Personalized Cancer Medicine – It's a MATCH! Focus on Refractory Solid Tumors in Pediatrics, Adolescents and Young Adults (AYA).

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Pharmacist
Children's Oncology Group

Disclosure

• No conflict of interest to disclose
• Off-label use of FDA-approved agents will be discussed

Objectives

• Discuss pediatric & AYA solid malignancies with opportunities to improve relapse/survival rates
• Evaluate the present and future role of Personalized Cancer Medicine
• Identify molecular targets of relevance to pediatric and AYA solid tumors
• Illustrate NCI's Molecular Analysis for Therapy of Choice (MATCH) initiative
• Illustrate COG-NCI Pediatric MATCH initiative
#### Definitions and Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>Anaplastic lymphoma kinase</td>
</tr>
<tr>
<td>MAPKs</td>
<td>Mitogen-activated protein kinases</td>
</tr>
<tr>
<td>ERK</td>
<td>Extracellular signal-regulated kinase</td>
</tr>
<tr>
<td>PI3K</td>
<td>Phosphoinositide 3-kinase</td>
</tr>
<tr>
<td>RAF</td>
<td>Poly(ADP-ribose) polymerase</td>
</tr>
<tr>
<td>TRK</td>
<td>Tropomyosin-related kinase (TRK)</td>
</tr>
<tr>
<td>SHH</td>
<td>Sonic hedgehog</td>
</tr>
<tr>
<td>MGMT</td>
<td>Methylguanine methyltransferase</td>
</tr>
<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
</tr>
<tr>
<td>PDGFR</td>
<td>Platelet-derived growth factor receptor</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
</tr>
<tr>
<td>JAK</td>
<td>Janus kinase</td>
</tr>
</tbody>
</table>

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### Observational Study

**Treatment inferred from mutations identified using massive parallel sequencing leads to clinical benefit in some heavily pretreated cancer patients**


Molecular portraits of numerous tumors have been studied with vast amounts of data. In parallel, effective inhibitors of certain pathways have been shown to enhance outcomes. Together, these studies have propelled clinical benefit for a select number of targeted treatments. The current study aims to identify informative mutations that would make clinical contributions.

A multidisciplinary team consisting of oncologists, molecular biologists, pathologists, and patients investigated clinical samples from 31 heavily pretreated cancer patients, taking into account mutations identified using exome or panel-based molecular testing, and relevant clinical data.

For 20 patients, the treating oncologists chose not to include the panel resequencing in the treatment plan for various reasons, such as patient factors or unstandardized protocols. However, for these patients, mutations were noted in the cancer panel.

The study concludes that the described approach can lead to individualized treatment plans, which may be especially beneficial for patients with advanced-stage disease, when standard therapies have failed. The authors recommend further studies to validate the findings and expand the application of this approach.

**Abbreviations:** mTOR = mammalian target of rapamycin, PD-1 = programmed death-1, PD-L1 = programmed death-ligand 1, PD-1/PD-L1 = programmed death-1/protein.

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### Trends in Cancer Incidence* and Death Rates in Children and Adolescents (0-19 Years), 1975-2014

*Note: The [53% decrease in mortality](https://www.cancer.gov/cancertopics/factsheet/incidence/death-rate) is visually represented in the graph. Additional information can be found on the [National Cancer Institute](https://www.cancer.gov) website.*
Cancer Deaths in Children & Adolescents with Solid Tumors 1975-2006

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Cancer Deaths Per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1975</td>
</tr>
<tr>
<td>Brain &amp; other CNS</td>
<td>0.93</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>0.36</td>
</tr>
<tr>
<td>Bones &amp; joints</td>
<td>0.35</td>
</tr>
<tr>
<td>Soft tissue (including heart)</td>
<td>0.27</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>0.14</td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>0.09</td>
</tr>
<tr>
<td>Gonad (ovary &amp; testis)</td>
<td>0.13</td>
</tr>
<tr>
<td>All other</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Smith MA et al. / J Clin Oncol 2010;28(15):2625-2634
Survival Rates

- 5-year overall survival (OS) rates for pediatric and adolescent solid tumors other than neuroblastoma (NBL) have not changed significantly over the past 1-2 decades.
- Pediatric and adolescent sarcomas (Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma) are particularly in need of better treatment options.
- Improvements in survival for pediatric brain tumors have been modest over the past 10 to 15 years for most age groups.
- Childhood cancer clinical researchers will need to focus on developing novel targeted therapies.


Audience Response Question #1

- You have a newly diagnosed 16 y.o male with stage III osteosarcoma being treated on your service. Your pharmacy student asked you about osteosarcoma research directions & probability of survival. Your answer is:
  - A) Tumors of bone & joints is the 3rd leading cause of cancer deaths among adolescents
  - B) There have been minimal improvements in OS for pediatric solid tumors (especially sarcomas) in the last couple of decades
  - C) Osteosarcoma research needs focus on development of novel targeted therapies
  - D) All of the above

What is Genomic Medicine?

- "An emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use."

National Human Genome Research Institute
Genomic Cancer Medicine

Background

- Systemic cancer treatment relies on drugs marginally more toxic to malignant cells than to normal tissues.
- Cancers have oncogenic dependencies that create "Achilles heels" that can be exploited for therapeutic benefit.
- Tretinoin (ATRA) for acute promyelocytic leukemia (APL).
- Imatinib for Ph+ acute lymphoblastic leukemia (ALL).
- Dinutuximab (Ch14.18) in high risk neuroblastoma.
- Genomics can help to identify and target molecular vulnerabilities of individual cancers.
- Adults with advanced disease have a higher ORR, longer PFS, and improved OS if they receive a phase 1 therapy "matched" to a molecular aberration in their tumor.

Genomics Driven Oncology – An Emerging Paradigm

- Specific tumor genomic changes may impact clinical management.
- A comprehensive catalog of the genomic abnormalities present in each childhood cancer needs to be established.
- Principles of cancer genomic information to guide oncology treatment choice.
  - 1) Molecular pathways involved in tumor survival and progression are often enacted by genetic alterations.
  - 2) Anticancer agents targeting oncogenic pathways have entered clinical trials.
  - 3) Genomic technologies enable robust tumor genomic profiling in the clinical arena.

Genomic Landscape of Childhood Cancer

- Tumors presenting in childhood have fewer somatic mutations and may be genetically less complex compared to adult malignancies.
- The spectrum of mutations in children is distinctive from that observed in adults.
- High variability of targetable genomic events.
- Genomic landscape at relapse is underexplored.
- Most genomic characterization of childhood cancers has been performed on diagnostic specimens.
- Transition from trials based on diagnosis to trials in which drugs are evaluated for activity in biologically defined populations.
Genomic Lesions That Provided Immediate Therapeutic Direction

- **NPM-ALK** fusion gene for anaplastic large cell lymphoma (ALCL)\(^1\)
- **ALK** point mutations for a subset of neuroblastoma\(^2\)
- Will be explored in ANBL1531 Arm E
- **BRAF** and other kinase genomic alterations for subsets of pediatric glioma\(^3\)
- Hedgehog pathway mutations for a subset of medulloblastoma\(^4\)

**Table: Potentially Targetable Genomic Mutations in Pediatric Solid Tumors**

<table>
<thead>
<tr>
<th>CANCER</th>
<th>MUTATION (frequency %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma (NBL)</td>
<td>ALK (5-10), PTPN11 (3)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma, embryonal (eRMS)</td>
<td>BRAF (1), FGFR4 (4), PIK3CA (3), CTNNB1 (2), RAS pathway activation (10-40), ALK (52)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma, alveolar (aRMS)</td>
<td>ALK (88), FGFR4</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>PIK3CA (3), MDM2 (10)</td>
</tr>
<tr>
<td>Wilms’ tumor</td>
<td>CTNNB1 (15), WTX (20)</td>
</tr>
<tr>
<td>Glioblastoma (GBM)</td>
<td>PDGFRα (8), EGFR (5), MGMT</td>
</tr>
<tr>
<td>Diffuse intrinsic pontine glioma (DIPG)</td>
<td>PDGFRα (36), PIK3CA (15), MGMT</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>CTNNB1 (12), PTCH1 (5)</td>
</tr>
<tr>
<td>Low Grade Glioma</td>
<td>BRAF (50-100)</td>
</tr>
</tbody>
</table>

**Diagram: Targeted Therapies For Known Pediatric Mutations**

FDA-approved Targeted Agents with Known Pediatric Doses

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Target</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>Imatinib</td>
<td>KIT, BCR-ABL, PDGFR</td>
<td>260-570 mg/m²/day (800 mg max)</td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td>BCR-ABL, Src, Lyn, FAK</td>
<td>60-85 mg/m²/dose BID</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
<td>EGFR</td>
<td>400 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td>EGFR, ERBB2, JAK2</td>
<td>85 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Lapatinib</td>
<td>EGFR, ERBB2</td>
<td>900 mg/m²/dose BID</td>
</tr>
<tr>
<td></td>
<td>Vandetanib</td>
<td>VEGFR-2, EGFR</td>
<td>145 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Sorafenib</td>
<td>Raf, PDGFR, VEGFR, Flt-3, KIT</td>
<td>200 mg/m²/dose BID</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>VEGFR-1/2/3, PDGFR-a, PDGFR-b, p-Akt</td>
<td>450 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Crizotinib</td>
<td>ALK, MET</td>
<td>280 mg/m²/dose BID</td>
</tr>
<tr>
<td></td>
<td>Ruxolitinib</td>
<td>Jak1, Jak2</td>
<td>50 mg/m²/dose BID</td>
</tr>
<tr>
<td>Other pathway inhibitors</td>
<td>Everolimus</td>
<td>mTOR</td>
<td>5 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Vandetanib</td>
<td>mTOR</td>
<td>10-150 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Vorinostat</td>
<td>HDAC</td>
<td>230 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Vismodegib</td>
<td>SMO/Hedgehog (Hh)</td>
<td>150 mg (0.67-1.32 m² BSA); 300 mg (1.33-2.2 m² BSA)</td>
</tr>
</tbody>
</table>

Genomically Guided Pediatric Efforts

- The Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative (http://target.cancer.gov)
  - Applies a comprehensive genomic approach to determine molecular changes that drive childhood cancers
  - Projects: ALL, AML, kidney tumors, neuroblastoma, osteosarcoma
- NCI Pediatric Preclinical Testing Consortium (http://www.ncipptc.org)
  - Focus on developing reliable preclinical testing data for pediatric drug candidates that can be used to inform new agent prioritization decisions.
- DFCI iCat (individualized cancer therapy) protocol
  - Multicenter study assessing tumor molecular profiles in advanced pediatric solid tumors (< 30 y.o. at enrollment with recurrent/refractory/high risk extracranial tumor)
- Genomic Assessment Informs Novel Therapy (GAIN)
  - Builds upon iCat protocol & will investigate the clinical impact of a precision cancer medicine approach in recurrent/refractory pediatric solid tumors
  - Plans to enroll 825 patients over 3 years.

Patient/Parent Perspective on Genomic Tumor Profiling (GTP): iCat experience

- Self-administered written survey following return of iCat results
- 53 were eligible for this substudy, 45 (83%) surveys were completed
- Surveys completed at median 13.5 months following return of results
- 89% (39/44) hoped it would help find cures for future patients
- 59% (26/44) hoped it would provide information or help to find cure for their/their child’s cancer
- 12% (5/43) worried they would learn that their/their child’s cancer was less treatable or more aggressive than previously thought
- 12% (27%) survey respondents received an iCat recommendation
  - only one participant (2%) received a targeted therapy
- Hopes exceeded the actual results experienced following receipt of GTP data, especially regarding increased hope for cure
- This warrants consideration during consent discussions about expectations of GTP research participation

Precision Medicine Clinical Trials in Pediatric Oncology

- A high proportion of low-grade gliomas in children have genomic changes that lead to activation of the MAP kinase
  - Selumetinib (MAP kinase inhibitor) in low grade gliomas
- Most children with anaplastic large cell lymphoma (ALCL) have genomic changes in the ALK gene.
  - ANHL12P1 investigated crizotinib (ALK inhibitor) in addition to standard chemotherapy
- Approximately 10 percent of children with acute myeloid leukemia (AML) have genomic changes in FLT3
  - AAML1031 investigated sorafenib (FLT3 inhibitor) in addition to standard chemotherapy
- NCI-COG pediatric MATCH for children with relapsed/refractory solid tumors opened for enrollment on July 24th, 2017

Audience Response Question #2

- A 7 y.o. female with relapsed/refractory high risk NBL after completing therapy on ANBL0032 is referred to your Phase I pediatric cancer center. The following is correct about her treatment options:
  - A) She is not a candidate for genomic testing because she relapsed after therapy on a high risk protocol utilizing targeted therapy with dinutuximab
  - B) She may be a candidate for genomic testing through TARGET, iCat or NCI pre-clinical testing initiatives
  - C) She has a very high probability of having a genomic mutation & will directly benefit from targeted therapy
  - D) She may be eligible for open Phase I or Phase II protocols utilizing targeted therapies
  - E) B and D only

NCI-MATCH [Molecular Analysis for Therapy Choice]

- Foundational treatment/discovery trial; assigns therapy based on molecular abnormalities, not site of tumor origin for patients without standard therapy
- Regulatory umbrella for phase II drugs/studies from > 20 companies; single agents or combinations
- Validated gene sequencing analysis of mutations in 143 genes; fresh biopsies at study entry
- Available nationwide (2400 sites); CIRB
- Accrual began mid-August 2015
**What is NCI-MATCH?**

This precision medicine trial explores treating patients based on the molecular profiles of their tumors.

NCI-MATCH is for adults with:
- Solid tumors (including rare tumors and lymphomas)
- Tumors that no longer respond to standard treatment

About 6,000 cancer patients will be screened with a tumor biopsy.

Now 6000

**NCI-MATCH Tumor Gene Testing**

The biopsied tumor tissue will undergo gene sequencing.

If a patient’s tumor has a genetic abnormality that matches one targeted by a drug used in the trial, the patient will be eligible to join the treatment portion of NCI-MATCH.

**NCI-MATCH Testing Expectations**

One in every four to five (23%) patients will have tumors with an abnormality that matches a drug being tested.

Not all patients will have tumors with an abnormality that matches a drug being tested.
NCI-MATCH Objective

- To determine whether matching certain drugs or drug combinations in adults whose tumors have specific gene abnormalities will effectively treat their cancer, regardless of the cancer type.
- This is a signal-finding trial—treatments that show promise can advance to larger, more definitive trials.

NCI-MATCH Step-by-Step Diagram

NCI-MATCH Structure

- Master protocol with multiple phase II treatment arms
  - Eligibility defined by molecular characteristics
  - IND for protocol template
  - Treatment arms open and close without affecting others
  - Single agents or combinations with recommended phase II dosage(s) known
  - FDA-approved for another indication or investigational
  - Central IRB required as the IRB of record
  - US-based sites across NCTN and NCORPs
Who is Eligible for NCI-MATCH Tumor Gene Testing?

- Adults ≥ 18 years of age
- Solid tumor or lymphoma whose disease has progressed following at least one line of standard systemic therapy
  - Or with a rare tumor that does not have standard therapy
- Good ECOG performance status
  - Fully active (PS-0) or restricted yet ambulatory (PS-1)
- Adequate organ function
- Able to tolerate being off treatment up to six weeks

Levels of Evidence for Drugs in NCI-MATCH

**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

NCI-MATCH’s 24 Current Gene Abnormalities and Expected Prevalence (Interim Analysis)
NCI-MATCH Mutation Prevalence Rates Per Arm (Actual vs Estimated)

- Overall 9% mutation match rate for first ten arms (56/645)
- Expected 10%

<table>
<thead>
<tr>
<th>colleague</th>
<th>arm activity</th>
<th>Actual MATCH Rate (%)</th>
<th>Estimated Prevalence Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q</td>
<td>Ado-trastuzumab emtansine in HER2 amplifications</td>
<td>1.7</td>
<td>5</td>
</tr>
<tr>
<td>U</td>
<td>Defactinib in NF2 loss</td>
<td>1.1</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>Afatinib in HER2 mutations</td>
<td>0.8</td>
<td>2.6</td>
</tr>
<tr>
<td>H</td>
<td>Dabrafenib+Trametinib in BRAF V600</td>
<td>0.8</td>
<td>7</td>
</tr>
<tr>
<td>R</td>
<td>Trametinib in BRAF non-V600</td>
<td>0.3</td>
<td>2.8</td>
</tr>
<tr>
<td>E</td>
<td>AZD9291 in EGFR T790M</td>
<td>0.2</td>
<td>1.2</td>
</tr>
<tr>
<td>F</td>
<td>Crizotinib in ALK translocation</td>
<td>0.2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>V</td>
<td>Sunitinib in cKIT mutations</td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>A</td>
<td>Afatinib in EGFR mutations</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td>G</td>
<td>Crizotinib in ROS1 translocation</td>
<td>0</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

Overall 9% mutation match rate for first ten arms (56/645)
Expected 10%

NCI-COG Pediatric MATCH (APEC1621)

- Collaboration between NCI and COG
- Modeled after adult NCI-MATCH - "umbrella" design with multiple molecularly-based phase II studies embedded within the overall clinical trial
- Goals:
  - Advance precision medicine for children with cancer
  - Increase knowledge about the genomics of relapse for pediatric cancers

Pediatric MATCH Study Design

- Patients with a solid tumor undergo biopsy at disease recurrence to have their tumors characterized for pre-defined "actionable" genomic alterations.
- Patients with a genomic alteration that matches the activity profile of one of the study agents are assigned to the treatment arm for this agent.
- Sequencing for eligibility to receive a study agent will be restricted to a set of genes for which there are relevant agents.
- The tissue specimens will additionally undergo comprehensive germline analysis of peripheral blood to detect whether mutations identified in the tumor are inherited.
- Treating MD will provide guidance to the patient’s family regarding the need for formal genetic testing, counseling, and follow-up care even if the patient does not match to a treatment arm.
### Target/Agent Prioritization

**Agent classes initially reviewed**
- ALK inhibitor
- MEK inhibitor
- BET bromodomain inhibitor
- PARP inhibitor
- BRAF inhibitor
- PDGFRA/B inhibitor
- CDK 4/6 inhibitor
- PI3K/AKT/mTOR inhibitor
- EGFR inhibitor
- ROS1 inhibitors
- ERK inhibitor
- SMO inhibitor
- FGFR inhibitor
- TRK inhibitor
- IDH inhibitor

**Agent classes not initially reviewed**
- MDM2 inhibitors
- Target (MDM2 amplification) uncommon
- ERBB inhibitors
- Target uncommon
- Met inhibitor
- Target (met amplification) uncommon
- Src/Syk inhibitor
- Target uncommon
- c-Kit inhibitor
- Target uncommon
- Anti-angiogenic (VEGF and Ang/Tie)
  - Not sufficiently targeted to define biomarker
- Pan-tyrosine kinase inhibitors
  - Not sufficiently targeted to define biomarker
- Aurora kinase inhibitors
  - Target/Biomarker not known
- Base excision repair inhibitor (TRC102)
  - Target/Biomarker not known
- ATR kinase inhibitor (VX-970)
  - Target/Biomarker not known
- FAK inhibitor
  - Target/Biomarker not known
- CK2 inhibitors
  - Target/Biomarker not defined by genomic alteration
- IGF1R inhibitors
  - Target/Biomarker not defined by genomic alteration

### APEC1621 Primary Aims

- To utilize clinical and biological data to screen for eligibility to phase 2 specific subprotocols of pathway-targeting agents in pediatric patients with advanced solid tumors, non-Hodgkin lymphomas, and histiocytic disorders.
- To determine the proportion of pediatric patients whose advanced tumors have pathway alterations that can be targeted by select anti-cancer drugs.
- To determine the objective response rates (ORR: complete response + partial response) in pediatric patients with advanced solid tumors, non-Hodgkin lymphomas, and histiocytic disorders harboring a priori specified genomic alterations treated with pathway-targeting agents.
APEC1621 Secondary Aims

- To estimate the PFS in pediatric patients receiving targeted therapies for advanced solid tumors, non-Hodgkin lymphomas, and histiocytic disorders.
- To obtain preliminary or additional information about the tolerability of targeted therapies in children with advanced cancers.
- To provide preliminary estimates of the pharmacokinetics of targeted therapies in children with advanced cancers.
- To obtain preliminary information on the response rate to targeted therapy in patients whose tumors lack actionable alterations as defined for the MATCH study, for selected agents for which efficacy is observed in the primary matched cohort.

Structure & Description

**STEP 1**

- **MATCH**
  - "Patient random in a study treatment
  - **No MATCH**
    - MTT screening study
    - **No MATCH**
      - MTT screening study

**STEP 2**

- **MATCH**
  - "Patient random in a study treatment
  - **No MATCH**
    - MTT screening study
    - **No MATCH**
      - MTT screening study

**STEP 2: Treatment**

- Investigational treatment part of the study.
  - If there is an investigational drug available through the Pediatric MATCH study that targets the mutations (if any) that are found in the tumor, upon obtaining consent and confirming eligibility, the patient will be enrolled on the subprotocol and then receive the study drug.
  - Patients must be enrolled onto a subprotocol within 8 weeks (56 days) of treatment assignment. The date subprotocol therapy is projected to start must be no later than 7 calendar days after the date of enrollment to the subprotocol.

Pediatric MATCH SubProtocols

<table>
<thead>
<tr>
<th>Agent Class</th>
<th>Agent Name</th>
<th>mMOI frequency</th>
<th>Study Chair</th>
<th>Protocol number</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRK inhibitor</td>
<td>Larotrectinib (LOXO-101)</td>
<td>2-3%</td>
<td>K. Janeway</td>
<td>APEC1621-A</td>
</tr>
<tr>
<td>FGFR inhibitor</td>
<td>Erdafitinib</td>
<td>2-3%</td>
<td>J. Cho</td>
<td>APEC1621-B</td>
</tr>
<tr>
<td>EZH2 inhibitor</td>
<td>Tazemetostat</td>
<td>2-3%</td>
<td>S. Chi</td>
<td>APEC1621-C</td>
</tr>
<tr>
<td>PI3K/mTOR inhibitor</td>
<td>LY3023414</td>
<td>5-10%</td>
<td>T. Laetsch</td>
<td>APEC1621-D</td>
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<tr>
<td>MEK inhibitor</td>
<td>Selumetinib</td>
<td>10-20%</td>
<td>C. Allen</td>
<td>APEC1621-E</td>
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<tr>
<td>ALK inhibitor</td>
<td>Ceritinib</td>
<td>2-3%</td>
<td>M. Irwin</td>
<td>APEC1621-F</td>
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<tr>
<td>BRAF inhibitor</td>
<td>Vemurafenib</td>
<td>5%</td>
<td>A. Kim</td>
<td>APEC1621-G</td>
</tr>
<tr>
<td>PARP inhibitor</td>
<td>Olaparib</td>
<td>2-3%</td>
<td>J. Glade-Bender</td>
<td>APEC1621-H</td>
</tr>
</tbody>
</table>
**Subprotocol Dosing Information**

- If a pediatric RP2D dose has been established, the patient will be treated at that dose.
- APEC1621A: LON2-001 (Larotrectinib)
- APEC1621E: Selumetinib
- APEC1621G: Vemurafenib
- If a pediatric RP2D dose has not been established:
  - For agents where the adult RP2D is below the adult MTD, the adult RP2D (normalized to body surface area or body weight) will be used for evaluation in the Pediatric MATCH, understanding that further dose optimization may be required in a future pediatric study.
    - APEC1621B: Erlotinib
    - APEC1621F: Enzastaurin
  - If adult RP2D is at the adult MTD, the pediatric subprotocol will evaluate an initial cohort of patients at a dose level approximately 30% below the adult MTD and then complete the study using the adult RP2D, assuming that both dose levels are tolerated.
    - APEC1621D: LY3023414
    - APEC1621H: Olaparib

**APEC1621 Eligibility Criteria**

- **Age:** Patients must be ≥ 12 months and ≤ 21 years of age at the time of study enrollment.
- **Diagnosis:**
  - Patients with recurrent or refractory solid tumors (including non-Hodgkin lymphomas, histiocytoses [e.g. LCH, JXG, histiocytic sarcoma], and CNS tumors) are eligible.
  - Patients must have had histologic verification of malignancy at original diagnosis or relapse except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG.
  - Certain subprotocols have diagnosis-specific exclusions, for example:
    - SEGA patients are excluded for APEC1621D
    - Low-grade glioma patients are excluded for APEC1621E, APEC1621G

**Concurrent Anticancer Therapy**

- Patients may receive concurrent cancer therapy while enrolled on the screening portion of APEC1621SC, but must meet criteria for prior therapy at the time of consent and enrollment to a subprotocol.
- Patients may receive investigational agents while enrolled on the screening portion of APEC1621SC, but must meet criteria for prior therapy (Section 4.2.3) at time of consent and enrollment to a subprotocol.
- No other investigational agents may be given while the patient is enrolled on an APEC1621 subprotocol and receiving protocol directed therapy.
**APEC1621-A: larotrectinib (LOXO-101)**

- Neurotrophin receptor tropomyosin-related kinase (TRK) fusions identified in diffuse intrinsic pontine glioma (DIPG) and other pediatric high grade gliomas
- LOXO-101 is an orally bioavailable, potent, ATP-competitive, selective inhibitor of TRKA, TRKB, and TRKC
- **Dose:**
  - 100 mg/m²/dose (max. 100 mg/dose) PO BID x 28 days
  - No starter supplies will be provided
  - Provided as 25 mg & 100 mg capsules and 20 mg/mL oral suspension
- **Exclusions:**
  - Strong inducers/inhibitors of CYP3A4 not permitted
  - Prior therapy with a specific inhibitor of TRK (including but not limited to entrectinib (RXDX-101), DS-6051b, and PLX7486)
  - Toxicities: anemia, GI (nausea, diarrhea, constipation, abdominal pain), transaminitis, fatigue, fever, pain, weight gain, delirium, cough, dyspnea.

**APEC1621C: Tazemetostat**

- EZH2 overexpression is mainly found in solid tumors
- EPZ-6438 (tazemetostat) is a selective small molecule inhibitor of the histone methyltransferase EZH2
- Patients must harbor gain of function mutations in EZH2, or loss of function mutations in the SWI/SNF complex subunits SMARCB1 or SMARCA4.
- **Exclusion:** strong inducers or inhibitors of CYP3A4
- **Dose:** 900 mg/m²/dose (max 1,600 mg)
  - Powder for oral suspension 30 mg/mL
- The most frequently occurring adverse events (≥ 15%): asthenia, anemia, decreased appetite, muscle spasms, nausea, vomiting, constipation, thrombocytopenia, and dyspnea.

**APEC1621D: LY3023414**

- LY3023414 is a potent orally bioavailable small molecule inhibitor of class 1 PI3K isoforms, MTOR, and DNAPK.
- **Dose escalation** PO BID x 28 days (50 mg & 100 mg tabs)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose (mg/m²)</th>
<th>Minimum BSA (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>0.75</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>115</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- **Inclusion criteria:**
  - must not have prior exposure to a PI3K inhibitor, an AKT inhibitor, an MTOR inhibitor, including rapalogs, or a combined PI3K/MTOR inhibitor.
  - normal blood glucose for age
  - serum triglyceride and cholesterol ≤ 300 mg/dL
- **Exclusion criteria:**
  - IDDM
  - SEGA tumors
- Prophylactic measures:
  - $5HT3$ antagonist, sunscreen and thick emollient creams BID.
APEC1621E: Selumetinib

- Selumetinib is a potent orally bioavailable small molecule inhibitor against ERK activation by activated MEK proteins.
- Patients with BRAF V600 aMOIs will be preferentially assigned to APEC1621G (vemurafenib) if that study is open & they are eligible for it.
- Inclusion criteria: BSA ≥ 0.5 m² at enrollment
- Exclusion criteria: strong CYP2C19 and 3A4 inducers or inhibitors
- known significant ophthalmologic conditions
- low grade glioma
- Dose: 25 mg/m²/dose (max 75 mg/dose) PO BID
- Take on an empty stomach
- Avoid VIT. E supplements
- ADRs: diarrhea, nausea, fatigue, edema, skin toxicity, HTN, CPK, paronychia, visual disturbances, transaminitis

APEC1621-F: Ensartinib

- ALK mutations/aberrations are found in ALCL, NBL & RMS
- Ensartinib: 2nd-generation oral ALK inhibitor that also has activity against ROS1, c-met, trkA, and axl
  - has 10-fold increased potency in blocking ALK phosphorylation in comparison to crizotinib
- Resistance to 1st generation ALK/ROS1 TKIs (crizotinib) does not confer resistance to ensartinib
- BSA ≥ 0.5 m² at enrollment
- Prior treatment with other ALK inhibitors is permitted if > 5 half-lives or 21 days have elapsed, whichever is greater.
- Exclusion: strong inducers or inhibitors of CYP 3A4, P-gp or BCRP
- Known cutaneous active squamous cell carcinoma
- Low grade glioma (WHO gr I-II)
- Dose: 130 mg/m² (max 225 mg) PO daily × 28 days
- Supplied as 25 mg & 100 mg capsules

APEC1621-G: Vemurafenib

- Vemurafenib is a selective oral inhibitor of the oncogenic BRAF V600 mutated kinase
- Patients must not have received prior exposure to a BRAF inhibitor (e.g. vemurafenib, dabrafenib or encorafenib).
- Exclusions:
  - Drugs that are strong inhibitors of CYP3A4, P-gp or BCRP
  - Known cutaneous active squamous cell carcinoma
  - Low grade glioma (WHO gr I-II)
- Dose: 550 mg/m²/dose (max 960 mg/dose) PO BID (120 mg & 240 mg tab)
- BSA:
  - ≥ 0.37 m² at enrollment while 120 mg tablets are available
  - ≥ 0.73 m² at enrollment once 120 mg tablet supply is exhausted
- Avoid QTc prolonging agents
- Toxicity: GI, arthralgia, skin cancers, skin rash, LFTs, headache, edema, Cre	
A 7 y.o. male with embryonal RMS relapsed after prior therapy and is enrolled on APEC1621SC. Molecular analysis demonstrated PI3K mutation and the patient is being screened for eligibility for APEC1621D subprotocol with LY3023414. All of the following may present an issue with patient's meeting eligibility requirements, except:

A) BSA = 0.8 m²
B) Inability to swallow tablets whole
C) Poorly controlled type 1 diabetes
D) Prior exposure to temsirolimus
E) Fasting triglycerides = 325 mg/dL
Audience Response Question #4

- AJ is 6 year old male (weight=20 kg, height = 111 cm, BSA=0.78 m²) with relapsed NBL who discontinued therapy with crizotinib as part of investigational protocol 1 month ago. After enrollment on APEC1621SC the patient is found to have MYCN and ALK amplifications. Please choose the correct statement(s) below:
  - A) This patient should not receive another ALK inhibitor like crizotinib because of cross-resistance potential
  - B) This patient is eligible for enrollment on APEC1621-F subprotocol with ensartinib if he can swallow capsules
  - C) AJ cannot be enrolled on APEC1621-F with ensartinib because < 5 half-lives have elapsed since crizotinib discontinuation
  - D) AJ can still be enrolled on APEC1621-F while receiving PO voriconazole for the treatment of invasive fungal infection of the liver

Conclusions

- The discovery phase is not over for childhood cancer genomics
- Many targeted therapies are now being offered on the basis of genomic alterations found in tumors
  - Few large-scale and coordinated efforts exist in pediatrics to measure the clinical efficacy of this approach.
- Return of incidental germline findings remains challenging
- Tumor heterogeneity offers another challenge to the translation of genomic medicine into the clinic, possibly requiring multiple biopsies at both diagnosis and relapse.
- Directions for future studies:
  - Less common cancers and rare subtypes
  - Tumors at relapse to define heterogeneity and evolution of clones over time
  - Tumors from multiple sites to define intra-patient spatial heterogeneity

Conclusions