NCI’s Childhood Cancer Data Initiative (CCDI)
Coordinated Collaborative Rare Pediatric and Young Adult Rare Cancer Effort

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For NCI CCDI

I have no disclosures
Rare Cancers Definition, Challenges, Ongoing Efforts

- **Definition:** Fewer than 15 per 100,000 people/year in US
- 25% of all adult cancers
- All pediatric cancers (approximately 20,000/year ages 0-19 years old)
- **Very rare pediatric cancer:**
  - Fewer than 2 cases per million per year (11% of all pediatric cancers)
  - Tumors not considered in clinical trials; lack of standard of care
- Definition in molecular era:
  - ALK mutated neuroblastoma 1 case/million/year
  - NTRK fusion cancers pediatrics: 1-3 cases/million/year
  - Frequently multiple histologies
- **Limitations:**
  - Focus on few cancers
  - Siloed
  - Insufficient patient numbers for most cancers
  - Data collection limited not standardized/structured

Landscape Analysis:
76 Rare Tumor Programs

Ferrari A. et al., European Journal of Cancer, 2019
Vivelo C. et al., The Oncologist 2023
Ultra-Rare Tumors

The Connective Tissue Oncology Society (CTOS) defines “ultra-rare” sarcomas as those with an annual incidence of <1 in 1,000,000 “entities whose rarity makes it extremely difficult to conduct well powered prospective clinical studies” - Stacchiotti et al 2021

Orphanet ranks rare diseases according to 6 prevalence bins, with the rarest being <1 in 1,000,000 (European-based)

- 1 in 1,000,000 is ~340 cases in the current US population

Review of data from Orphanet and CTOS analysis suggests there are ≥ 222 ultra-rare tumors, of which ≥ 60 have characteristic molecular alterations

- ~75,000 people affected by ultra-rare tumors each year
- ≥ 29 ultra-rare tumors with fusions
- ≥ 38 with disease-causing germline or somatic mutations

Examples of Disease-Causing Gene Mutations in Ultra-Rare Tumors

<table>
<thead>
<tr>
<th>APC</th>
<th>CSF3R</th>
<th>IDH1</th>
<th>NPM1</th>
<th>SMARCA4</th>
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<tr>
<td>ASXL1</td>
<td>CTNNB1</td>
<td>IDH2</td>
<td>PRKAR1A</td>
<td>TERT</td>
</tr>
<tr>
<td>ATP4A</td>
<td>DICER1</td>
<td>KIT</td>
<td>SDHB</td>
<td>TET2</td>
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<td>DNMT3A</td>
<td>MET</td>
<td>SDHC</td>
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<tr>
<td>CDKN2A</td>
<td>FLT3</td>
<td>NF1</td>
<td>SDHD</td>
<td>ZNRF3</td>
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</tbody>
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MyPART: My Pediatric and Adult Rare Tumor Network

- Focusing on rare solid tumors affecting children, teens, and young adults (≤39 yo)
- Engaging patients, family members, advocates, clinicians, scientists, as partners in research
- Collecting longitudinal molecular, clinical, and patient reported outcome data through the Natural History Study of Rare Solid Tumors (NCT03739827)
- Holding workshops and symposia on rare tumors to develop expert consensus
- Hosting multi-day clinics for rare tumors to bring patients and nationwide experts together
- Building a multi-institutional network of sites to collaborate on data collection
Natural History Study of Rare Solid Tumors (NCT03739827)

- Standardized longitudinal evaluation: Retrospective and prospective
  - Medical and family history, patient reported outcomes, clinical evaluation
  - Extensive medical record data extraction

- Children and adults with rare solid tumors and biological relatives
  - Off or on site participation
  - Treatment recommendations

- Comprehensive molecular profiling
  - Tumor tissue, blood, saliva

- Molecular tumor board

- Genetic counseling

- Annotated biospecimen repository

- Development of interventional trials

Wedekind et al 2023 Pediatric Blood and Cancer
Enrollment on Natural History Study of Rare Solid Tumors:
- >570 participants enrolled with >68 different rare tumor histologies
- Study opening at 2 extramural sites in upcoming year (TXCH and OHSU)

Biospecimens Collected and Analyzed:
- Biospecimens collected from 447 participants; return of results to >270 participants
- Addition of cfDNA liquid biopsies and tumor-germline deep WGS to analyses

New Models of Rare Tumors:
- Sdhb-loss/Raf^V600E-gain mouse model of SDH-deficient GIST
- PDX models and organoids from rare tumor patients (collab with POB Mouse Hospital and DTB)

Engagement with Patients and Advocates:
- Partnerships with 31 advocacy organizations
- Website (~70,000 unique visitors/mo); Newsletter (13,500 subscribers); POB Twitter (1700 followers)
- Translation of website to Spanish, summer 2023

Joint Adult-Pediatric Trials with DTC:
- Phase II Trial of Tiragolumab + Atezolizumab

In-person Specialty Clinics:
- GIST and Chordoma

NIDAP POB Data Analysis Portal:
- Data cleaning, visualization, and data integration with Lab of Pathology, BTRIS, PACS, Halo
- Clinical and Biospecimen Data Submitted to dbGAP (est rel Q4 2023)
- 10062 data fields on 1st 500 participants, 57245 data fields on 1st 200 participants
- Variant calls for 193 tumors; 2370 biospecimen annotation fields

Publications and in press FY23:
- Ilanchezhian et al Front Endocrinol Oct ‘22
- Li et al J Clin Endocrin Metab Nov ‘22
- Fierro Pineda et al Curr Opin Ped Feb ‘23
- Ioakeim-Ioannidou et al Neuro Onc Apr ‘23
- Flores-Tores et al JCO Jun ‘23
- Wedekind et al Ped Blood Canc Jun ‘23
- Liny et al Ped Blood Canc Jun ‘23
- Ahmed et al Can Res Commun, accepted
- Vivelo et al The Oncologist, accepted

To make progress in many rare tumors, a national/international effort is needed.
NIH Rare Tumor Clinics

- Clinics bring 10-15 patients with select very rare tumors to the NIH CC
  - Disease experts (intra- and extramural) and advocates
  - Detailed clinical and biospecimen evaluations
  - Patient reported outcomes, focus groups
  - Patients meet with each other and with experts
  - Communication of expert opinion

- Established new rare tumor clinics
  - WT-GIST; planning Sept 2023 clinic
  - Medullary Thyroid Carcinoma
  - Chordoma; 4th yearly clinic held May 2023

- Remote and in-person participation
- Planning new clinics
Pediatric Chordoma: Paradigm for Very Rare Tumor Research

- **Interest within IRP**
  - CCR/DCEG Chordoma Working Group
  - 27 members

- **Workshop of national leaders in research and advocacy**
  - June 15, 2018

- **Formalized partnership with Chordoma Foundation**

- **Natural history study**
  - Chordoma subprotocol

- **Grant applications and new treatment trials for chordoma patients**

- **Pediatric chordoma working group**
  - Pathology
  - Med Onc
  - Rad Onc
  - Surg Onc

  - 45 extramural members
  - July 2020 to present

- **Multi-Institution virtual tumor boards**

- **First pediatric chordoma clinic at the NIH Clinical Center**
  - April 16-18, 2019
Phase II trial of Tiragolumab + Atezolizumab

Expression of PD-L1 and TIGIT in SMARCB1 deficient tumors
- Tiragolumab: Monoclonal antibody against TIGIT
- Atezolizumab: Monoclonal antibody against PD-L1

Eligibility:
- SMARCB1 or SMARCA4 deficient tumors
- Ages ≥ 12 months
- Cohorts:
  - Poorly differentiated chordoma
  - Renal medullary carcinoma
  - Malignant rhabdoid tumor (extra-CNS)
  - Atypical teratoid rhabdoid tumor (CNS)
  - Epithelioid sarcoma
  - Other SMARCB1 or SMARCA4 deficient tumors

NCI-CTEP: Multi-site, PEP-CTN coordinated
- Collaboration with NCI DTC, UOB, POB
- Correlative studies supported by MyPART

Figure adapted from Manieri et al. Trends Immunology 2017

Classified as public by the European Medicines Agency
Rare Tumor Experience/Future

- **Advocacy** and clinical/scientific **rare tumor expertise** are critical
- **NIH Rare Tumor Clinics** provide insight one could not get through evaluation of single patients at multiple sites
- Building meaningful cohorts is **resource and time intensive**
- **Focus on select tumor types** is needed to accrue sufficient patient numbers
- **Partnership** with consortia / COG / community hospitals / advocacy and national experts will be critical to **accelerate** rare tumor progress

**NCI CCDI vision for rare tumors**

- A national/international effort will allow enrolling adequate numbers of participants to more rapidly, efficiently, and consistently study multiple rare cancers
NCI Childhood Cancer Data Initiative (CCDI)

Learn from and use data
- EHR pilots
- Cohorts
- Survivorship
- Data catalog

Aggregate and generate data
- Preclinical models
- Molecular characterization initiative
- National rare tumor initiative

Build foundational infrastructure
- Data ecosystem
- CCDI participant index
- Computable consent
- Tools interoperability
- Federated infrastructure
- Clinical data commons

Gregory Reaman
SD, CCDI

Learn from and use data

aggregate and generate data

build foundational infrastructure

NCI Childhood Cancer Data Initiative (CCDI)
CCDI Molecular Characterization Initiative (MCI)

- Partnership between NCI and COG Project: EveryChild
- State-of-the-art molecular characterization at diagnosis (WES, fusions, methylation)
- Results returned to participants and treating physicians within 21 days
- Identification of molecular tumor subtypes
- In its first year, MCI enrolled more than 1,000 participants from 47 states, Canada, Australia, and New Zealand

Enrollment as of Aug 2023 is 3035 patients

Specimens for Sequencing (monthly)

Classification as public by the European Medicines Agency
Objectives

- Feasibility of a national observational protocol for very rare pediatric and AYA solid cancers and hematologic malignancies
- Longitudinally evaluate the disease course of participants with rare cancers
  - Structured and real world data
  - External control for interventional trials
  - Meaningful comparison across multiple cancer types
- Collect clinical and research molecular characterization
  - Identification of therapeutic targets and inform clinical trials
- Feasibility of national / international molecular/clinical tumor boards for rare cancers
  - Facilitation of patient navigation and treatment recommendations
CCDI-Cooordinated Rare Pediatric/AYA Tumor Study

CCDI Rare Cancer Study
Recruitment through:
• COG – PEC
• Self referral

CCDI Molecular Characterization Initiative pipeline or equivalent

Clinical Sequencing (CLIA)
- Targeted exome seq
- Archer fusion
- EPIC methylation array
- Clinical/demographic

Research Characterization (non-CLIA)
- WGS
- RNA-seq
- Proteomics
- Metabolomics
- Other, Clinical

Clinical characterization (core/comprehensive)
- Etiology, family history, medical history
- Clinical, PRO, imaging, treatment
- Pathology
- Detailed treatment info
- AEs / Toxicity
- PROs
- Follow-Up / Survival

Return clinical results to patients & providers

CCDI Data Ecosystem (Integrated clinical & -omic data)

De-Identification

Patient remains on CCDI Rare Tumor Protocol during follow-up.

Patient may be enrolled on interventional trials

Clinical Data Collection

De-Identification

Classified as public by the European Medicines Agency
Centralized Coordination with Distributed “Champions”

Preexisting Programs Could Participate as Disease Champions or Integrate Data for Rare Tumor Comparisons

International Collaboration: EU Beating Cancer Plan

Marketplace Administrator

Disease Champion PIs
Advocacy/Research Partners
Disease-Specific Data Collection

Centralized Overall Study PI
Remote Enrollment
Core Data Collection

EU Beating Cancer Plan
NCI-European Union Collaboration

EU Beating Cancer Plan – NCI Cancer Moonshot / National Cancer Plan

Aims:
- Develop a focused international research collaboration that requires sharing of patient-level data
- Develop a database of clinical, genomic, potentially etiologic and exposure, treatment, outcome, and social determinants of health data across the spectrum of very rare cancers in children and young adults

Output:
- Joint natural history study with identical data collection on specific rare tumors

Technical working groups:
- Co-Chairs:
  - **EU**: Ruth Ladenstein; **US**: Brigitte Widemann

Next steps:
- EU and NCI determine technical working group members and meet to develop demonstration project
- Presentation to EU-US taskforce on Cancer Health Cooperation Leadership
European Union Collaboration Opportunities

Data collection:
- Substantially increase number of patients with very rare cancers for analysis
  - Identical clinical core data for rare tumors
  - Make utility of CCDI resources, tools, data ecosystem
- Building external control for clinical trials
- Streamlined molecular characterization

Molecular tumor boards:
- International representation for virtual rare tumor boards (disease champions)

Evidence based recommendations for evaluation and management of rare cancers

Interventional clinical trials:
- In collaboration with FDA/EMA, consortia and industry
Regulatory Rare Cancer Efforts

- **FDA guidance**: Rare tumor natural history studies, external controls, real world data
- **Regulatory approvals for very rare cancers pediatric and adult**:

**Atezolizumab**: Alveolar soft part sarcoma
- ≥ 2 years old
- ORR 24%, DOR ≥ 12 months 42%
- 47 adult, 2 pediatric patients

**Larotrectinib**: NTRK gene fusion cancers
- Pediatric and adult patients, histology agnostic
- ORR 75%, DOR ≥ 9 months 63%
- 43 adult, 12 pediatric patients

Chen A. et al.: NEJM 2023
Drilon A. et al.: NEJM 2018
Conclusions

- Increasing number of pediatric and adult rare tumor efforts
- Increasing regulatory efforts on advancing rare tumor therapies through innovative trial designs including non randomized studies and natural history as external control
- Substantial advances in individual rare cancers
- CCDI is working to create the foundational infrastructure for data collection and sharing to benefit pediatric and AYA cancer patients
- A CCDI coordinated national (international) observational rare pediatric tumor study is in development to allow advancing the understanding of many rare tumors simultaneously
  - Collaboration with COG MCI, adult oncology and many others
  - Distributed disease champions
  - Tumor boards, evidence based recommendations
  - Interventional trials and regulatory approvals
If you work on frequent cancers: Do randomized trials
If you work on rare cancers: FIND FRIENDS
Acknowledgements

• NCI
• CCDI
• COG
• Cancer Moonshot™
• NCI-EU Task Force
• MyPART
• NIH Clinical Center
• Intramural and extramural collaborators

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