Update on Clinical Trial Design for New Therapies in Children with Cancer

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Disclosures

Disclosures: none

I will discuss the following off label use or investigational use: selumetinib, ulixertinib

This presentation reflects my opinion, based on referenced data available in the public domain, and does not reflect the opinion of the institutions, sponsors, cooperative groups or consortia with whom I am affiliated.

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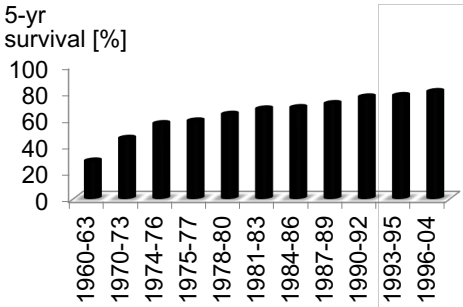
Objective

Demonstrate how the evolution of therapy for childhood cancer has impacted trial design

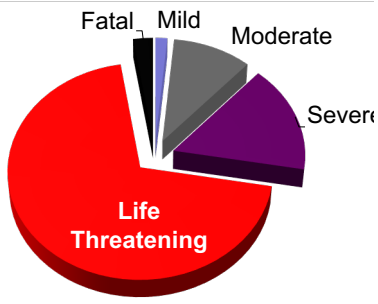
3

Unifying Goal of Childhood Cancer Drug Development

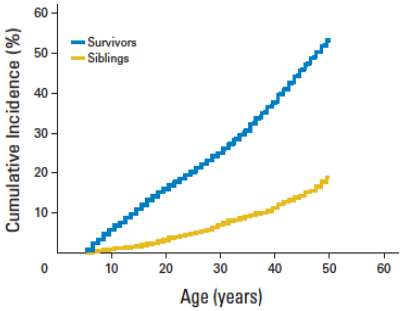
Improve cure rates. Diminish acute toxicity. Eliminate late effects.



Treatment year



Acute Side Effects

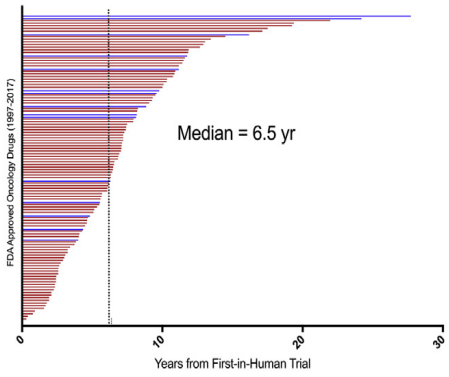


Grade 3 to 5 chronic health conditions
Survivors of Childhood Cancer

Armstrong et al JCO 2014

4

Realities of Clinical Research in Children with Cancer



Interval From First in Human to First in Child Trials for Oncology Drugs

Neel et al Eu J Cancer 2019

- Relatively low incidence study population, sub-classification and risk groups mandate **multi-center and multi-disciplinary clinical trials**
- Improved outcome, accrual rates, **integration of biology** -evidence of success of **NCI Cooperative Groups**
- **Lag time** to initiation trials in children and **formulation constraints impact trial design**

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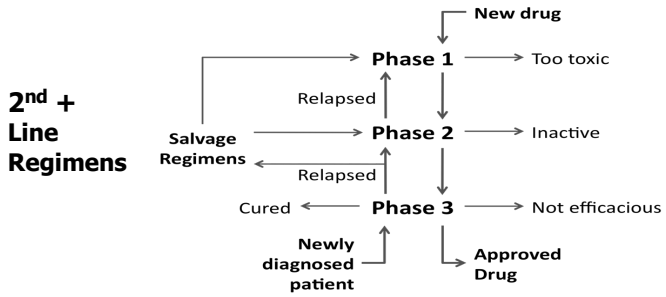
Drug Development Paradigms

Goal	Historically	Current
Dose and Safety	Phase 1 toxicity based	Dose confirmation
Anti-Cancer Activity	Phase 2 response	Signal Seeking
Clinical Benefit	Phase 3 Survival	Survival and QOL/PRO



Balis FM & Fox E, Clinical Investigation 2012 2(3)

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Targeted Therapy Evolution of Paradigm in the Era of Targeted Therapy

Therapy Related

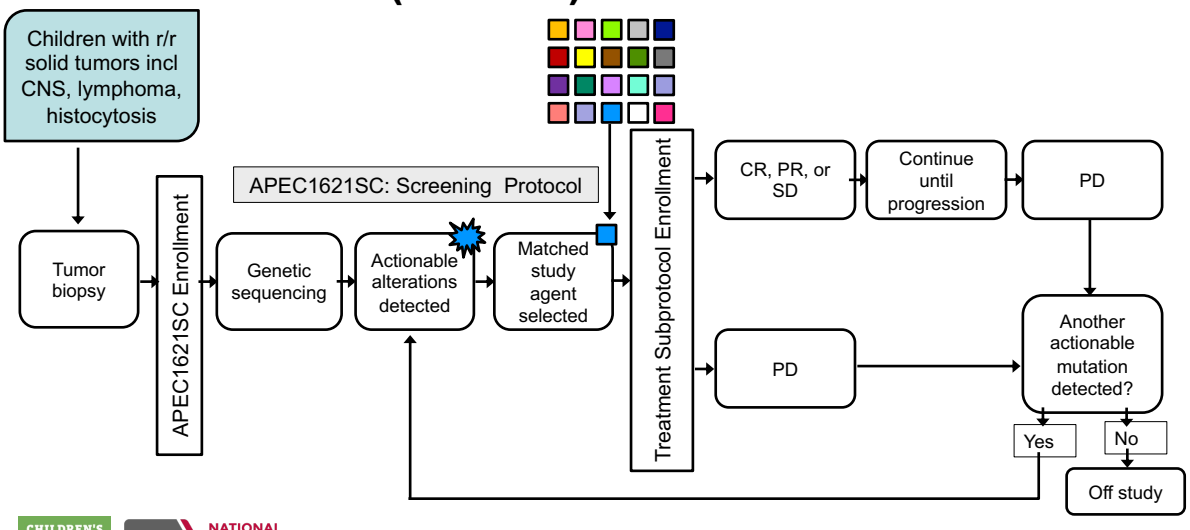
- Continuous oral dosing
- Long Half life
- Formulation
- Less myelosuppressive

Trial Design

- Maximum tolerated dose and acute toxicity are no longer used to determine dose
- Definitions of Toxicity
- Biomarker selection
- Hybrid designs (Phase 1/2, Phase 2/3)

7

NCI-COG Pediatric Molecular Analysis for Therapy Choice (MATCH) Trial Overview



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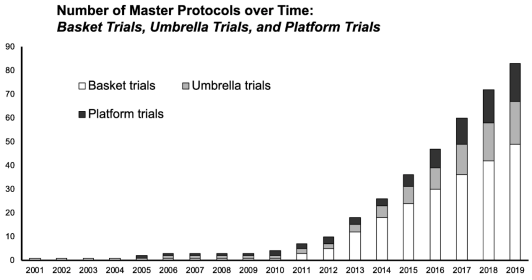
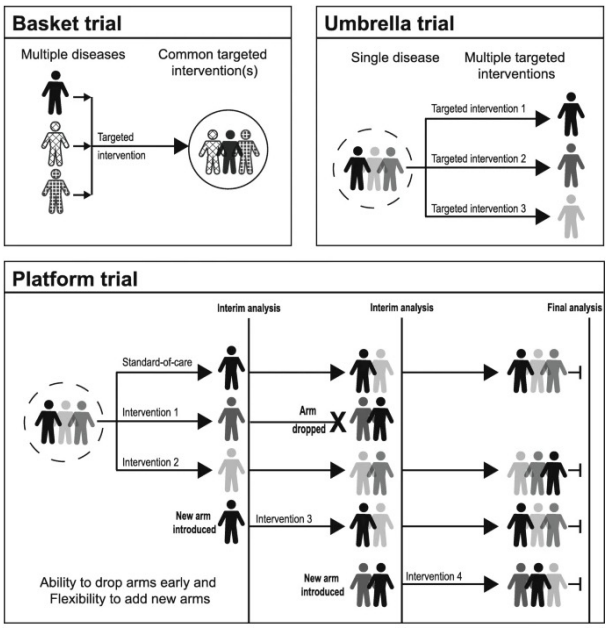
Trial Designs



Park et al Trials 20 572, 2019



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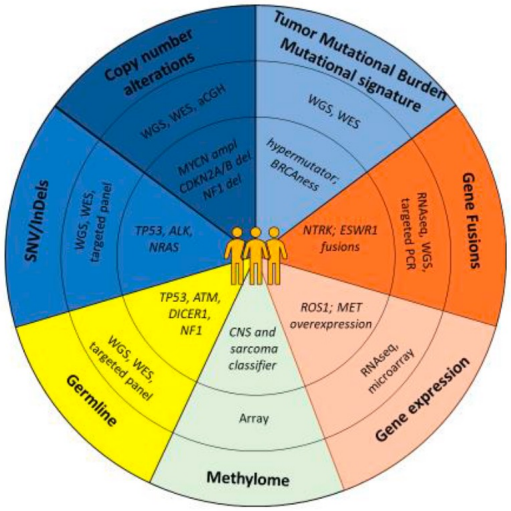
Biomarker Selection for Patient Eligibility

- Clinical Test or Research Test
- Centralized vs Sites
- Method and Turn around time
- Definitions and Thresholds
- Prevalence of Biomarker



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Langenberg et al Cancers 13, 4324, 2021

10

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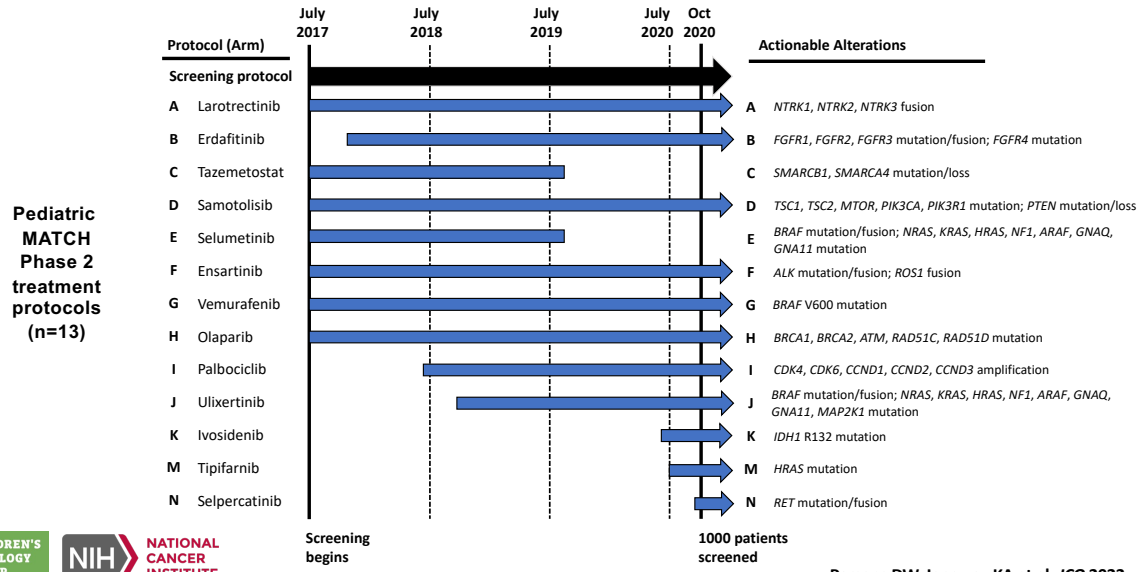
Pediatric MATCH Trial Subprotcols



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Parsons DW, Janeway KA et al. *JCO* 2022

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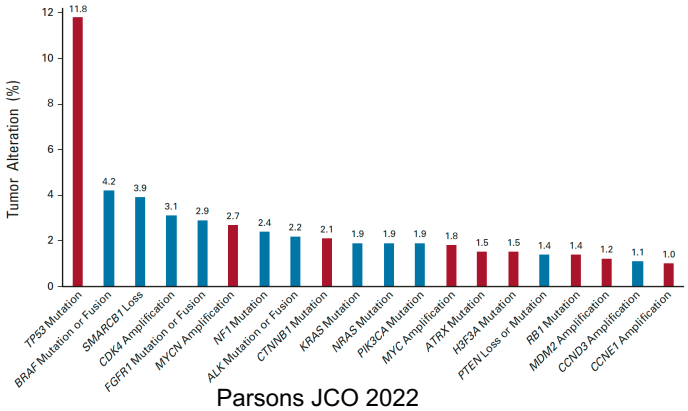
Interim Summary of Pediatric MATCH Screening

1000 Patients ≤ 21y submitted tumor for molecular profiling

- July 2017- October 2020
- Patients with relapsed or refractory solid tumors were eligible

315 patient's cancer had actional mutation

131 Patients were enrolled on therapeutic sub-protocols



Parsons JCO 2022

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Pediatric MATCH SubProtocol E: MAP Kinase Pathway Inhibitor Selumetinib

Single Stage Phase 2 Trial

Actional Alterations: ARAF, BRAF, NRAS, KRAS,HRAS, MAP2K1, GNA11, GNAQ, NF1, and BRAF

Pediatric Dose established

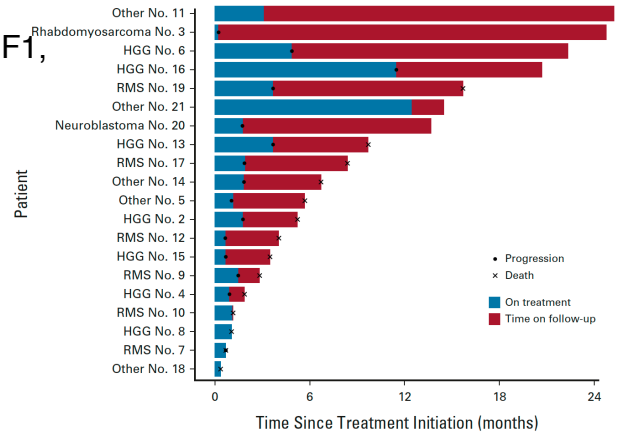
Primary Endpoint: Objective Response

58 patients MATCHED to Arm E

21 were enrolled; 20 Treated

Response

- No objective responses
- 3 patients had prolonged stable disease (HGG x 2, plexiform neurofibroma x1)



Eckstein et al JCO 2022

13

Pediatric MATCH SubProtocol J: MAP Kinase Pathway Inhibitor Ulixertinib

Limited Dose Escalation Trial and Single Stage Phase 2 Trial

Actional Alterations: *ARAF*, *BRAF*, *HRAS*, *KRAS*, *NRAS*, *MAPK1*, *MAP2K1*, *GNA11*, *GNAQ* hotspot mutations; *NF1* inactivating mutations; *BRAF* fusions

Establishing Pediatric Dose

- 2 dose levels 260 or 350 mg/m^2 twice daily evaluated in Rolling 6 design
- Dose Limiting Toxicity in the dose escalation and primary cohorts included fatigue, anorexia, rash, nausea, vomiting, diarrhea, dehydration, increased creatinine, hypoalbuminemia, hypernatremia, and hip fracture.

Primary Endpoint: Objective Response

20 were enrolled and treated

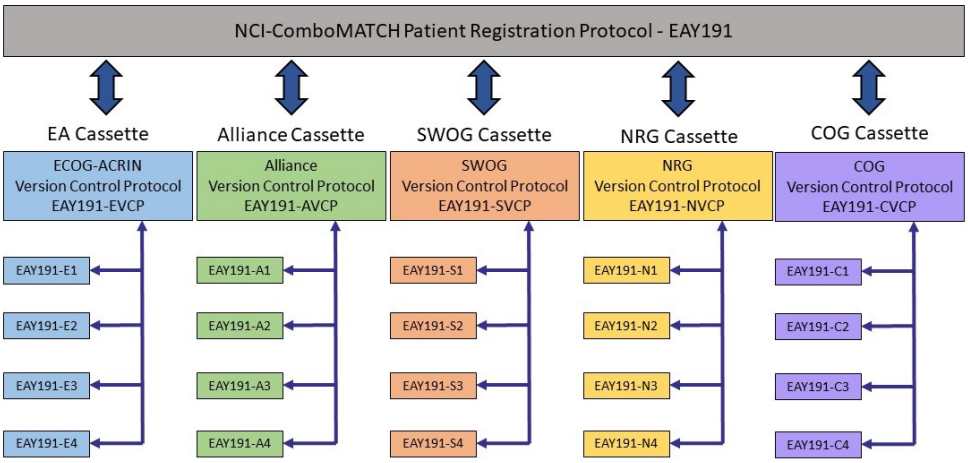
Response

- No objective responses
- 3 patients with BRAF altered glioma or neuroglial tumors had prolonged stable disease

Vo et al ASCO 2021

14

NCI-ComboMATCH Protocol Organization



Prototype as of February 19, 2020. Number of studies in each cassette likely to vary.

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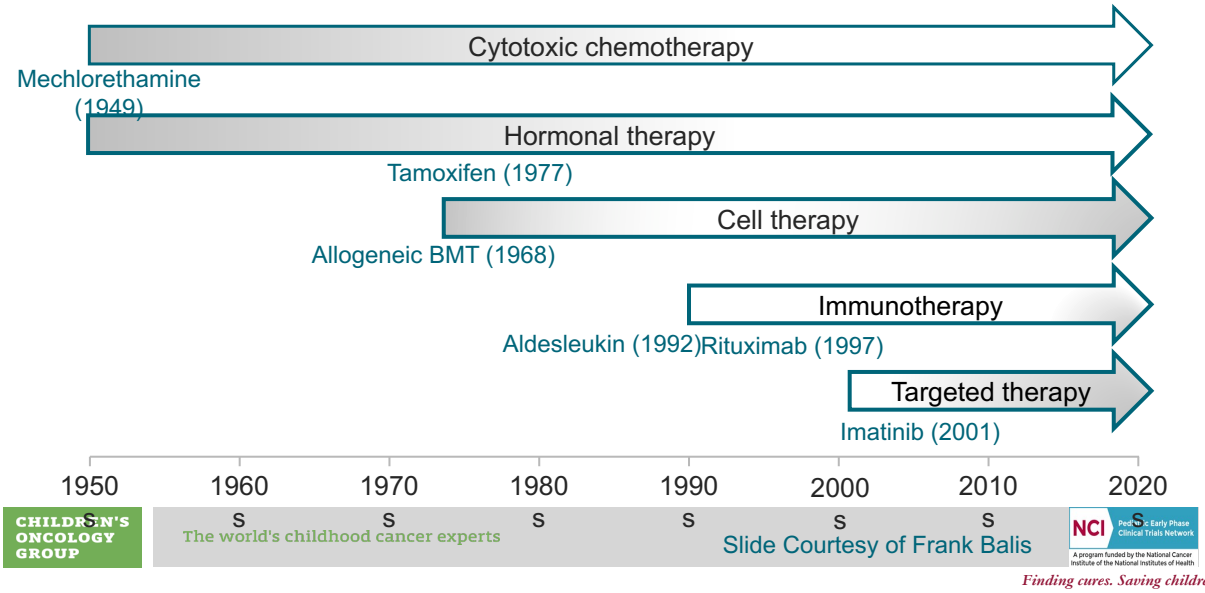
Evolution of Anticancer Drugs



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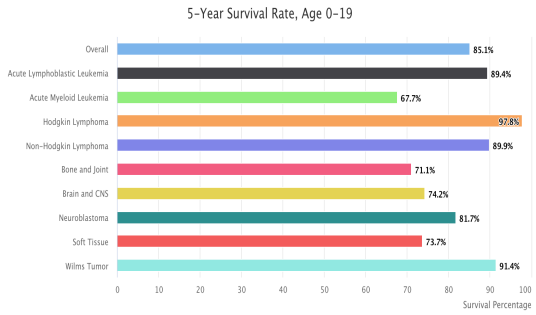
Evolution of Principles of Chemotherapy

Goal of curative therapy is to eradicate all malignant cells and precursors



Curesearch based on Nov 2020 SEER Data

3 Principles of Chemotherapy for Childhood Cancer				
	Cytotoxic Era	Cellular Tx Era	Immuno Tx Era	Targeted Tx Era
Combination Therapy	✓	✓	✓	✓
Adjuvant Therapy	✓	?	✓	✓
Dose Intensity	✓	✓	?	?

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Evolution of Trial Design and Conduct

Molecularly Targeted Therapy necessitates Biomarker Selected Trials and therefore Smaller patient populations

- Impact Dose Determination:
  - Target Concentrations may be preferred endpoint
  - Targeted therapy is less myelosuppressive, not non-toxic
  - Toxicity beyond Cycle 1 should be incorporated (BOIN)
  - Dose confirmation and limited dose exploration
- Basket and Umbrella Trials are feasible in children
  - The trial design is still radiographic response- based phase 2
  - Multi-Center and International Trials are required

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18