Master Protocol in Pediatric Cancer Trials

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Disclaimer: The presentation represents the opinion of the presenters, and do not reflect the position of the U.S. Food and Drug Administration, nor BeiGene

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Slides courtesy from all

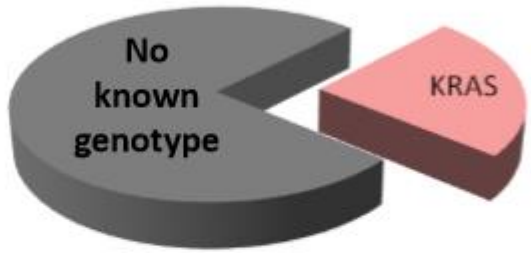
Outline

- Background
  - Precision Medicine and Pediatric Oncology Drug Development
  - Master Protocol Guidance
- NCI-COG Pediatric MATCH Design and Structure
- Challenges and Opportunities
- Summary

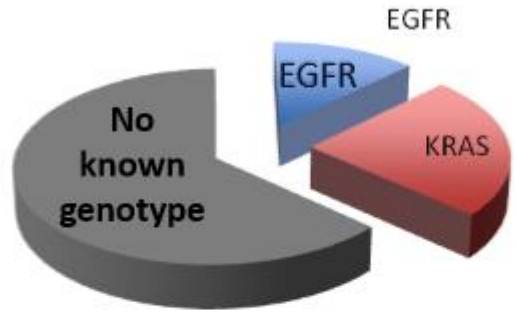
Precision Medicine and Oncology Drug Development

- Precision cancer medicine: **targeted therapy** selection by identifying **key gene variants**
- Evolutionary Paradigm shift: **Human genome** (2003) – wide-spread availability of NGS
- Genomic and proteomic interrogation of individual cancers screened: resulted in creation of multiple rare subsets (defined by **molecular phenotype**) of previously common cancers

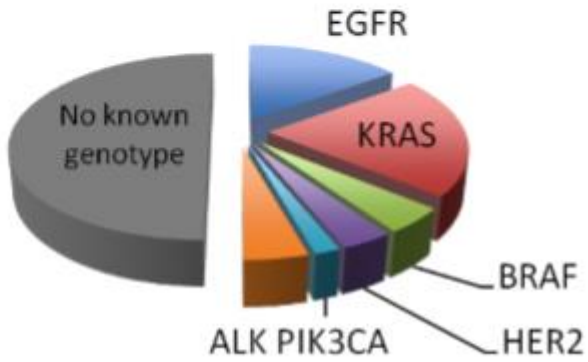
Evolution of Identification of Genomic Alterations in Lung Adenocarcinoma



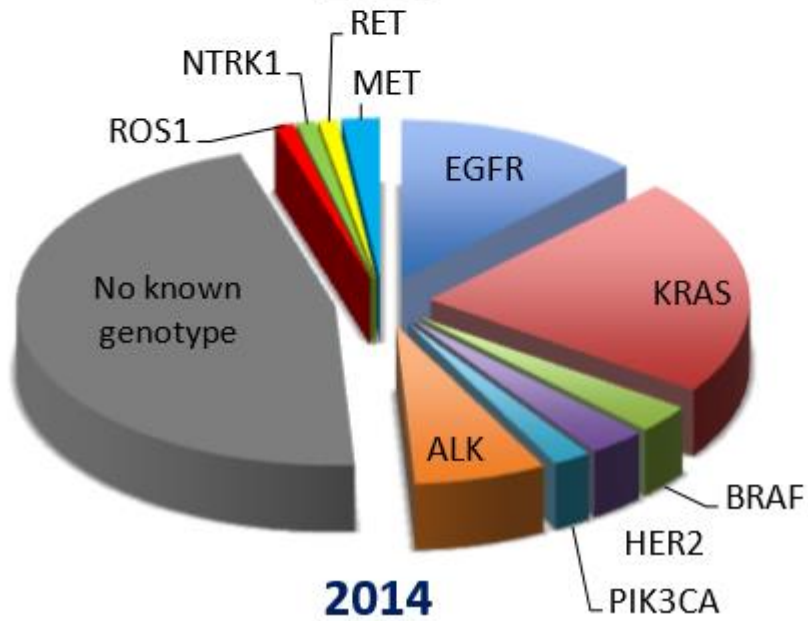
1984 - 2003



2004

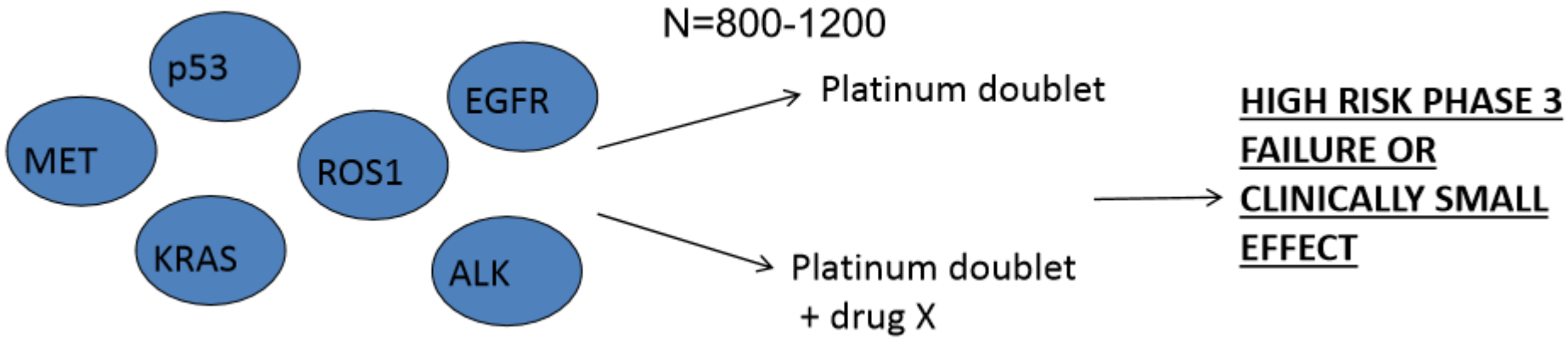


2009



2014

Challenges with “Old Paradigm”



Challenges with “New Paradigm”

- 1% Prevalence of even common tumors: Number needed to screen > 100 patients→ need to reduce screen failure rate
- 1 drug/ 1 biomarker per trial unsustainable→ Need common multi-analyte platform(s)
- Need Rapid Learning/ Failure/ Confirmation

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Precision Medicine in Pediatric Oncology

- Most childhood cancers (embryonal origin) – low mutation frequency
- Initial therapy (H.D. chemo/XRT)
- Some childhood cancers have very few recurrent events
- Post-therapy sequencing of relapse samples accumulate more mutations in targetable oncogenic pathways
- Few opportunities for extrapolation: 5 out of 40 written requests in 2001-2019*

*A review of the experience with pediatric written requests issued for oncology drug products, submitted and under review

Characteristics of an Ideal Master Protocol

- One protocol
- Central governance structure
- Central IRB
- Central DMC
- Central Independent Review Committee
- Central repository of Data and Specimens
- Central screening platform

- Study multiple drugs
  - Targeting more than one marker
  - More than one drug for one marker
- Study multiple markers
  - Overlapping expression of markers
- Leverage common control
- Flexibility to add/remove agents (Adaptive)

FDA draft guidance on master protocol (2018)

Background: NCI-MATCH –Genomically-Driven Trial 2013

A Disease Agnostic Basket Trial: NCI-MATCH

THIS PRECISION MEDICINE TRIAL EXPLORES TREATING PATIENTS BASED ON THE MOLECULAR PROFILES OF THEIR TUMORS

NCI-MATCH[1] IS FOR ADULTS WITH:

- solid tumors (including rare tumors), lymphomas, and myeloma
- tumors that no longer respond to standard treatment

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05/27/2018 6

NCI-COG Pediatric MATCH Trial

- Funded by NCI
- Developed jointly by NCI and Children's Oncology Group (COG)
- Conducted by COG
- Refractory and recurrent pediatric Solid tumor, including non-Hodgkins lymphomas and CNS tumors or histiocytosis
- Goal: deliver targeted anticancer therapy that produces a clinically meaningful objective response rate

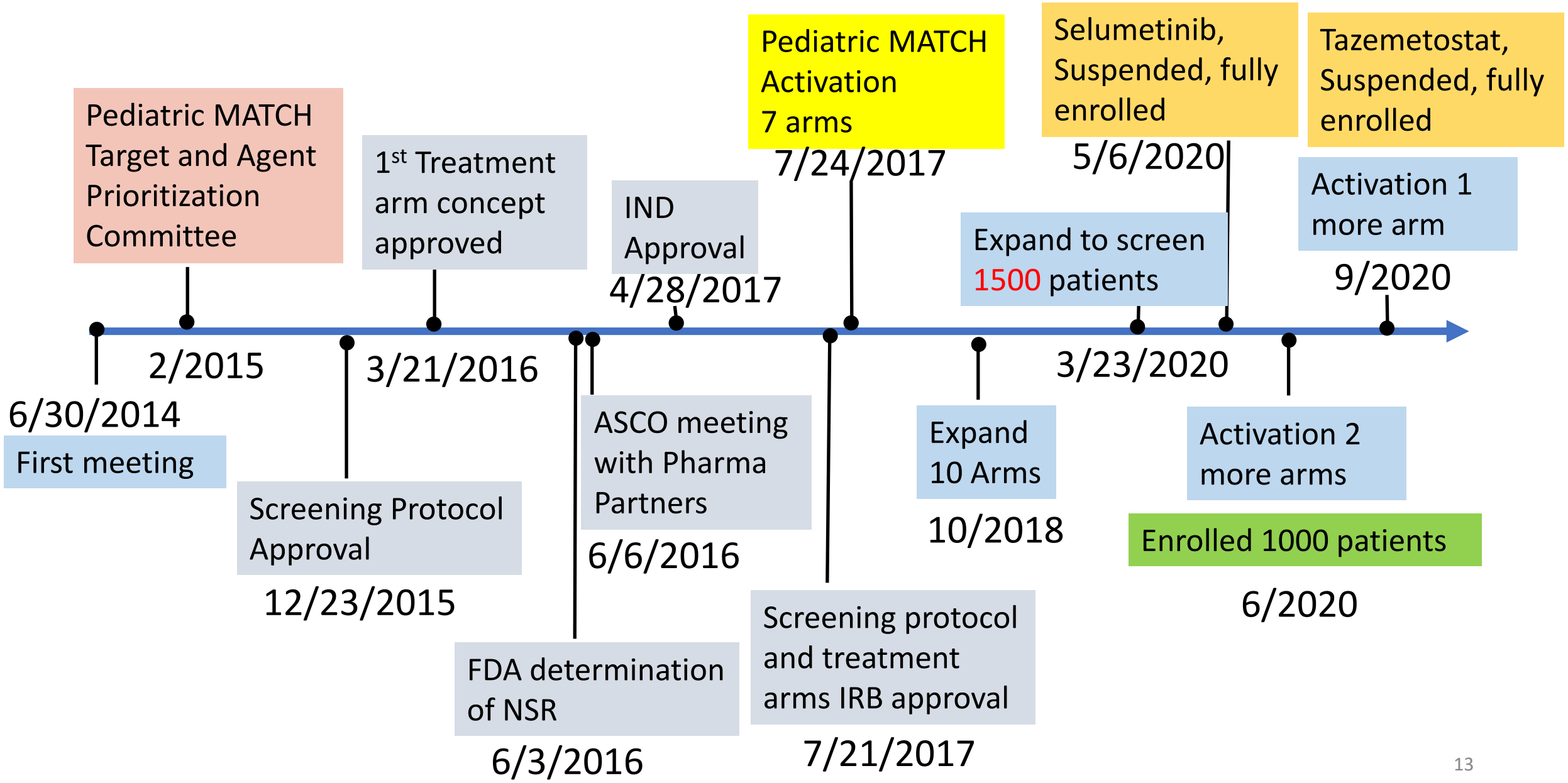
NCI-COG Pediatric MATCH Master Protocol

- Single IND held by CTEP
- Central Governance Structure
- NCI Pediatric Central IRB
- Master Protocol review by CIRB, each marker-drug subprotocol
- Central DMC by COG
- Central screening platform, leverage Adult MATCH trial
- Central Repository of data and specimen

NCI-COG Pediatric MATCH Design Features

- Non-histology driven
- Test many children and adolescents to find widely distributed genetic alterations
- Biopsies from the time of recurrence except for DIPG (from dx)
- Single stage Phase 2 studies
- Inclusion of agents with adult RP2D, without formal pediatric phase I testing
- Blood sample acquisition and return of germline sequencing results related to inherited cancer susceptibility

NCI-COG Pediatric MATCH Timeline



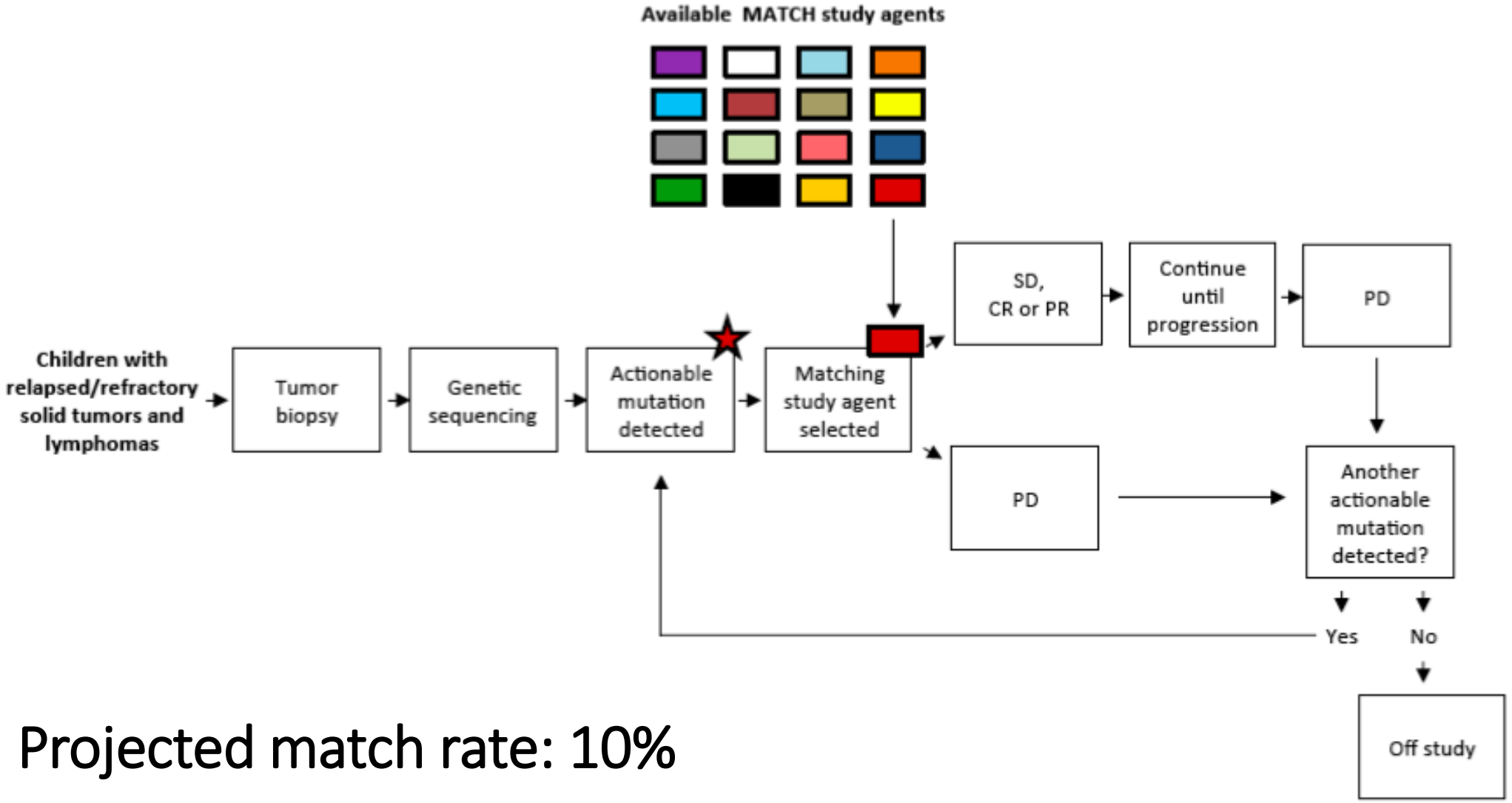
Level of Evidence for Drugs

- Level 1: FDA approved for any indication for that target
- Level 2: Agent met a clinical endpoint (objective response, PFS or OS) with evidence of target inhibition
- Level 3: Agent demonstrated evidence of clinical activity with evidence of target inhibition at some level

Level of Evidence for Target Selection

- Level 1: Gene variant credentialed for selection of an approved drug
- Level 2a: Variant is eligibility criteria for an ongoing clinical trial for that drug
- Level 2b: Variant identified in an N of 1 response (s)
- Level 3: Preclinical inferential data
  - Models with variant response; without variant do not
  - Gain of function mutation demonstrated in preclinical model
  - Loss of function (tumor suppressor genes or pathway inhibitor e.g. NF1); stop codon or demonstrated loss of function in preclinical model

NCI-COG Pediatric MATCH Schema



Projected match rate: 10%

Later re-match can occur at physician's request (if slots are available)

Study Designs and Statistical Consideration

- Primary endpoint: Objective Response Rate
- Secondary endpoint:
  - Progression-free survival (PFS)
  - Tolerability
  - PK: erdafitinib, ensartinib, LY3023414, ivosidenib, ulixertinib
- Simon's 2-stage Design, no interim stopping
- Evaluation per arm: ORR and DOR, PFS
- No cross-arm comparison or pooling
- N=20/arm

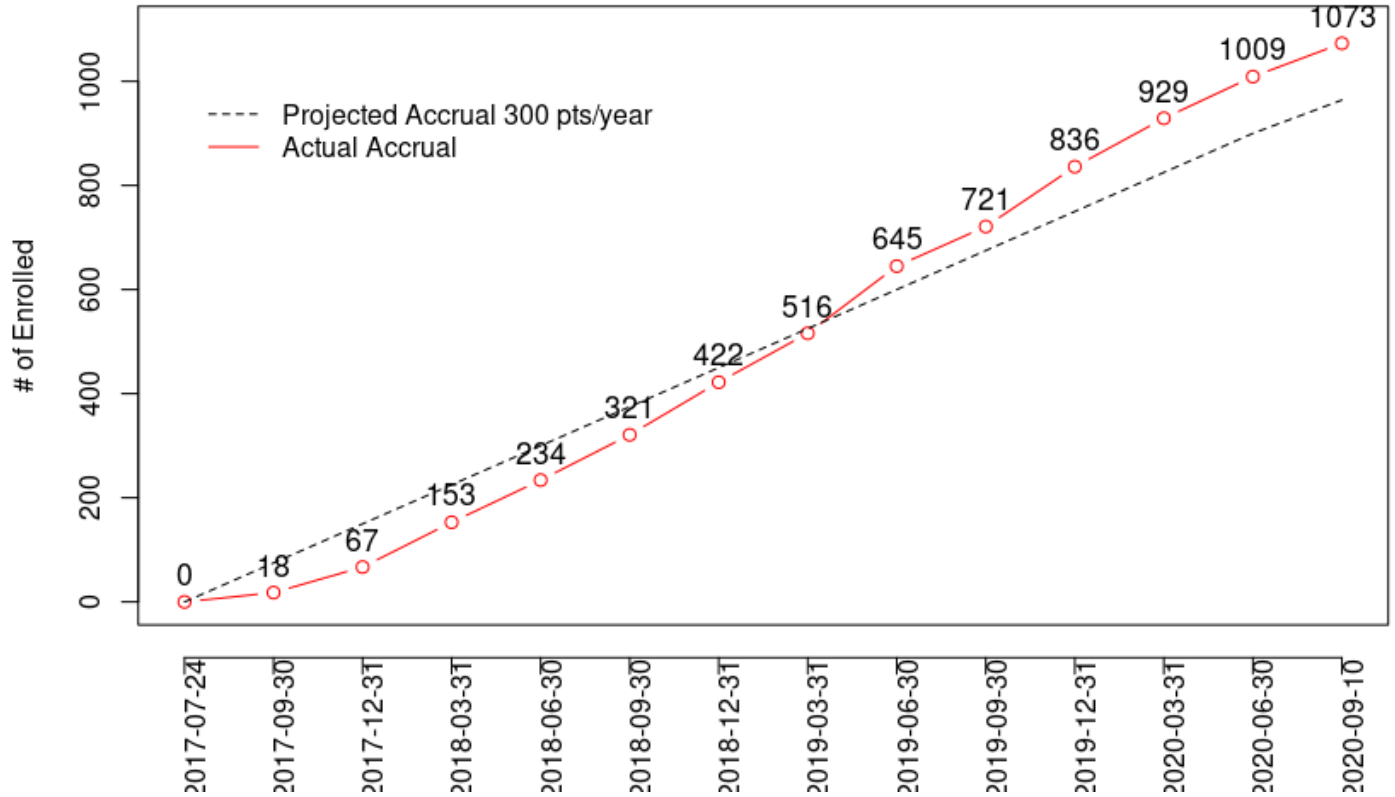
Treatment Subprotocol Status

Protocol ID	Agent	Agent Class	aMOI Frequency	Activation Date	Current Status	Adult Approval
APEC1621-A	Larotrectinib	TRK inhibitor	2-3%	7/24/2017	Recruiting	11/26/2018
APEC 1621-B	Erdafitinib	FGFR inhibitor	2-3%	11/06/2017	Recruiting	4/12/2019
APEC 1621-C	Tazemetostat	EZH2 inhibitor	2-3%	7/24/2017	Suspended, full enrollment – Planned analysis	1/23/2020
APEC 1621-D	LY3023414	PI3K/mTOR inhibitor	5-10%	7/31/2017	Recruiting	
APEC 1621-E	Selumetinib	MEK inhibitor	10-20%	7/24/2017	Suspended, full enrollment – Planned analysis	4/10/2020
APEC 1621-F	Ensartinib	ALK inhibitor	2-3%	7/24/2017	Recruiting	
APEC 1621-G	Vemurafenib	BRAF inhibitor	5%	7/24/2017	Recruiting	8/17/2011
APEC 1621-H	Olaparib	PARP inhibitor	2-3%	7/24/2017	Recruiting	12/19/2014
APEC 1621-I	Palbociclib	CDK4/6 inhibitor	2-3%	6/25/2018	Recruiting	2/3/2015
APEC1621-J	Ulixertinib	ERK1/2 inhibitor	5-10%	10/01/2018	Recruiting	
APEC1621-K	Ivosidenib	IDH1 Inhibitor	1-2%	6/08/2020	Recruiting	7/20/2018
APEC1621-M	Tipifarnib	HRAS Inhibitor	1-3%	7/13/2020	Recruiting	
APEC1621-N	Selpercatinib	RET inhibitor	1-2%	9/14/2020	Recruiting	5/8/2020

Screening Protocol Enrollment

- 1074 patients from 100 COG sites enrolled between 7/24/2017 and 9/10/2020

Subjects enrolled



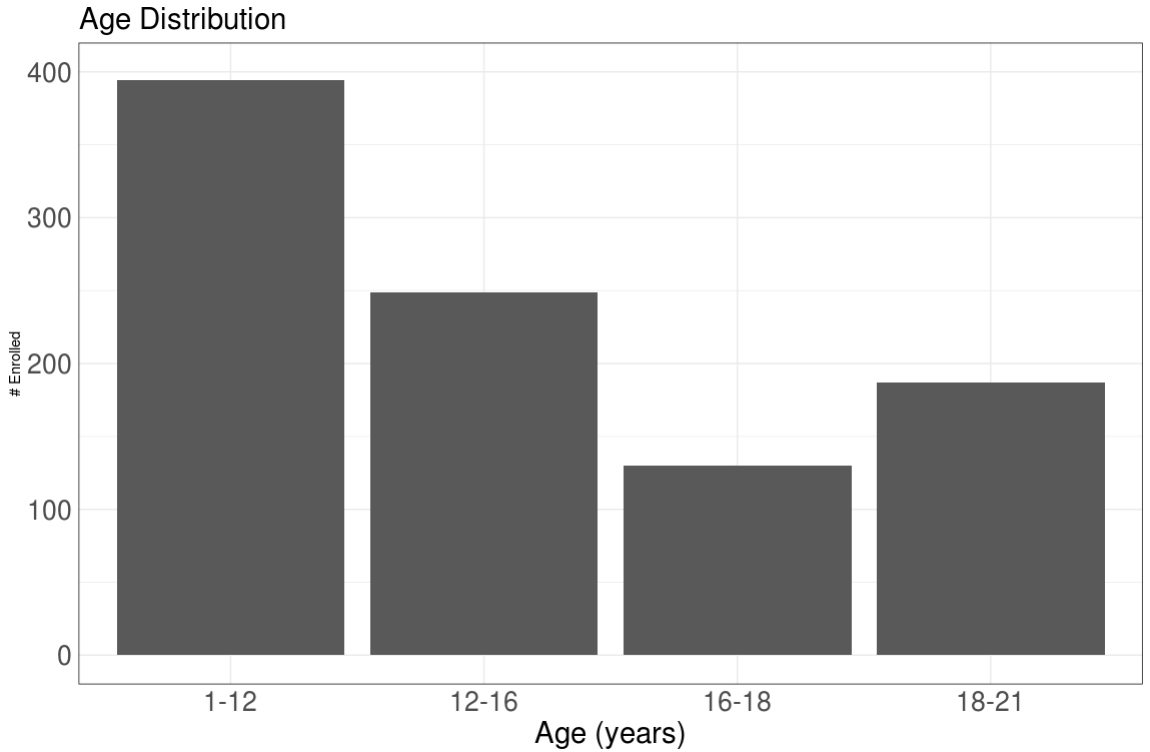
COVID-19

	Dates	N
Q1	7/24/17-9/30/17	18
Q2	10/1/17-12/31/17	49
Q3	1/1/18-3/31/18	86
Q4	4/1/18-6/30/18	81
Q5	7/1/18-9/30/18	87
Q6	10/1/18-12/31/18	101
Q7	1/1/19-3/31/19	94
Q8	4/1/19-6/30/19	129
Q9	7/1/19-9/30/19	76
Q10	10/1/19-12/31/19	115
Q11	1/1/20-3/31/20	93
Q12	4/1/20-6/30/20	80
Q13	7/1/20-9/10/20	64

Screening Protocol Enrollment (as of 4/30/2020)

- Patient age
  - Age range 1 to 21 years (median = 13)
  - 59% of patients from 12-21 years

Patients enrolled



Patient sex, race, ethnicity

Gender	Number (%)
Male	553(58)
Female	407 (42)
Racial	
White	657(68)
Black	134 (14)
Asian	38 (4)
American Indian/Alaskan Native	3 (0.3)
Multiple	15 (2)
Unknown/not reported	105 (11)

Regulatory Agency Discussion in NCI-COG Pediatric MATCH

- Discussion initiated early in the development
- Under one new IND: subprotocol reviewed by different division based on disease
- Alignment on biomarker-driven targeted therapies
- Alignment on testing in pediatric when toxicity acceptable
- Alignment on starting dosing once RP2D in adult determined
- Evaluation by arm
- No IDE required – reviewed as Adult MATCH trial

Challenges and Opportunities

- Existing clinical trial infrastructure
- Abundance of targeted agents
- Biopsy requirement for eligibility
- Evolving standard of care and comparator selection
- Combinations
- Safety oversight and monitoring

Summary

- NCI-COG Pediatric MATCH: collaborative framework for efficient collection, processing and sequencing of refractory pediatric cancers
- ~25% of study patients with tumor submitted assigned to a treatment arm, with 40% enrolled on the trials
- Ability to evaluate a wide spectrum of childhood cancers (from common to ultra-rare)

Summary

- Master protocols expand the promise of Precision Oncology to children
- Efficient mechanism for evaluating novel agents (dose-finding and activity screening)
- Biomarker-driven tissue agnostic cancer drug development strategies must include children
- Early communication with both CDER and CDRH on study design and research use of IVDs and IDE

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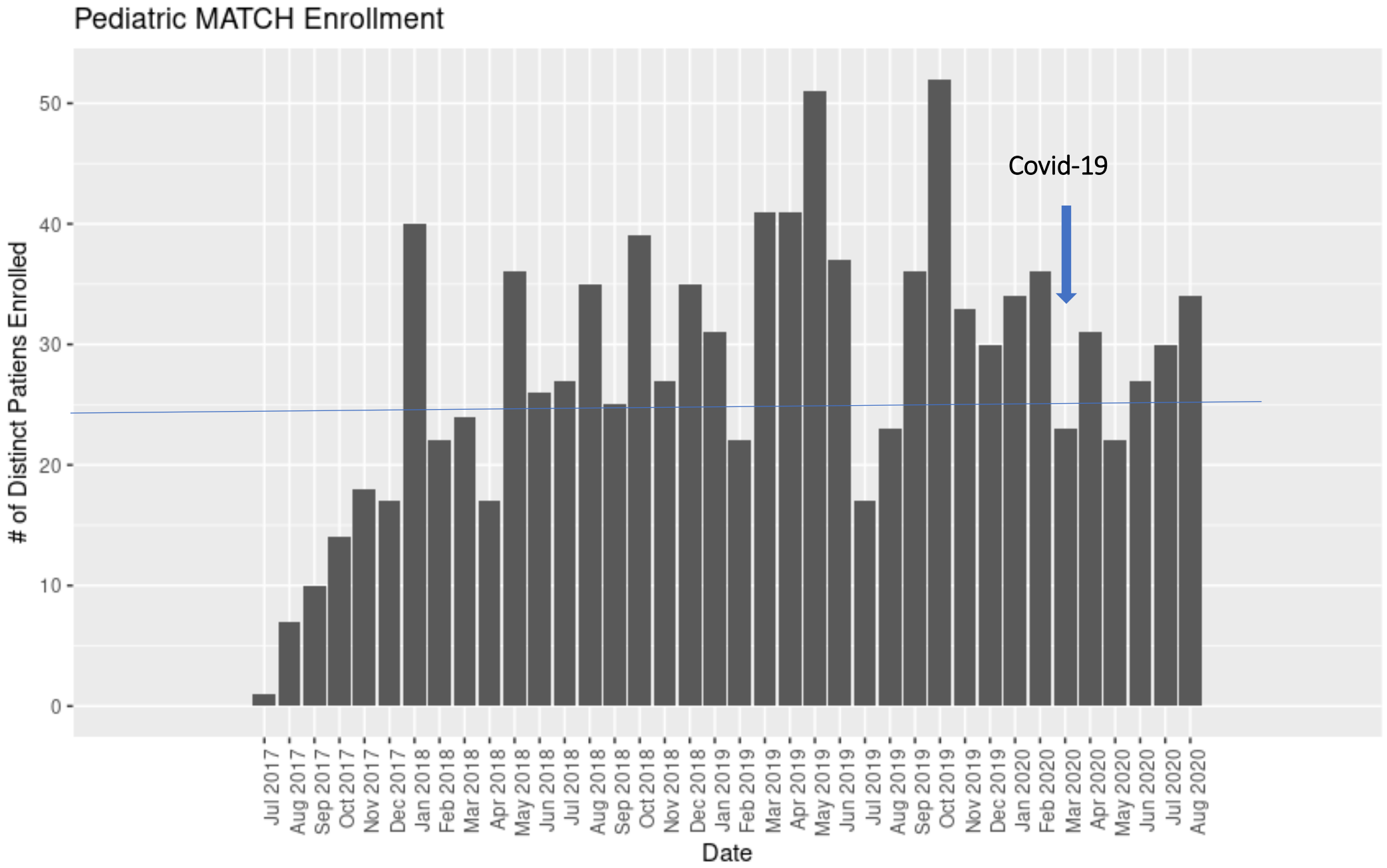
Back-up


Pediatric MATCH Enrollment
# of Distinct Patiens Enrolled
50
40
30
20
10
0
Covid-19
Jul 2017
Aug 2017
Sep 2017
Oct 2017
Nov 2017
Dec 2017
Jan 2018
Feb 2018
Mar 2018
Apr 2018
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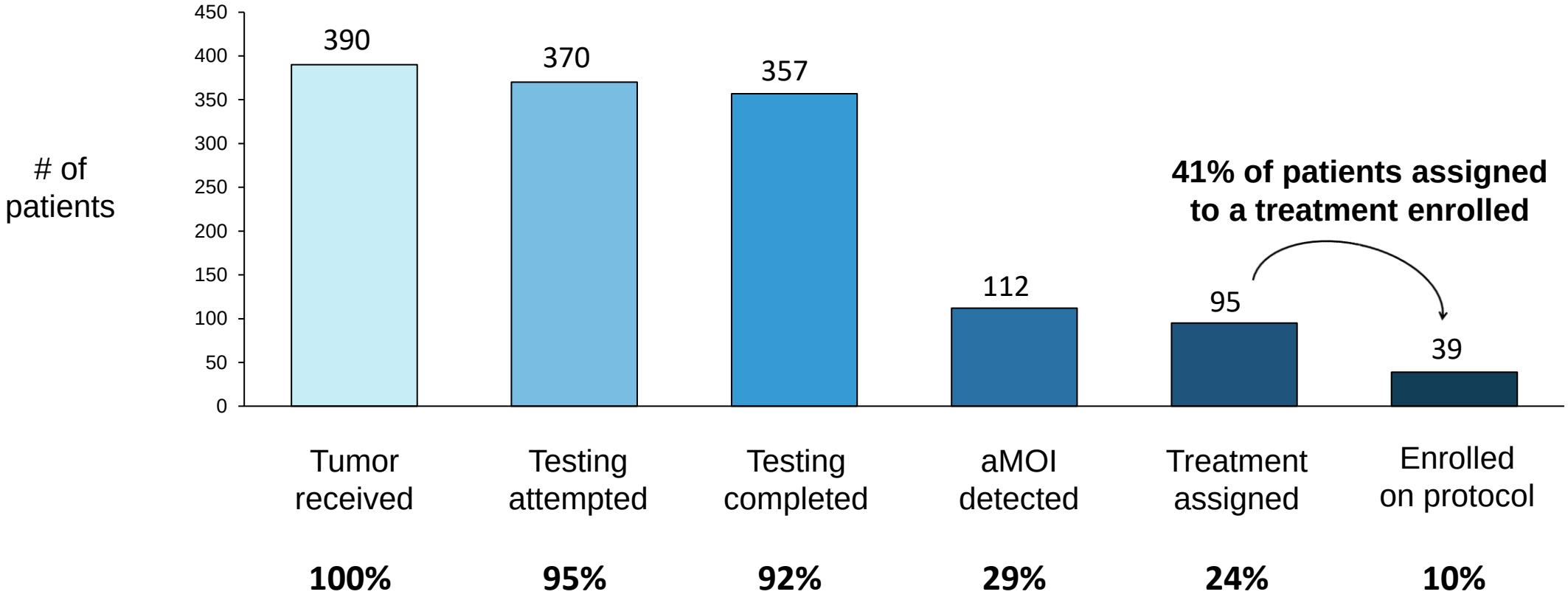
May 2020
Jun 2020
Jul 2020
Aug 2020
Date

Tumor testing and matching (as of ASCO2019)

- Tumor sample was received for 390/422 (92%) enrolled patients, as of 12/31/2018
- Tumor sample was received for 909/960 (95%) enrolled patients, as of 4/30/2020



Median turnaround time (tumor receipt to assignment): 15 days

Subprotocol matching and enrollment

- 95 of 390 (24%) with tumor submitted had at least one match assigned
- 39 of 390 (10%) with tumor submitted enrolled on treatment subprotocol

Protocol ID	Agent	Matched	Enrolled	Enrolled (%)
APEC1621-A	Larotrectinib	3	3	100%
APEC1621-B	Erdafitinib	4	2	50%
APEC1621-C	Tazemetostat	9	4	44%
APEC1621-D	LY3023414	13	4	31%
APEC1621-E	Selumetinib	31	11	35%
APEC1621-F	Ensartinib	8	3	38%
APEC1621-G	Vemurafenib	7	3	43%
APEC1621-H	Olaparib	11	4	36%
APEC1621-I	Palbociclib	8	2	25%
APEC1621-J	Ulixertinib	1	0	0%

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Data shown for highest priority match only (n=95);
Treatment subprotocol enrollment as of 12/31/18