Master Protocols in Pediatric Oncology: Access to Precision Medicine

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Center for Drug Evaluation and Research
U.S. FDA

Outline

- Precision Medicine and Oncology Drug Development
- Few opportunities for extrapolation
- New paradigm for leveraging adult experience in cancer drug development
- Current and planned “Precision Medicine Studies” – Biomarker derived treatment assignment in pediatrics
- Challenges and Opportunities

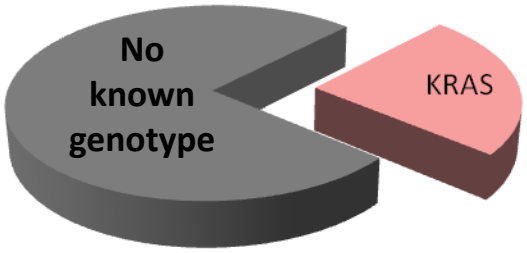
Precision Medicine and Oncology Drug Development

- Precision oncology requires novel study platforms for evaluating new targeted therapies
  - Multiple new targeted agents (including same in class)
  - Combinations
  - Standard control arms
  - Centralized biomarker platforms
  - Efficiency in setting of small populations (rare subsets)
- Precision cancer medicine: **targeted therapy** selection by identifying **key gene variants.**

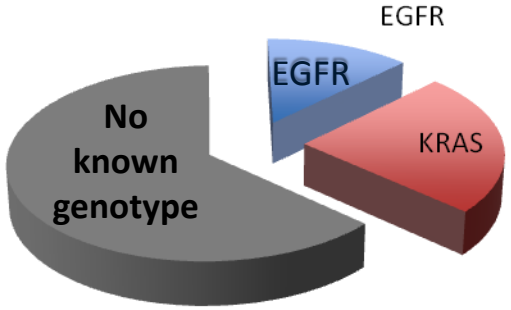
Precision Medicine and Oncology Drug Development

- Evolutionary Paradigm shift: Human genome (2003) – wide-spread availability of NGS
- Genomic and proteomic interrogation of individual cancers screened for specific molecular abnormalities for which “highly specific” targeted agents are available
- Resulted in the creation of multiple rare subsets(defined by molecular phenotype) of previously common cancers
- Early example: HER2 (ERB2) – breast cancer hormone receptors

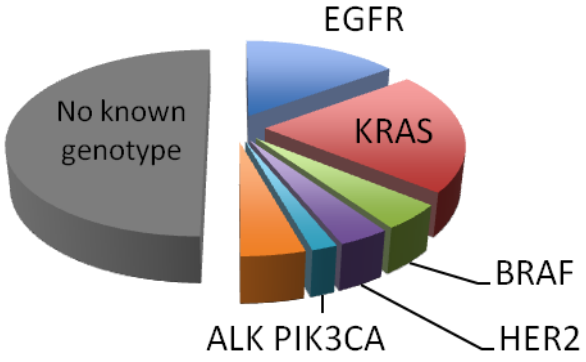
Evolution of Identification of Genomic Alterations in Lung Adenocarcinoma



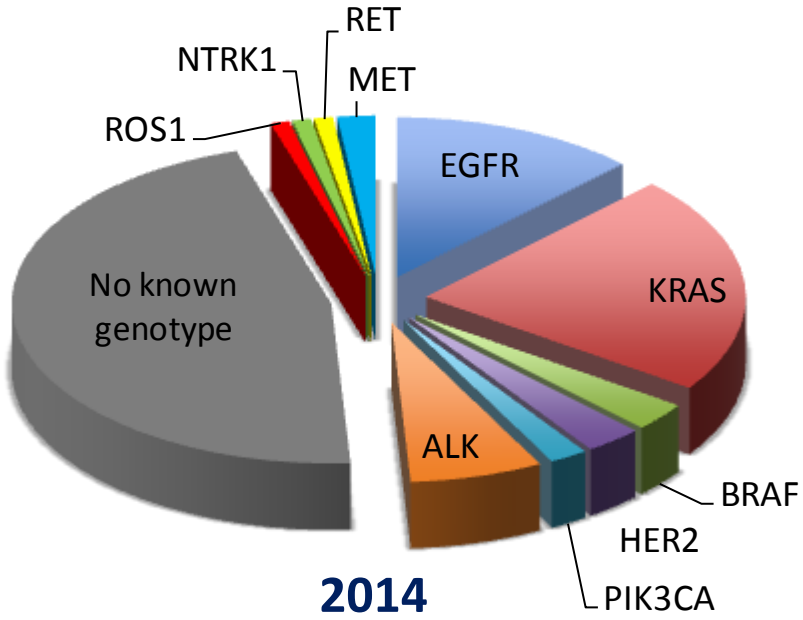
1984 - 2003



2004

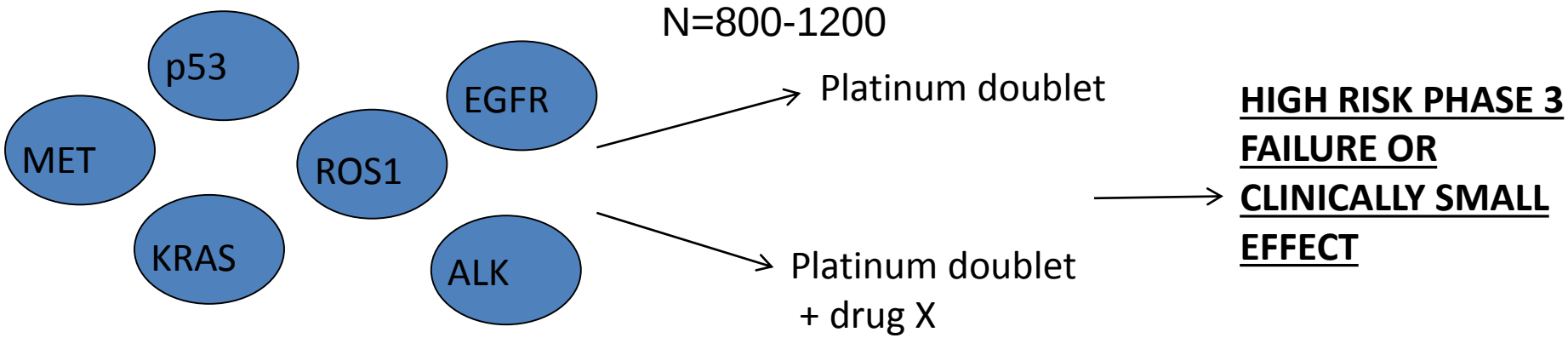


2009

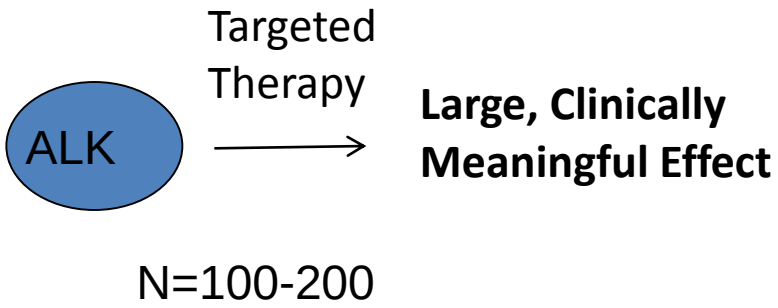


2014

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

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 group (s)
- Flexibility to add/remove agents (Adaptive)

Umbrella

Test impact of different drugs on different mutations in a single type of cancer

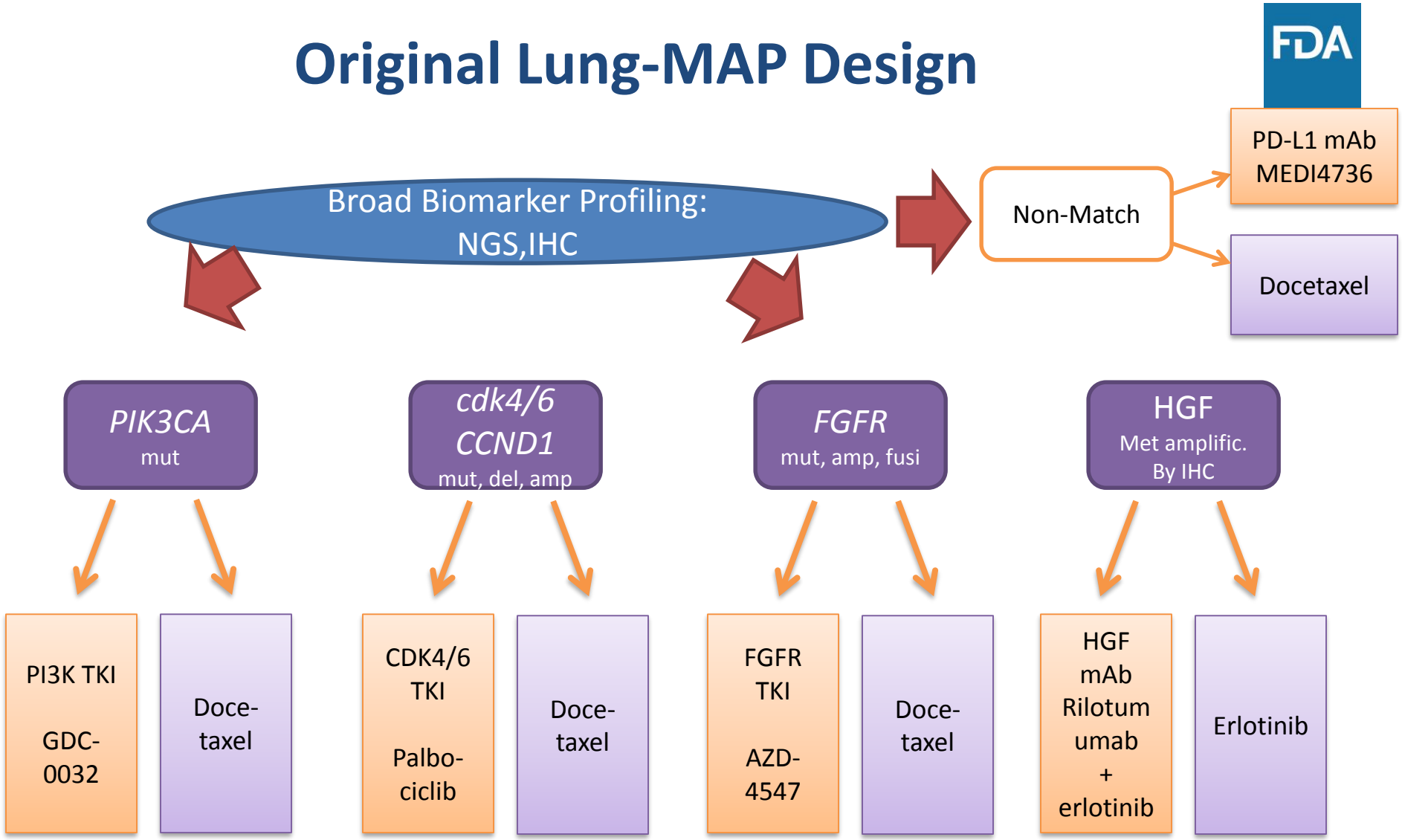
- BATTLE
- I-SPY2
- Lung-MAP
- NEPENTHENE

Basket

Test the effect of a drug(s) on a single mutation(s) in a variety of cancer types

- Imatinib Basket
- BRAF+
- NCI MATCH
- Pediatric MATCH
- iCAT1
- Peds MiOncoseq (PMTB)
- iMatrix Trial

Original Lung-MAP Design



- Interim Analysis (Phase 2 part): IRR PFS; futility/efficacy
- Final Analysis (Phase 3 part): Co-primary OS (powered) and PFS

New information and rapidly evolving landscape in NSCLC

- *November 2014*: Amgen announces termination of rilotumumab (HGF-MET inhibitor) in gastric cancer
- *March 2015*: FDA approves nivolumab in 2nd line squamous NSCLC- Docetaxel no longer SOC

What's next for master protocols

- More comprehensive 'omics profiling?
- Novel-novel combinations?
- Guidance on best practices for expansion cohorts and master protocols?
  - IRBs
  - DSMBs
  - Statistical Methodologies
- Instituting pediatric expansion cohorts when appropriate

Ongoing and Planned Precision Medicine Initiatives in Pediatric Oncology

- Most childhood cancers (embryonal origin) – low mutation frequency
- Some childhood cancers have very few recurrent events
- Initial therapy (H.D. chemo/XRT)
- Post-therapy sequencing of relapse samples accumulate more mutations in targetable oncogenic pathways

Resistance mechanisms

- Proof of principle: UM PedsMiOncoseq/PMTB-102 pts.
  - 46% Actionable genomic results
  - 15% Action-change Rx
  - 75% clinical benefit (ModyR, JAMA 214: 913-25, 2015

The First Multi-Institution PCM Study in Pediatric Oncology: the iCat1 Study

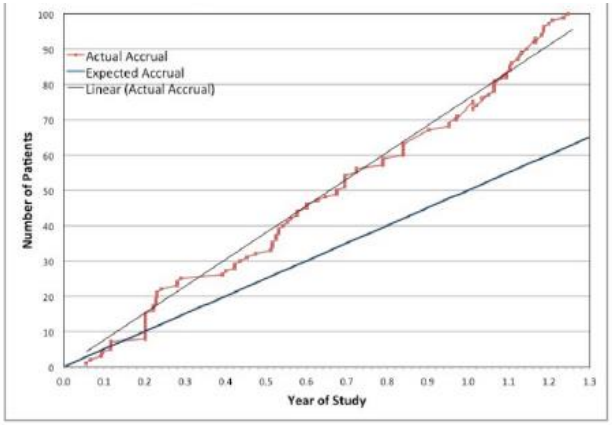
– Goal: to determine whether it is feasible to identify key gene mutations and make an **i**ndividualized **ca**ncer **t**herapy or **iCat** recommendation using currently available clinical gene tests

Eligibility: High risk solid tumors

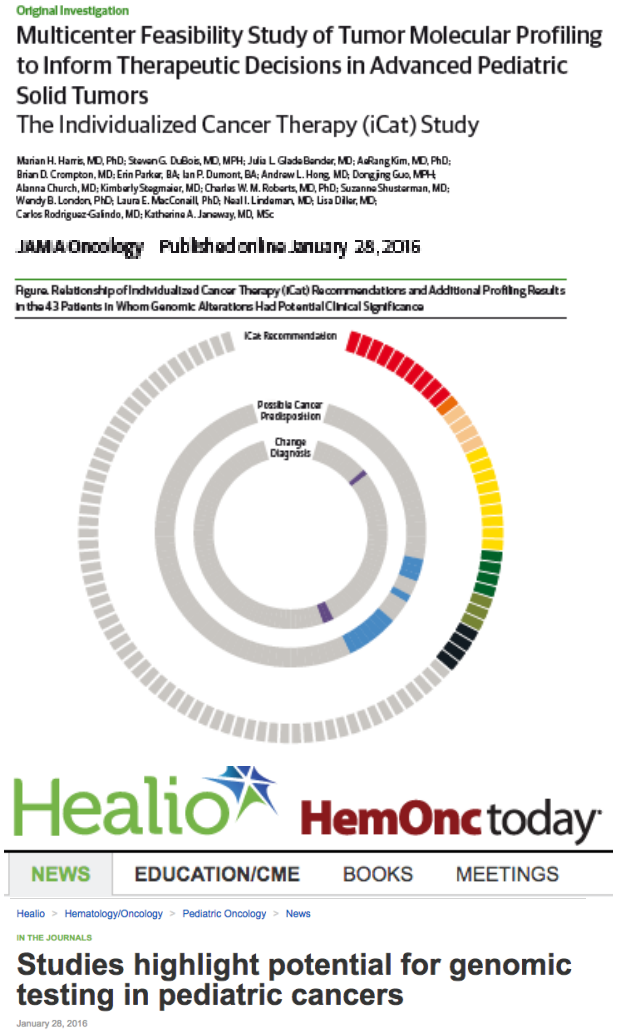
Expert Panel

The iCat1 Study, Results

- High degree of physician and patient engagement



- Conducting a multi-institution study is feasible
  - 40% patients enrolled from 3 collaborating Institutions
- 30% of patients received an iCat recommendation
- 40% had a result with implications for care
- >90% would participate again (Marron J,, PBC, in press)



Original Investigation

Multicenter Feasibility Study of Tumor Molecular Profiling to Inform Therapeutic Decisions in Advanced Pediatric Solid Tumors

The Individualized Cancer Therapy (iCat) Study

Marian H. Harris, MD, PhD; Steven G. DuBois, MD, MPH; Julia L. Glade Bender, MD; AaRang Kim, MD, PhD; Brian D. Crompton, MD; Erin Parker, BA; Ian P. Dumont, BA; Andrew L. Hong, MD; Dongjing Guo, MPH; Alanna Church, MD; Kimberly Stegmaier, MD; Charles W. M. Roberts, MD, PhD; Suzanne Shusterman, MD; Wendy B. London, PhD; Laura E. MacConaill, PhD; Neal I. Lindeman, MD; Lisa Diller, MD; Carlos Rodriguez-Galindo, MD; Katharine A. Janeway, MD, MSc

JAMA Oncology Published online January 28, 2016

Figure. Relationship of Individualized Cancer Therapy (iCat) Recommendations and Additional Profiling Results in the 43 Patients in Whom Genomic Alterations Had Potential Clinical Significance

Healio HemOnc today

NEWS EDUCATION/CME BOOKS MEETINGS

Healio > Hematology/Oncology > Pediatric Oncology > News

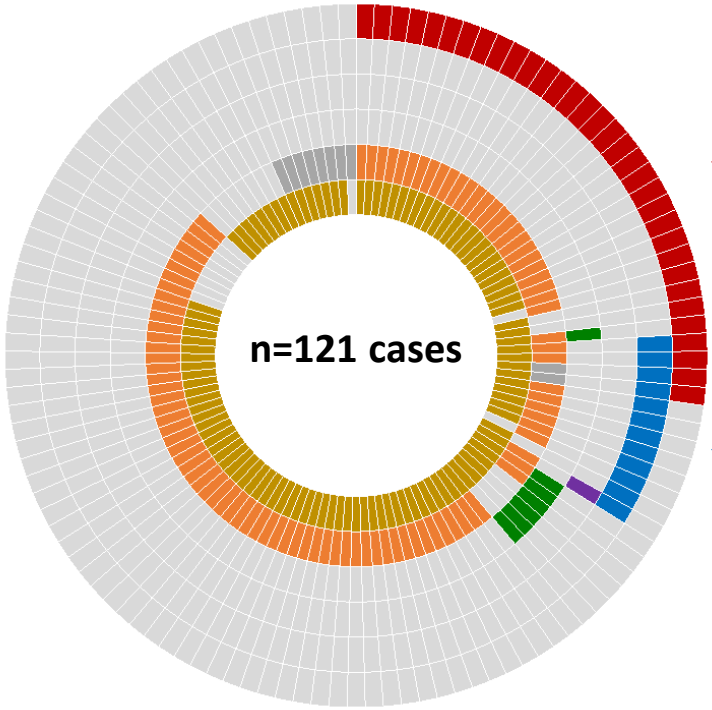
IN THE JOURNALS

Studies highlight potential for genomic testing in pediatric cancers

January 28, 2016

Harris M et al., JAMA Oncology 2016

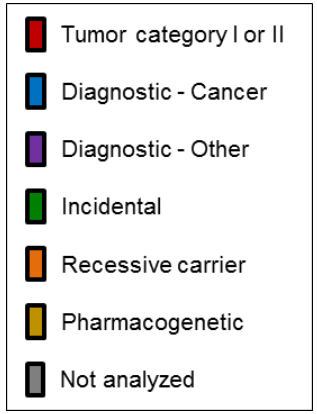
Putting the puzzle pieces together



Combined tumor and germline exome results

"Potentially" clinically-relevant tumor mutations (many not currently targetable) in 25%

Inherited cancer mutations in 10%



Slide Credit: Will Parsons
Parsons et al, *JAMA Oncology*

Lesson 3: Germline cancer predisposition is more common than previously appreciated

G·A·I·N

Genomic Assessment Informs Novel Therapy

CONSORTIUM

- Boston Children's Hospital
- Children's Hospital at Montefiore
- Children's Hospital of Philadelphia
- Children's National Medical Center
- Columbia University Medical Center
- Dana-Farber Cancer Institute
- Huntsman Cancer Institute, University of Utah
- Nationwide Children's Hospital
- Seattle Children's Hospital
- UCSF Benioff Children's Hospital
- University of Chicago Comer Children's Hospital
- Children's Hospital Colorado
- UT Southwestern Medical Center

12 institutions collaborate on the design and conduct of clinical genomic or tumor profiling protocols investigating the clinical impact of a precision cancer medicine approach in recurrent/refractory pediatric cancers

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

A phase 2 precision medicine cancer trial
Co-developed by the Children's Oncology Group and the National Cancer Institute

NIH NATIONAL CANCER INSTITUTE

June 22, 2016

NCI-Molecular Analysis for Therapy Choice (NCI-MATCH or EAY131)

Study Chairs: **Keith T. Flaherty[1], Alice P. Chen[2], Peter J. O'Dwyer[3], Barbara A. Conley[2], Stanley R. Hamilton[4], Mickey Williams[5], Robert J. Gray[6], Shuli Li[6], Lisa M. McShane[6], Lawrence V. Rubinstein[2], Susanna I. Lee[1], Frank I. Lin[7], Paolo F. Caimi[8], Albert A. Nemcek, Jr.,[9] Edith P. Mitchell[10], James A. Zwiebel[2]**

[1]Massachusetts General Hospital, Boston, MA; [2]National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis, Bethesda, MD; [3]University of Pennsylvania, Philadelphia, PA; [4]MD Anderson Cancer Center, Houston, TX; [5] NCI Frederick National Laboratory for Cancer Research, Frederick, MD; [6]Dana-Farber Cancer Institute, Boston, MA; [7]NCI Cancer Imaging Program, Rockville, MD [8]Case Western Reserve University, Cleveland, OH, [9]TNorthwestern University, Chicago, IL, [10]Thomas Jefferson University, Philadelphia, PA

Slides 27-35: Courtesy of Dr. N. Seibel

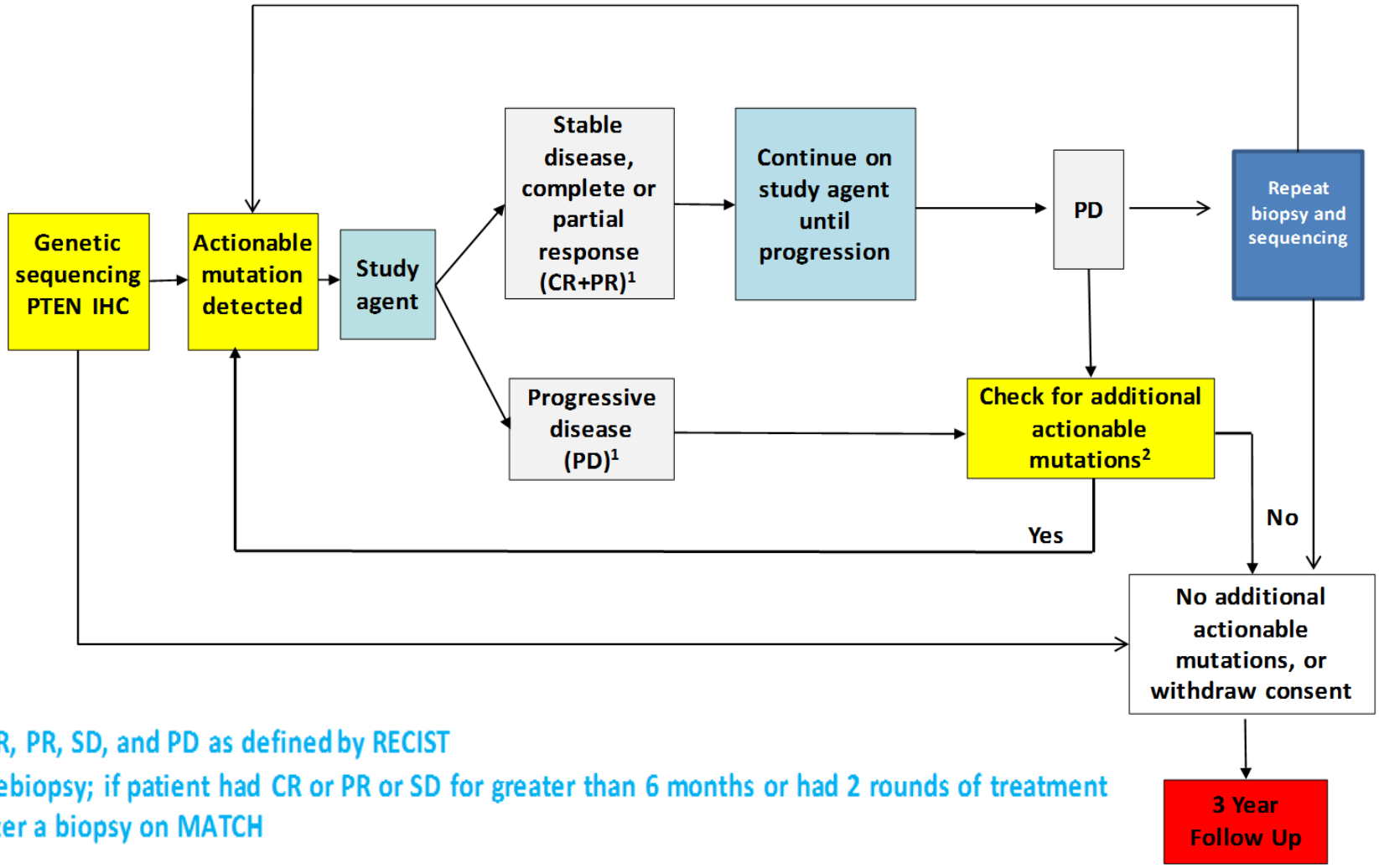
Reporting and Actionable Mutations by NCI-MATCH Assay

- **Total genes: 143**
- **Mutations of interest (MOI) reported by assay:**
  - 4066 pre-defined hotspot
    - 3259 SNVs
    - 114 Small indels
    - 435 Large indels (gap >=4bp)
    - 75 CNVs
    - 183 Gene fusions
  - Deleterious mutations in 26 tumor suppressor gene
  - EGFR exon 19 inframe deletions and insertions
  - ERBB2 exon 20 inframe insertions
  - KIT exons 9 and 11 inframe deletions/ insertions
- **Actionable MOI (aMOI):**
  - Subset of MOIs with level of evidence

NCI-MATCH Trial Status

- Trial opened on Aug 12, 2015, with 10 treatment arms
  - And plan to add at least 14 more arms in coming months
- Initial goal of 3000 patients for tumor gene testing
  - Estimated mutation matching rate of 30% when all arms open
  - But 10% for first 10 arms
- Registration of *new* patients was paused on Nov 11, 2015
- By the time 500 patients had undergone tumor testing, several hundred more had begun the initial screening process-total of 795 patients screened
- 9% actionable aberration actually matching a treatment arm
- Reopened and expanding to 24 arm

NCI-MATCH Schema



[1]CR, PR, SD, and PD as defined by RECIST

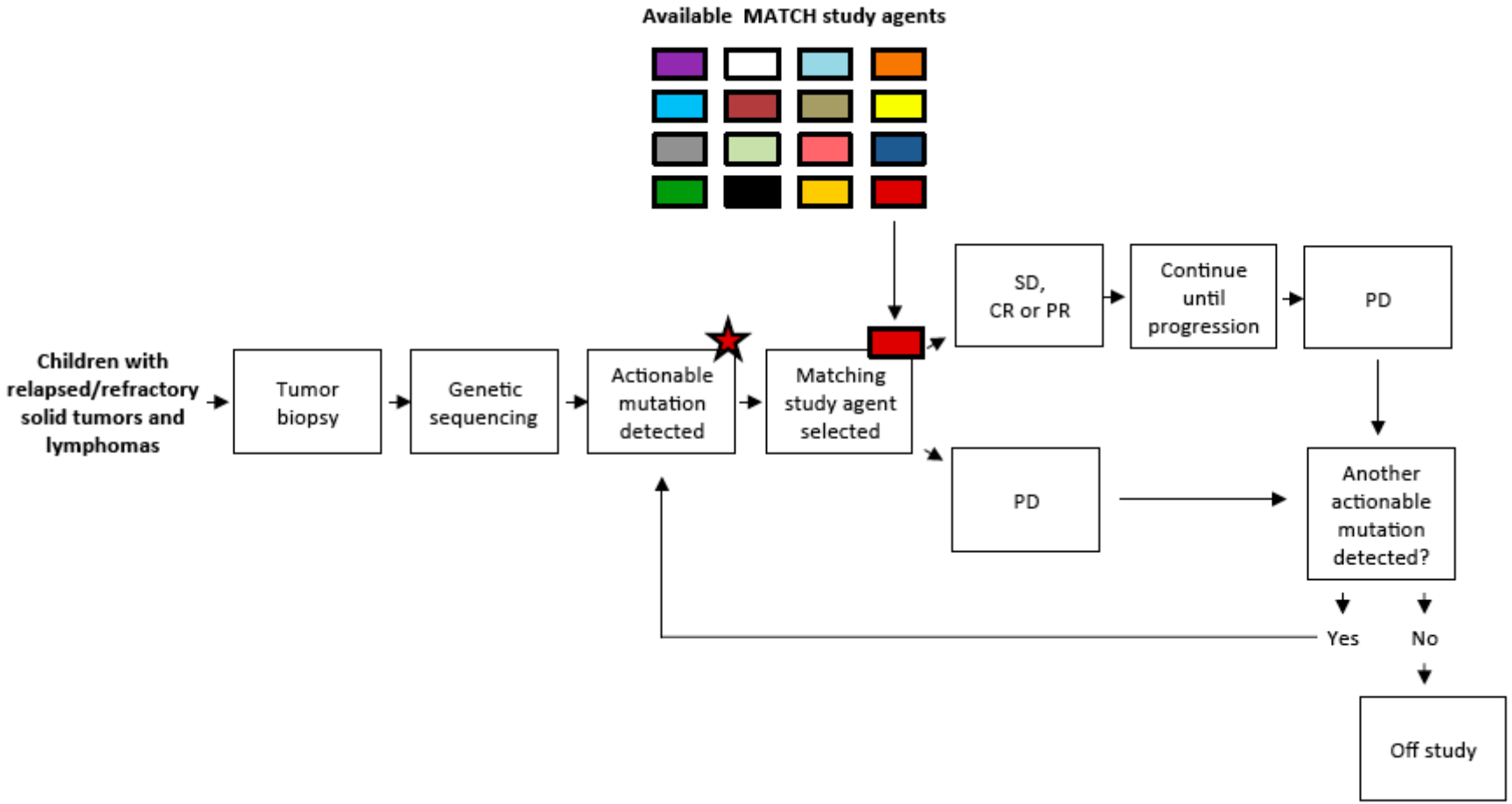
[2]Rebiopsy; if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH

NCI-Pediatric MATCH
Design Features

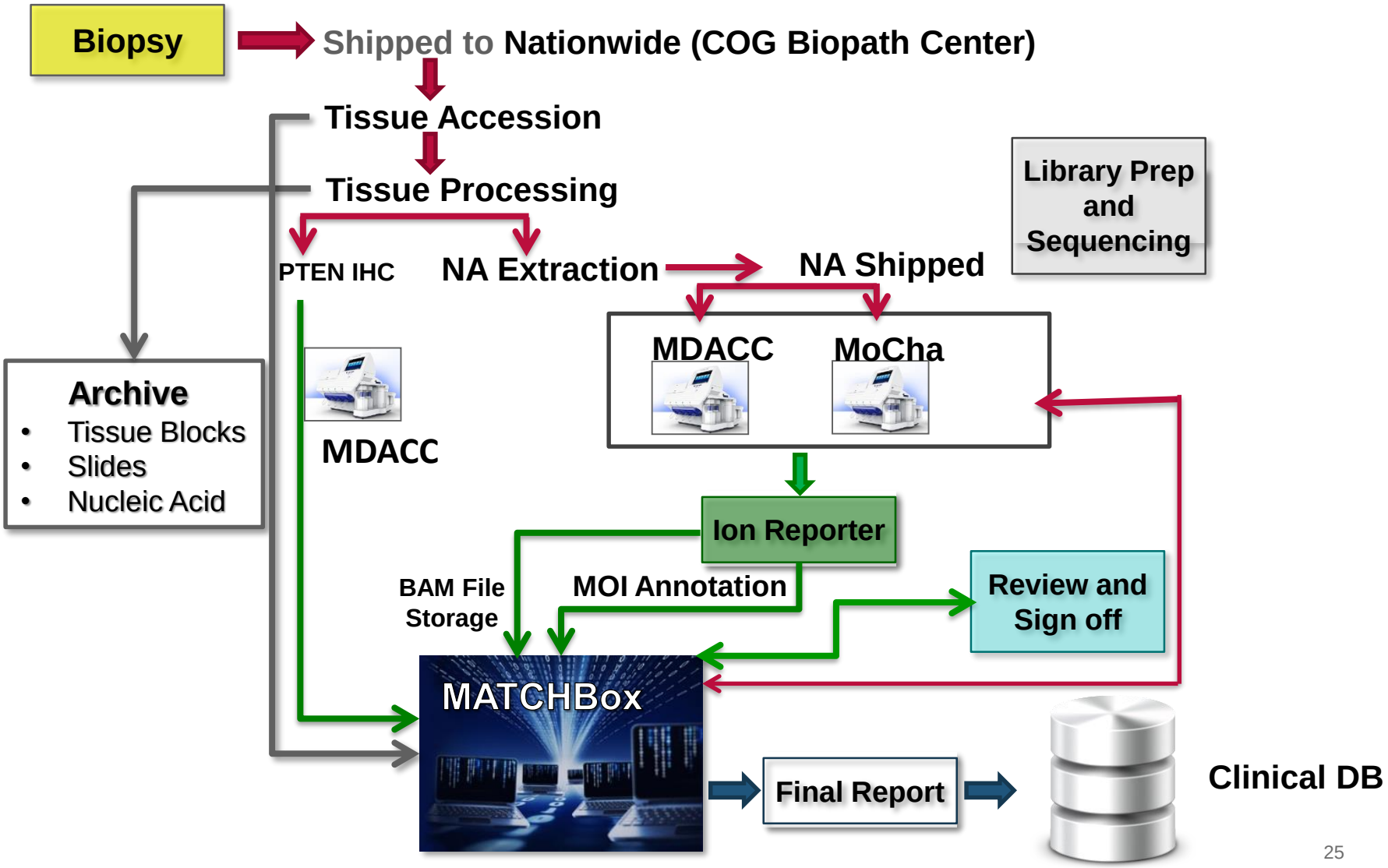
- Test many children and adolescents to find widely distributed genetic alterations
- Biopsies from the time of recurrence except for DIPG (from dx)
- Inclusion of agents with adult RP2D
- Response rate (tumor regression) will be primary efficacy measure
- Blood sample acquisition and return of germline sequencing results related to inherited cancer susceptibility
- Possibility of assignment of patients with non-target-bearing tumors to selected agents that have demonstrated activity in target-bearing tumors

Slides 27 thru 33: Courtesy Dr. N. Seibel

NCI-Pediatric MATCH Schema



NCI-Pediatric MATCH Assay System & Work Flow



NCI-Pediatric MATCH Treatment Arms

Agent Class	aMOI Frequency	Subarm chair	Subprotocol ID
Pan-TRK inhibitor	2-3%	Katie Janeway	APEC 1621-A
FGFR inhibitor	2-3%	Jae Choi	APEC 1621-B
EZH2 inhibitor		Susan Chi	APEC 1621-C
PI3K/mTOR	5-10%	Ted Laetsch	APEC 1621-D
MEK inhibitor	10-20%	Carl Allen	APEC 1621-E
ALK inhibitor	2-3%	Meredith Irwin	APEC 1621-F
BRAF inhibitor		Aerang Kim	APEC 1621-G

GOAL AND OBJECTIVES OF iMATRIX TRIAL

GOAL:

- To ensure earlier access to innovative molecules for children and young adults and to optimize early stage data collection for confirmatory trial decision-making

OBJECTIVES :

- Maximize early access to new therapies across a range of pediatric tumor types
- Reduce number of patients subjected to potentially sub-therapeutic doses
- Enrich the proportion of patients that have the potential to gain benefit on the basis of tumor biology or drug target prevalence
- Produce a robust data package for PK/PD, dosing, tolerability, and safety
- Faster and more reliable data acquisition for decision-making for confirmatory trials

*Note: The Sponsor has already initiated two independent, pediatric early-phase studies for atezolizumab and cobimetinib based on the MOA as stand-alone protocols

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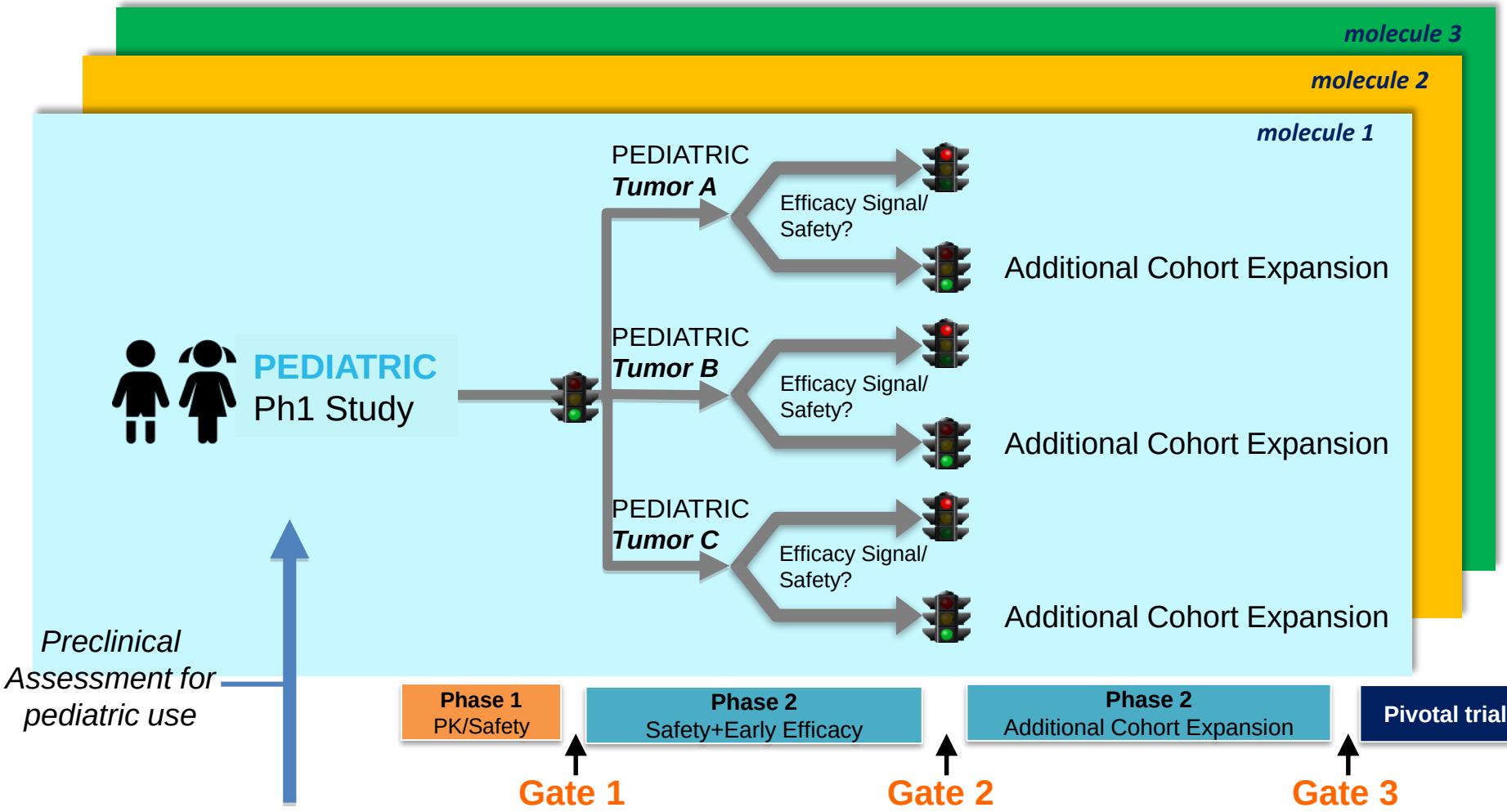
iMATRIX TRIAL STRUCTURE

MoA-driven in disease context, Gated design, Multiple molecules



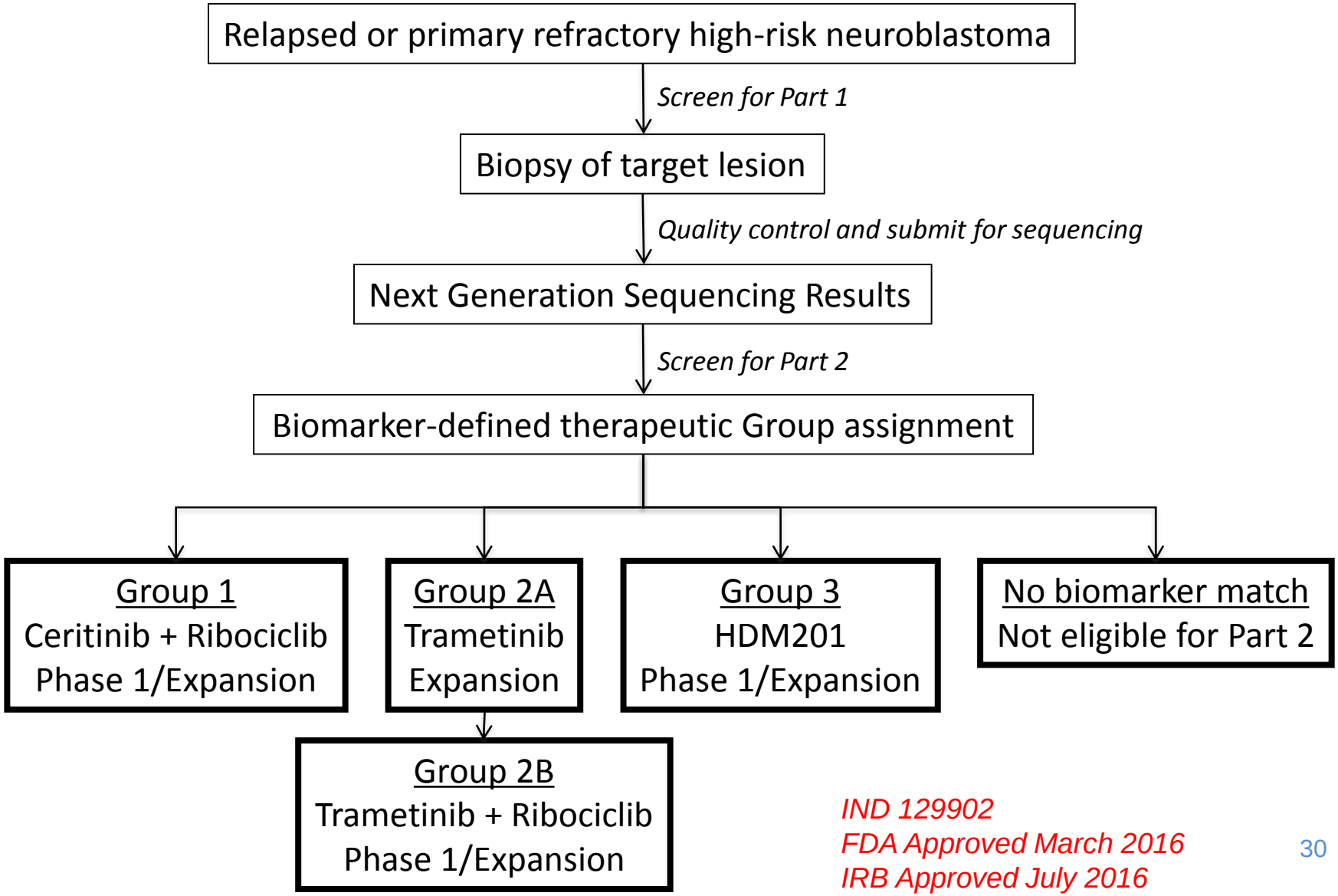
ADULT

Ph1/2 Studies **Ph3 – Disease 1** // **Ph3- Disease 2** // **Ph3 – Disease 3**

iMatrix Trial

- Regulatory agency support
- Enrichment (biomarker directed) maximizes potential benefit
- Single IND Master Protocol with individual substudies (amendment)
- Frequent consultation/engagement with regulatory agencies and investigator community
- Limited to sponsor pipeline
- Opportunity for pre-competitive space collaboration
- Parallel Scientific Advice – EMA Qualification Procedure

NExt generation PErsonalized Neuroblastoma THErapy (NEPENTHE)



IND 129902
FDA Approved March 2016
IRB Approved July 2016

NEPENTHE

Next Generation personalized Neuroblastoma THERAPY

- High risk NBL harbors subpopulations that confer resistance to therapy, but may be exploited with rationally selected targeted agents
- First pediatric cancer clinical trial to match genomic aberrations at time of relapse to rationally designed biomarker-defined **combinations** of molecularly targeted agents that show synergistic activity in a variety of preclinical models
- Expect 90% of patients to have treatment choices
- Master protocol will continue to bring additional agents to the clinic based on ongoing preclinical work
- Blueprint for similar trials in other childhood cancers

Slides 40-43: Courtesy: Dr. Y. Mosse

Assignment of treatment based on molecular alteration detected at progression

		Inclusion Biomarkers				Exclusion Biomarkers	
Group	**Therapy**	**Mutation***	**Amplification****	**Deletion*****	**Fusion******	**Mutation***	**Deletion*****
1	~~ceritinib~~+ ribociclib	*ALK**	*ALK*		*ALK*	*RB1*	*RB1*
2A°	Trametinib	*BRAF, HRAS, NRAS, PTPN11, NF1*		*NF1*	*BRAF*	*RB1*	*RB1*
2B	Trametinib + ribociclib	*BRAF, HRAS, KRAS, MAP2K1, MAP2K2, MAP2K4, MYCN, NRAS, PTPN11,*	*BRAF, CCND1, CCDN2, CCND3, CDK4, CDK6, MYCN*	*CDKN2A, CDNK2B, NF1, NF2*	*BRAF*	*RB1*	*RB1*
3	HDM201		*MDM2, MDM4*			*TP53*	*TP53*

**ALK mutation defined as: Mutations within the tyrosine kinase domain of ALK at any of the three hotspot residues- R1275, F1174 and F1245; additionally, the following ALK TKD sequence variations are also known to be activating I1170N, I1170S, I1171N, Y1278S, R1192P, M1166R, L1196M and G1128A*{Bresler, 2014 #7255}.. *Any sequence variation in ALK must be biochemically proven to be activating for patient to be eligible for this therapy group*

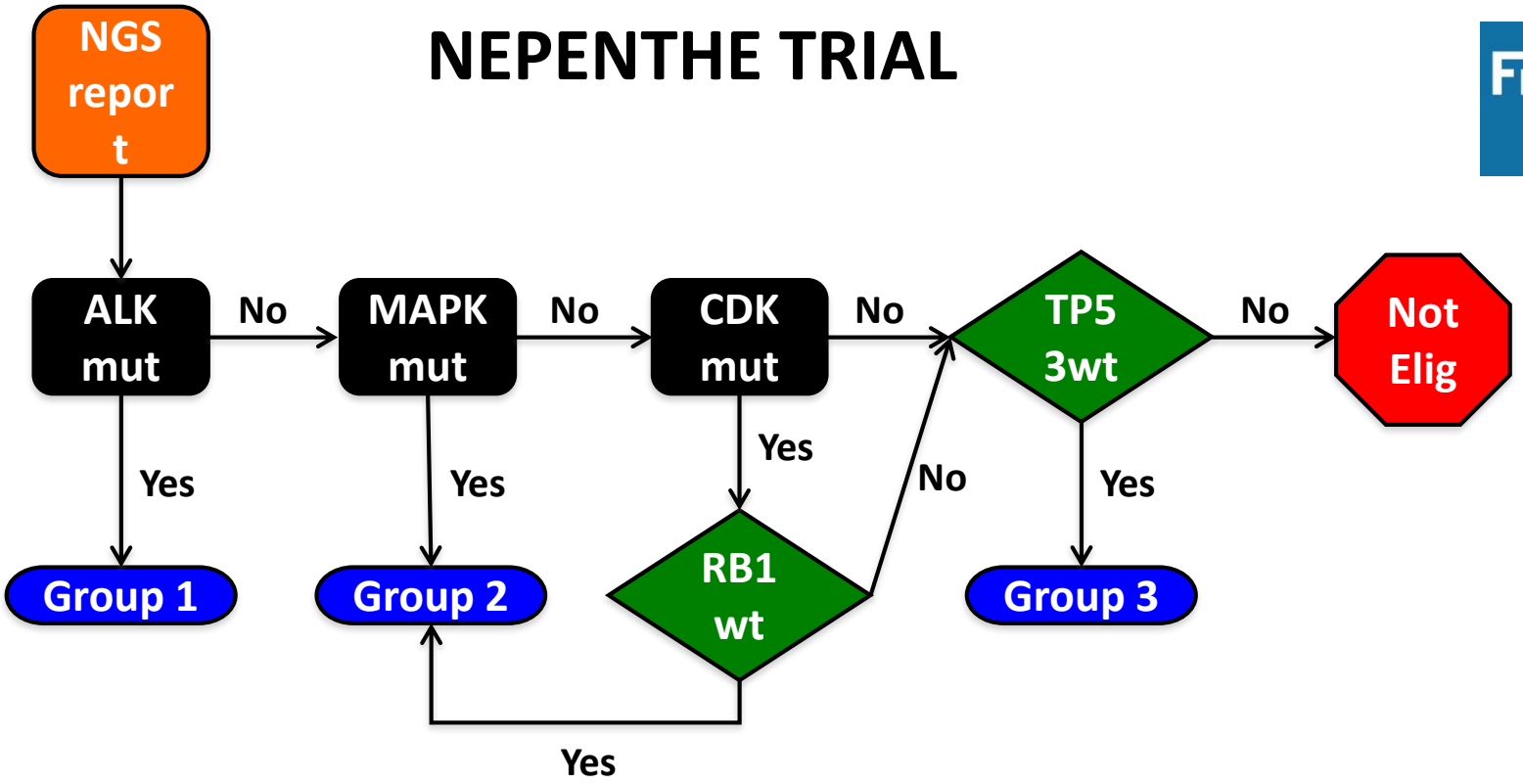
***Amplification is defined as greater than 4-fold increase in the gene copy number as compared to reference genes located on the same chromosome (see below for details)*

****Must have evidence for bi-allelic deletion.*

***** The presence of any ALK or BRAF fusion protein consistent with kinase activation that arises from a chromosomal translocation.*

° *Mutations for assignment to group 2 will initially be limited to these specific mutations (Group 2A). Upon initiation of the trametinib + ribociclib combination cohort (Group 2B), the list of mutations will be expanded.*

NEPENTHE TRIAL



- **Primary objectives:** safety and ORR within context of a phase 1/1b biomarker-driven trial
- **Secondary objectives:** define genomic landscape of relapsed NB; determine frequency by which a drug-target match leads to objective benefit
- **Correlative biology studies:**
  - Serial detection of mutations in circulating cfDNA
  - Generate Patient-Derived Xenograft models
  - Define clonal evolution

Master Protocols in Pediatric Oncology: Challenges/Opportunities

- Existing clinical trial infrastructure
- Limited number of actionable mutations
- Abundance of targeted agents
- Key genomic drivers of pediatric cancers – targeted inhibitors currently unavailable
- Focus restricted to genome simplistic – proteome and epigenetic factors

Challenges/Opportunities

- Biopsy requirement for eligibility
- Evolving standard of care and comparator selection
- Addressing combinations
- Adaptive designs and expansion cohorts
- Safety oversight and monitoring

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