Master Protocols in Pediatric Oncology: Access to Precision Medicine

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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


• 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

- No known genotype
- KRAS

2009

- KRAS
- EGFR
- ROS1
- PIK3CA
- BRAF
- ALK
- HER2

2004

- KRAS
- EGFR
- RET
- NTRK1
- MET
- ROS1

2014

- KRAS
- ALK
- EGFR
- PIK3CA
- HER2
- BRAF
Challenges with “old paradigm”

- p53
- MET
- ROS1
- KRAS
- EGFR
- ALK

N=800-1200

- Platinum doublet
- Platinum doublet + drug X

HIGH RISK PHASE 3
FAILURE OR CLINICALLY SMALL EFFECT

Challenges with “new paradigm”

- Targeted Therapy
- ALK

N=100-200

Large, Clinically Meaningful Effect

- 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

Broad Biomarker Profiling: NGS,IHC

Non-Match

PD-L1 mAb MEDI4736

Docetaxel

- PIK3CA mut
  - PI3K TKI GDC-0032
  - Docetaxel

- cdk4/6 CCND1 mut, del, amp
  - CDK4/6 TKI Palbociclib
  - Docetaxel
  - Doce-taxel

- FGFR mut, amp, fusi
  - FGFR TKI AZD-4547
  - Docetaxel

- HGF Met amplific. By IHC
  - HGF mAb Rilotumumab + erlotinib
  - Erlotinib

- 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 nivolumub 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
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 individualized cancer therapy 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)
Putting the puzzle pieces together

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

Inherited cancer mutations in 10%

Combined tumor and germline exome results

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

Slide Credit: Will Parsons
Parsons et al, JAMA Oncology
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

June 22, 2016
NCI-Molecular Analysis for Therapy Choice (NCI-MATCH or EAY131)

*Study Chairs*: Keith T. Flaherty¹, Alice P. Chen², Peter J. O'Dwyer³, Barbara A. Conley², Stanley R. Hamilton⁴, Mickey Williams⁵, Robert J. Gray⁶, Shuli Li⁶, Lisa M. McShane⁶, Lawrence V. Rubinstein², Susanna I. Lee¹, Frank I. Lin⁷, Paolo F. Caimi⁸, Albert A. Nemcek, Jr.,⁹ Edith P. Mitchell¹⁰, James A. Zwiebel²

¹Massachusetts General Hospital, Boston, MA; ²National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis, Bethesda, MD; ³University of Pennsylvania, Philadelphia, PA; ⁴MD Anderson Cancer Center, Houston, TX; ⁵NCI Frederick National Laboratory for Cancer Research, Frederick, MD; ⁶Dana-Farber Cancer Institute, Boston, MA; ⁷NCI Cancer Imaging Program, Rockville, MD; ⁸Case Western Reserve University, Cleveland, OH; ⁹TNorthwestern University, Chicago, IL, ¹⁰Thomas 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. Genetic sequencing PTEN IHC
2. Actionable mutation detected
3. Study agent
4. Stable disease, complete or partial response (CR+PR)\(^1\)
5. Continue on study agent until progression
6. PD
7. Repeat biopsy and sequencing
8. Progressive disease (PD)\(^1\)
9. Check for additional actionable mutations\(^2\)
10. Yes
11. No additional actionable mutations, or withdraw consent
12. 3 Year Follow Up

\(^1\)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 Assay System & Work Flow

Biopsy

→ Shipped to Nationwide (COG Biopath Center)

Tissue Accession

→ Tissue Processing

- PTEN IHC

→ NA Extraction

→ NA Shipped

Archive
- Tissue Blocks
- Slides
- Nucleic Acid

→ MDACC

→ MoCha

Library Prep and Sequencing

→ Ion Reporter

- MOI Annotation

- BAM File Storage

MATCHBox

→ Review and Sign off

- Final Report

→ Clinical DB
## NCI-Pediatric MATCH Treatment Arms

<table>
<thead>
<tr>
<th>Agent Class</th>
<th>aMOI Frequency</th>
<th>Subarm chair</th>
<th>Subprotocol ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-TRK inhibitor</td>
<td>2-3%</td>
<td>Katie Janeway</td>
<td>APEC 1621-A</td>
</tr>
<tr>
<td>FGFR inhibitor</td>
<td>2-3%</td>
<td>Jae Choi</td>
<td>APEC 1621-B</td>
</tr>
<tr>
<td>EZH2 inhibitor</td>
<td></td>
<td>Susan Chi</td>
<td>APEC 1621-C</td>
</tr>
<tr>
<td>PI3K/mTOR</td>
<td>5-10%</td>
<td>Ted Laetsch</td>
<td>APEC 1621-D</td>
</tr>
<tr>
<td>MEK inhibitor</td>
<td>10-20%</td>
<td>Carl Allen</td>
<td>APEC 1621-E</td>
</tr>
<tr>
<td>ALK inhibitor</td>
<td>2-3%</td>
<td>Meredith Irwin</td>
<td>APEC 1621-F</td>
</tr>
<tr>
<td>BRAF inhibitor</td>
<td></td>
<td>Aerang Kim</td>
<td>APEC 1621-G</td>
</tr>
</tbody>
</table>
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*
iMATRIX TRIAL STRUCTURE
MoA-driven in disease context, Gated design, Multiple molecules

**Preclinical Assessment for pediatric use**

**PEDIATIC**
Ph1 Study

**Gate 1**
Phase 1
PK/Safety

**Gate 2**
Phase 2
Safety+Early Efficacy

**Gate 3**
Phase 2
Additional Cohort Expansion

Pivotal trial

**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)**

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
  - Phase 1/Expansion

- **Group 3**
  - HDM201
  - Phase 1/Expansion

- **No biomarker match**
  - Not eligible for Part 2

**Group 2B**
- Trametinib + Ribociclib
- Phase 1/Expansion

*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
Assignment of treatment based on molecular alteration detected at progression

<table>
<thead>
<tr>
<th>Group</th>
<th>Therapy</th>
<th>Inclusion Biomarkers</th>
<th>Exclusion Biomarkers</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Mutation*</td>
<td>Amplification**</td>
</tr>
<tr>
<td>1</td>
<td>cediranib + ribociclib</td>
<td>ALK*</td>
<td>ALK</td>
</tr>
<tr>
<td>2A</td>
<td>Trametinib</td>
<td>BRAF, HRAS, NRAS, PTEN, NF1</td>
<td>NF1</td>
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<tr>
<td>2B</td>
<td>Trametinib + ribociclib</td>
<td>BRAF, HRAS, KRAS, MAP2K1, MAP2K2, MYCN, NRAS, PTEN</td>
<td>BRAF, CCND1, CCND2, CDK4, CDK6, MYCN</td>
</tr>
<tr>
<td>3</td>
<td>HDM201</td>
<td>MDM2, MDM4</td>
<td></td>
</tr>
</tbody>
</table>

*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.
• **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