IMPLICATIONS OF THE 2017 FDA REAUTHORIZATION ACT ON PEDIATRIC CANCER DRUG DEVELOPMENT: AN INDUSTRY PERSPECTIVE

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AMGEN
I have the following financial relationships to disclose:

I work full time for Amgen

I will not discuss off label use and/or investigational use in my presentation.
BPCA AND PREA WORK TOGETHER

• Intended to work together to maximize information in labeling on dosing, safety, and efficacy for products that may be used in children
  – Even if studies are negative/uninterpretable, study information still placed in labeling because information is deemed critical

• Not mutually exclusive
  – Therapies with required studies under the Pediatric Research Equity Act (PREA) are eligible for exclusivity under the Best Pharmaceuticals for Children Act (BPCA)
FDA has required post marketing commitments outside of PREA.

Examples include:
- 2000, Aresenic Trioxide (Trisenox) – Acute promyelocytic leukemia
- 2001, Imatinib mesylate (Gleevec) – Ph+ Leukemias
- 2006, Panitumumab (Vectibix) – solid tumors

Before 2017, submissions with Orphan Drug Designation (ODD) were exempt from PREA requirements
Since early 2000s, improved knowledge of tumor biology is informing treatment

- Precision medicine has delivered more targeted therapies
  - Impact on unmet medical need large,
  - Populations with greatest potential to benefit are smaller

- Products may qualify for ODD
  - Critical regulatory pathway for development of medicines
Remarkable progress has been made in our understanding of the genomic landscapes of pediatric cancers

Products approved for use in adult cancers can provide a health benefit for pediatric patients

Despite the lack of a PREA requirement, these products are studied in the pediatric population

Not always performed for regulatory review nor product labeling
Approximately 77 new BLAs or NDAs, approved since 2012
- 26 applications waived,
  - Disease did not occur or was rare in the pediatric population
- 50 applications exempt
  - Orphan designation
- One had no clear information

Clinicaltrials.gov search
- Of 77 above, 48 have pediatric studies (62.3%)
- Regulatory utility of studies unknown (intended for submission)
CHANGES IN PEDIATRIC LEGISLATION UNDER FDARA

• BPCA:
  – No changes

• PREA:
  – Requires evaluation of new molecularly targeted drugs and biologics “intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer.”
  – Elimination of the PREA exemption when the application is for a orphan designated cancer drug being studied in adults
PLEA now allows industry an early opportunity to discuss pediatric studies with the FDA
- Smaller study populations will require the development innovative study designs
- It is a chance for closer collaboration between NCI, COG, other collaboratives, FDA, Industry, and Advocacy groups
- Independent regulatory review of data and availability in labeling may increase access for patients
LEGISLATIVE CHANGES COME WITH CHALLENGES
WHAT MOLECULES SHOULD BE STUDIED?
THE “LISTS”

• Legislation requires lists
  – May represent an opportunity for stakeholders to come together to discuss emerging science
  – Intended to limit regulatory uncertainty, but nonbinding
  – Therapies must be individually assessed for appropriate conditions
    • This could change over time as more information becomes available
PRIORITIZATION IS REQUIRED

• Many products share same molecular target, studies could be competing for the same small pool of patients
  – Recruitment in pediatric trials difficult
  – Pediatric studies often international by nature
    • Requires some level of harmonization

• On going surveillance of pipelines required to ensure that the most promising therapies are studied first
  – FDA and NCI are often aware of pipelines across companies
  – Convert deferrals to waivers as appropriate
SAFETY REQUIREMENT

• Safety information for any product is critical to assure that benefit out weighs risk
  – Inherent risks for patients participating in clinical studies
    • Recent adult examples of studies of immunotherapies in combination with other drugs that were placed on hold while safety concerns examined
  – Previous studies in pediatrics (including non-oncology) have identified adverse events unique to or amplified in the pediatric population
    • Some toxicities difficult to identify from adult studies and/or nonclinical studies
REGULATORY STABILITY

• Intent of legislation was not to provide prescriptive directions for implementation, and lists do not provide certainty

• As science advances, it will be incumbent upon the FDA to more clearly define what therapies will have study requirements

• Regulatory certainty is an ideal that is hard to realize, and Business uncertainty is not sustainable
  – Must know what study requirements will be for a given therapy over time
• While not the primary driver, must be assessed for business
• $1 million - $35 million for studies (depending on source)
  – Exclusivity seen by many companies to off set the cost of studies
CONCLUSIONS

• We have been here before
  – More than 20 years ago, people said pediatric studies could not be conducted.
    • Now there are 728 products with pediatric information in label, largely from studies

• There will be challenges prioritizing products to study
  – The best minds are poised to solve the challenges presented by the new legislation

• The new requirements may provide an opportunity for collaboration across industry, academia and government
Investigator Perspectives on New Agent Prioritization and Challenges with Multiple Same in Class Agents

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee

Elizabeth Fox, MD
20 June 2018
Disclosure Information

Elizabeth Fox, MD

Consultant (travel compensation only) from: Bayer, Bristol Myers Squibb

Institutional research support for clinical trials from: Novartis, Ignyta, Merck

Data Safety Monitoring Board (compensated): Helsinn Therapeutics

All data in this presentation is publically available and referenced. My interpretation of data and opinions are not intended to reflect opinions of my institutional or cooperative group affiliations or trial sponsors.

I will discuss the following off label use and/or investigational use in my presentation:
atezolizumab, cabozantinib, entrectinib, larotrectinib, nivolumab, pazopanib, pembrolizumab, vismodegib
Research to Accelerate Cures & Equity for Children Act
FDARA 2017 Title V

• Mandates earlier discussion of the pediatric plan for an oncology drug or biological product directed at a specific molecular target in cancer that is germane to children

• Agents classified as relevant, non-relevant or other

• Opportunity for collaboration among US government agencies, EMA/PDCO, global pharmaceutical industry, academic investigators, and patient and policy advocates
Oncology Drug Approvals

<table>
<thead>
<tr>
<th>Decade</th>
<th>Total NME</th>
<th>Annual Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>1951-1960</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>1961-1970</td>
<td>17</td>
<td>1.7</td>
</tr>
<tr>
<td>1971-1980</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>1981-1990</td>
<td>18</td>
<td>1.8</td>
</tr>
<tr>
<td>1991-2000</td>
<td>44</td>
<td>4.4</td>
</tr>
<tr>
<td>2001-2010</td>
<td>49</td>
<td>4.9</td>
</tr>
<tr>
<td>2011-2018</td>
<td>75</td>
<td>10.7</td>
</tr>
</tbody>
</table>

1950-1990: 57 drugs

1990-2018: 168 drugs

Drug Disc Today 19: 1831-5, 2014
Anticancer Drugs

New FDA Approved Oncology Drugs

<table>
<thead>
<tr>
<th>Generic Name Stem</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>-tinib</td>
<td>Tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>-anib</td>
<td>Angiogenesis inhibitor</td>
</tr>
<tr>
<td>-clicib</td>
<td>Cyclin-dependent kinase inhibitor</td>
</tr>
<tr>
<td>-zomib</td>
<td>Proteasome inhibitor</td>
</tr>
<tr>
<td>-lisib</td>
<td>PI3 kinase inhibitor</td>
</tr>
<tr>
<td>-parib</td>
<td>PARP inhibitor</td>
</tr>
<tr>
<td>-stat</td>
<td>Enzyme inhibitors</td>
</tr>
<tr>
<td>-ase</td>
<td>Enzyme</td>
</tr>
<tr>
<td>-kin</td>
<td>Interleukin (-leukin is IL-2)</td>
</tr>
<tr>
<td>-mab</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>-leucel</td>
<td>Cell therapy</td>
</tr>
<tr>
<td>-stim</td>
<td>Colony stimulating factors</td>
</tr>
<tr>
<td>-tide</td>
<td>Peptide</td>
</tr>
</tbody>
</table>

![Graph showing the average annual NME approved for new FDA approved oncology drugs by decade.]
<table>
<thead>
<tr>
<th>Childhood Cancer Diagnosis (%)</th>
<th>Common Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Lymphoblastic Leukemia (20%)</td>
<td>&lt;8 y</td>
</tr>
<tr>
<td>Brain/ CNS Tumors (18%)</td>
<td>0-19 y</td>
</tr>
<tr>
<td>Hodgkin Lymphoma (8%)</td>
<td>10-19y</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma (7%)</td>
<td>0-19 y</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia (5%)</td>
<td>&lt;2 y; &gt;12 y</td>
</tr>
<tr>
<td>Neuroblastoma (5%)</td>
<td>&lt;4 y</td>
</tr>
<tr>
<td>Bone: Osteosarcoma+Ewing Sarcoma (5%)</td>
<td>10-19 y</td>
</tr>
<tr>
<td>Thyroid Carcinoma (4%)</td>
<td>15-19 y</td>
</tr>
<tr>
<td>Wilms/Kidney (3%)</td>
<td>&lt;5 y</td>
</tr>
<tr>
<td>Germ Cell Tumors (3%)</td>
<td>15-19 y</td>
</tr>
<tr>
<td>Rhabdomyosarcoma (2%)</td>
<td>0-19 y</td>
</tr>
<tr>
<td>Retinoblastoma (2%)</td>
<td>&lt;1 y</td>
</tr>
<tr>
<td>Melanoma (2%)</td>
<td>&gt;12 y</td>
</tr>
<tr>
<td>Other (16%)</td>
<td></td>
</tr>
</tbody>
</table>

Each year **15,780 Children** in the US are diagnosed with Cancer

Adapted from Siegel et al  CA Cancer J Clin 2017
Single Agents, Same in Class

- Unique aspects of biomarker in cancers in children/adolescents (Strength on the Oncogenic Driver)
- Rare Tumors among Childhood Cancer
- Number of agents/trials in a rare patient population will depend on agent properties and efficiency of trial design
  - Endpoints (Safety, dosing, PK)
  - Biomarker/Companion Diagnostic
  - Disease specific response criteria
RACE for Children Act defines *Cures* as the Goal

- Majority of childhood cancers will require assessment of combinations
  - Disease specific backbone therapy (multimodality, cytotoxic)
  - Combinations of targeted agents for pathway inhibition
- Consideration of age distribution of specific cancers, histologic and molecular subtypes
Prioritization

• Evidence of drug-target-response relationship
  • Less data from trials in adults
    • PKPD endpoints and modeling
    • PBPK models/assumptions
  • Biomarker Validation/Companion Diagnostics
  • Resources for Pediatric Cancer Specific Animal Models

• Toxicity profile
  • Developmental considerations; Juvenile toxicology
  • Severity and Reversibility
  • Combinations relevant to childhood cancer and additive toxicity

• Pharmacological properties and formulation

• Global Collaborations
Preclinical Models: Prerequisite for Prioritization

• Selection of models with fidelity of the oncogenic drivers of disease
• Evaluation of biomarkers
• Drug distribution (CNS penetration)
• Validation of concentration thresholds and necessary duration of inhibition
• Demonstrate relationship between target inhibition and activity
• Clinically meaningful efficacy thresholds
• Evaluation of pathway redundancy, innate and acquired resistance
• Mechanistic rationale for synergy for combinations
Biomarkers

• Childhood cancer is rare disease, biomarker selection will further limit number of eligible patients

• Need for resources for assessment of agents in pediatric preclinical *in vivo* and *in silico* models

• Limited Re-Validation of Biomarker/Companion Diagnostics
  • Tumor Biopsies
  • Circulating Tumor DNA

• Relevance of single genetic aberrations and genomic signatures from carcinomas in adults

• Complexities of fusion transcripts and multiple fusion partners
## Checkpoint Inhibition in Childhood Cancer

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>74</td>
<td>46</td>
<td>66</td>
</tr>
<tr>
<td>Age (years)</td>
<td>14 (2-29)</td>
<td>13 (1-25)</td>
<td>13 (1-17)</td>
</tr>
<tr>
<td>PD-1/PDL-1 selection</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>DLT Gr3 LFT; Gr4 DKA</td>
<td>No DLT</td>
<td>Gr3 ALT</td>
</tr>
<tr>
<td>Objective Response Rate</td>
<td>5% 2/9 HL; 1/11 EWS 1 MRT (unconfirm)</td>
<td>0% EWS, RMS, Osteo</td>
<td>6% 1 HL; 1ACC; 1GMB; 1 mesothelioma</td>
</tr>
</tbody>
</table>
Checkpoint Inhibition in Childhood Cancer

**Where we started:**
- Enthusiasm from studies in adults and lack of preclinical models led to multiple large, multi-strata clinical trials
- Uncertainty of biomarker selection

**What we learned:**
- Single agent PD-1/PDL-1 inhibitors are tolerated for short durations
- Many children exposed, few with clinical benefit
- Multiple studies can simultaneously accrue when the effort is global

**What we would like to know:**
- HL cohorts included in trials in adults, can medical and pediatric centers collaboration can be realized?
- Can we define hyper-mutated cancers in children and will those children benefit?
- Will combinations work better?
# Dose Finding Trials in Childhood Cancer

<table>
<thead>
<tr>
<th>Dose Escalation Trial</th>
<th>Dose Confirmation Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended Dose in Adults is MTD</td>
<td>Recommended Dose in Adults is not MTD</td>
</tr>
<tr>
<td>Concern for toxicity: CNS, irreversible/serious organ damage</td>
<td>Toxicology and Toxicity profile reversible</td>
</tr>
<tr>
<td>Myelosuppressive/impact of prior Tx</td>
<td>Non-myelosuppressive</td>
</tr>
<tr>
<td>Highly variable PK, age related metabolism, or saturable CL</td>
<td>PK is dose proportional, limited variability</td>
</tr>
<tr>
<td>Untested formulation or schedule</td>
<td>Ability to deliver dose and similar schedule</td>
</tr>
<tr>
<td>Childhood cancer requires different target concentration</td>
<td>Target inhibition across broad concentration or exposure range</td>
</tr>
<tr>
<td>Rationale for early combination</td>
<td>Single agent or prior combination trial</td>
</tr>
</tbody>
</table>
### Challenges of Same in Class Comparison

<table>
<thead>
<tr>
<th></th>
<th>Larotrectinib</th>
<th>Entrectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Laetsch et al Lancet Oncology 2018</td>
<td>Desai et al ASCO 2018</td>
</tr>
<tr>
<td>Population</td>
<td>Biomarker enriched/selected</td>
<td>Solid tumor Dose Escalation; biomarker expansion</td>
</tr>
<tr>
<td>N</td>
<td>24 (17 fusion positive)</td>
<td>16 (3 fusion positive)</td>
</tr>
<tr>
<td>Median Age (years)</td>
<td>4.5</td>
<td>10</td>
</tr>
<tr>
<td>DLTs</td>
<td>increased ALT</td>
<td>pulmonary edema, fatigue, dysguesia, elevated creatinine</td>
</tr>
<tr>
<td>MTD</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pediatric RP2D</td>
<td>100 mg/m² BID (max 100 mg/dose)</td>
<td>550 mg/m² Daily</td>
</tr>
<tr>
<td></td>
<td>100 mg BID</td>
<td>600 mg/day (~350 mg/m²)</td>
</tr>
<tr>
<td>Adult RP2D</td>
<td>14/15 patients with fusion positive tumors</td>
<td>3/3 patients with fusion positive tumors</td>
</tr>
<tr>
<td>Formulations</td>
<td>25 or 100 mg capsules; 20 mg/mL oral solution</td>
<td>100 and 200 mg capsules</td>
</tr>
</tbody>
</table>
Dosing Considerations Based on Pharmacokinetics

Larotrectinib
Laetsch et.al Lancet Oncol 2018

- Estimated plasma AUC_{0-24h} (ng*h/mL)
  - n=6, 99 mg/m²
  - n=9*, (98 mg/m²)
  - n=5, 126 mg/m²
  - n=29, 100 mg

Adult

Entrectinib
Desai et.al ASCO 2018

- Concentration-time profiles of entrectinib (multiple dose)
- Efficacy Target from Preclinical Models: 550 mg/m², 250 mg/m², 400 mg/m²
- Mean ± SD concentration (nM)
  - Time (hours): 0, 4, 8, 12, 16, 20, 24
Formulation

- Bioavailability
- Taste
- Palatability
- Concentration
- Stability
- Preparation
- Administration
Formulation, Deliverable Dose and PK

Cabozantinib

AUCₜₐ₂₄ₙ (µg·h/mL)

Dose Level (mg/m²):
- 30
- 40
- 55

Ave. Daily Dose (mg/m²/d):
- (30.8 ± 3.6)
- (31.5 ± 10.3)
- (46 ± 11.1)

Chuk et al PBC 2018
## Toxicity Profile of Targeted Therapy: Small Molecules

<table>
<thead>
<tr>
<th>Target</th>
<th>Drugs</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK/ROS1</td>
<td>Ceritinib, Crizotinib, Ensartinib</td>
<td>Arrhythmia, Hyperglycemia, Neuropathy/Neuromuscular, Respiratory, PE, Vision</td>
</tr>
<tr>
<td>BCR-ABL1, KIT, PDGFR</td>
<td>Dasatinib, Imatinib, Nilotinib, Ponatinib</td>
<td>Cardiac, Edema, Growth, Pulmonary HTN, Thyroid, Vascular events</td>
</tr>
<tr>
<td>BRAF</td>
<td>Dabrafenib, Vemurafenib</td>
<td>Hyperglycemia, SMN, QT prolong, radiation sensitivity</td>
</tr>
<tr>
<td>CDK</td>
<td>Palbociclib, Ribociclib</td>
<td>Hepatic, SOS</td>
</tr>
<tr>
<td>HDAC</td>
<td>Etinostat, Vorinostat</td>
<td>PE, QTc</td>
</tr>
<tr>
<td>MEK/MAPK</td>
<td>Selumetinib, Trametinib</td>
<td>Cardiac, skin, Vision</td>
</tr>
<tr>
<td>mTOR</td>
<td>Everolimus, Sirolimus, Temsirolimus, ABI-009</td>
<td>Dyslipidemia, hyperglycemia</td>
</tr>
<tr>
<td>PI3K</td>
<td>CYDC-907, LY3023414</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>TRK</td>
<td>Entrectinib, Larotrectinib</td>
<td></td>
</tr>
<tr>
<td>MTKI: VEGFR, PDGRF, RET, MET</td>
<td>Axitinib, Bevacizumab, Cabozantinib, Lenvatinib, Vandetanib</td>
<td>Cardiac, Bleeding/Clotting, HTN, Thyroid Dysfunction</td>
</tr>
</tbody>
</table>

Adapted from Chow et al JCO 2018
<table>
<thead>
<tr>
<th>Target</th>
<th>Drugs</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>Blinatumomab</td>
<td>Cytokine release syndrome, Neurotoxicity</td>
</tr>
<tr>
<td>CD19</td>
<td>Blinatumomab, CAR Tcells</td>
<td>Cytokine release syndrome, Neurotoxicity, B cell aplasia</td>
</tr>
<tr>
<td>CD20</td>
<td>Rutuximab</td>
<td>B cell aplasia</td>
</tr>
<tr>
<td>CD30</td>
<td>Brentuximab vendotin</td>
<td>Neuropathy, PML</td>
</tr>
<tr>
<td>CD33</td>
<td>Gemtuzumab ozogamicin</td>
<td>Hepatic, SOS</td>
</tr>
<tr>
<td>GD2</td>
<td>Dinutuximab, 3F8, Hu14.18K322A</td>
<td>Capillary Leak, Neuropathic Pain, RPLE</td>
</tr>
<tr>
<td>PD-1, PDL-1, CTLA4</td>
<td>Atezolozumab, Avelumab, Durvalumab, Ipilimumab, Nivolumab, Pembrolizumab, JS001, MEDI4736</td>
<td>AutoImmune/ Inflamatory including: Endocrinopathies, Myopathies, Neurotoxicity, Pneumonitis</td>
</tr>
</tbody>
</table>

Adapted from Chow et al JCO 2018
Unique Toxicities: Growth Plate Abnormalities

Pazopanib
Voss et al Ped Blood Cancer, 2015

• Serial Evaluations
• Pediatric Specific Grading Criteria
  • Hypertension
  • Neuropathy

Vismodegib
Robinson et al Oncotarget, 2017
Attributes for Prioritization and Collaboration

**Adaptability**
- Expected prevalence of biomarker/disease and primary endpoint determine number of sites necessary, additional sites after safety cohort

**Agility**
- Timely scientific/clinically relevant results require shorter protocol lifecycles with rapid readouts of endpoints and outcome measures

**Allegiance**
- Goals of cure rather than individual drug or trial
- Mechanism to continue assessment of agents without adult indications

**Alignment**
- International alignment of goals, risk stratification and strategies: Hepatic Tumors, NBL, GCT
Future of Cancer Therapy in Children

• Increased preclinical models (*in vivo* and *in silico*)
• Personalized (individualized) therapy based on tumor biology
• Extinction of cytotoxic chemotherapy and increased role for molecularly targeted and immunotherapy
• Challenges of combination therapy
• Age-appropriate Formulations
• Toxicity
  - Chronic oral outpatient therapy with targeted drugs or long half-life
  - Non-myelosuppressive, chronic non-hematological toxicity, impact on growth and development,
  - Unknown late effects
Industry Perspective on Prioritization of Pediatric Relevant Targets and Molecules

June 20\textsuperscript{nd}, 2018 Pediatric Subcommittee of the Oncologic Drug Advisory Committee (pedsODAC) Meeting

Hubert Caron, MD. PhD.
Principle Medical Director
Pediatric Oncology Drug Development Group
Roche
Basel, Switzerland
Disclosure Information

• I am an Employee and Stock Holder of Hoffmann-La Roche AG

• The presentation describes the Roche/Genentech perspective on target & drug prioritization, as part of the approach adapted by the Company towards pediatric drug development
Outline

• Perspective on current pediatric regulatory landscape
• Revisions to PREA – FDARA 2017
  – Impact on the Industry and its challenges
• Roche/Genentech vision for pediatric drug development
  • Pediatric target & molecule prioritization
    • MOA-based pediatric potential
    • Pediatric molecule developability
    • Across company prioritization
• Case study on prioritization
• Key Messages
Pediatric Research Equity Act
What it means post-FDARA 2017?

• Implemented on both drugs and biologics

• Pediatric studies are **mandatory**

• Requires **molecularly targeted pediatric cancer investigation** of new molecular entities (drugs and biologics) “intended for the treatment of adult cancers and directed at a **molecular target** substantially relevant to the growth or progression of a pediatric cancer.”

• Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets

• Once completed, pediatric studies must inform the **product label**
Changing Landscape

Industry-Sponsored Pediatric Oncology Drug Development Needs Innovation

- Sponsors are required to submit ‘initial Pediatric Study Plan’ (iPSP) for marketing applications for new molecular entities submitted after August 2020 unless the PREA requirement is waived.

- Submitting an iPSP outlining the clinical study design to evaluate dose, safety and preliminary efficacy of the drug would require:
  - Pre-clinical data
  - Pediatric formulation and starting dose for pediatric study
  - Adult safety and efficacy data (if available)
Innovative Pediatric Oncology Drug Development

Roche’s Vision and Mission

Our Vision

• Provide children with unmet medical needs with innovative, safe, life-saving therapies

Our Missions

• Ensure **early access** to medicines with a strong scientific rationale for children with high unmet medical needs

• Increase **treatment options** through clinical trials aimed at pediatric product labeling for children with cancer

• Fulfill pediatric regulatory obligations to ensure **timely registrations in adults**

• Facilitate **industry innovation and change in policies** in collaboration with regulatory authorities, to increase drug development in pediatric oncology
Developing the Roche Pipeline for Children with Cancer

With the intent to inform the product label

All Oncology Molecules

Prioritized list for inclusion in Matrix Trial

Matrix Trial Phase I/II Data*

Product Pediatric Labeling

Sponsored Pivotal Trials

Supported Academic Investigation

Terminated Pediatric Development

Matrix Trial data may directly support product labeling

Pediatric Developability Assessment

*Safety, PK, Preliminary Efficacy
The iMATRIX Trial Concept
MOA-driven, gated for safety + early efficacy, molecule combinations, across multiple diseases

The iMATRIX Trial Concept
MOA-driven, gated for safety + early efficacy, molecule combinations, across multiple diseases

PEDIATRIC gated phase 1-2

preclinical assessment for pediatric use

Adult Phase 1-2 Studies

Gate 1
Gate 2
Gate 3

Pivotal trial

© 2016 Genentech, a Member of the Roche Group.
## Pediatric Molecule Developability

*An multifactorial approach across the portfolio*

### Regulatory:
- Do we have an existing or likely future regulatory obligation for this molecule?

### Molecule Feasibility:
- MOA match with pediatric biology?
- Is there an unmet medical need?
- Suitable safety (preclinical+adult) profile?
- Is the formulation appropriate for children?

### Clinical Feasibility:
- Prevalence of matching patients?
- Perceived improvement over SOC?
- Competing molecules in class?

### Incentives:
Can we qualify for regulatory incentives for this molecule?

### De-risk
- adult filings by addressing EU & US regulatory obligations

### Deliver
- High-potential molecules to rare pediatric populations with significant unmet need

### Leverage
- Opportunities for regulatory incentives (LOE extension, PRV)
Matching MOA with Pediatric Tumor Biology

*Strength of the ‘MOA match’ guides pediatric developability*

**Compound**
- Mechanism of Action

**Pediatric Tumor Biology**
- Pediatric Target Actionability

**Pediatric Potential**

**Target classes:**
- Tumor dependence
  - Genomic
  - Expression (lineage)
- Tumor delivery
- Tumor microenvironment
  - Immunology
  - Angiogenesis

**FDA Target Classes:**
- Gene Abnormality Targets
- Cell Lineage Targets
- Non-cancer cell Targets
- Other Targets

**Preclinical Proof-of-Concept Molecule Testing in Pediatric Models**

**Systematic Literature Reviews of Target Actionability**

**Target Prevalence in Pediatric Clinical Series**

*Neuroblastoma, Rhabdomyosarcoma, Synovial Sarcoma, MPNST, Ewing sarcoma, Osteosarcoma, ATRT/RH30, Nephroblastoma, Hepatoblastoma, Inflammatory Myofibroblasts, GCT, Mu Mu Ex Mu*
<table>
<thead>
<tr>
<th>Module</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1</td>
<td>Target Activation Status in clinical series</td>
</tr>
<tr>
<td>Module 2</td>
<td>Target Dependence: ‘in vitro’ (molecular validation)</td>
</tr>
<tr>
<td>Module 3</td>
<td>Target Dependence: ‘in vivo’ (molecular validation)</td>
</tr>
<tr>
<td>Module 4</td>
<td>Molecule Sensitivity Patterns ‘in vitro’</td>
</tr>
<tr>
<td>Module 5</td>
<td>Molecule Efficacy ‘in vivo’</td>
</tr>
<tr>
<td>Module 6</td>
<td>Biomarkers; Predictive and Biological Efficacy (PD)</td>
</tr>
<tr>
<td>Module 7</td>
<td>Resistance mechanisms</td>
</tr>
<tr>
<td>Module 8</td>
<td>Rational combinations</td>
</tr>
</tbody>
</table>

**Clinical data**

*Pediatric Clinical trials*
Systematic Target Actionability Reviews
Cochrane-like methodology supported by ITCCP4 R2 data platform

STEP 0: Expert reviewers
- Identify 2 or more reviewers
- Derive specifics for target patterns and target validation from basic target (pathway) biology in cancer

STEP 1: Sensitive literature search for papers on pediatric tumors
- Sensitive PubMed search
- Select relevant papers, based on Title + Abstract

STEP 2: Critical evaluation of papers and scoring of main findings
(independent by each reviewer)
- Extract Main Finding(s) per paper
- Categorize each main finding for disease entitie(s) and for class(es) of POC data
- Appraise + score main findings for Experimental Quality and for Effect Quantity (standardized guidance tables)

STEP 3: Comparison of the scoring from independent reviewers
- Reviewer discussion of main findings and evidence scores per tumor entity
- Resolve+adjudicate discrepancies by discussion

STEP 4: visualization in R2 datatool
- Derive POC heatmap from evidence scores
Step 1: enter Papers

Step 2: Extract ‘main findings’

Step 3: score for ‘Quality’ and ‘Quantity’

Step 4: adjudicate between reviewers
## Scoring of Evidence Quality

<table>
<thead>
<tr>
<th>Module</th>
<th>Criteria</th>
<th>Scoring</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Target pattern</td>
<td>number of samples/pediatric patients</td>
<td>3</td>
<td>n&gt;20, two or more different methods</td>
</tr>
<tr>
<td></td>
<td>type of analysis</td>
<td>2</td>
<td>n&gt;10-&lt;20, at least one reliable method</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>n&lt;10, one method</td>
</tr>
<tr>
<td>2. Target validation in vitro</td>
<td>knockdown/knockout</td>
<td>3</td>
<td>Different methods to induce knockdown/knockout of &gt;3 cell lines + phenotypic analysis of knockdown</td>
</tr>
<tr>
<td></td>
<td>Confirmation and analysis of knockdown</td>
<td>2</td>
<td>Single methods to induce knockdown/knockout of &lt; 3 cell lines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>questionable knockdown/knockout</td>
</tr>
<tr>
<td>3. Target validation in vivo</td>
<td>type of in vivo model used</td>
<td>3</td>
<td>transgenic mouse model and/or at least 2 different xenographs with an appropriate control and/or</td>
</tr>
<tr>
<td></td>
<td>validation in vivo</td>
<td></td>
<td>different methods of genetic modification in vivo (shRNA/CRISPR) + validation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>at least 2 different xenographs without appropriate control + validation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>no validation of the developed tumors</td>
</tr>
<tr>
<td>4. Drug efficacy in vitro</td>
<td>number of cell lines</td>
<td>3</td>
<td>5 cell lines or more + at least two appropriate controls + validation</td>
</tr>
<tr>
<td></td>
<td>validation including PD biomarkers or phenotypic response</td>
<td>2</td>
<td>2-5 cell lines + at least one appropriate controls + validation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>1 cell line and/or lack of control +/- validation</td>
</tr>
<tr>
<td>5. Drug efficacy in vivo</td>
<td>number and type of in vivo models used</td>
<td>3</td>
<td>2 or more xenograph models or one transgenic mouse model with appropriate control + validation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>1 xenograph model with appropriate control + validation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>1 xenograph model w/o appropriate control or w/o validation</td>
</tr>
<tr>
<td>6. Biomarkers</td>
<td>confirmation of correlation</td>
<td>3</td>
<td>correlation molecularly confirmed in 2 or more models (e.g. silencing, overexpression, etc.), patient</td>
</tr>
<tr>
<td></td>
<td>patient selection</td>
<td></td>
<td>selection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>correlation confirmed in one model, patient selection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>correlation not confirmed</td>
</tr>
<tr>
<td>7. Resistance</td>
<td>development of resistance</td>
<td>3</td>
<td>reported resistance + comprehensive analysis + reversing/overcoming resistance</td>
</tr>
<tr>
<td></td>
<td>molecular analysis</td>
<td>2</td>
<td>reported resistance + analysis of molecular changes underlying or due to resistance</td>
</tr>
<tr>
<td></td>
<td>overcoming resistance</td>
<td>1</td>
<td>only reporting resistance</td>
</tr>
<tr>
<td>8. Combinations</td>
<td>concentrations tested</td>
<td>3</td>
<td>&gt;4 concentrations of each compound are tested + CI + in vivo</td>
</tr>
<tr>
<td></td>
<td>combination index (CI) in vitro /vivo combination</td>
<td>2</td>
<td>1-4 concentrations of each compound are tested + CI +/- in vivo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>1 concentration of each compound is tested</td>
</tr>
<tr>
<td>Module</td>
<td>Criteria</td>
<td>Scoring</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>1. Target pattern</td>
<td>Prevalence of abnormal expression/amplification/mutation in cohort (separate scoring)</td>
<td>3  More than 10% in the cohort</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  Between 2-10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3  No</td>
<td></td>
</tr>
<tr>
<td>2. Target validation in vitro</td>
<td>Level of dependency and phenotypic recapitulation</td>
<td>3  Full dependency (&gt;75% cell death OR transformation) after knockdown/knockout</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  Partial dependency (&lt;75% death OR growth arrest)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3  No dependency</td>
<td></td>
</tr>
<tr>
<td>3. Target validation in vivo</td>
<td>Level of dependency and phenotypic recapitulation</td>
<td>3  Full dependency (CR / complete tumor regression) after knockdown/knockout or transformation in GEMM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  Partial dependency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3  No dependency</td>
<td></td>
</tr>
<tr>
<td>4. Drug efficacy in vitro</td>
<td>IC50 observed after 72hr exposure</td>
<td>3  &lt; 500 nM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  500-1500 nM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1  &gt;1500 nM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3  No activity (&gt; 10uM)</td>
<td></td>
</tr>
<tr>
<td>5. Drug efficacy in vivo</td>
<td>In vivo tumor response extrapolation (preferably using clinically relevant dose)</td>
<td>3  Response comparable to PR/CR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  Response comparable to SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1  Very minor response (between SD and PD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3  No activity or clear PD, comparable to control</td>
<td></td>
</tr>
<tr>
<td>6. Predictive biomarker</td>
<td>Confirmation of correlation</td>
<td>3  Strong correlation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  Moderate correlation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3  No correlation</td>
<td></td>
</tr>
<tr>
<td>7. Resistance</td>
<td>Reported resistance</td>
<td>3  Resistance reported with drug exposure (at clinically relevant dose) with identification of mechanism of resistance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  Resistance reported with no identification of mechanism of resistance</td>
<td></td>
</tr>
<tr>
<td>8. Combination</td>
<td>Synergy - CI</td>
<td>3  Strong synergy reported - CI &lt;0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  Moderate synergy/additive effect - CI 0.5-0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1  Very minor synergy/additive effect observed - CI 0.9-1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3  No synergy</td>
<td></td>
</tr>
</tbody>
</table>
## R2 heatmap of POC results

Merging of disease-specific data per POC data module

<table>
<thead>
<tr>
<th>Target/pathway:</th>
<th>MDM2-TP53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version Date:</td>
<td>13 April 2018</td>
</tr>
<tr>
<td>Author:</td>
<td>Nil Schubert, Guillaume Bergthold, Caitlin Lowery, Ana Rodriguez, Jan Molenaar, Hubert Caron</td>
</tr>
</tbody>
</table>

### Target/pathway:
- Neuroblastoma
- Rhabdomyosarcoma
- STS non-RMS: Synovial Sarcoma
- Ewing sarcoma
- ATRT / Rhabdoid
- Wilms tumor (Nephroblastoma)
- GCT extracranial
- Retinoblastoma
- NCC (inc. GBM)
- LGG
- Ependymoma
- Medulloblastoma

### Preclinical:
- 1. Target activation in pediatric clinical series
  - p53 functionality
  - MDM2 amplified
  - MDM2 expressed
- 2. Tumortarget dependence (in vitro models)
- 3. Tumortarget dependence (in vivo models)
- 4. Compound sensitivity (in vitro models)
- 5. Compound POC Efficacy (in vivo models)
- 6. Biomarker (Predictive and PD)
- 7. Resistance Mechanisms
- 8. Combinations

### Work in progress
<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Target activation in pediatric clinical series</th>
<th>p53 functionality</th>
<th>MDM2 amplified</th>
<th>MDM2 expressed</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Tumor target dependence (in vitro models)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3. Tumor target dependence (in vivo models)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>4. Compound sensitivity (in vitro models)</th>
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<th>5. Compound POC Efficacy (in vivo models)</th>
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<th>6. Biomarker (Predictive and PD)</th>
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<th>7. Resistance Mechanisms</th>
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</thead>
</table>

<table>
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<tr>
<th>8. Combinations</th>
</tr>
</thead>
</table>

**Target/pathway:** MDM2-TP53  
**Version Date:** 13 April 2018  
**Author:** Nil Schubert, Guillaume Bergthold, Caitlin Lowery, Ana Rodriguez, Jan Molenaar, Hubert Caron

- Neuroblastoma
- Rhabdomyosarcoma
- STS non-RMS: Synovial Sarcoma
- Ewing sarcoma
- ATRT / Rhabdoid
- Wilms tumor (Nephroblastoma)
- Hepatoblastoma
- GCT extracranial
- Retinoblastoma
- HGG (incl GBM)
- LGG
- Ependymoma
- Medulloblastoma

**Work in progress**
Remarks:
Amplification or gain of 12q13-15 (includes MDM2) was found in 32% of the 44 primary ARMS samples (CGH analysis).
Curator: Nil Schubert

Remarks:
1/26 ERMS and 1/17 ARMS had an MDM2 amplification and very high RNA expression (WGS, FISH, IHC). (9/26 ERMS and 3/17 ARMS had copy number gains for MDM2 between 0.5 and 10 copies).
Curator: Nil Schubert

Remarks:
No MDM2 amplification was found in 22 pediatric RMS tumor samples (differential PCR).
Curator: Nil Schubert

Remarks:
MDM2 amplification (qPCR) was found in 2/22 RMS tumors and over-representation of MDM2 was found in 3/22 tumors. The amplification-positive tumors were only of the ARMS and anaplastic ERM type and not of the classic ERM type. High MDM2 mRNA expression correlated with protein expression (IHC).
Curator: Nil Schubert

Remarks:
MDM2 was overexpressed (IHC) in 9/72 cases and amplified (PCR) in 3/18 cases, but there was no correlation between amplification and overexpression. MDM2 status was not associated with prognosis or other clinicopathologic parameters.
Curator: Nil Schubert

Remarks:
No MDM2 amplifications were detected in a cohort with 67 high-grade round cell sarcomas, including ES/PNET (23), SS (5) and RMS (11) samples (FISH).
Curator: Nil Schubert

Remarks:
### Regulatory Obligations

**Molecule feasibility:**
- MOA-based rationale for PEDS
- Biomarkers
- Safety (preclinical + adult)
- PK + Formulation

**Clinical feasibility:**
- Unmet need & prevalence
- Perceived efficacy over SOC
- Other molecules in class

**Incentives:**
- Development costs
- Regulatory incentives

---

**Future Obligation likely**
- Likely

**Time to 1st filing**
- <1 year

**MOA**
- Well-understood MOA
  - MOA and/or clear target population

**Biomarker**
- BM under evaluation
  - Limited safety info available

**Safety**
- Requires development

**Formulation feasibility**
- Requires development

**Pediatric incidence & prevalence**
- Medium

**Perceived improvement over SOC**
- Low

**Competing programs in class**
- 2-3 drugs

**Potential for regulatory incentives**
- Green
Prioritization across Molecules & Companies

Accelerate multi-stakeholder strategy forums

• Setup:
  – Molecules in same class OR disease-specific
  – Multi-stakeholder (academia, patient advocates, pharma, health authorities)
  – Formatted data sharing across molecules:
    • MOA
    • Safety (juvenile toxicity / adult safety profile)
    • Pharmacokinetics (biodistribution, CNS penetration, dosing schedules)
    • Adult efficacy data
    • Stage of adult development
    • Formulation (pediatric?)
    • Available pediatric data
  – Hosted by European Medicines Agency (EMA) in London

• Experience: ALK Strategy forum (Jan. 2017: 7 ALK-inh from 6 companies)
  BNHL Strategy forum (Nov. 2017: 20 molecules from 15 companies)
  Immuno-checkpoint inh. (Sept. 2018: in preparation)
A Case Study

Prioritization of Molecules for pediatric B-cell Non Hodgkin Lymphoma (B-NHL)
Do we need a Pediatric B-NHL Strategy?

Molecule prioritization

I need 280 patients for my Pixatrone studies

I need 36 patients for my Idelalisib Phase I study

I need 72 patients for my Ibrutinib study

Any patients left for my CAR-T studies?

We may need patients for Polatuzumab studies!

…and some for the Pralatrexate!

What about the Nivolumab study?

Don’t forget Venetoclax!

I need patients for my Acalabrutinib
What are the Issues Faced in Pediatric B-NHL?

<table>
<thead>
<tr>
<th></th>
<th>B-NHL patients numbers (EU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0-19 yr)</td>
</tr>
<tr>
<td>Total B-NHL</td>
<td>1L</td>
</tr>
<tr>
<td></td>
<td>2000</td>
</tr>
<tr>
<td>Burkitt Lymphoma</td>
<td>800</td>
</tr>
<tr>
<td>DLBCL (Diffuse large B-cell Lymphoma)</td>
<td>250</td>
</tr>
<tr>
<td>FL (Follicular Lymphoma)</td>
<td>10-20</td>
</tr>
</tbody>
</table>

Source: Adapted from Dr. Thomas Gross’s presentation at the Accelerate Strategy Forum, November 2017

- Too many drugs to test and not enough pediatric patients
- Current pediatric studies facing recruitment challenges due to competition for future PIPs
  - High risk of early study closure without sufficient data to support a label update
- High resource burden on companies to maintain pediatric studies with low chance of obtaining incentives
- Difficulty to obtain Product Specific Waiver (PSW) vs. PIP based on non-feasibility of conducting pediatric trial
  => 9 ongoing PIPs and 4 future PIPs

- Few pediatric patients in both 1L and r/r B-NHL
  - ‘MabThera + LMB-96’ 1L treatment has 94% EFS => high bar for new molecules and less r/r patients expected in the future

<table>
<thead>
<tr>
<th></th>
<th>Burkitt Lymphoma</th>
<th>DLBCL</th>
<th>FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0-19 yr)</td>
<td>800</td>
<td>250</td>
<td>10-20</td>
</tr>
<tr>
<td>(0-19 yr)</td>
<td>40</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>(≥20 yr)</td>
<td>9000</td>
<td>54,000</td>
<td>72,800</td>
</tr>
</tbody>
</table>

B-NHL patients numbers (EU) (0-19 yr) (0-19 yr) (≥ 20 yr)
Internal Prioritization of Roche B-NHL Molecules

Rationale and Strategy moving forward

- 3 Molecule are pursuing same/similar adult indications for pivotal studies in DLBCL and FL
- Timing of adult programs overlap, which translates into overlapping PIP obligations in pediatric DLBCL/BL/mature BLL
- iPODD Team solicited feedback from the 3 EU Forums on which B-NHL molecule they would prioritize and how:
  - EMA PedOnc Portfolio meeting 22 Sept 2017
  - Advisory Board 11 Oct 2017
  - Pediatric Strategy B-NHL Forum 13-14 November 2017
- Key feedback received
  1. The preferred drugs to be investigated in pediatric B-NHL are CAR-T, T-cell bispecific antibodies and some ADCs (depending on target and on toxicity profile of drug-conjugate)
  2. Feasibility is not grounds for waiver but, if justified with supportive evidence, could be considered
Outcome

• The iPODD team was successfully able to conduct the prioritization of the molecules across its portfolio in B-NHL space receiving EMA-PDCO agreement on its proposal based on:
  – Strong scientific rationale to move ahead with the molecule(s) whose MOA and overall profile would most likely to be effective
  – Feasibility challenges to successfully enroll pediatric patients in all programs for a meaningful outcome
  – Feedback received from academic experts to support the above

• The team is currently working on a multi-arm early phase clinical design to study prioritized molecule
Key Messages

• Revision of PREA to direct MOA-based pediatric drug development is the right approach and is much needed for the timely development and access of cancer drugs to the pediatric patients

• It will enforce the proactive and early consideration of integrating pediatric development as part of overall clinical development plan for the molecule

• Strong collaboration among Regulators, Sponsors and, Academic Partners, detailed preclinical POC testing, global harmonization of study designs, and molecule prioritization will be critical for it successful implementation

• Innovative trial designs, establishing clinical development matching pediatric potential and molecule developability and shifting mindsets to take a MOA-based portfolio approach will be the new norm
Thank You
Pediatric Oncology Subcommittee of ODAC:
Mechanisms to assure efficiency and to enhance global coordination through international collaboration

Recommendations for International Collaborations and Coordination

Gilles Vassal
Gustave Roussy, France

June 20, 2018
The oncology paradox in 2018

Many drugs in adults
Adult disease – based pediatric developments

- Waived or delayed pediatric developments
- Poor access to pediatric patients

Rare patients

- Poor access to innovation
New oncology drug development for children: the goal

Many drugs in adults

MOA* – based development and prioritisation

Specific pediatric drugs

NEEDS

*Mechanism of action

SCIENCE

A favorable regulatory environment, now!

FDA REAUTHORIZATION OF 2017

SEC. 504. DEVELOPMENT OF DRUGS AND BIOLOGICAL PRODUCTS FOR PEDIATRIC CANCERS: molecular targets regarding cancer drugs and biological products........ if the drug or biological product is .......

“(i) intended for the treatment of an adult cancer;

and

“(ii) directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer.”


Revised Class Waiver List Enters into force July 28, 2018
Early evaluation of MOA relevance

- Early pipeline discussions between scientists, ped oncologists and Pharma
- Easy access to data and high quality preclinical platforms
- International consensus on required biological and preclinical data

Vassal et al. Lancet Oncol, 2013, 14, 117
Easy access to preclinical platforms

First joint PPTC ITCC-P4 meeting at the 2018 American Association for Cancer Research annual meeting
an international scientific consensus on preclinical evaluation that will be published in a peer-reviewed journal and will serve as a basis for a guidance to be submitted to regulatory authorities for qualification.
Access to molecular data at diagnosis and at relapse (examples)


https://www.pedpancan.com
International cooperation to run trials

- Track record of successful phase III academic trials
  - Burkitt lymphoma, Hepatoblastoma, Osteosarcoma, Ewing, ........
- But major regulatory and administrative hurdles for academic trials
- Most industry trials are international
• Pediatric oncology drug development is global
• This is NECESSARILY a multistakeholder endeavor
International Multistakeholder Paediatric Oncology Platform

To improve new oncology drug development for children

Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer

Gilles Vassal a,*, Raphaël Rousseau b, Patricia Blanc c, Lucas Moreno d, Gerlind Bode e, Stefan Schwoch f, Martin Schrappe g, Jeffrey Skolnik h, Lothar Bergman i, Mary Brigid Bradley-Garelik j, Vaskar Saha k, Andy Pearson l, Heinz Zwierzina m

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

www.accelerate-platform.eu

Created in December 2015
The value of working together

No blame! No shame!
Generate data and find solutions
Current Perspective

Implementation of mechanism of action biology-driven early drug development for children with cancer

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Mechanism of action – driven development plans in pediatric oncology

along with

Prioritisation of compounds among those developed in adults
Paediatric Strategy Forum - scientific meeting to share information and advance learning on a topic which will inform a paediatric drug development strategy and subsequent decisions:

**Define the needs and facilitate prioritization**

**Principle**: dialogue and constructive interactions between **ALL relevant international stakeholders**: clinicians, academics, patients advocates, pharmaceutical companies and regulators

**Output**: Summary on websites and Article in a peer-reviewed journal
Paediatric Strategy Forums

Forum n° 1 - January 2017
Alk inhibition

- Very substantially relevant target for 3 paediatric malignancies (NB, ALCL, IMT)
- 6 drugs (4 approved) and no PIPs
- Clear activity in ALCL and IMT through academic trials

Forum n° 2 - November 2017
Mature B-cells malignancies

- Rare diseases with 94% cure rate with new standard treatment
- Many drugs in development in adults (20 were discussed)
Paediatric Strategy Forums

Forum n° 3 - September 2018
Checkpoint inhibitors in combination

• Several PD1 and PDL1 inhibitors approved
• Many in development with a vast majority likely to be approved in adults
• Very limited activity in paediatric malignancies, qualified as “cold” tumors

Forum n° 4 - April 2019
Pediatric acute myeloid leukemias

• Rare conditions
• Many drugs in adults
• Several PIPs in competition for access to patients in phase III trials
Proposal for International Paediatric Strategy forums

• Co-organised by ACCELERATE, EMA and FDA (permanent preparatory team)
• A dedicated Programme Committee for each forum with experts from EU and US Cooperative Groups
  = a single international forum for each topic
• Invitation of academia, pharma and patients advocates following expression of interest
• Venue: alternatively in Europe and the US
• Up to 4 Forums in paediatric oncology per year
• Re-organised with an International Steering Committee
• Working and interactive meetings
• An International platform for multistakeholder discussions to facilitate and accelerate a coordinated global agenda in the new regulatory environment in the US and Europe
• Need to engage more pediatric oncologists and scientists.

Next meeting – February 2019, Brussels
New oncology drug development for children: an international collaboration

SCIENCE

*Mechanism of action

NEEDS

Work together (all stakeholders)
In a favorable regulatory environment

Many drugs in adults
MOA* – based development and prioritisation

Specific pediatric drugs

Improve access
Addressing Challenges to Global Coordination

Christina Bucci-Rechtweg MD, Global Head Pediatric Health Policy
FDA, CDER, PedsODAC Meeting
20 June 2018
The presenter is an employee of Novartis Pharmaceuticals Corporation (‘Novartis’)

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Agenda

1. Setting the scene
2. Global solutions focused approaches
   - Population specific
   - Identification of unmet need
   - Regulatory pathway to agreeing a pediatric plan
3. Parting Thoughts
Setting the scene
Setting the scene

Advances in genomics and precision medicine

Promising new avenues for cancer drug development (e.g., Immuno-oncology)

Growing body of knowledge related to the underlying biological mechanisms promoting cancer cell growth

Integration to inform scientific and regulatory policy related to pediatric cancer drug development

Advances in regulatory science facilitating statistical approaches to analysis of small clinical trial populations

Pediatric Policy, Regulatory Affairs, Global Drug Development
Promise in the Pipeline: More than 200 Immuno-oncology Medicines in Development

Number of Medicines in Development in the United States, May 2017, Selected Classes of Immunotherapy

- Adoptive Cell Therapies: 40
- Bispecific Antibodies: 30
- Cytokines: 23
- Oncolytic Cell Therapies: 14
- Vaccines: 96

“In the past 5 years, immunotherapy has emerged as one of the most exciting new approaches to cancer treatment that has ever entered the clinic.”

- American Association for Cancer Research


Slide courtesy PhRMA - Used with permission
CAR-T therapy is an individualized adaptive immunotherapy

Pediatric acute lymphocytic leukemia (pALL) is the leading cause of childhood cancer with ~3,100 new cases annually in the US

Treatment options for r/r pALL are limited & outcomes are suboptimal

- Allo-HSCT is the only potential curative option, but is limited by eligibility requirements and presents less than optimum outcomes:
  - 5-yr OS in children receiving HSCT during the 2nd and ≥ 3rd remission is approximately 40% and 30% respectively
  - HSCT is associated with 10-20% treatment-related mortality and serious adverse effects (e.g. GVHD and infections)
- Other treatment options are mainly considered “bridges” to HSCT

Response rate of 83% ORR\(^1\) in pediatric patients with r/r ALL when treated with tisagenlecleucel suspension

\(^1\) ORR = Overall Remission Rate; Source: KYMRIAH\(^{\text{TM}}\) (tisagenlecleucel) suspension USPI
Global Burden of Disease: Causes of Death in Children < 5 years

Global Burden of Disease: Causes of Death in Children 5-14 years

Pediatric Policy, Regulatory Affairs, Global Drug Development

Promise in the Pipeline: More than 1,100 Medicines in Development for Various Cancers

“These are exciting times… the pace of discovery and application of new knowledge to patient care is rapidly accelerating.”

— Dr. Jose Baselga, Physician-in-Chief, Memorial Sloan Kettering Cancer Center

Medicines and Vaccines in Development for Cancer by Tissue of Origin (Selected) – May 2018

*Some medicines may be in more than one therapeutic category.

Sources: PhRMA, Medicines in Development for Cancer, May 2018; American Association for Cancer Research. "Jose Baselga, MD, PhD” http://cancerprogressreport.org/2015/Pages/baselga.aspx.
Industry pipelines are expanding

- 5212 active drugs in development pipelines for Anticancer therapies
- Cancer pipeline candidates posted a 7.6% increase in this year
  - Close to three times that of the overall industry pipeline

Source: Pharmaprojects: track pharma R&D
https://pharmaintelligence.informa.com/resources/product-content/undefined
In today’s environment, pediatric oncology trials face significant recruitment challenges

**Trial recruitment in Acute Lymphoblastic Leukemia (ALL)**

- Patients required for trials: 23,009
- US pediatric patients diagnosed per year: 534
- US recurrent or relapsed pediatric patients per year: 2,670

- The total number of patients needed to enroll in active trials often surpasses the number of available patients that could be enrolled
- Initiating additional clinical trials would likely further slow recruitment

SOURCE: Cancer.gov; ClinicalTrials.gov; team analysis

1 Total interventional trials in the US with active recruitment status compiled from Clinicaltrials.gov online database
2 Pediatric ALL relapse rate is ~20% Slide courtesy PhRMA - Used with permission
“New generation of cell therapies helps Chinese emerge as industry leaders”

There are already more clinical trials in the country than in the US, and executives and scientists say it has several strategic advantages that could allow China to challenge US dominance, including an accommodating regulatory regime, low labour costs and expertise in precision manufacturing.

- 116: Number of CAR-T clinical trials in China, compared with 96 in the US
- 4.3m: New diagnoses of invasive cancer in China in 2015
- $10bn: Investment in 2017 in Chinese biotechnology companies
An improved regulatory environment & changes in strategic focus are enhancing access to new therapies globally

Population specific approaches

- Pediatric only cancers
- Ultra rare cancers
- Cancers with high mortality despite research investment
- Cancers occurring in both adults and children
<table>
<thead>
<tr>
<th>Pediatric cancer</th>
<th>Proposed solutions</th>
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<tbody>
<tr>
<td><strong>Pediatric only cancers</strong></td>
<td></td>
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<tr>
<td>Retinoblastoma</td>
<td>Few novel therapies in development</td>
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<td></td>
<td>✓ Drive innovation → Investment in foundational science and discovery</td>
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<tr>
<td></td>
<td>✓ <strong>Market drivers</strong> → Meaningful incentives, funding models, manufacturing models, pricing models</td>
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<tr>
<td><strong>Ultra rare cancers</strong></td>
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<tr>
<td>Infantile fibrosarcoma</td>
<td>Extremely limited populations for trial participation</td>
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<tr>
<td></td>
<td>✓ Drive regulatory science → Role for non-traditional quantitative approaches to data analytics (Bayesian, etc)</td>
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<td>✓ <strong>Dedicated Global pediatric regulatory advice</strong> pathway to facilitate convergence</td>
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<tr>
<td><strong>Cancers with persistently high mortality</strong></td>
<td></td>
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<tr>
<td>Diffuse Intrinsic Pontine Gliomas (DIPG)</td>
<td>Clinical advancement remains limited despite research</td>
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<tr>
<td></td>
<td>✓ Define and target critical <strong>unmet needs</strong> → Coalesce research community in identifying scientific basis of disease</td>
</tr>
<tr>
<td></td>
<td>✓ Investment in <strong>foundational science</strong> and discovery</td>
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<tr>
<td><strong>Cancers occurring in both adults and children</strong></td>
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<tr>
<td>Certain bone sarcomas</td>
<td>Translational research of novel therapies generally excludes adolescent eligibility in adult oncology studies</td>
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<td></td>
<td>✓ Regulatory guidance to facilitate <strong>earlier inclusion</strong> of adolescents (where appropriate)</td>
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<td>✓ Regulatory agreement to key program design elements (not details) on <strong>high-level pediatric plans</strong> prior to availability of adult data</td>
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Global coordination on identification of unmet need

Pediatric Policy, Regulatory Affairs, Global Drug Development

Neutral arbiter

Global multi-stakeholder forum to discuss, align on critical pediatric cancer needs

To converge (1) mapping of therapies to therapeutic target and (2) enhance efficiencies in development of scientifically and commercially viable pediatric therapies

To identify and align on the RIGHT
- Indication
- Population
- End-points

To enhance program and development viability
And
To reduce waste of resource-consuming activities to agree unfeasible programs

Competitive environment

Early Phase Planning
Assumptions
Attrition

Standard of care
## EU: 2017 paediatric planning

**Source:** EMA Annual Report 2017


### Opinions on paediatric investigation plans and waivers

<table>
<thead>
<tr>
<th>Year</th>
<th>PIP agreed (with or without deferral)</th>
<th>Modification of PIP agreed</th>
<th>Compliance check with a PIP</th>
<th>Full waiver granted</th>
<th>Negative opinions</th>
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<td>2013</td>
<td>184</td>
<td>96</td>
<td>53</td>
<td>6</td>
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<td>2017</td>
<td>221</td>
<td>83</td>
<td>53</td>
<td>12</td>
<td>6</td>
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</tbody>
</table>

### Paediatric investigation plans agreed and waivers granted (2017)

- **Anaesthesiology:** 75 agreements, 25 waivers
- **Cardiovascular diseases:** 22 agreements, 1 waiver
- **Dermatology:** 2 agreements
- **Diagnostic:** 3 agreements
- **Endocrinology-gynaecology-fertility-metabolism:** 7 agreements, 6 waivers
- **Gastroenterology-hepatology:** 7 agreements
- **Haematology-haemostaseology:** 12 agreements
- **Infectious diseases:** 7 agreements, 9 waivers
- **Immunology-rheumatology-transplantation:** 3 agreements
- **Neonatology-paediatric intensive care:** 2 agreements, 9 waivers
- **Oncology:** 15 agreements, 17 waivers
- **Ophthalmology:** 5 agreements
- **Other:** 6 agreements
- **Oto-rhino-laryngology:** 2 agreements
- **Pain:** 1 agreement
- **Pneumology-allergology:** 3 agreements
- **Psychiatry:** 2 agreements
- **Uro-nephrology:** 1 agreement
- **Vaccines:** 6 agreements
Agreeing a “pediatric plan”

THE PAEDIATRIC REGULATION

THE ACTORS

EUROPEAN MEDICINES AGENCY

SAWP

CHMP

Division

FDA

Applicant

THE ACTORS

VARIOUS HAs
INTERACTIONS

SA

PRIME

BREAKTHROUGH DESIGNATION

Pre-IND / IND Meeting

Type B / C Meeting

Parallel Advice

WHEN TO DO WHAT?

APPLICATION

PAEDIATRIC STRATEGY

BPCA

RfM

Type B / C

Meeting

Pre-IND / IND

Meeting

Pre-IND / IND

Meeting

Breakthrough

Designation

Parallel Advice

When to do what?

Breakthrough

Designation

Parallel Advice

When to do what?

Breakthrough

Designation

Parallel Advice

When to do what?
Timelines to agree a EU and U.S. “pediatric plan”: Overview

**Europe**
- Scientific Advice: 5 months
- PIP Application: 10 months
- Initial PSP: 7 months
- Written Request: 3 months

**U.S.**

NOTE: European and U.S. process may or may not run in parallel

* Assuming sponsor does not receive an ‘Inadequate Response’ letter
Why do sponsor’s seek regulatory advice?

SA can help to guide changes in the pivotal clinical development towards improved regulatory acceptability

- Obtaining and complying SA is strongly associated with a positive outcome of a MAA: almost 90% of those who obtain and follow SA receive a positive opinion compared to 40% for those who do not follow SA; **Hofer et al. 2015**
Regulatory cooperation: Pediatric Cluster & ‘Common Commentary

- **Pediatric Cluster** facilitates conversation **between regulatory bodies** to enhance the science of pediatric trials and to **avoid exposing children to unnecessary trials**
  - FDA, EMA, Health Canada, PMDA, TGA
  - Aug 2007 - Oct 2017: Discussions on 456 products and 153 general topics

- **Common Commentary** is used to inform sponsors of products discussed at the Pediatric Cluster
  - **Informal**, non-binding comments on pediatric development plans that have been submitted to both **FDA** and **EMA**

![Graph showing Pediatric Cluster discussed topic numbers per year](https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM451789.pdf)
Parallel Scientific Advice

- Mechanism for EMA, FDA and sponsors to exchange views on scientific issues during program development
  - Increased dialogue between the agencies and sponsors
  - Optimizes development and avoids unnecessary trial replication and divergence of testing methodologies (where applicable)
- Intended for breakthrough drugs or to address important safety issues for:
  - Oncology, Vaccines, Orphan Drugs, drugs in the Pediatric Population, Nanotechnologies, Advanced Therapies, Pharmacogenomics and Blood products
- Especially useful in early phase development where there is limited precedence
- Focused on sharing information and perspectives, rather than specific harmonization of study or regulatory requirements*

*Advice of each agency may still differ after joint discussion
European Mutual Recognition Procedure*

- A European authorization route resulting in a mutually recognized product

- Can be used when a product is already authorized in at least one Member State (MS) on a national basis and the Marketing Authorization Holder (MAH) wishes to obtain a Marketing Authorization (MA) for the same product in at least one other Member State
  - The MS that has already authorized the product is known as the Reference Member State (RMS)
  - The RMS submits their evaluation of the product to other MSs, or the Concerned Member States (CMS)
  - The CMS is asked to mutually recognize the MA of the RMS

- If the applicant is successful, the CMS will then issue a MA for that product permitting the marketing of that product in their country

* Legal basis: Directive 2001/83/EC
Role for global regulatory cooperative pathway to agree a pediatric plan (Expand, refine, or create)

- Life-threatening nature of pediatric cancers
- Small populations
- Complexity of existing treatment paradigms
- Molecularly targeted development approaches
- Assay development

➢ Could consideration be given to a pediatric-cancer specific parallel advice pathway, that includes observer agencies?
➢ Could consideration be given to establishment of a “mutual recognition” pathway (between EMA-FDA) for agreed pediatric plans?
  ➢ If joint guidance was developed (by molecular target/pediatric cancer)?
  ➢ Other?
Parting thoughts
Parting thoughts

We have an opportunity to facilitate meaningful change in how we develop medicines for children with cancer.

Small pediatric oncology patient numbers creates an opportunity for **global collaboration** and avenues for **innovative** approaches.

Successful transformational change requires **trust**.

The children are depending on us.
Thank you

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