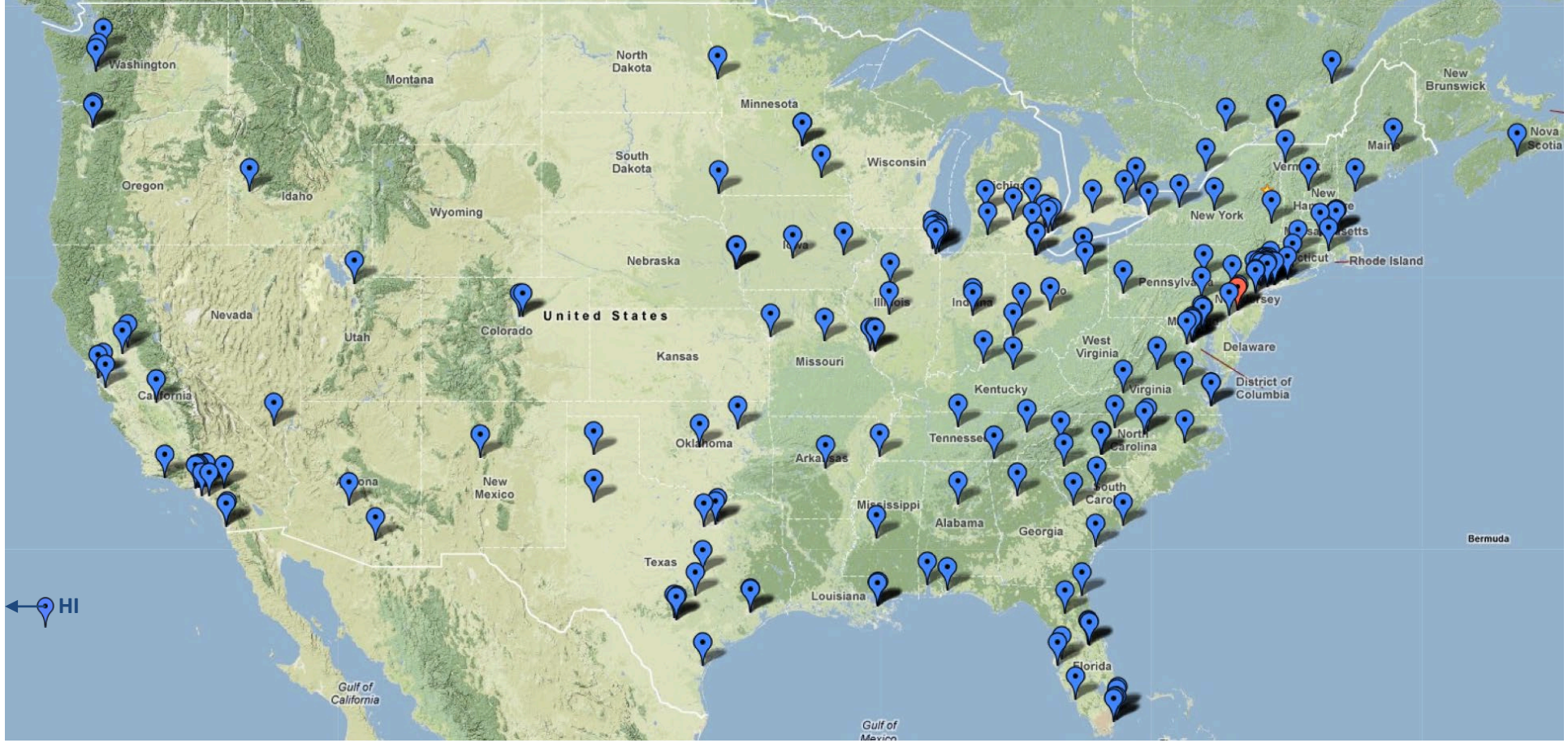
PEDIATRIC CANCER U.S. Incidence (S.E.E.R. Program)

- Adult:Pediatric
  - 125-150:1

- *Rate 1 in 7,000 in children 0-15 years*
  - 9,000 cases/ yr — Ages 0-15 y
  - 3,700 cases/ yr — Ages 15-19 y
  - 1,500cases/ yr — Ages 19-21 y
  - 14,200
- Cancer Deaths
  - 2,500-2,800/yr

Realities of Pediatric Cancer Research

- Relatively low incidence: study population
- Sub-classification and risk groups
- Mandates **multi-center** and **multi-disciplinary** clinical trials
- Improved outcome, accrual rates, integration of biology - evidence of success of NCI Cooperative Group Program



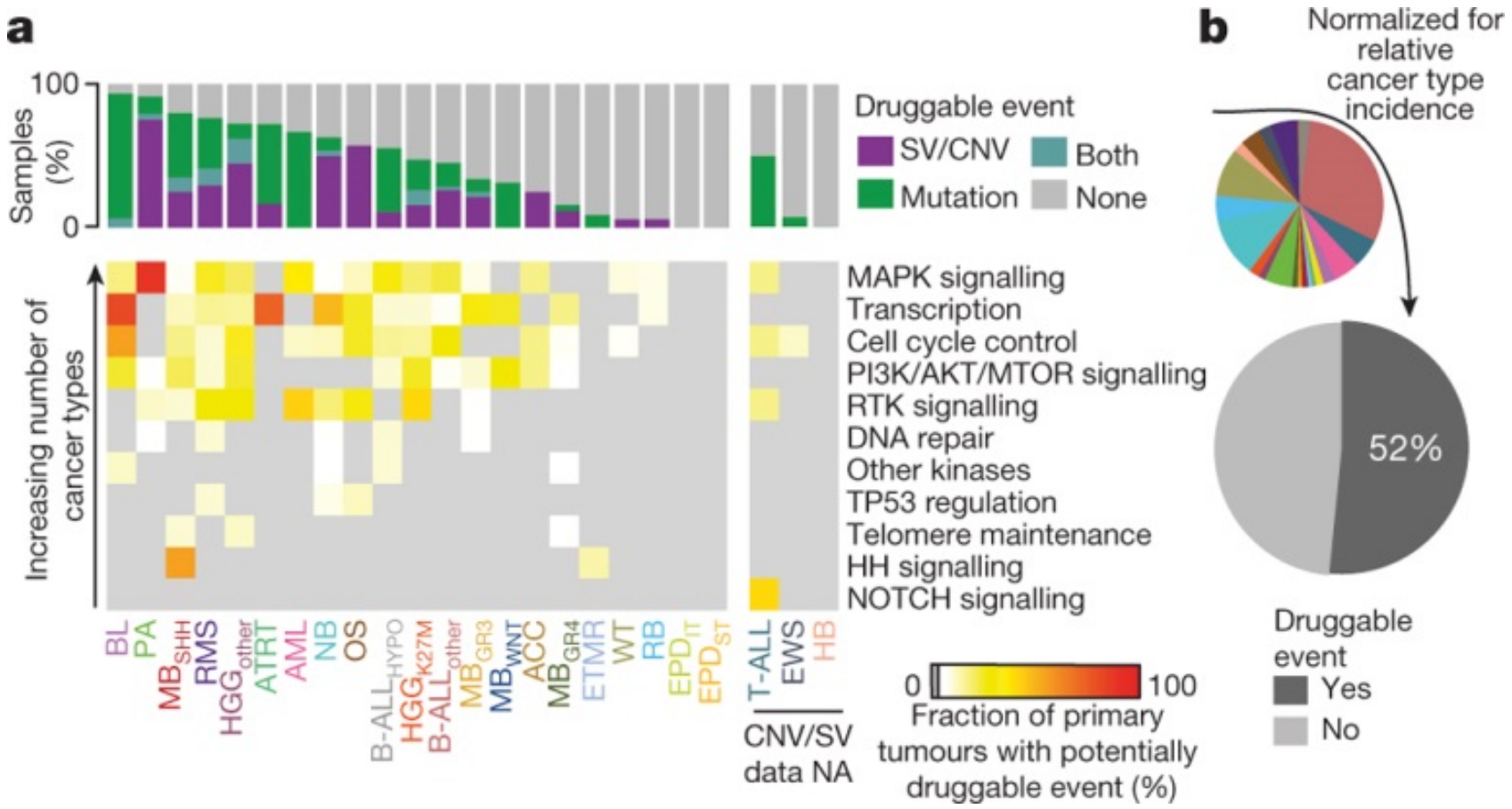
- Children's Oncology Group
  - ~ 200 research sites throughout United States
  - Clinical trials opportunities for ~ 90% of children diagnosed with cancer in the US

Children's Oncology Group

Evolving and Changing Landscape of Cancer Drug Development

- Result of expanded understanding of the genetic epidemiology and molecular etiology of cancer
- Genomic/proteomic profiling of human cancers and identification of highly specific targeted agents
- Tissue/histology agnostic drug development
- Large treatment effects observed in small subsets of patients; seamless, adaptive study designs leading to drug approvals in defined cohorts
- **Precision Cancer Medicine**
- Transformative: NSCLC, Breast, Melanoma, AML, and rare cancers
- Target vulnerabilities extend to pediatric cancers.

Potentially Druggable Alterations



Gröbner SN et al. Nature. 2018 Mar 15;555(7696):321-327.

Examples of Pediatric Precision Oncology Trials

Trial type	Examples of precision trials	Sponsor	ClinicalTrials ID
Basket in relapsed/refractory cancers across multiple diagnoses	NCI–COG Pediatric MATCH AcSé-ESMART	COG/NCI Gustave Roussy	NCT03155620 NCT02813135
Disease-specific umbrella in patients with progressive disease	Ruxolitinib or Dasatinib with Chemotherapy in Ph-Like ALL NEPENTHE (Neuroblastoma)	MD Anderson CHOP	NCT02420717 NCT02780128
Single-agent targeted therapy in advanced cancers	Larotrectinib in NTRK Fusion Positive Tumors EZH2 Inhibitor Tazemetostat in INI-1 Negative tumors Crizotinib for Tumors with an ALK, MET or ROS1 alteration LDK378 (Ceritinib) in ALK-activated Pediatric Tumors Dabrafenib with Trametinib for BRAF V600 Positive Tumors Afatinib in Pediatric Tumors with ErbB Pathway Deregulation	LOXO Oncology Epizyme UNICANCER Novartis Novartis Boehringer Ingelheim	NCT02637687 NCT02601937 NCT02034981 NCT01742286 NCT02684058 NCT02372006
Disease-specific trials in newly diagnosed patients	Total Therapy XVII JAK/STAT Mutations in ALL and Lymphoma Addition of Dasatinib for ALL with TKI-targetable Fusions Combination Therapy Plus Dasatinib for Ph-Like B-ALL Clinical and Molecular Risk-Directed Therapy (Medulloblastoma) BIOMEDE (DIPG)	St. Jude DFCI COG/NCI St. Jude Gustave Roussy	NCT03117751 NCT03020030 NCT02883049 NCT01878617 NCT02233049

ALL, acute lymphoblastic leukemia; AcSé-ESMART, Secured Access Program of the French National Cancer Institute (INCa); COG, Children's Oncology Group; ESMART, European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors in Children; MATCH, Molecular Analysis for Therapy Choice; NCI, National Cancer Institute; NEPENTHE, Next Generation Personalized Neuroblastoma Therapy; Ph-like, Philadelphia chromosome-like.

Precision medicine in pediatric oncology.
Forrest, Suzanne; Geoerger, Birgit; Janeway, Katherine
Current Opinion in Pediatrics. 30(1):17-24, February 2018.

Laroterctinib: FDA Approved in Pediatrics

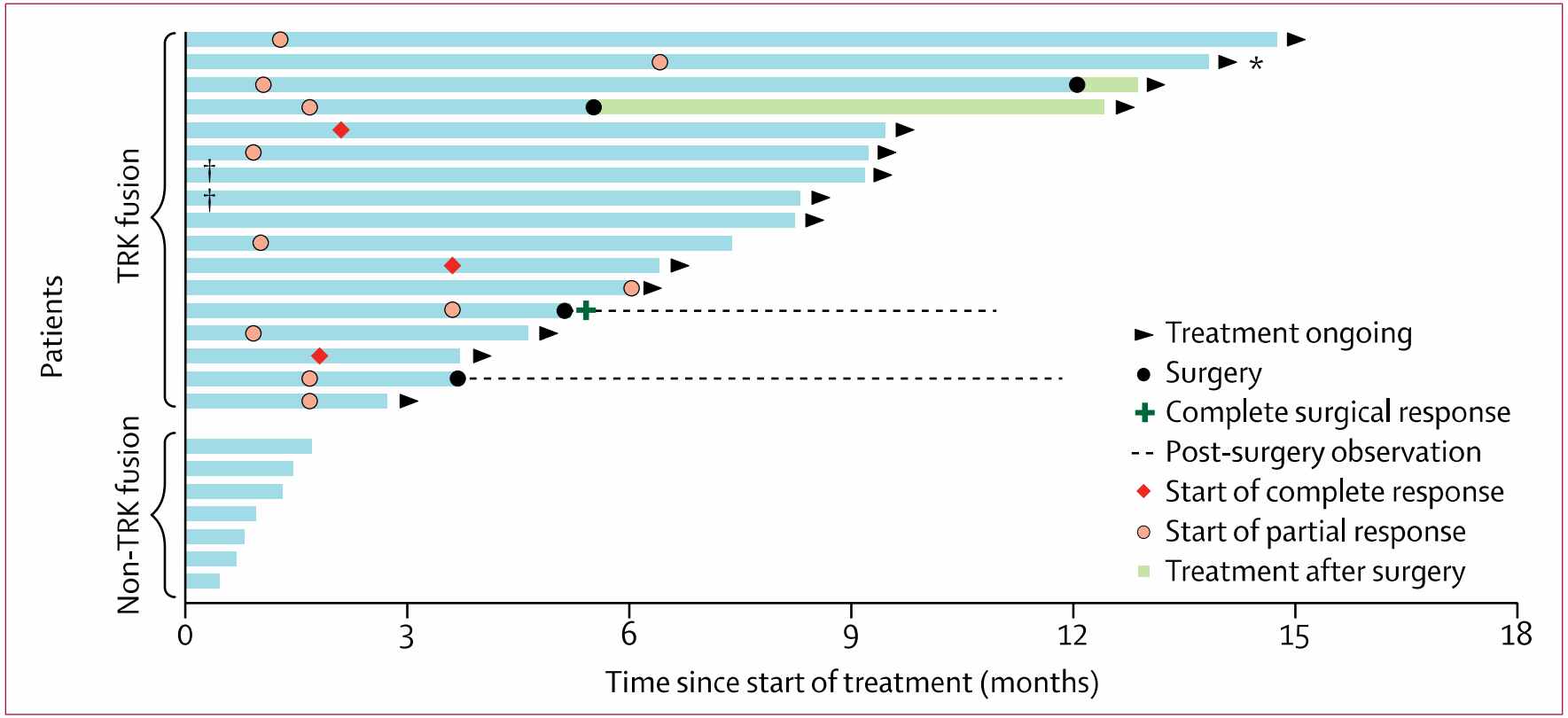
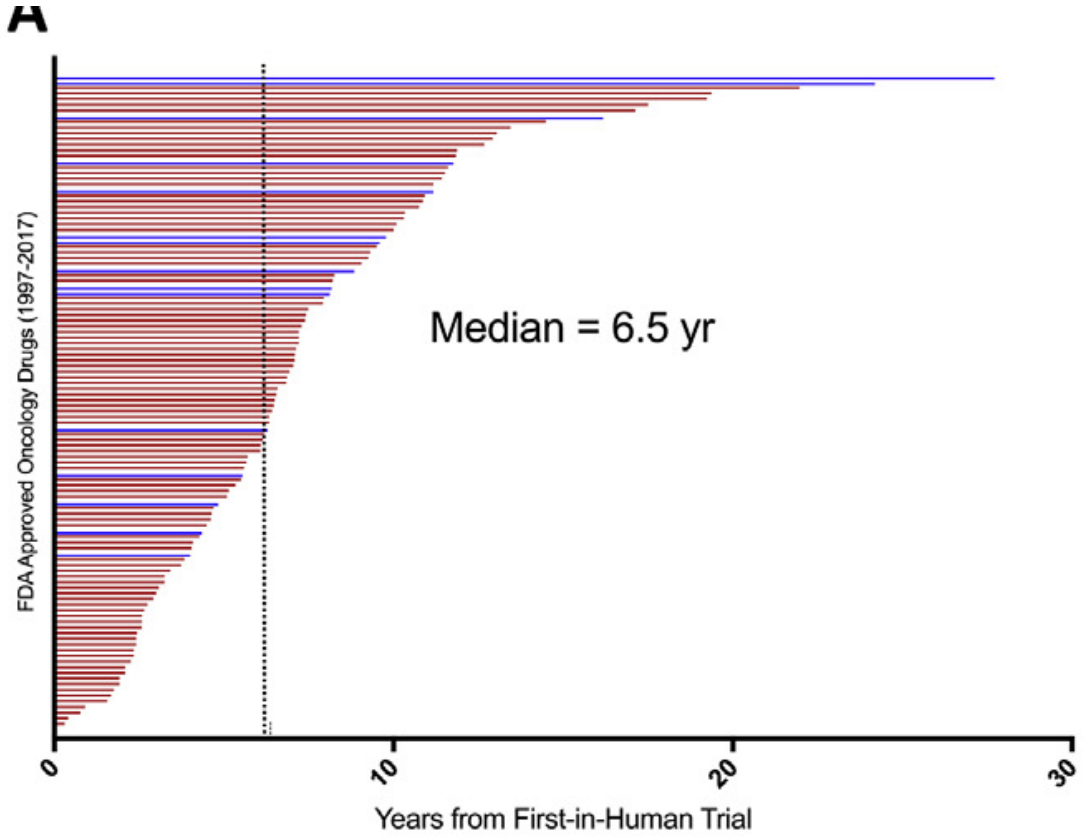


Figure 2: **Swimmer plot of all enrolled patients (n=24) by NTRK fusion status**

Many Challenges Applying the Precision Approach to Pediatric Oncology

- Limited understanding of the spectrum of biologically and clinically-relevant alterations
- Limited number of pre-clinical models
- Limited experience with clinical application of genomic sequencing technologies
- Challenges of clinical trial design
  - Small numbers of patients with each tumor subtype
  - Biopsies of refractory tumors often not performed
- **Limited number of available drugs**

Average of 6.5 yrs to Start Pediatric Trial



Neel DV et al. *Eur J Cancer*. 2019

RACE for Children Act:

- **Requires** evaluation of new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and directed at a **molecular target** substantially relevant to the growth or progression of a pediatric cancer."
- **Molecularly targeted pediatric cancer investigation**: clinically meaningful study data, "using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling." [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)].
- Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets.

Factors Related to Relevance

- Identification of the target in a pediatric cancer
- Target function related to etiology or resistance
- Effect of target modulation- *in vivo, in vitro;* synergy in biologic/rational combination
- Clinical experience: adult and pediatric
- Availability of predictive and response biomarkers

Biology and Pre-clinical Data

- Valid and relevant cell lines and models limited in pediatric oncology
- Many ‘targets’ evaluated late
  - eg Alk and crizotinib
- Limited relevant human tumor data
  - Different tumors
  - Relative rarity

Target/Drug Selection

- Pediatric pre-clinical data to suggest possible role in a pediatric tumor
  - To justify a phase ½ trial or expansion cohort minimal data required
    - Cell lines
    - Pathway knowledge
    - Broad mechanism e.g immune check point

Drug Formulation

- IV is easy
  - All ages eligible
- Oral
  - May limit based on size to allow for dosing in pediatrics but wouldn’t base on age but size and the available strengths/formulation
  - Currently most companies delay development until an adult indication is clear: RACE Act may help change this

Key Considerations

Pediatric formulation requirement

- Molecularly targeted pediatric cancer investigation: clinically meaningful study data, **"using appropriate formulations, regarding dosing, safety and preliminary efficacy** to inform potential pediatric labeling."

  [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)].
- Importance of early development of pediatric formulations:

  eg: larotrectinib vs entrectinib in NTRK oncofusion positive cancer
- Impact on accuracy and feasibility of drug administration to children
- Develop pediatric appropriate formulation in stages

  Start with existing formulation and concurrently develop pediatric appropriate formulation as data emerge

Key Considerations

- Clinical benefit: risk analysis
  - Safety and toxicity profile
    - Pre-clinical
      - Growth and development
    - Clinical
      - Toxicities from adults

Key Considerations

Rare target patient populations require collaboration

- International clinical trial collaboration
- Coordination of regulatory requirements

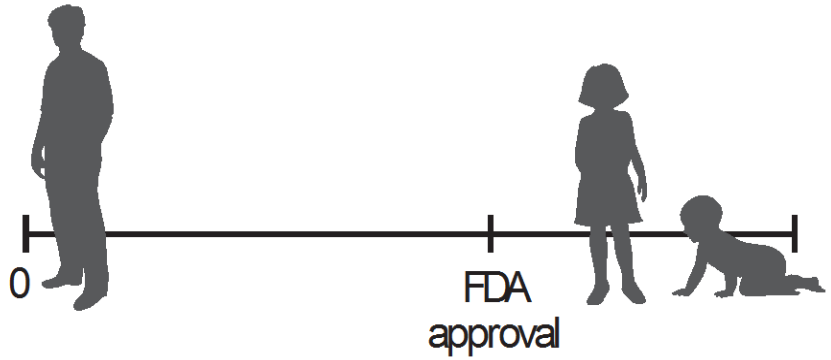
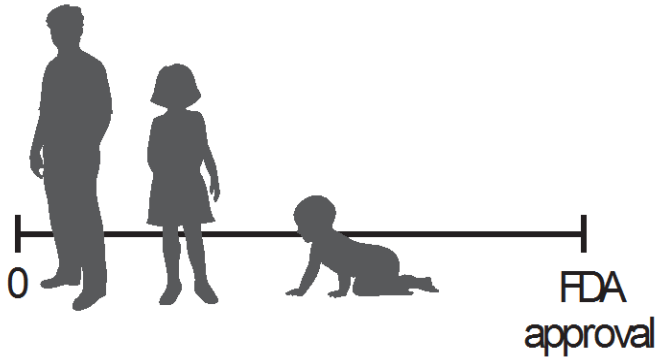
Adequate safety and dosing data in children and adolescents

- Age of eligibility and appropriate formulations
- FDA recommendation on adolescent cohorts *Chuk et al Clin Cancer Res 2017 23:9-12*

Impact on trial design

- Master protocols
- Rolling 6 design with expansions to ensure adequate toxicity and PK data
- Starting dose based on adult recommended phase 2 dose
- Limit pediatric dose finding

Changing the Future of Pediatric Oncology Drug Development

TRIAL ASPECT	PAST	FUTURE
Timeline for trials in pediatrics		
	First-in-child occurs several years after f rst-in-human	Adolescents enrolled in trials concurrent with adults Plan for trials in children in place early in drug development

Dubois S et al. *Science*. 2019

NCI Pediatric Early Phase Clinical Trials Network
A program funded by the National Cancer Institute of the National Institutes of Health

Conclusions

Development of new agents to improve the outcome of children and adolescents with cancer requires:

- Coordination of pre-clinical, clinical, and biologic resources
  - Improved understanding of the tumor/host/drug factors
  - Development of Biomarkers and standardized genomic testing
  - Access to agents of interest
- Collaboration
  - NCI/Academia/Industry
  - International