US Regulatory Perspective: Rare Tumors

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Disclosures

- No financial relationships to disclose
- No discussion of off label or investigational use of specific products/devices

Outline

- Trial design for rare tumors indication
  - General considerations
  - Endpoints
  - Natural history of disease
- Pathways to Approval
- Innovative pediatric oncology trial designs in an era of precision medicine
  - Case examples of pediatric master protocols

Challenges of Drug Development for Rare Tumors

- Small numbers
- Heterogeneous populations
- Incompletely characterized natural history
- Choice of endpoint often unclear
- Limited resources
  - patients
  - funding sources
- Rare disease drug development is a global exercise
  - collaboration and information sharing is critical

General attributes of clinical endpoints

- Clinical endpoints should:
  - be clinically meaningful
  - reflect how a patient feels, functions, or survives
  - be reliably measured
- Showing a treatment effect is dependent on:
  - the disease and its manifestations
  - the course of disease over time
  - what is being assessed and when assessed
  - the effect of the drug

Regulatory endpoints

- Measures of direct clinical benefit
  - Feels/Functions/Survives
  - Overall survival
- Other/Surrogate endpoints
  - Durable response rate
  - Progression free survival, event free survival, etc.
    - *Advantages*: smaller sample size, shorter follow up, includes stable disease, not confounded by cross-over or subsequent therapies
    - *Disadvantages*: assessment bias, frequent radiologic assessments and balanced timing between tx arms, prone to missing data

Use of clinical outcome assessments (COAs) in oncology

- Endpoints that reflect how a patient **feels or functions**
  - Improvement in *disease-specific* sx or functional impairment
- COA endpoints
  - Knowledge of disease mechanism, manifestations and course
  - Impacts choice of study population (baseline impairment)
  - Consider early in development
  - Systematic comprehensive data collection vital
- Correlation with tumor-based assessments (e.g. durable ORR)

Role of natural history of disease

- Knowledge of the natural history of disease helps guide an efficient drug development program
  - Defining the disease population
  - Choosing appropriate study duration, patient subpopulations
  - Selecting sensitive and specific outcome measures
  - Developing biomarkers
- Not always well-described in rare diseases
- Natural history study-prospective longitudinal design preferable
- Best to apply available knowledge of disease pathophysiology and clinical manifestations early in development

Pathways to approval

- Any approval requires “substantial evidence” of safety and effectiveness supported by “adequate and well-controlled” clinical data

Regular approval

Substantial evidence of clinical benefit is demonstrated prior to approval based on demonstration of direct clinical benefit or an established surrogate for clinical benefit.

Accelerated Approval

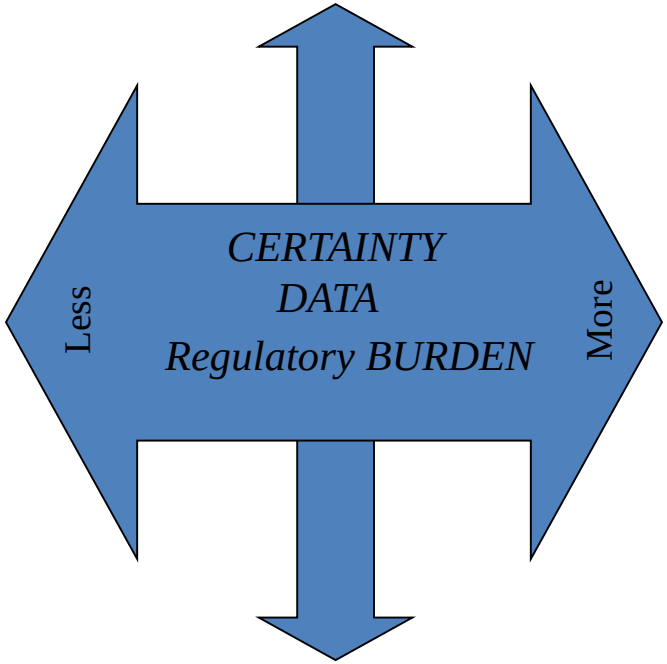
Designed to facilitate delivery of products appearing to provide a benefit for a serious or life-threatening illness lacking satisfactory treatment.

Elements of accelerated approval pathway

- "Serious and life-threatening diseases"
- Clinical data show an effect on a surrogate endpoint "reasonably likely to predict clinical benefit"
  - Durable objective response, progression-free survival, etc.
- Provide meaningful benefit over available therapies
- Approval generally earlier in drug development process
- Require post-marketing trials to confirm clinical benefit

Striking the Balance

Flexible, Efficient, Interactive



"Toxic deaths!

Delayed safety findings!

FDA asleep at the Wheel"

"Too Cautious!

Stifling Innovation!

Reduce regulatory burden!"

Consistent, Thorough, Insular/Regulatory Silo

Active ingredient: pentobarbital

Indications:

- "when little patients balk at scary, disquieting examinations"
- "when they're frightened and tense (and growing more fearful by the moment)"
- "when they need prompt sedation"

With short-acting nembutal, the dosage required is small and the margin of safety is wide. And-since the drug is quickly and completely destroyed in the body-there is little tendency toward morning after hangover. Keep a supply of all four sizes on hand. Be ready for the frightened ones before their fears begin.

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Precision Medicine and Master Protocols in Pediatric Oncology

Precision Medicine

- Tailors treatment to the genetic aberrations present in a specific tumor type
- Calls for innovative trial designs
  - Single drug/single test/all comer clinical trial model may be suboptimal for developing targeted therapies in rare cancers
  - Biomarker-driven model leads to more complex clinical trials requiring more upfront preparation but offers efficiencies
    - FDA partnership with industry/cooperative groups crucial throughout the process
    - Co-development of in vitro diagnostic(s) critical

Challenges to Childhood Cancer Research in Precision Medicine Era

- The (fortunately) relatively small numbers of patients with any specific cancer makes design and conduct of trials that can reliably identify effective new treatments challenging
- These challenges are increased by further subdividing of cancers based on tumor genomic characteristics
  - medulloblastoma: 4 subtypes
  - high-grade glioma: only 5-10% have BRAF genomic alterations; 3% EGFR mutations evaluations of inhibitors challenging for this population
- Upside: potential for dramatically increased effectiveness for small subgroups!

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 or remove agents
  - Adaptive designs

Umbrella

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

- BATTLE
- I-SPY2
- Lung-MAP
- NEPENTHE

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

Adapted from slide from Dr. Greg Reaman

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

NCI-COG Pediatric Molecular Analysis for Therapy Choice (MATCH) APEC1621

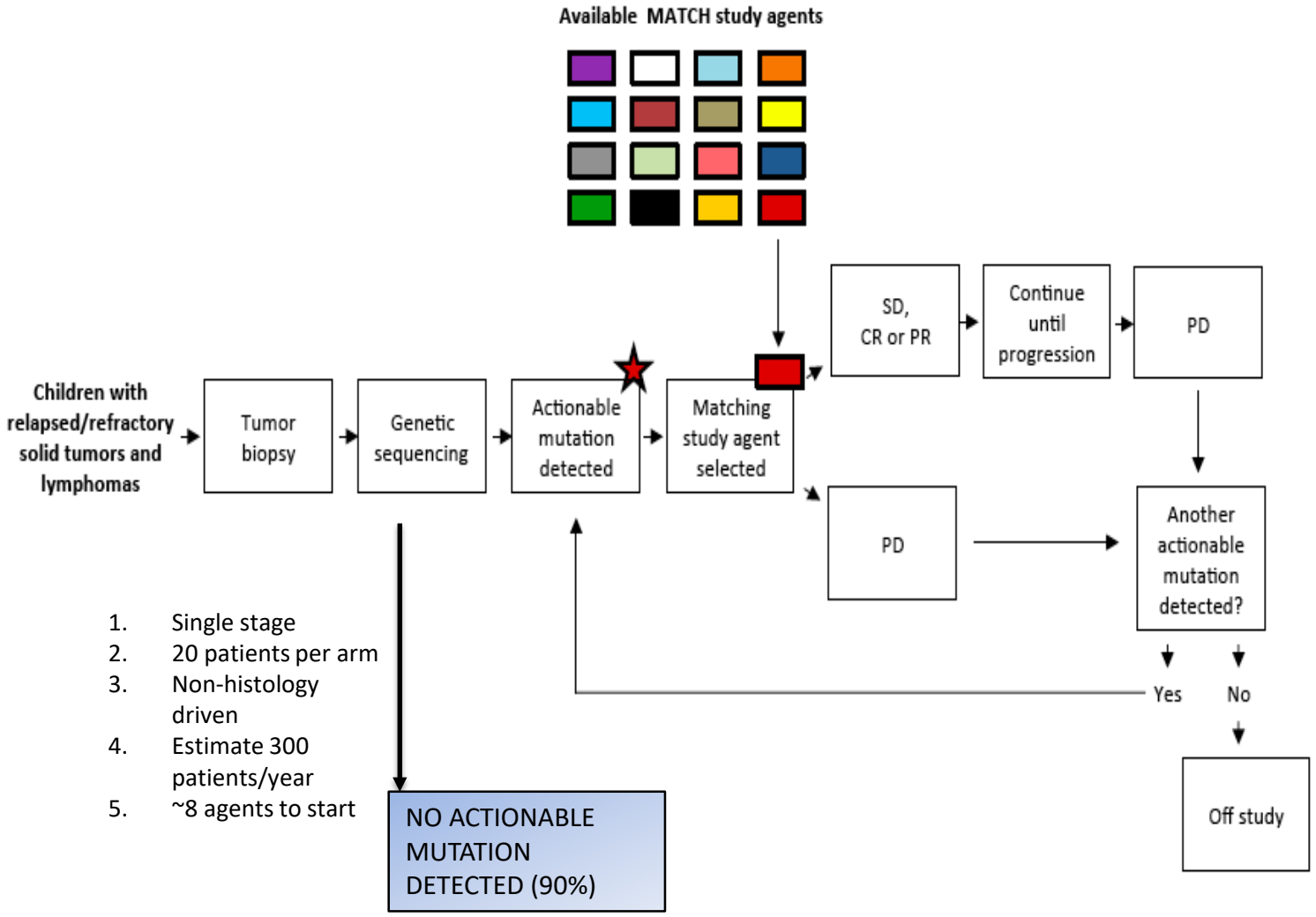
A phase 2 precision medicine cancer trial
Co-developed by the Children's Oncology Group
and the National Cancer Institute

NCI-Pediatric MATCH Design Features

- Test many children and adolescents to find widely distributed genetic alterations
- Biopsies required post-relapse except for DIPG
- 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
- Most patients screened will be biomarker negative and will not match to a treatment arm
- Possibility of assignment of patients with non-target-bearing tumors to selected agents that have demonstrated activity in target-bearing tumors

Slide adapted from Dr. N. Seibel

NCI-COG Pediatric MATCH



NIH NATIONAL CANCER INSTITUTE CHILDREN'S ONCOLOGY GROUP

Slide adapted from Dr. N. Seibel

COG APEC1621: Pediatric MATCH Study

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COG APEC1621A: LOXO-101

20 pts. → ≥3 responses → Biomarker Positive, Histology-Specific (7 pts., up to 3 cohorts)

COG APEC1621C: Tazemetostat

20 pts. → ≥3 responses → Biomarker Positive, Histology-Specific (7 pts., up to 3 cohorts)

COG APEC1621D: LY3023414

Primary Cohorts A (TSC1/2) &B (PI3K/MTOR) 20 pts. each → ≥3 responses

- Single histology → Biomarker Positive, Histology-Specific (7 pts., up to 3 cohorts per Primary Cohort)
- Single histology → Biomarker Negative, Histology-Specific (10 pts., up to 3 cohorts total)
- Responses in different histologies → Biomarker Negative, Histology-Agnostic (10 pts.)

If >1 histology-specific cohort open at same time as histology-agnostic cohort, accrual to agnostic cohort stops if activity has not been observed.

COG APEC1621E: Selumetinib

20 pts. → ≥3 responses → Biomarker Positive, Histology-Specific (7 pts., up to 3 cohorts)

COG APEC1621F: Ensartinib

Primary Cohorts A (ALK/ROS1 fusions) &B (ALK missense) 20 pts. each → ≥3 responses → Biomarker Positive, Histology-Specific (7 pts., up to 3 cohorts)

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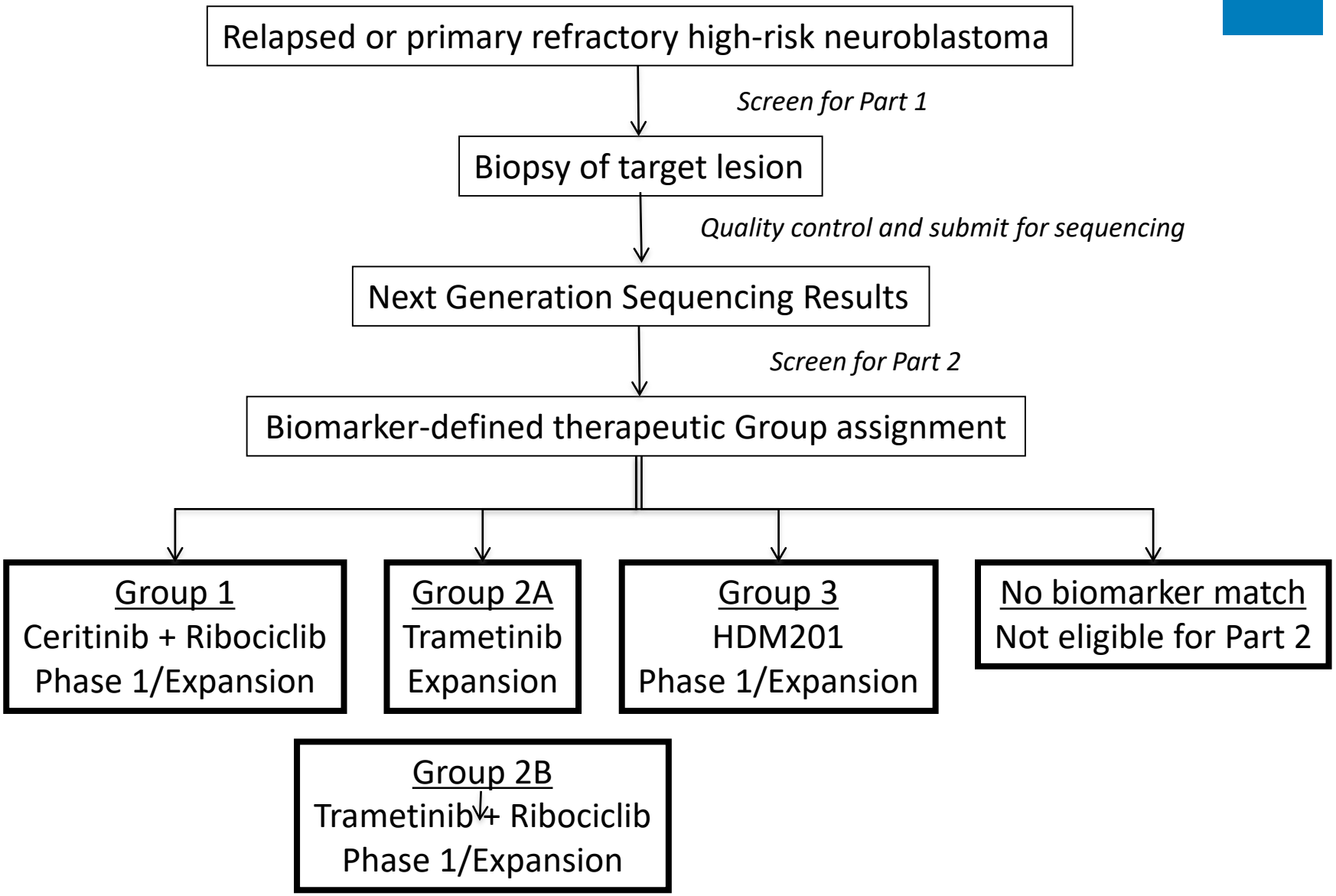
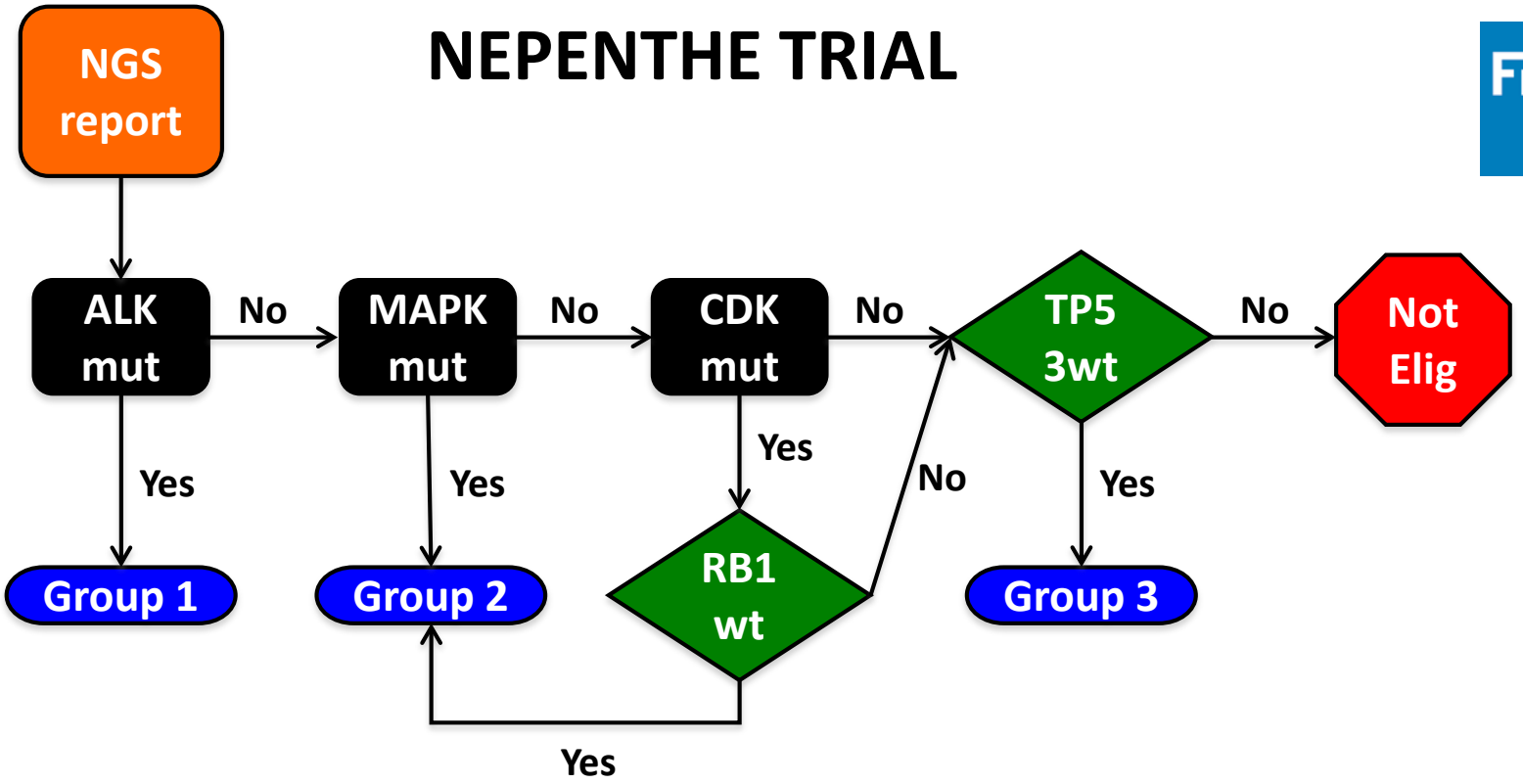
NExt generation **PE**rsonalized **N**euroblastoma **THE**rapy (**NEPENTHE**)

NEPENTHE trial

- Background: High risk NBL harbors subpopulations that confer resistance to therapy, but may be exploited with rationally selected targeted agents
- Objective: 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 design will allow additional agents to be evaluated based on ongoing preclinical work
- Blueprint for similar trials in other childhood cancers


Relapsed or primary refractory high-risk neuroblastoma
Screen for Part 1
Biopsy of target lesion
Quality control and submit for sequencing
Next Generation Sequencing Results
Screen for Part 2
Biomarker-defined therapeutic Group assignment
Group 1
Ceritinib + Ribociclib
Phase 1/Expansion
Group 2A
Trametinib
Expansion
Group 3
HDM201
Phase 1/Expansion
No biomarker match
Not eligible for Part 2
Group 2B
Trametinib + Ribociclib
Phase 1/Expansion

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

Summary

- FDA can apply scientific judgment and regulatory flexibility when making decisions about drug development and approval in rare diseases such as pediatric cancers, when appropriate.
- Timely development of safe and effective therapies for pediatric patients with cancer requires thoughtful, innovative, and efficient clinical trial designs and drug development plans.
- Global collaboration of all stakeholders is required to fully leverage scientific discoveries.
- Precision medicine and use of Master protocols will hopefully prioritize and facilitate development of products that will provide clinical benefit.

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Thank you!

Resources

- Draft Guidance: Rare Diseases: Common Issues in Drug Development

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf

- Office of Orphan Products Development

(http://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/default.htm

- Clinical Outcome Assessment Qualification Program

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm

- Critical Path Innovations Meeting

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm

- Kakkis et al. Recommendations for the development of rare disease drugs using the accelerated approval pathway and for qualifying biomarkers as primary endpoints. *Orphanet Journal of Rare Diseases* 2015

http://www.ojrd.com/content/10/1/16

	Fast Track	Breakthrough Therapy	Priority Review	Accelerated Approval
Program	Designation	Designation	Designation	Approval Pathway
Qualifying Criteria (all require condition to be serious)	Nonclinical or clinical data demonstrate potential to address unmet need	Preliminary clinical evidence demonstrates substantial improvement over available therapies	If approved would result in significant improvement in safety or efficacy	Demonstrates effect on endpoint reasonably likely to predict clinical benefit over available therapies
When to Submit	IND or after	Ideally no later than EOP2	With (s)BLA, (s)NDA	Discuss during development
Features	Expedite development and review Rolling review	Intensive development guidance Organizational commitment Rolling review	6 month vs. 10 month review clock for regulatory action after filing	Approval based on effect on endpoint that is reasonably likely to predict clinical benefit

In Vitro Companion Diagnostic Device (IVD)

- A medical device which provides essential information for the safe and effective use of a drug
- Companion diagnostics can:
  - identify patients who are most likely to benefit from a particular drug
  - identify patients likely to be at increased risk for serious side effects as a result of treatment with a drug
  - monitor response to treatment
- If the diagnostic test is inaccurate, then the treatment decision based on that test may not be optimal
- https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM510824.pdf

Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on: July 15, 2016

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact CDRH's Office of *In Vitro* Diagnostics and Radiological Health at 301-796-5711 or Pamela Bradley at 240-731-3734 or Pamela.Bradley@fda.hhs.gov; CBER's Office of Communication, Outreach and Development, at 1-800-835-4709 or 240-402-8010; or for CDER, please contact Christopher Leptak at 301-796-0017 or Christopher.Leptak@fda.hhs.gov.

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