Introduction

Gilles Vassal
an international multistakeholder organisation working to solve the central challenges in the development of innovative anticancer medicines for children and adolescents

OUR NAME IS OUR MISSION
<table>
<thead>
<tr>
<th>Geographical origin</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>55 Industry</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>33 Academia</td>
</tr>
<tr>
<td>Belgium</td>
<td>18 Patient Advocates</td>
</tr>
<tr>
<td>Netherlands</td>
<td>17 Regulators</td>
</tr>
<tr>
<td>Switzerland</td>
<td>15 European Commission</td>
</tr>
<tr>
<td>France</td>
<td>12 Staff</td>
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<td>Italy</td>
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<td>Sweden</td>
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<td><strong>TOT</strong></td>
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8th ACCELERATE Conference
Two anticancer medicines approved for children

- US August 15, 2019
  - Entrectinib – ROZLYTEK™
    - a pan-TRK, ROS1 and ALK inhibitor
    - solid tumors with NTRK fusion (12 years and older)

- EU September 19, 2019
  - Larotrectinib – VITRAKVI™
    - a pan-TRK inhibitor
    - solid tumors with NTRK fusion
ACCELERATE-ing Pediatric Oncology Drug Discovery and Development

ATLANTA
April, 2, 2019
10:30am
DAY -194

2017
FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act Guidance for Industry

December 2019
Additionally, **FDA encourages participation in international multi-stakeholder meetings including the Pediatric Strategy Forums organized by the ACCELERATE Platform** which bring sponsors, investigators, patient advocates, and regulators together to discuss development strategies for specific pediatric cancers in the context of the number of investigational drugs available **for assessment and the highly variable unmet medical needs** of distinct pediatric populations with specific childhood cancers.

We recommend stakeholders, including sponsors, investigators, and patient advocates consider coordinating **early multi-stakeholder input** to inform decision-making related to the initial pediatric clinical evaluation of appropriate
1. To set-up the 5th Pediatric Strategy Forum in the US and to implement the break out session recommendations

2. To develop the agenda of the FAIR Working Group and create 2 new working groups (see next slide)

3. To define a plan to implement break out session recommendations on International Collaboration

4. To explore the field of HTA evaluation across specialties and the ongoing initiatives to make a proposal at the next ACCELERATE meeting

5. To define a communication strategy for ACCELERATE
FAIR Working Group – Nathalie Gaspar and Chris Copland
Objectives: Develop the survey, implement the tool kit, new webpage, monitor implementation

**NEW** LTFU Working Group – Mark Kieran and Daniele Horton
Objective: Create an international data repository

**NEW** Fit For Filing Working Group – Elly Barry and Pam Kearns
Objective: Develop best principles on how to design and deliver a trial with a dataset that can be included in a package for filing

**NEW** International Collaboration – Nicole Scobie and Greg Reaman

Working Groups
79 participants
5. **New private sector initiatives to accelerate paediatric oncology drug development**

**Chairs:** Brenda Weigel, University of Minnesota / Delphine Heenen, KickCancer

6. **The global perspective**

**Chairs:** Donna Ludwinski, Solving Kids’ Cancer / Christina Bucci Rechtweg, Novartis
7. Preparing for the new regulatory environment

**Chairs:** Guillaume Bergthold, Roche / Susanne Gatz, University of Birmingham

8h30 – 08h45  Implementation of the Race for Children ACT  
Greg Reaman, Food and Drug Administration

08h45 – 09h00  Perspectives for the European Regulatory Environment  
Fabio D’Atri, European Commission

09h00 – 09h30  Assets to generate biological and preclinical data  
1. The IMI2 ITCC-P4 public private partnership project  
   Louis Stancato, Eli Lilly Company  
2. The FNIH public private partnership project  
   Stacey J. Adam and David Wholley, FNIH
Break Out Sessions

<table>
<thead>
<tr>
<th>Meeting</th>
<th>Group 1A</th>
<th>Group 1B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Challenges in prioritisation – The way forward</td>
<td>Andy Pearson + Scott Diede</td>
<td>Sam Blackman + Andy Kolb</td>
</tr>
<tr>
<td>3. Preclinical testing in order to benefit children</td>
<td>Hubert Caron + Nicole Scobie</td>
<td>Leona Knox + Stefan Pfister</td>
</tr>
<tr>
<td>4. Implementing the Race for Children Act</td>
<td>Elly Barry + Pam Kearns</td>
<td>Peter Adamson + Davy Chiodin</td>
</tr>
</tbody>
</table>
EUROPE’S BEATING CANCER PLAN
LET’S STRIVE FOR MORE

4 February 2020, European Parliament, Brussels

Horizon Europe
THE NEXT EU RESEARCH & INNOVATION PROGRAMME (2021–2027)

#HorizonEU

THE SIOP STRATEGIC PLAN
A European Cancer Plan for Children and Adolescents
10. Report from Breakout sessions

Chair: Gilles Vassal

14h00 – 16h00  Report from Breakout sessions and discussion

11. Wrap-up and 2019 Action Plan

16h00 – 16h20  Defining the 2020 ACCELERATE Action Plan

16h20 – 16h30  Conclusions and end of Conference
A catalyst and a sentinel*

*ACCELERATE is a sentinel whose goal is to warrant that implementation of new regulatory measures benefit children
OUR NAME IS OUR MISSION

The value of working together
Link: https://live.voxvote.com
PIN: 23124
The ACCELERATE Paediatric Strategy forum initiative and further development

Andy Pearson, ACCELERATE
ACCELERATE-EMA-FDA Paediatric Strategy Forums

• Progress, *evolution* and achievements over 2019-2020
• Paediatric Strategy Forum Medicinal Product Development of Epigenetic Modifiers in Children
• Future Directions
**ACCELERATE-EMA-FDA Paediatric Strategy Forums**

- **Goal** - To *share* information between all stakeholders, to *evaluate* science, to *inform* paediatric drug development strategies and *subsequent* decisions – multi-stakeholder meeting

- Improve the selection *and prioritisation* of innovative drugs being evaluated for children and adolescents cancer, this will be driven by science and meet patients’ unmet needs
ACCELERATE-EMA-FDA Paediatric Strategy Forums

Output – Paediatric Strategy Forums

• Summary and manuscripts – make conclusions public
• Prioritisation of medicinal products with follow up meetings when needed
• New initiatives such as platform trials to accelerate drug evaluation
• Monitoring changes in regulatory submissions and approvals both in Europe and the US (changing from adult-condition based waivers to scientifically and medically relevant waivers)
ACCELERATE-EMA-FDA Paediatric Strategy Forums

• **First Forum** for ALK Inhibition in Paediatric Malignancies - EMA - January 2017 - 6 products; 5 companies

• **Second Forum** - Medicinal Product Development for Mature B cell Malignancies in Children - EMA - November 2017 - 20 products; 14 companies

• **Third Forum** - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies - EMA - September 2018 - 20 products; 16 companies (32 EOI)

  ➢ **Fourth Forum** - Medicinal Product Development for Acute Myeloid Leukaemia - with EMA and FDA - Rotterdam - April 2019 - 26 products; 18 companies

  ➢ **Fifth Forum** - Epigenetic modifiers in Paediatric Malignancies - EMA and FDA - Philadelphia, USA (Alex Lemonade Stand) – January 2020 - 17 products; 11 companies

• **Sixth Forum** - Topic to be identified through consultation - EMA and FDA - EMA Amsterdam - 3 &4 November 2020

  **Target or disease focussed - Continually developing and adapting to needs**
Paediatric Strategy Forum Medicinal Product Development of Epigenetic Modifiers in Children

Medicinal Product Development for Mature B cell Malignancies in Children

- Consensus of clinicians - products which have the greatest probability of being beneficial in relapse
  - International ITCC European intergroup For Childhood NHL COG platform trial
  - Increase in the number of drugs with a lower scientific priority and relevance for children with cancer which are waived
Paediatric Strategy Forum Medicinal Product Development of Epigenetic Modifiers in Children

Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Six major conclusions including the need for international inter-company registry of early and late adverse effects
Paediatric Strategy Oversight Committee

- Reports to the ACCELERATE Steering Committee
- Responsible for:
  - recommending, after consultation, the choice of topics, for the Forum
  - proposing dates for the Forums
  - identifying 2-3 representatives from relevant international cooperative trial groups from both sides of the Atlantic for the preparation of each Forum (members of the Program Committee)
  - monitoring the impact of Forums

<table>
<thead>
<tr>
<th>Name</th>
<th>Representing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andy Pearson</td>
<td>ACCELERATE</td>
</tr>
<tr>
<td>Gilles Vassal</td>
<td>ACCELERATE</td>
</tr>
<tr>
<td>Dominik Karres</td>
<td>EMA</td>
</tr>
<tr>
<td>Koen Norgia</td>
<td>PDCO</td>
</tr>
<tr>
<td>Greg Reaman</td>
<td>FDA</td>
</tr>
<tr>
<td>Alberto Pappo</td>
<td>ODAC</td>
</tr>
<tr>
<td>Peter Adamson</td>
<td>Cooperative trial groups</td>
</tr>
<tr>
<td>Nicole Scoble</td>
<td>Patient Advocate</td>
</tr>
<tr>
<td>Susan Weiner</td>
<td>Patient Advocate</td>
</tr>
<tr>
<td>Anjali Sharma</td>
<td>Industry Trade Associations</td>
</tr>
<tr>
<td>Fiona Hemmings</td>
<td>Industry Trade Associations</td>
</tr>
</tbody>
</table>
Paediatric Strategy Forum Medicinal Product Development of Epigenetic Modifiers in Children

Medicinal Product Development for Acute Myeloid Leukaemia

**Developments**
- EMA and FDA
- Disease experts on Organising Committee
- Held in Rotterdam
- Linked with Leukaemia Lymphoma Society

**Outputs**
- Prioritisation of products – CD123
- PedAL/EUPAL Platform Trial
- FLT3 & CD123 focused meetings academia and industry - conclusions
- Novel agents in front-line should be embedded in cooperative group trials
- If rare mutations are more frequent in adolescents - extrapolation
ACCELERATE-EMA-FDA Paediatric Strategy Forums

• Progress, evolution and achievements over 2019-2020

• Paediatric Strategy Forum Medicinal Product Development of Epigenetic Modifiers in Children

• Future Directions
Paediatric Strategy Forum Medicinal Product Development of Epigenetic Modifiers in Children

Specific aspects

• First - Early in development of epigenetic modifiers
• First to be held in United States - Philadelphia
• RACE for Children Act implemented 18 August 2020 - drugs have to be considered for paediatric development if the target is relevant to paediatric cancer → early consideration
• Kimberly Stegmaier and Franck Bordeaut – topic experts
• Objective of the Forum-
  • To identify epigenetic targets or mechanisms of action relevant to paediatric cancer
  • To define the landscape for paediatric drug development of epigenetic modifiers in children and adolescents
Paediatric Strategy Forum Medicinal Product Development of Epigenetic Modifiers in Children

Priority targets

• Menin-MLL – Evaluate role in ALL and AML – Very high priority
• DOT1L - potential role in combination with Menin-MLL Inhibitor
• EZH2 - importance combination
• EDD - potential role in combination with EZH2
• PRMT5 - Adult data, pre-clinical data to be presented and knowledge of CNS access
• LSD1 - Very interesting pre-clinical activity in Ewings
• Retinoic acid receptor alpha agonist - Role in PedAL/EUPAL
• BET - At least three specific roles in paediatric malignancies and at least 7 pan BET inhibitors in development – specific follow up meeting
Paediatric Strategy Forum Medicinal Product Development of Epigenetic Modifiers in Children

General principles

• What is the best strategy to exploit viral mimicry in paediatrics
• Importance of combinations
• What pre-clinical data is needed? - the extent of required pre-clinical data depends on the context
  ▪ How can that pre-clinical data be provided?
• What is the strategy for multiple compounds of the same class, especially if there is a small potential paediatric population for evaluation?
ACCELERATE-EMA-FDA Paediatric Strategy Forums

- Progress, evolution and achievements over 2019-2020
- Paediatric Strategy Forum Medicinal Product Development of Epigenetic Modifiers in Children

Future Directions
ACCELERATE-EMA-FDA Paediatric Strategy Forums

Breakout Session  Accelerate 2019 – Future development of Paediatric Strategy Forums - Recommendations

- To develop forums alternatively in Europe and North America
- Continue to improve the preparation and the meetings
- To set up action plan with follow up for each forum in order to evaluate the impact of the forum and monitor its implementation
- To define the process for deciding forum topics
  - Increase the number of Forums

Next forum
In a class of compounds with no drugs yet approved in adults to discuss paediatric development earlier than previously – proposal BET inhibitors and epigenetic modifiers

Other potential forum topics
- Disease Focused: High Grade Glioma, Sarcomas
- Target focused: DNA Repair, CSF1 inhibitors and other immune-oncology targets
ACCELERATE-EMA-FDA Paediatric Strategy Forums

Future Directions

• Improving the selection and prioritisation of innovative drugs
• Alternate venues Europe and the US
• Mixture of topics - late versus early in development where the Forum can define the landscape
• Complement Race Act
• Present more pre-clinical data
• Continually refine and develop
Therapeutic targets and unmet medical needs in children with acute myeloid leukaemia

Todd M. Cooper, *Seattle Children's Hospital*
Therapeutic Targets in Pediatric AML: Outline

• Pediatric AML: Historical Perspective
  • Survival Plateau
  • Clinical Trial Designs at relapse: Historical Challenges
  • Incidence of AML in children

• Biology of Childhood AML: Should we treat children as adults?

• Reviewing Targets in Childhood AML

• Opportunities for alignment on pediatric drug development for Phase I/II studies in childhood AML
Our Challenge: Improving Survival for Childhood AML

De Novo Survival: COG

Relapse Survival: i-BFM
Rasche et al., Leukemia 2018

Standard risk
High-risk

De Novo Survival: -BFM
recent plateau in EFS
### Clinical Trials for Childhood AML in First Relapse

<table>
<thead>
<tr>
<th>Author</th>
<th>group (yrs)</th>
<th>n=</th>
<th>CR2, %</th>
<th>pOS %</th>
<th>(yrs)</th>
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</thead>
<tbody>
<tr>
<td>Stahnke</td>
<td>BFM (1987-1996)</td>
<td>134</td>
<td>51</td>
<td>21</td>
<td>(5 yrs)</td>
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<tr>
<td>Sander</td>
<td>BFM (1997-2001)</td>
<td>63</td>
<td>59</td>
<td>23</td>
<td>(5 yrs)</td>
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<tr>
<td>Rubnitz</td>
<td>St. Jude (1987-2002)</td>
<td>60</td>
<td>69</td>
<td>23</td>
<td>(5 yrs)</td>
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<tr>
<td>Webb</td>
<td>MRC (1988-1995)</td>
<td>125</td>
<td>69</td>
<td>24</td>
<td>(3 yrs)</td>
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<tr>
<td>Wells</td>
<td>CCG (1997-2001)</td>
<td>101</td>
<td>77</td>
<td>24</td>
<td>(2 yrs)</td>
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<tr>
<td>Gorman</td>
<td>TACL (1995-2004)</td>
<td>91</td>
<td>56</td>
<td>29</td>
<td>(5 yrs)</td>
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<tr>
<td>Abrahamsson</td>
<td>NOPHO (1988-2003)</td>
<td>146</td>
<td>77</td>
<td>34</td>
<td>(5 yrs)</td>
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<tr>
<td>Nakayama</td>
<td>JPLSG (&gt;2000)</td>
<td>71</td>
<td>50</td>
<td>37</td>
<td>(5 yrs)</td>
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<tr>
<td><strong>Kaspers</strong></td>
<td>I-BFM-SG (2001-2009)</td>
<td>394</td>
<td>64</td>
<td>38</td>
<td>(4 yrs)</td>
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<tr>
<td><strong>Karlsson</strong></td>
<td>NOPHO (1993-2012)</td>
<td>208</td>
<td>70</td>
<td>39</td>
<td>(5 yrs)</td>
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<tr>
<td><strong>Cooper</strong></td>
<td>COG (2016-2018)</td>
<td>38</td>
<td>68</td>
<td>50</td>
<td>(2 yrs)</td>
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</table>

Courtesy: G. Kaspers
Clinical Trial Development Challenges: Patient Numbers Affect Designs

• Clinical Trial Designs heavily influenced by available patients for study

• Historically, about 50% of children enroll on relapse trials for AML

• De Novo AML: ~900 children enrolled on international trials yearly

• 1st Relapse AML: ~300 annually, about half expected to enroll

• 2nd Relapse AML: ~100-150 annually, about half expected to enroll

• Targeted agents: e.g. FLT3/ITD
  • ~90-115 de novo
  • ~40 in first relapse
Genomic Era Confirms Pediatric AML is Biologically Distinct

Tarlock, Meshinchi, ASH 2016
Boulori et al, Nature Medicine 2018
Impact of Gene Fusions on Clinical Outcome

Bolouri, Nature Medicine 2018
Pediatric AML: Relevant Targets

adapted from Tasian, Börnhauser, and Rutella Biomedicines 2018
The most impactful cell lineage target to date: CD33

- Gemtuzumab ozogamicin (GO) in COG AML trials demonstrated minimal increased risk of VOD/SOS and improved DFS in subgroups of patients
- Bright CD33 expression and CC genotype associated with improved DFS
- Despite years of study, no approval for de novo AML in children
- CD33 ADC developed to improve upon this experience abandoned due to toxicities in older patients.
Landscape of FLT3 inhibitors for pediatric AML

• FDA approval for several in adults
  • Midostaurin approved for adults
  • Quizartinib break through designation, fast track for adults
  • Gilteritinib fast track for adults, approved in adults

• Pediatrics:
  • De novo (~150/yr)– Gilteritinib in COG Phase III study; Quizartinib – St. Jude study; Midostaurin – 34 European sites in 14 countries
  • Relapse: (~40/yr) Quizartinib in international Phase I/II; Gilteritinib in international Phase I/II; Midostaurin study completed.

• Nov 2019: Accelerate Paris: Specific recommendation for development of FLT3 inhibitors in children
### CD123 Directed Agents

- Expressed in B-ALL, AML, BPDCN, and hairy cell leukemia
- Differentially overexpressed in 93% of AML patients
  - High CD123 expression associated with lower CR and OS
  - Also present on quiescent leukemic stem cells

<table>
<thead>
<tr>
<th>Monoclonal Ab</th>
<th>Product</th>
<th>Company/Institution</th>
<th>Phase</th>
<th>Trial</th>
<th>Status</th>
<th>Results (ORR)</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Talacotuzumab</td>
<td>Xencor/J&amp;J</td>
<td>3</td>
<td>NCT01632852</td>
<td>Completed</td>
<td>20%</td>
<td>Discontinued (efficacy)</td>
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<th>Antibody Drug Conjugate</th>
<th>SGN-CD123A</th>
<th>Seattle Genetics</th>
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<th>NCT02848248</th>
<th>Terminated</th>
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<tr>
<td>IMGN632</td>
<td>ImmunoGen</td>
<td>1</td>
<td>NCT03386513</td>
<td>Recruiting</td>
<td>33%</td>
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<th>SL-401</th>
<th>Stemline Therapeutics</th>
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<th>NCT02270463</th>
<th>Recruiting</th>
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<tr>
<td>JNJ-63709178</td>
<td>Genmab/J&amp;J</td>
<td>1</td>
<td>NCT02715011</td>
<td>Recruiting</td>
<td>Hold (x2)/lifted</td>
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<tr>
<td>XmAb14045</td>
<td>Xencor/Novartis</td>
<td>1</td>
<td>NCT02730312</td>
<td>Hold</td>
<td>23%</td>
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</tbody>
</table>

| Bispecific Antibody | Flotetuzumab | MacroGenics | 1 | NCT02152956 | Recruiting | 26% |
|---------------------|-------------|------------|---|-------------|------------|
| JNJ-63709178 | Genmab/J&J | 1 | NCT02715011 | Recruiting | Hold (x2)/lifted |
| XmAb14045 | Xencor/Novartis | 1 | NCT02730312 | Hold | 23% | Hold/2 deaths |

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<tr>
<th>CART</th>
<th>UCART123 3</th>
<th>Cellectis (MD Anderson)</th>
<th>1</th>
<th>NCT03190278</th>
<th>Recruiting</th>
<th>Hold/lifted 1 death (BPDCN)</th>
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<tr>
<td>MB-102</td>
<td>Mustang Bio (City of Hope)</td>
<td>1</td>
<td>NCT02159495</td>
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<tr>
<td>CAR123</td>
<td>UPenn</td>
<td>1</td>
<td>NCT03766126</td>
<td>Recruiting</td>
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## Prioritization of New Agents in Childhood AML

<table>
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<th>Agent</th>
<th>Target</th>
<th>PIP?</th>
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</thead>
<tbody>
<tr>
<td>IMGN632 (Immunogen)</td>
<td>Anti-CD123 ADC</td>
<td>Planned</td>
</tr>
<tr>
<td>Anetumab Ravtansine (Bayer)</td>
<td>Anti-Mesothelin ADC</td>
<td>No</td>
</tr>
<tr>
<td>Trametinib (Novartis)</td>
<td>Mek inhibitor</td>
<td>Not in AML</td>
</tr>
<tr>
<td>Uproleselan</td>
<td>E-selectin inhibitor</td>
<td>Planned</td>
</tr>
<tr>
<td>SNDX-5613 (Syndax)</td>
<td>Menin</td>
<td>Planned</td>
</tr>
<tr>
<td>Flotetuzumab (Macrogenics)</td>
<td>CD123 DART</td>
<td>Yes</td>
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<tr>
<td>Venetoclax</td>
<td>BCL2</td>
<td>Yes (needs amendment)</td>
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<tr>
<td>CPX-351</td>
<td>Liposomal dauno/araC</td>
<td>Yes</td>
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</table>

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>PIP?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivosidenib (Agios)</td>
<td>IDH1</td>
<td>Yes</td>
</tr>
<tr>
<td>Enasidenib (Celgene)</td>
<td>IDH2</td>
<td>Yes</td>
</tr>
<tr>
<td>Cusatuzumab (Janssen)</td>
<td>CD70</td>
<td>Planned 3/20</td>
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<tr>
<td>AMG-330, AMG-673 (Amgen)</td>
<td>CD33 BiTE</td>
<td>Planned Q2 2020</td>
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<tr>
<td>AMG-427 (Amgen)</td>
<td>FLT3 BiTE</td>
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<td>TC-210 (TCR²)</td>
<td>Mesothelin TCR</td>
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<tr>
<td>Magrolimab (Forty Seven)</td>
<td>CD47 blocking antibody</td>
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<tr>
<td>MGB453 (Novartis)</td>
<td>TIM3</td>
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<tr>
<td>IMGN853 (Immunogen)</td>
<td>FOLR1-ADC</td>
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</tbody>
</table>
Opportunities: Clinical Trial Development in Pediatric AML

- Patient numbers limited, lack of good historical controls making efficacy assessments challenging.
- Often competing agents of same class in rare populations. Ex. FLT3 inhibitors
- Align on mechanism for prioritization and development for pediatric specific new agents.
- Early alignment on pediatric new agent prioritization, endpoints, clinical trial designs and development
- LLS Master Trial in development for pediatric acute leukemia: Early international collaboration between academia, industry, regulatory bodies
  - Unique opportunity for international alignment
Thank You!
The PedAL/EUPAL consortium to speed up innovation and prioritize

Edward Anders Kolb, Nemours Al DuPont Hospital for Children
Dirk Reinhardt, AML-BFM Study Group
University Children’s Hospital Essen
Our vision is for young cancer patients to not just *survive*, but to *thrive* in their lives after treatment.
Pedal master trial

Working with Pharmaceutical Partners

• The PedAL LLS is the sponsor in the US
  • The PedAL LLC will apply for and hold the IND (US) and CTA (Canada)
  • Princess Maxima Centre will be the ITCC accredited EU international sponsor to join with LLS support and a CTA with COG
  • The PedAL LLC will utilize NCI-funded infrastructure for maximal efficiency in trial design and implementation

• LLS and PedAL LLC advisors will perform all regulatory activities related to trial
  • Pharmaceutical Partners are responsible for development costs associated with individual sub-studies

• The PedAL LLC will advance promising molecules through proof of concept or Phase II
• The PedAL LLC will work with Pharmaceutical Partners to help advance molecules to a potential regulatory filing
Clinical Trial Goals and Design - Standardization

1. **Safety/Feasibility/Signal Finding studies** – Mono- and combination therapy safety and PK in patients with second or greater relapse/refractory AML
   - Simon 2 Stage Design Efficacy Expansion to up to 40 patients based on response confirmed by central flow cytometry.
     - Fail fast (n=10 at the end of the first stage).
     - Central flow cytometry at diagnosis and end of evaluation period to confirm response.

2. **Efficacy trial with intent for a regulatory filing**
   - Disease-free survival primary endpoint
   - Randomized or single arm trials depending on the estimated number of eligible patients

3. **DLT Assessments** – Currently non-standard and drifting
Clinical Trial Goals and Design - Standardization

3. DLT Assessments – Currently non-standard and drifting

<table>
<thead>
<tr>
<th>DLT Exclusions</th>
<th>AAML1421</th>
<th>ADVL1812</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
<td>Grade 3 or 4 AST or ALT elevation that improves to Grade ≤ 2 within 14 days</td>
<td>Grade 3 or 4 elevation of ALT/AST that returns to Grade ≤ 1 within 7 days. Hy’s law cases are to be considered a DLT</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Early intervention</td>
<td>Early intervention clearly and incontrovertibly unrelated to protocol therapy.</td>
</tr>
<tr>
<td>Hematological</td>
<td>Count recovery equal to 50 days from the start of the therapeutic cycle</td>
<td>Count recovery 42 days from the start of a therapeutic cycle.</td>
</tr>
</tbody>
</table>

Miller et al, ASH 2019 – Based on automated EHR Data Extraction

Induction ALT DLTs in 13% of patients
Near term ongoing activities

• Prioritize Pharma/NMEs of interest to be included in the trial - ongoing
  • Tier 1/ 1st wave: strong interest and have NMEs ready to go in the clinic
  • Tier 2/ 2nd wave: strong interest but are not quite ready to go in peds by Q3 2020 (early 2021)
  • Tier 3/ following wave(s): too early (not yet in human/early stages of FIH) 1-2 yrs after IND (2021-2022)

• Agreement on Process for approval of protocol – ongoing
  • MOU drafted and submitted to NCI in final stages of legal review

• Engage Scientific Steering Committee - ongoing
  • 1st Steering Committee meeting Oct 18, 2019
  • International Advisors – concept review and comment

• Dialog with COG - ongoing
  • Detailed list of RACI for LLS, COG, CRO, NCI is being agreed upon
  • Alignment and clarification on roles and responsibilities among the various parties was reached at high level
  • Scientific Council Approval (with Stipulations) of first 3 sub-trials and Master Protocol

• European involvement - ongoing
Collaboration LLS PedAL (North America +) and EUpAL-Consortium
EuPAL Consortium

**Consortium board:** 3 chairs and representatives of collaborative groups\(^1\) + representative of associated subgroups\(^2\), MD foundation

- Strategy
- Project selection
- Governance

**Steering Committee:** CB representatives (2), WP leader
+ 2 supporting project coordinator
conducting / developing projects
Cooperations ⇔ PEDAL / EU-Projects etc.

**Activities:** Grant application, private and public funding, international collaboration

---

\(^1\) The AIEOP-BFM, NOPHO and MyeCHILD will be represented by 3 delegates each.

\(^2\) Actually ITCC
Founding Members
1. Princess Máxima Center for Pediatric Oncology B.V.
2. AIEOP-BFM Pediatric AML Study group, representing the following countries: Italy, Austria, Czech Republic, Germany, Greece, Poland, Slovakia, Slovenia
3. NOPHO-DBH pediatric AML collaborative group, representing the following countries: Belgium, Netherlands, Denmark, Norway, Finland, Sweden, Island, Lithuania, Estland, Latvia, Spain
4. MyeChild pediatric AML consortium, representing the following countries: France, United Kingdom, Ireland
5. Innovative Therapies for Children with Cancer in Europe ("ITCC"), representing the European early phase clinical trial consortium
6. SIOP-Europe
7. German Society of Pediatric Oncology and Hematology (GPOH) gGmbH
8. Pediatric Research Network gGmbH

Interested Groups and/or Institutions are invited to join
European Foundation pediatric Acute myeloid Leukemia („Stichting“ according to Dutch law)

EuPAL

**Foundation** (legal entity)

**Board:** Consortium board

Managing director (by law)
Project coordinators (employed)

- contracting
- projects
- grant applications
- employer
- accounting

Will be founded by Princess Maxima
- statutes (given by law; defining aims/topics; should be general to cover all possible activities
EuPAL Consortium

**Consortium board:** 3 chairs and representatives of collaborative groups\(^1\) + representative of associated subgroups\(^2\), MD foundation

- Strategy
- Project selection
- Governance

**Steering Committee:** CB representatives (2), WP leader + 2 supporting project coordinator conducting / developing projects

Cooperations ↔ PEDAL / EU-Projects etc.

**Foundation (legal entity)**

- **Board:** Consortium board

- Managing director (by law)
- Project coordinators (employed)

  - contracting
  - projects
  - grant applications
  - employer
  - accounting

**Activities:** Grant application, private and public funding, international collaboration

---

\(^1\) The AIEOP-BFM, NOPHO and MyeCHILD will be represented by 3 delegates each.

\(^2\) Actually ITCC
Thank You!
Proofs of Principle: clarifying past developments & Innovation and Acceleration for 2020 (FLT3 and CD123)

Michel Zwaan, MD, PhD, Prof of Pediatric Oncology, Princess Máxima Center & Erasmus MC
Many drugs recently approved for *adult* AML

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Approval status</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPX-351</td>
<td>Liposomal formulation of cytarabine and daunorubicin</td>
<td>t-AML or AML with myelodysplasia-related changes (AML-MRC)</td>
<td>Blair HA, Drugs 2018; 78:1903–1910</td>
</tr>
<tr>
<td>Enasidenib mesylate</td>
<td>IDH2 inhibitor</td>
<td>RR AML with IDH2 mutation.</td>
<td>Stein EM, Blood 2017;130:722-31</td>
</tr>
<tr>
<td>Ivosidenib</td>
<td>IDH1 inhibitor</td>
<td>RR AML with IDH2 mutation.</td>
<td>Dhillon S, <em>Drugs</em>. 2018 Sep;78(14):1509-1516</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>BCL2 inhibitor</td>
<td>Elderly unfit AML with HMA/LD Ara-c</td>
<td>DiNardo CD,Blood 2019 133:7-17</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>Hypomethylating agent</td>
<td>adult AML and MDS.</td>
<td></td>
</tr>
</tbody>
</table>

Backbone in ped AML often different from the ‘elderly unfit population’ where adult AML drug development takes place (HMA/LD Ara-C): not easy to extrapolate.
<table>
<thead>
<tr>
<th>Study Group</th>
<th>Study</th>
<th>Patients (n)</th>
<th>EFS (%)</th>
<th>OS (%)</th>
<th>Relapse (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIEOP</td>
<td>AML2002/01 (2002-2011)</td>
<td>482</td>
<td>8-yr 55.0±2.6</td>
<td>8-yr 67.7±2.4</td>
<td>24</td>
<td>Pession et al 2013</td>
</tr>
<tr>
<td></td>
<td>AAML0531 (2006-2010)</td>
<td>1022</td>
<td>3-yr 53.1 vs 46.9</td>
<td>3-yr 69.4 vs 65.4</td>
<td>32.8 vs 41.3</td>
<td>Gamis et al, 2014</td>
</tr>
<tr>
<td>JACLS</td>
<td>AML99 (2000-2002)</td>
<td>240</td>
<td>5-yr 61.6±6.5</td>
<td>5-yr 75.6±5.3</td>
<td>32.2</td>
<td>Tsukimoto et al 2009</td>
</tr>
<tr>
<td></td>
<td>AML05 (2006-2010)</td>
<td>443</td>
<td>3-yr 54.3±2.4</td>
<td>3-yr 73.2±2.3</td>
<td>30.3</td>
<td>Tomizawa et al 2013</td>
</tr>
<tr>
<td>SJCRH</td>
<td>AML02 (2002-2008)</td>
<td>216</td>
<td>3-yr 63</td>
<td>3-yr 71</td>
<td>21</td>
<td>Rubnitz et al 2010</td>
</tr>
</tbody>
</table>
### Nr of available newly diagnosed pts

<table>
<thead>
<tr>
<th>Study group</th>
<th>Countries</th>
<th>New patients per year</th>
<th>FLT3-mutated pts 10-15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOPHO-DBH</td>
<td>Ice,N,S,Fin,DK,Es,Li,La,NL,B,S,Is,HK</td>
<td>~120</td>
<td>~15</td>
</tr>
<tr>
<td>BFM</td>
<td>D,A,CH, CZ, SK, Slo, Poland, AIEOP</td>
<td>~215</td>
<td>~27</td>
</tr>
<tr>
<td>MyeChild</td>
<td>UK, F, Irl</td>
<td>~150</td>
<td>~19</td>
</tr>
<tr>
<td>JCCG</td>
<td>Japan</td>
<td>~100</td>
<td>~12</td>
</tr>
<tr>
<td>COG</td>
<td>US, Canada</td>
<td>~300</td>
<td>~37</td>
</tr>
<tr>
<td>St Jude</td>
<td>US</td>
<td>~40</td>
<td>~5</td>
</tr>
<tr>
<td>All groups</td>
<td></td>
<td>925</td>
<td>115</td>
</tr>
</tbody>
</table>
Pediatric Strategic Forum meetings

ALK inhibitors 30/31 Jan 2017

Mature B-cell malign. 13/14 Nov 2017

Checkpoint inh 5/6 Sept 2018

AML 11/12 April 2019 Rotterdam

Follow-up meeting 5-11-2019 Paris: CD123 and FLT3
Currently approved PIPS in ped AML (April 2019)

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>Gemtuzumab ozogamicin</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Jazz Pharma</td>
<td>Vyxeos (CPX-351)</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Takeda</td>
<td>Pevonedistat</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Sanofi</td>
<td>Isatuximab</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>AbbVie</td>
<td>Venetoclax</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Boehringer-Ingelheim</td>
<td>Volasertib</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Janssen-Cilag</td>
<td>Decitabine</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Celgene</td>
<td>Azacitidine</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Astex</td>
<td>Guadecitabine</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Novartis</td>
<td>Midostaurin</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Daiichi Sankyo</td>
<td>Quizartinib</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Astellas</td>
<td>Giltertinib</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Celgene</td>
<td>Enasedinib</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Agios</td>
<td>Ivosedinib</td>
<td>PIP agreed</td>
</tr>
<tr>
<td>Clovis</td>
<td>Elacytarabine</td>
<td>PIP agreed; withdrawn</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Glasdegib</td>
<td>Product-specific waiver</td>
</tr>
</tbody>
</table>
### Class of medicinal product

<table>
<thead>
<tr>
<th>Class of medicinal product</th>
<th>Product</th>
<th>Target</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLT3 Inhibitors</strong></td>
<td>Midostaurin</td>
<td>FLT3</td>
<td>Novartis Pharmaceutical Industry AG</td>
</tr>
<tr>
<td></td>
<td>Gilterinib</td>
<td>FLT3</td>
<td>Astellas</td>
</tr>
<tr>
<td><strong>IDH 1&amp;2 Inhibitors</strong></td>
<td>FT-2102</td>
<td>IDH1</td>
<td>FORMA Therapeutics</td>
</tr>
<tr>
<td></td>
<td>Ivosidenib</td>
<td>IDH1</td>
<td>Agios</td>
</tr>
<tr>
<td></td>
<td>Enasedinib</td>
<td>IDH2</td>
<td>Celgene</td>
</tr>
<tr>
<td><strong>MoAb, BITE and ADC</strong></td>
<td>Flotetuzumab - Bispecific CD123-CD3 DART</td>
<td>CD123</td>
<td>Les Laboratoires Servier</td>
</tr>
<tr>
<td></td>
<td>XmAb®14045 (SQZ622) (Bi-specific CD123-CD3) (intermittent dosing)</td>
<td>CD123</td>
<td>Novartis Pharmaceutical Industry AG</td>
</tr>
<tr>
<td></td>
<td>SAR440324 (BiTE CD3-CD123)</td>
<td>CD123</td>
<td>Sanofi</td>
</tr>
<tr>
<td></td>
<td>Gemtuzumab ozogamicin (ADC)</td>
<td>CD33</td>
<td>Pfizer</td>
</tr>
<tr>
<td></td>
<td>AMG 330 &amp; AMG 673 (BiTE CD33)</td>
<td>CD33</td>
<td>Amgen</td>
</tr>
<tr>
<td></td>
<td>AMG 427 (BiTE FLT3)</td>
<td>FLT3</td>
<td>Amgen</td>
</tr>
<tr>
<td></td>
<td>Anetumab ravtansine (ADC)</td>
<td>Mesothelin</td>
<td>Bayer</td>
</tr>
<tr>
<td></td>
<td>Cusatuzumab (monoclonal antibody)</td>
<td>CD70</td>
<td>Janssen</td>
</tr>
<tr>
<td></td>
<td>Isatuximab (monoclonal antibody)</td>
<td>CD38</td>
<td>Sanofi</td>
</tr>
</tbody>
</table>
Outputs - Paediatric Strategy Forum for Acute Myeloid Leukaemia in Children 11-12 April 2019

- FLT3: proof of concept for cleaning the landscape of approved PIPs to focus on most promising developments – consensus biopharmaceutical companies and academia
- CD123: very interesting new target for ADC, DART and CART. How many studies can be delivered as several companies are developing CD123 targeted drugs? Need to accelerate – proof of concept
- Future approach for inhibitors of rare mutations - if more frequent in adolescents - inclusion of adolescents in adult trials and extrapolate from adolescent and adult data (if scientifically justified)
- Leukaemia Lymphoma Society PedAL initiative
- MRD as a surrogate marker for outcome – Meeting at ASH and then a consensus
FLT3 Inhibitors in children and adolescents

- Approximately 100 children present at diagnosis and 30 children relapse each year with FLT3 mutations in North America, Europe, Australia and Japan.

- Three agreed PIPs for FLT3 inhibitors with 3 front-line and 2 relapse studies in paediatrics – too many studies – too late.

- It is highly unlikely that these trials could be completed in view of the numbers of available patients.
Medicinal products targeting CD123 in children and adolescents

- CD123 is a high priority target - Paediatric Strategy Forum
- CD123 products are very early in development in paediatrics
- Consensus between relevant biopharmaceutical companies & academics - prioritisation (particularly within same class of agent, but also between agents with different mechanisms of action) - discussion with regulatory agencies
- In the relapsed population ADCs, which are administered with chemotherapy, have the advantage of not being reliant on a competent immune environment
Relapsed Studies
Currently there are two relapse studies in PIPs of Quizartinib and Gilterinib.

Proposal
Both the relapse studies should proceed but their size should be smaller with the aim only to describe pharmacokinetics and safety in children.

Front-line studies
The objective is to assess activity of the different FLT 3 inhibitors and also to provide access to FLT 3 inhibitors in children with FLT3 inhibitors.
Currently there are three frontline studies of Midostaurin, Quizartinib and Gilterinib.

Proposal
All three studies to proceed
• North America – COG Gilterinib
• Italy, Germany, Austria, Czechoslovakia and Poland – Midostaurin
• Netherlands, NOPHO, Belgium, Neth, Spain and Portugal – Quizartinib

An interim analysis of the Midostaurin study is carried out demonstrating the pharmacokinetics in combination and safety profile.
**CD123 Follow-up**

**Available drugs**

- **ADC**
  - IMGN632 (CD123-targeting ADC) ImmunoGen

- **T-cell engagers**
  - Long half life - Bispecific CD123XCD3 DART - Flotetuzumab - Macrogenics
  - Short half-life - Bi-specific T-cell engager CD3-CD123 Sanofi
  - CD123-bi-specific mAb Novartis Pharma AG

**Proposal**

- *IMGN632 (ADC)* is evaluated in Pedal North American and European randomised phase II trial (120 pts)

- *Bispecific CD123XCD3 T-cell engager Macrogenics* is evaluated in a phase I study by COG (just opened). When this is complete, it is evaluated in Pedal North American and European randomised phase II trial

- The lower age of entry for the *T-cell engager CD3-CD123 Sanofi* adult phase I is reduced to 12 years and patients are enrolled in Europe. When this is complete it is evaluated in Pedal North American and European randomised phase II trial.

- CD123-bi-specific T-cell engager mAb Novartis Pharma AG is not pursued in paediatrics at present.
Phase I
Dose Finding
DL1 = IMGN632 90mcg/kg q3wk x2 doses
(DL-1 = IMGN632 45mcg/kg q3wk x2 doses)

Phase II
(First Relapse of AML)

Randomized

Standard Arm
Cycle 1: CPX-351
Cycle 2: Fludarabine Cytarabine

Experimental Arm
Cycle 1: CPX-351 IMGN632
Cycle 2: Fludarabine Cytarabine IMGN632

Randomized study of IMGN632 on a backbone of CPX-351 (Vyxeos)

Studies in PEDAL are ‘Intent to file’:
- added value of IMGN632
- Vyxeos in the control arm

Vyxeos may replace the SOC defined by Kaspers et al in 1st relapse of AML. We need this as DNX is no longer available.
How to proceed with the Vyxeos/IMGN632 trial?

• Regulatory approval in NA and Europe
  - How to get *alignment* in an acceptable time-frame (end of 2020)?
  - Joint FDA/PDCO review?

• Can we consider a regulatory *fast-track approval process* after this very successful interaction during the Accelerate multi-stake-holder meetings
Thank you, and welcome to the beautiful world of liquid malignancies !!
ACCELERATE relapsed/refractory B-NHL Platform

Amos Burke, Cambridge University Hospitals
Paediatric Strategy Forum for Medicinal Product Development for Mature B cell Malignancies in Children

EMA
13-14 November 2017
• Standard of care results in > 94% 5 year EFS but substantial acute toxicity
• As frontline therapy is so successful de-escalation only undertaken when there is:-
  ▪ An effective salvage regimen
  ▪ There is a promising new product
• New drugs for mature B Cell malignancies in children should be first evaluated in relapse and not frontline
• Challenges of designing a relapse strategy include the very small number of patients (90 - US and Europe relapsed B cell malignancies per year) and the rapid progression
• Due to very small numbers of patients, a global strategy for novel drug development in is the most feasible approach
• These protocols should be designed and conducted to a very high quality standard with “intent to file”
Antibody drug conjugates (excluding a vinca alkaloid drug)
T-cell Engagers
CAR-T cells (as take 4 weeks for production - not products for initial use but only for consolidation)

These represent the greatest probability of being significantly beneficial in relapse
ACCELERATE and EMA Paediatric Strategy Forum for medicinal product development for mature B-cell malignancies in children

Abstract

Global, industry-supported, academic-sponsored studies testing compounds from different pharmaceutical companies simultaneously should be considered in rare populations, and it was proposed that an international working group be formed to develop an overarching clinical trials strategy for these disease groups. Future Forums are planned for other relevant paediatric oncologic diseases with a high unmet medical need and relevant molecular targets.
 Proposed model for prioritisation of drugs

<table>
<thead>
<tr>
<th>Class of therapeutics</th>
<th>First relapse or subsequent-Window/Induction</th>
<th>Consolidation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>With/without backbone chemotherapy</td>
<td>With/without backbone chemotherapy</td>
<td>Without backbone chemotherapy</td>
</tr>
<tr>
<td>ADC</td>
<td></td>
<td>CAR-T cell</td>
</tr>
<tr>
<td>Bispecific T cell Engagers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTK *</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* on going trial NCT02703272 – no further small molecule inhibitors until completion of the SPARKLE trial
First meeting of the ACCELERATE Paediatric relapsed/refractory B-NHL Strategy Forum Working Group
2nd May 2019

- Involved academic and industry partners
- Broad consensus achieved on the following:
  - Statistical design of the trial will likely incorporate Bayesian methodology due to number of patients
  - Classes of agents to be included
  - Platform will incorporate a drug prioritisation process by utilising a Trial Steering Committee with an independent chair
  - Funding model for the platform will be creative, with a proposal that industry partners make an initial payment on submission of a drug for review for prioritisation, as well as governmental, charitable and other philanthropic sources
  - Each experimental arm will be costed and paid for by the industry partner
  - Data output will be ‘fit for filing’
Platform organisation and structure

- A Trial Steering Committee will be appointed, and will consist of:
  - Independent Chair
  - Equal membership from European and American partners
  - Chief Investigator
  - Sponsor representatives
  - Patient/parent members
- University of Birmingham will be the platform Sponsor, with the Cancer Research UK Clinical Trials Unit (CRCTU) acting as the Trials Unit
The EICNHL-ITCC-COG platform trial for relapsed/refractory mature B-cell lymphoma

- **Trial Conduct**
  - Sponsored by the University of Birmingham
  - Delivered - Clinical Trials Unit (CRCTU)
  - Hub and spoke model - single trial sponsor working in partnership with national coordinating centres responsible for the conduct of the trial in their country
Progress

- 2\textsuperscript{nd} Working Group meeting 31\textsuperscript{st} October 2019
- 1\textsuperscript{st} Trial Steering Committee meeting 21\textsuperscript{st} January 2020
- 3\textsuperscript{rd} Working Group meeting 5\textsuperscript{th} February 2020
- 2\textsuperscript{nd} Trial Steering Committee meeting 5\textsuperscript{th} February 2020

Protocol in development is underway
Thank you
Paediatric developments of anticancer drugs for non-Hodgkin lymphoma in adults: current landscape

**8th ACCELERATE Paediatric Oncology Conference**

6- 7 February 2020, Brussels

Presented by Franca Ligas and Dominik Karres
Paediatric Medicines Office – European Medicines Agency
Disclaimer

The views expressed in this presentation are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.
### Outcome of the 2nd Paediatric Strategy Forum (13-14 Nov 2017)

<table>
<thead>
<tr>
<th>Medicinal products with greatest probability of being beneficial in relapse in mature B-cell malignancies in children</th>
<th>Scientific rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR T-cells</td>
<td>Mechanism of action with a rapid onset of effect. Significant advance in relapsed/refractory leukemias with same target. Potential to replace high-dose therapy, which is required for cure of relapsed/refractory B-cell non-Hodgkin’s lymphoma.</td>
</tr>
<tr>
<td>T-cell engagers</td>
<td>Mechanism of action with a rapid onset of effect. Immune cellular therapy with significant promise in leukemias with shared targets for B-cell non-Hodgkin’s lymphoma.</td>
</tr>
<tr>
<td>Antibody drug conjugates</td>
<td>Mechanism of action with a rapid onset of effect. Immunochemotherapy has shown substantial efficacy in frontline high-risk B-cell non-Hodgkin’s lymphoma in adults. Antibody-conjugates could provide increased efficacy in relapsed/refractory patients who may have received naked antibody as frontline therapy.</td>
</tr>
<tr>
<td>Checkpoint inhibitors</td>
<td>Biology of PMLBL associated with enhanced target for checkpoint inhibitors similar to Hodgkin’s lymphoma</td>
</tr>
</tbody>
</table>

### Table 3

Rationale for the consensus of the clinicians regarding the medicinal products which have the greatest probability of being beneficial in relapse

**Table 3**

<table>
<thead>
<tr>
<th>Medicinal products with lower probability of being beneficial in relapse in mature B-cell malignancies in children</th>
<th>Scientific rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td>Mechanism of action with a slow onset of effect—lack of significant therapeutic benefit. In future, most relapsed/refractory patients will have received naked monoclonal antibodies as part of frontline therapy. Adult studies do not suggest that changes of antibody against the same target in relapsed/refractory setting are effective.</td>
</tr>
<tr>
<td>Cell signalling inhibitors</td>
<td>Mechanism of action with a slow onset of effect demonstrated in adults—lack of significant therapeutic benefit and uncertainty about activity of Bruton’s tyrosine-kinase inhibitors ongoing trial</td>
</tr>
<tr>
<td>IMiDs and CELMoD</td>
<td>Mechanism of action with a slow onset of effect demonstrated in adults—lack of significant therapeutic benefit</td>
</tr>
<tr>
<td>Cytotoxics</td>
<td>Mechanism of action not different from established cytotoxics used in therapy of mature B-cell malignancies in childhood</td>
</tr>
</tbody>
</table>

**Table 3**

PMLBL, primary mediastinal B-cell lymphoma; IMiD, immunomodulatory inside drugs.

---

### Paediatric developments of anticancer drugs for non-Hodgkin lymphoma in adults: current landscape

**Table 3**

Pearson ADJ et al; European Journal of Cancer 110 (2019) 74e85

---

*Classified as public by the European Medicines Agency*
Current landscape for condition of mature B cell malignancies: paediatric applications

Methodology

• Number of EMA decisions issued within the condition of mature B cell malignancies from July 2007 until October 2019

• Number of EMA decisions issued before and after 2\textsuperscript{nd} Paediatric Strategy Forum (Cut-off date December 2017)

• Not including modifications requesting to turn a PIP into a full-waiver
**Results**

**July 2007 – December 2017**

- # of EMA decisions for Paediatric Investigation Plans → 15/27 (56%)
- # of EMA decision for Full-waivers → 12/27 (44%)

**July 2015- July 2018 Revision of the class waiver list (CW/0001/2015)**

**November 2017- 2nd Paediatric Strategy Forum**

**January 2018 – Oct 2019**

- # of EMA decisions for Paediatric Investigation Plans → 5/16 (31%)
- # of EMA decisions for Full-waivers → 11/16 (69%)

**Increased number of paediatric applications in the last years (16 in ~ 2 years vs 27 in ~ 10 years) and a more focussed approach in agreeing PIPs**
Take home message

• Continuous high number of applications in this condition driven by the development in adults
• Revision of the class waiver list (CW/0001/2015) has led to a higher number of procedures being discussed at the PDCO
• Scientific outputs of Paediatric Strategy Forums inform regulatory discussions clarifying unmet medical needs and identifying ways to address them
• Paediatric Strategy Forums initiate follow-up activities that lead to further interactions among stakeholders
Acknowledgments

• EMA PME office (Giovanni Lesa, Ralph Bax)
• PDCO delegates
Thank you for your attention!

Further information

[Franca.Ligas@ema.europa.eu]

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Classified as public by the European Medicines Agency
Choosing the topic of the next Paediatric Strategy Forums
Choosing the topic of the next Paediatric Strategy Forums

Process

• Survey
• Review by Paediatric Strategy Oversight Committee
• Voting by attendees of ACCELERATE Conference

Identify three topics for the next three Forums
Choosing the topic of the next Paediatric Strategy Forums

Survey

• Academia (via SIOPE Clinical Research Council in Europe and COG in the US)
• Industry attendees at previous ACCELERATE Conferences or Paediatric Strategy Forums Phrma and EFPIA
• Regulators
Choosing the topic of the next Paediatric Strategy Forums

Responses

• 47 proposals
  ▪ Class of compound based (17)
  ▪ Disease based (13)
  ▪ Class of compound within a disease (6)
  ▪ “Other” (11)
• 14 duplicate topics
• 33 topics

Reviewed by Oversight Committee
Choosing the topic of the next Paediatric Strategy Forums

Class of compounds

- BRAF and MEK inhibition (3)
- MYC inhibition and targeting in childhood cancer (2)
- Targeting defects in DNA repair (2)
- Retargeted T cells (2)
- Cyclin inhibition
- NK inhibitors
- Targeting energetic metabolism
- Cell based therapy
- PI3 K inhibitors
- FAP targeted therapies
- Epigenetic modifiers - covered in Fifth Paediatric Strategy Forum
Choosing the topic of the next Paediatric Strategy Forums

**Class of compound within a disease**

- TKI in sarcoma
- CAR T cell in solid tumours
- Proteasome inhibition in acute lymphoblastic leukaemia
- Immunotherapies in leukaemia
- Epigenetic modifiers in CNS tumours - in Fifth Paediatric Strategy Forum (2)

**Disease**

- Acute Lymphoblastic leukaemia, including B cell (4)
- Sarcoma / rhabdomyosarcoma (3)
- Brain tumours / brainstem tumours (3)
- Neuroblastoma (2)
- Post-transplant lymphoproliferative disorders (PTLD)
Choosing the topic of the next Paediatric Strategy Forums

Other

- Microbiome: new partner
- Loco-regional drug administration
- The future of precision trials in paediatric oncology
- Data sharing to facilitate clinical trial design
- Diagnosis and Management of PTLD
- Synergizing new FDA guidelines with EMA existing legislature
- Paying for paediatric studies: new models
- Molecular diagnostics
- Tumour microenvironment
Choosing the topic of the next Paediatric Strategy Forums

Principles for selection

• The goal is that discussion of the topics chosen will be timely, impactful and have an influence on future drug development

• To date the successful Paediatric Strategy Forums have focussed on areas where there have been a number of medicinal products available, however there is a limited paediatric population to evaluate the products and therefore prioritisation is required. In the future also defining the landscape
Choosing the topic of the next Paediatric Strategy Forums

Principles for selection

• It is important that the Paediatric Strategy Forum can solve the problem addressed for example, for the Forum to be effective in a disease with a dismal prognosis, there must be available medicinal products

• Defined topic
Choosing the topic of the next Paediatric Strategy Forums

• Targeting defects in DNA repair
• Tyrosine Kinase inhibitors in sarcoma
• BRAF and MEK inhibition
• Cyclin inhibition
• PI3K/AKT pathway
• Car-T Cells
• MYC inhibition and targeting in childhood cancer

Vote for three topics
<table>
<thead>
<tr>
<th>Topic 1</th>
<th>Targeting defects in DNA repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent insight has shown significant sensitivity of paediatric tumours to compounds that interfere in DNA damage signalling. The objective would be to determine: i) which DNA damage response targets are relevant in paediatric patients and ii) which tumours may be targeted with DNA damage response inhibitors.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topic 2</th>
<th>Tyrosine Kinase inhibitors in sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within paediatric and young people's tumours sarcomas represent an unmet need for curative treatment second only to brain tumours. The many tyrosine kinase inhibitors have demonstrated biological activity against a wide range of sarcomas in vitro, in vivo and efficacy in clinical trials in sarcoma patients. As several competing products are under development for the broad condition for sarcomas, prioritisation is required.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topic 3</th>
<th>BRAF and MEK inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activating mutations of the MapKinase pathway are frequently associated with high grade glioma and low-grade glioma, relapsed acute lymphoblastic leukaemia rhabdomyosarcoma and langerhans cell histiocytosis. A range of inhibitors for the MAPKinase pathways have been developed and have been investigated or come into clinical practice. The cancer subtypes in question constitute a substantial proportion of patients for whom there are not sufficiently effective therapies and who make up a substantial proportion of childhood cancer deaths. It is unknown which inhibitors should be prioritised.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topic 4</th>
<th>Cyclin inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Several cyclin inhibitors have been approved for adult breast cancer (palbociclib, abemaciclib, ribociclib) and additional agents are under development. Two PIPs are approved, both in Ewing sarcoma. Given the number of drugs being developed in this space, it would be worthwhile to discuss which paediatric populations should be studied and if there is a need to prioritise new agents in this class.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topic 5</th>
<th>PI3K/AKT pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Several compounds in paediatric development are targeting the same pathway and therefore discussion is warranted on the relevance in paediatric cancers.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topic 6</th>
<th>Car-T Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are many new compounds coming. T cell engagers and CAR T cells have high impact in B cell malignancies and potential also for other cancers. They have a specific mode of action and a new spectrum of toxicities. There is a need to prioritize new agents in this class.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topic 7</th>
<th>MYC inhibition and targeting in childhood cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYC is of high relevance in several paediatric solid cancers. There remains an urgent clinical need to disrupt the MYC-driven accelerated tumorigenesis in glioblastoma, high risk neuroblastoma, medulloblastoma and some types of lymphoma. MYC-dependent signalling pathways and molecular partners are emerging as attractive therapeutic targets for potential novel treatment regimens. Dialogue with industry and support for pre-clinical and early clinical trials in relapsed/refractory and/or high risk paediatric patients is both a hot topic and an urgent priority.</td>
<td></td>
</tr>
</tbody>
</table>
Thank You!
NTRK inhibitors: what we learned and where to go

Michela Casanova,
Fondazione IRCCS Istituto Nazionale dei Tumori
Milano, Italy
TRK receptors mediate neurotrophin signaling

- Neurotrophins are important growth factors involved in the growth, differentiation, and survival of neurons
- Neurotrophin signaling occurs through activation of the TRK receptor family

<table>
<thead>
<tr>
<th>TRK Receptor</th>
<th>Gene (Chromosomal Location)</th>
<th>Functions</th>
<th>Natural Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRKA</td>
<td>NTRK1 (1q23.1)</td>
<td>Developmental: Cellular differentiation/sensory neuron subtype specification and development of pain and thermoregulation modalities Adult: Pain signaling, thermoregulation</td>
<td>Nerve growth factor (NGF), neurotrophin-3 (NT-3)</td>
</tr>
<tr>
<td>TRKB</td>
<td>NTRK2 (9q21.33)</td>
<td>Development of sensory neurons in the brain</td>
<td>Regulation of movement, memory, mood, appetite, body weight</td>
</tr>
<tr>
<td>TRKC</td>
<td>NTRK3 (15q25.3)</td>
<td>Neuronal differentiation, axon outgrowth/guidance, and synaptic plasticity</td>
<td>Proprioception</td>
</tr>
</tbody>
</table>
Gene fusions: an important class of oncogenes

- Associated with a diverse range of solid tumours and hematologic malignancies
- *NTRK* gene fusions are associated with many human cancers
  - Associated with ≥19 tumour types
  - Implicated in up to 1% of all solid tumours

**TRK fusion proteins are primary oncogenic drivers**

---

Landscape of recurrent kinase fusions in solid tumours

<table>
<thead>
<tr>
<th>Gene Fusion Partner</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>3</td>
</tr>
<tr>
<td>BRAF</td>
<td>9</td>
</tr>
<tr>
<td>EGFR</td>
<td>5</td>
</tr>
<tr>
<td>FGFR1</td>
<td>4</td>
</tr>
<tr>
<td>FGFR2</td>
<td>1</td>
</tr>
<tr>
<td>FGFR3</td>
<td>3</td>
</tr>
<tr>
<td>FGR</td>
<td>2</td>
</tr>
<tr>
<td>MET</td>
<td>1</td>
</tr>
<tr>
<td>NTRK1</td>
<td>5</td>
</tr>
<tr>
<td>NTRK2</td>
<td>1</td>
</tr>
<tr>
<td>NTRK3</td>
<td>4</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>1</td>
</tr>
<tr>
<td>PKCα</td>
<td>1</td>
</tr>
<tr>
<td>PKMN1</td>
<td>1</td>
</tr>
<tr>
<td>PRKCA</td>
<td>1</td>
</tr>
<tr>
<td>PRKCB</td>
<td>1</td>
</tr>
<tr>
<td>RAF1</td>
<td>3</td>
</tr>
<tr>
<td>RET</td>
<td>2</td>
</tr>
<tr>
<td>ROS1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Pro-differentiation genes**

- MAPK
- PLCγ
- PK3

**Pro-survival genes**

- Tumorigenesis

**Transcription factors**

- Known fusion
- Known kinase — novel partner
- Known kinase — novel indication
- New fusion

---

**Gene fusions**

- Associated with a diverse range of solid tumours and hematologic malignancies
- *NTRK* gene fusions are associated with many human cancers
  - Associated with ≥19 tumour types
  - Implicated in up to 1% of all solid tumours
TRK fusion cancer occurs across a wide range of childhood and adult tumour types

- Rare tumours with high NTRK gene fusion frequency
- Common tumours with low NTRK gene fusion frequency

Paediatric (infants) high-grade glioma
Infantile fibrosarcoma
Spitz nevi
Congenital mesoblastic nephroma
Sarcoma (multiple)

Brain cancer (glioma, GBM, astrocytoma)
Salivary MASC
Thyroid cancer
Lung cancer
Secretory breast cancer
Intrahepatic cholangiocarcinoma
Pancreatic
Colon
Melanoma
Sarcoma

GBM, glioblastoma multiforme; MASC, mammary analogue secretory carcinoma; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.
What we are learning: brain tumors

Single-driver tumors particularly suitable for precision medicine

Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas

High unmet need both in terms of chance of relapse but also current therapies can lead to significant treatment burden and long term side effects
What we learned: rapid clinical development

- Identification of nerve growth factor (NGF), the first neurotrophin
- Identification of TRKA, TRKB and TRKC as high-affinity neurotrophin receptors
- Severe neuropathies developed by Ntrk knockout mice
- BDNF–TRKB pathway involvement in neuroblastoma progression
- Data emerge implicating the involvement of TRK signalling in ovulation
- Loss-of-function NTRK1 mutations identified in patients with congenital insensitivity to pain with anhidrosis (CIPA)
- Crystal structure of NGF in complex with TRKA determined
- First activating TRKA alternative variant identified
- Crystal structures of the kinase domains of TRKA and TRKB determined

1950s
- Identification of NTRK as an oncogene: TPM3–NTRK1 found in a human colorectal carcinoma

1982
- Identification of NTRK1 fusions in papillary thyroid carcinoma

1989–1991
- Identification of the first NTRK3 fusion (ETV6–NTRK3) in infantile fibrosarcoma

1993–1994
- Identification of NTRK2 fusions in pilocytic astrocytoma

2000
- TRKB downregulation associated with hyperphagia and hyperdipsia in mice

2010
- First-generation TRK inhibitors enter clinical trial testing

2015
- Second-generation TRK inhibitors enter clinical trial testing

2017
- Larotrectinib achieves histology-agnostic and age-agnostic responses in NTRK fusion-positive solid tumours

2018
- Larotrectinib and entrectinib receive FDA breakthrough designation for the treatment of NTRK fusion-positive solid tumours
Larotrectinib

- Larotrectinib is the first and only selective TRK inhibitor
- Highly potent against TRKA, TRKB, and TRKC
  - $IC_{50}$ 5–11 nM
- Highly selective
  - Limited inhibition of other kinases
  - No inhibition of 229 other kinases at 1000 nM
- Demonstrate activity in CNS disease
Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children


Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study

Larotrectinib

Study design: paediatric subset (non-CNS tumours; N=52)

- SCOUT phase I/II trial (NCT02637687)
  - Age <21 years
  - Advanced solid tumours
  - N=49

- Adult/adolescent phase II ‘basket’ trial NAVIGATE (NCT02576431)
  - Age ≥12 years
  - Advanced solid tumours
  - TRK fusion cancer
  - N=3

- 52 children and adolescents (aged <18 years) with non-CNS TRK fusion cancer

- Dosing
  - (Cohort 1; n=3): 8.6–55 mg/m² BID
  - (Cohort 2; n=6): 17.5–120 mg/m² BID
  - (Cohort 3; n=43): maximum dose 100 mg/m² BID

- TRK fusion status
  - Determined by local CLIA (or similarly accredited) laboratories

- Primary endpoint
  - Objective response rate (RECIST 1.1, investigator-assessed)

- Secondary endpoints
  - Duration of response
  - PFS
  - OS
  - Safety

Data cut-off February 19, 2019
BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; CNS, central nervous system; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase

No child should die of cancer
Larotrectinib

Best change in target lesions (INV-assessed by RECIST v1.1)

Data cut-off: Feb 19, 2019. *Patient with 0% change in tumour size (TPM3-TRK1 melanoma).
Pathological complete response. † One patient (ETV6-TRK3 IPS) was not evaluable due to lack of first post baseline assessment at data cut-off. Total values for complete and partial responses include 5 and 6 patients, respectively, pending confirmation. RECIST, Response Evaluation Criteria in Solid Tumors

What we learned: efficacy
Entrectinib

Proposed mechanism of action: Entrectinib inhibits constitutively activated TRK/ROS1/ALK tyrosine kinases thereby decreasing growth and proliferation signals from MAPK and PI3K pathways.
Entrectinib activity in NTRK fusion-positive solid tumours: individual patient responses by tumour type

<table>
<thead>
<tr>
<th></th>
<th>NTRK+ patients (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>57.4% (43.2–70.8)</td>
</tr>
<tr>
<td>SD</td>
<td>9 (16.7)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>Non-CR/PO, missing or un evaluable</td>
<td>10 (18.6)</td>
</tr>
</tbody>
</table>

Results per Blinded Independent Central Review (BICR)

Note: Patients (n=6) without matched pre/post therapy scans were excluded from the plot.
CI: confidence interval; CRC: colorectal cancer; MASC: mammary analogue secretory carcinoma; NSCLC: non-small cell lung cancer.
Entrectinib in pediatric solid tumors: individual patient responses

28 children treated between 5/2016-10/2018

Data cut-off: October 31, 2018. Investigator assessed
Includes only patients with measurable disease at baseline and tumor assessment
Entrectinib

Measureable and durable responses in CNS tumors
### Entrectinib/Larotrectinib

<table>
<thead>
<tr>
<th>Type</th>
<th>Entrectinib</th>
<th>ORR</th>
<th>Larotrectinib</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-CNS NTRK+</td>
<td>3/3 (3 PR)</td>
<td>100% (29-100%)</td>
<td>32/34 (11 CR, 21 PR)</td>
<td>94% (80-99%)</td>
</tr>
<tr>
<td>CNS NTRK +</td>
<td>3/4 (1 CR, 2 PR, 1 PR)</td>
<td>75% (19-100%)</td>
<td>5/11 (2 CR, 3 PR)</td>
<td>45% (17-77%)</td>
</tr>
<tr>
<td>CNS ROS1 +</td>
<td>2/2 (1 PR, 1 uPR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra-CNS ROS1 +</td>
<td>1/1 (1 PR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra-CNS ALK +</td>
<td>Fusion: 2/2 (2 CR) Mut: 1/1 (1 CR)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Difference response rate to extra-CNS and CNS tumor related to CNS penetrance?
- Larotrectinib was designed to have limited CNS penetration to reduce the potential for on-target toxicity due to inhibition of normal TRK receptors in the brain
- Entrectinib was first developed as an ALK inhibitor
Larotrectinib

Time to response and treatment duration

Duration of treatment: 1.3+ to 34.0+ months

75% of patients (n=39) continuing treatment at the time of data cut-off

Larotrectinib

Secondary efficacy endpoints

- **Duration of response**
  - Median DOR: NE (range 1.6+ – 29.5+)
  - Median follow-up: 11.1 months

- **Progression-free survival**
  - Median PFS: NE (range 0.03+ – 30.4+)
  - Median follow-up: 9.9 months

- **Overall survival**
  - Median OS: NE (range 1.3+ – 34.0+)
  - Median follow-up: 12.8 months

Data cut-off: Feb 19, 2019. DOR, duration of response, NE, not estimable.
Larotrectinib

Adverse events in ≥20% of pediatric patients (N=52)

<table>
<thead>
<tr>
<th>Treatment-emergent adverse events (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>38</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>50</td>
</tr>
<tr>
<td>ALT Increased</td>
<td>35</td>
<td>12</td>
<td>2</td>
<td>–</td>
<td>48</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>31</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>AST Increased</td>
<td>31</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>40</td>
</tr>
<tr>
<td>Cough</td>
<td>35</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>38</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>31</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>38</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>4</td>
<td>12</td>
<td>15</td>
<td>4</td>
<td>35</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>31</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>25</td>
</tr>
<tr>
<td>Leukocyte count decreased</td>
<td>19</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>23</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>12</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>23</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4</td>
<td>19</td>
<td>–</td>
<td>–</td>
<td>23</td>
</tr>
<tr>
<td>Anaemia</td>
<td>12</td>
<td>4</td>
<td>6</td>
<td>–</td>
<td>21</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>15</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>21</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>17</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>21</td>
</tr>
<tr>
<td>Nausea</td>
<td>19</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-related adverse events (%)</th>
<th>Grade 3/4</th>
<th>Total</th>
</tr>
</thead>
</table>
| Discontinuation due to AE related to study drug occurred in 1 (2%) patient
Potential NTRK inhibitors toxicities

No data on late effects

The phase I adult trial of larotrectinib enrolled patient starting in March 2015
Entrectinib

STARTTRK-NG summary of safety: Dose discontinuations, reductions, and adverse events

- **Discontinuations:**
  - 2 patients (6.9%) discontinued drug
    - One treatment-related AE (pulmonary edema)
    - One event not related to treatment (dyspnea)

- **Reductions:**
  - 11 patients (39.7%) were dose reduced for treatment-related AE – see table

- **Notable adverse events:**
  - **Elevated Creatinine**
    - 41% of all patients – all G1/G2
    - May not reflect true renal impairment since Entrectinib inhibits the MATE1 transporter which is involved in creatinine excretion.
  - **Weight gain**
    - Possible on-target effect (hyperphagia, obesity) 1-4
    - Most common reason for dose reduction
    - More common in patients on the drug for prolonged period (i.e. responders)
    - 2 patients have experienced bilateral femoral neck fractures possibly related to study drug, rapid weight gain, and steroid use.
  - **Dysgeusia/Ataxia/Falling**
    - Also possible on-target effects 1-4
    - Sensory impairments from TRK protein inhibition?
    - Dysgeusia 21% total - G1/G2
    - Ataxia and falling < 10% total

---

<table>
<thead>
<tr>
<th>AE leading to dose reductions by patient</th>
<th>Phase 1 dose escalation (n=5/16)</th>
<th>Phase 1b (n=6/13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased blood creatinine</td>
<td>Weight gain</td>
<td></td>
</tr>
<tr>
<td>Weight gain (2 episodes)</td>
<td>Ataxia</td>
<td>Intermittent falling episodes</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>Intermittent falling episodes</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema (3 episodes)</td>
<td>Weight gain</td>
<td>Headache</td>
</tr>
<tr>
<td>Increased blood creatinine</td>
<td>Prolonged QT interval</td>
<td></td>
</tr>
</tbody>
</table>
# NTRK inhibitors approved in NTRK-fusion positive tumours

<table>
<thead>
<tr>
<th><strong>Larotrectinib</strong></th>
<th><strong>Entrectinib</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved:</strong> FDA 2018; Brazil, Canada, EMA 2019</td>
<td><strong>Approved:</strong> FDA and Japan 2019</td>
</tr>
<tr>
<td><strong>Indication:</strong> For the treatment of patients with solid tumours harbouring NTRK fusions in paediatric or adult patients</td>
<td><strong>Indication:</strong> For the treatment of NTRK fusion-positive advanced or recurrent solid tumours in adult patients and paediatric patients aged ≥12 years old</td>
</tr>
</tbody>
</table>
| **Dose:** 25-mg or 100-mg oral capsule or 20-mg/mL oral solution  
  - Adults and children with BSA ≥1.0m²: 100 mg orally BID  
  - Children with BSA ≤1.0m²: 100 mg/m² orally BID | **Dose:** 100-mg and 200-mg oral capsule  
  - Adults: 600 mg orally once daily  
  - Children: Recommended dose based on BSA |
Where to go?

Identification of NTRK fusions in pediatric patients

Treatment: when? how long?

Toxicity and late effects

Resistances and second generation NTRKi
ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research

As a confirmatory technique use FISH, RT-PCR or targeted RNA NGS assays with specific probes for the fusion involving the known NTRK gene

Is the histologic tumour type known to harbour highly recurrent NTRK fusions?

Is there a sequencing platform available?

Use IHC as a screening tool

Detection of TRK expression

IHC to confirm protein expression in positive cases

Use front line NGS reliably detecting NTRK fusions, preferably including RNA testing when possible
No in tumor with activating mutation mutually exclusive to NTRK
TRK Fusion Cancers in Children: A Clinical Review and Recommendations for Screening

Catherine M. Albert, MD; Jessica L. Davis, MD; Noah Federman, MD; Michela Casanova, MD; and Theodore W. Laetsch, MD

(A) Immunohistochemistry
- Detects protein expression, which may be attributable to a fusion event.
  (A) Strong panNTRK antibody expression in NTRK1 fusion–positive IFS.

(B) FISH
- Detects gene rearrangements in DNA that may generate a fusion transcript.
  (B) ETV6 FISH break-apart probe demonstrating an ETV6 rearrangement.

Reverse Transcriptase Polymerase Chain Reaction
- Detects known fusion transcripts in RNA.
- Detects 5'3' imbalance as a fusion signature, but cannot determine novel partner.

(C) Next-Generation Sequencing
- Detects known and novel fusions with arbitrary breakpoints in DNA or RNA.
- Exact capabilities depend on enrichment strategy and data analysis pipeline.
  (C) Sequencing read piles aligned to the human genome and visualized using the Integrative Genomics Viewer. The rainbow plot shows discordant mate pairs in the tumor with one mate mapping to intron 7 of TPM3 on chromosome 1 and the other mapping to intron 8 of NTRK1 also on chromosome 1.

Need for specific recommendations for children
<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Clinical summary</th>
<th>Screening methodology</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infantile fibrosarcoma</strong></td>
<td>• Most common soft tissue sarcoma in children &lt;1 year</td>
<td>IHC/FISH (ETV6 and/or NTRK3) RT-PCR; NGS if negative</td>
<td>High frequency of ETV6-NTRK3 fusion; variant NTRK3 and NTRK1 fusions have been described</td>
</tr>
<tr>
<td><strong>Cellular congenital mesoblastic nephroma</strong></td>
<td>• Most common kidney tumour in the first month of life</td>
<td>IHC/FISH (ETV6 and/or NTRK3) RT-PCR; NGS if negative</td>
<td>High frequency of ETV6-NTRK3 fusion; variant NTRK3 and NTRK1 fusions have been described</td>
</tr>
<tr>
<td><strong>Secretory breast cancer</strong></td>
<td>• Rare subtype of breast cancer (&lt;0.02% of patients)</td>
<td>IHC/FISH (ETV6 and/or NTRK3) RT-PCR; NGS if negative</td>
<td>High frequency of NTRK3 fusions</td>
</tr>
<tr>
<td><strong>MASC of the salivary gland</strong></td>
<td>• Histologically resembles secretory breast cancer</td>
<td>IHC/FISH (ETV6 and/or NTRK3) RT-PCR; NGS if negative</td>
<td>High frequency of NTRK3 fusions</td>
</tr>
</tbody>
</table>
Tumours with medium-frequency TRK fusions (10% to 40%)

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Clinical summary</th>
<th>Screening methodology</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| Spitzoid melanomas                 | • Rare melanocytic lesions (ranging from benign to malignant spitzoid melanoma)  
• 90% of patients diagnosed are <30 years old  
• Children aged 10–18 years are at greater risk of metastatic spread and death vs younger children  
• Recently, recurrent kinase fusions have been described                                                                                                                                         | IHC/NGS               | TRK fusions occur in 15–25% of paediatric melanocytic neoplasms                                                                                                                                               |
| Papillary thyroid cancer            | • Thyroid cancers account for ~4% of malignancies in children; >90% of these are PTC cases  
• Good prognosis, with >95% overall survival rate at 5 years  
• Treatment consists of thyroidectomy for localised tumours, and radioactive iodine for metastatic tumours  
• TRK fusions may be associated with higher-stage disease                                                                                                                                       | IHC/NGS               | TRK fusions (NTRK1 and NTRK3) occur in approximately 25% of children, and BRAF activating mutations occur in ~50% of patients                                                                                  |
| High-grade gliomas, especially in young children | • Gliomas are the most common brain tumours in children  
• Poor survival outcomes in children with high-grade gliomas (<25% 3-year overall survival rate)  
• NTRK fusions shown to occur in ~40% of high-grade gliomas in children <3 years old                                                                                                                                                      | NGS                   | TRK fusions occur, especially in tumours of children <3 years of age; patients have poor prognosis; IHC has not been validated in gliomas, which can have normal physiologic expressions of TRK |

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER
### Tumours with unknown or low-frequency TRK fusions (<5%)

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Clinical summary</th>
<th>Screening methodology</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| **Undifferentiated sarcoma (without known defining fusion)** | • Link with TRK fusions largely anecdotal, so frequency has not been estimated  
• Historically, treatment of undifferentiated sarcoma has been variable, more recently risk-based chemoradiotherapy | NGS                   | Prevalence of TRK fusions unknown but described; in addition to NTRK, other targetable fusions have been described |
| **Inflammatory Myofibroblastic Tumour**  | • Locally aggressive neoplasms  
• Median age at diagnosis: 9 years  
• Metastases are rare (<5%), and complete surgical resection is usually curative  
• Patients with ALK fusions (50–60% of cases) have a good treatment response with crizotinib | NGS                   | TRK fusion tumours may share inflammatory myofibroblastic tumour-like morphology; mutually exclusive fusions of ALK and ROS1 also occur |
ICH: sensitivity and specificity is high in mesenchymal tumors useless in brain tumors

Pan-Trk Immunohistochemistry Identifies NTRK Rearrangements in Pediatric Mesenchymal Tumors

Erin R. Rudzinski, MD,* Christina M. Lockwood, PhD,† Bradley A. Stohr, MD, PhD,‡ Sara O. Vargas, MD,§ Rachel Sheridan, MD,¶ Jennifer O. Black, MD,¶ Veena Rajaram, MD,# Theodore W. Laetsch, MD,** and Jessica L. Davis, MD,‡‡†

Expanding the Spectrum of Pediatric NTRK-rearranged Mesenchymal Tumors

Jessica L. Davis, MD,*† Christina M. Lockwood, PhD,‡ Bradley Stohr, MD, PhD,† Carolin Boecking, MD,† Alyaa Al-Ibraheemi, MD,§ Steven G. DuBois, MD,¶ Sara O. Vargas, MD,§ Jennifer O. Black, MD,¶ Michael C. Cox, PharmD,# Mark Luquette, MD,** Brian Turpin, DO,†† Sara Szabo, MD,‡‡ Theodore W. Laetsch, MD,§§ Catherine M. Alberti, MD,¶¶ David M. Parham, MD,¶¶ Douglas S. Hawkins, MD,¶¶ and Erin R. Rudzinski, MD##
Molecular profiling programs at relapse

1. Generate individual molecular information at relapse

- **MAPPYACTS** (France, Spain, Italy, Ireland, Israel)
- **INFORM** (Germany, Austria, Sweden, Switzerland, Belgium)
- **iTHER** (The Netherlands)
- **SM-PAEDs** (UK)

2. Match treatment and tumor profile

SHARE

- **EU Clinico Biological** (WES/RTA/seq Data Base)

3. Evaluate activity of drugs and combinations

- **Phase 1 Trials** (Industry and ISTs)
- **Phase 2 Trials** (Industry and ISTs)
- Genentech Roche
  - Matrix Trial
- **ESMART Multiarm trial**
  - European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors in children (ESMART)

4. Generate new knowledge, new druggable pathways

ACCELERATE

Innovation for Children and Adolescents With Cancer
MYCKID STUDY:
MOLECULAR IDENTITY CARD FOR KIDS, ADOLESCENT AND YOUNG ADULT WITH NON RHABDOMYOSARCOMAS SOFT TISSUE SARCOMA
Frozen material (molecular characterization):
- Whole exome sequencing (WES), RNAseq for fusion detection, DNA methylation
- Ancillary studies (organoids, single cell RNA sequencing)

FFPE material (molecular characterization):
- RNAseq, CGH: CINSARC, GI
- Transcript fusion, clustering: diagnosis

Diagnosis purpose

Research purpose

Center 1
Local pathology

Center 2
Local pathology

Center 3
Local pathology

Center 4
Local pathology

Lyon

Utrecht

EpSSG Country A

EpSSG Country B

EpSSG Country C
Additional data are coming in the next years in adults and children

<table>
<thead>
<tr>
<th>Study/Identifier</th>
<th>Design</th>
<th>Patients</th>
<th>Objectives</th>
<th>Estimated primary completion</th>
<th>Estimated total enrollment</th>
</tr>
</thead>
</table>
| Pediatric MATCH (phase 2) NCT03213704 | Patients receive larotrectinib orally or via nasogastric or gastric tube BID for up to 2 years | • Children and young adults (12 months to 21 years)  
• Relapsed or refractory advanced solid tumors, NHL or histiocytic disorders with NTRK gene fusions | • ORR  
• PFS  
• Tolerability  
• PK | March 2022 | 49 |
| Pediatric MATCH (phase 2) NCT03155620 | Patients are tested for genetic alterations, and receive corresponding targeted therapy for up to 2 years (6 therapies available; patients with NTRK gene fusion receive larotrectinib) | • Children (12 months to 21 years)  
• Recurrent or refractory solid tumors | • ORR  
• Toxicity  
• PK  
• PFS | December 2021 | 1500 |
| NCI MATCH (phase 2) NCT02465060 | Patients are tested for genetic alterations, and given a corresponding targeted therapy for up to 2 years (30 therapies available; patients with NTRK gene fusion receive larotrectinib) | • Adults (≥18 years)  
• Solid tumor or lymphoma | • ORR  
• OS  
• PFS  
• TTP | June 2022 | 6452 |
Larotrectinib in Treating Patients With Previously Untreated TRK Fusion Solid Tumors and TRK Fusion Relapsed Acute Leukemia – COG ADVL1823

- **Primary outcome measure**
  ORR of children with infantile fibrosarcoma (IFS) treated with neoadjuvant larotrectinib prior to local control

- **Secondary outcome measures**
  EFS/OS/DoR in IFS treated with neoadjuvant larotrectinib

  ORR/EFS/OS/DoR in newly diagnosed TRK fusion solid tumors other than IFS treated with neoadjuvant larotrectinib prior to local control

  Incidence of adverse events

  Percentage of patients with TRK fusion solid tumors with detectable ctDNA
### Chemotherapy versus Larotrectinib as first-line therapy in IFS

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Larotrectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV (catheter)</td>
<td>Oral</td>
</tr>
<tr>
<td>Effective (75%)</td>
<td>Effective (&gt;90%), rapid response</td>
</tr>
<tr>
<td>Acute toxicity (VOD)</td>
<td>No severe acute toxicity</td>
</tr>
<tr>
<td>Duration of therapy: median 4 months</td>
<td>Duration of therapy?</td>
</tr>
<tr>
<td>Long term toxicity only to second line therapy (alkylating agents, anthracycline)</td>
<td>Long term effects?</td>
</tr>
<tr>
<td>Costs: cheap</td>
<td>Cost: very expensive</td>
</tr>
<tr>
<td>Available</td>
<td>Current availability only within trials</td>
</tr>
</tbody>
</table>
EpSSG/EXPeRT guidelines for IFS recommend conservative surgery or neoadjuvant chemotherapy as first-line therapy

**Tumour assessment**
Resectability without any functional or mutilating consequences with RO intent

- **Yes:** Surgery first
  - IRS I–II: no further therapy
  - IRS III: chemotherapy
- **No:** Neoadjuvant chemotherapy until maximum tumour shrinkage
  - Conservative surgery
  - RO, R1 margins, complete necrosis; no further therapy
  - R2: post-operative chemotherapy

**VA regimen recommended initially**
- If response to VA is not sufficient to permit conservative surgery, ifosfamide and/or cyclophosphamide and/or doxorubicin should be added
- If no response to VA, the IFO-DOXO regimen should be adopted

**New targeted therapies**
The use of TRK inhibitor drugs should be certainly considered when conventional chemotherapy fails
Toxicity and late affects

Neurocognitive outcome
  - Very young children
  - Patients who remain on treatment for years

Discussion with parents on this topic is essential
Multiple initiative

Brussels 5\textsuperscript{th} Feb: Readdressing the need for long-term follow up
Accelerate group: Danielle Horton Taylor/Mark Kieran
Acquired resistance mechanisms

Resistance to NTRK inhibition by larotrectinib and entrectinib is mediated by recurrent mutations to the kinase domain of NTRK gene at three different locations (solvent-front mutations, gatekeeper and xDFG)

The kinase solvent-front mutation is mediated through G595R substitution in the TRKA protein and G623R substitution in the TRKC protein.

The gatekeeper mutation is found at F589L substitution in the TRKA.

The xDFG motif mutation is found at G667C substitution in the TRKA protein and G696S substitution in the TRKC protein.
Second generation NTRK inhibitors are being developed to overcome acquired resistance

<table>
<thead>
<tr>
<th>Drug (company)</th>
<th>Objective</th>
<th>MoA</th>
<th>Development stage (Clinicaltrials.gov identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selitrectinib (formerly known as LOXO-195)* (Bayer)</td>
<td>To overcome resistance mediated by solvent-front mutations, and xDFG substitutions</td>
<td>Selectively targets NTRK 1/2/3 gene fusions</td>
<td>Phase 1/2 trial (NCT03215511)</td>
</tr>
<tr>
<td>Repotrectinib** (Turning Point Therapeutics)</td>
<td>To overcome resistance due to solvent-front substitutions</td>
<td>High selectivity for wild-type and mutated TRKA, TRKB, TRKC, ROS1, and ALK proteins</td>
<td>Phase 1/2 trial (NCT03093116)</td>
</tr>
</tbody>
</table>
Thank you

michela.casanova@istitutotumori.mi.it
ACCELERATE FAIR trial group

Nathalie GASPAR, *Gustave Roussy, France*
Chris COPLAND, *University of York, UK*

*Carole LECINSE, ITCC*
Fostering Age Inclusive Research Group

https://www.accelerate-platform.org/fair-trials/

Objective 1
To identify successful trials

Objective 2
Awareness Raising to the professionals involved in trial design and approval and the general public

Objective 3
Tools ready to use to facilitate the understanding of the problem and the initiation of trial

Objective 4
Endorsement of the adolescent strategy

Associated members
- National authorities
- Regulatory representatives
- Ethics Committees
- Academics from the main European countries

Core group
- Academic drug development
- Pediatric and medical oncology
- Pharma Roche Genentech BMS Novartis
- Patient/parent representatives AYA

Fostering Age Inclusive Research Group
Objective 1
To identify successful trials

2020
User return
Better completeness

Early Drug Development for Adolescents:
Oncology Protocols Survey

Fostering Age Inclusive Research (FAIR) Trials for Adolescents & Young Adults

- If you work in Pharma or Research, please complete our survey on current standards.

To be completed anytime of the year
Reminders from October to January
The Survey:

- Early phase 1/2 trials
- Intended for academic PIs for academic trials through ITCC
- Intended for ACCELERATE pharma partners for pharma trials

More companies have completed the survey
Still few adult trials including adolescents

### Objective 1
To identify successful trials

**Trial phase**

<table>
<thead>
<tr>
<th>Trial phase</th>
<th>Ped. Trial with YA</th>
<th>Adult trial with Ado.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1/1b</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(+2 confidential)</td>
<td></td>
</tr>
<tr>
<td>Phase 2/3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(+1)</td>
<td></td>
</tr>
</tbody>
</table>

**Responses**

<table>
<thead>
<tr>
<th></th>
<th>Academia</th>
<th>Pharma</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019 trials</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Academia</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Pharma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

More companies have completed the survey
Still few adult trials including adolescents

Very difficult to interpret
- Not all items completed
- Separate excel file sent
- Results ergonomy
Paediatric oncologists

Medical oncologists


cs

National networks

Representatives of the main EU countries .... Meeting and cancer societies

European networks

Paediatric oncology

Medical oncology

Specific AYA cancer groups

General public

Online

Broadcast media

Media release

In 2020

Contact with Other organisations

Objective 2

Raising Awareness through NETWORKS
European networks

E-learning Tools

Access to Clinical Trials for Adolescents and Young Adults With Cancer: A Meta-Research Analysis

Teresa de Rojas, Anouk Neven, Mitsumi Terada, Miriam García-Abós, Lucas Moreno, Nathalie Gaspar, Julien Péron

Abstract

Background: The 18-year-old age limit for inclusion in clinical trials constitutes a hurdle for adolescents and young adults (AYAs) with cancer. We analyzed the impact of this age barrier on the access of AYAs to cancer trials and novel therapies.

Methods: ClinicalTrials.gov was searched to identify all the trials including patients with 10 malignancies relevant for AYAs (January 2007 to July 2015). The trials were categorized as pediatric (patients <18 years), adolescent (18-21 years), and transitional (including adult and pediatric patients). Transitional trials with a lower limit between 12 and 18 years and an upper limit younger than 40 years were considered AYA-specific.

Results: Of 2,764 identified trials, 2,176 were included: 79% adult, 19% transitional, 2% pediatric. Five trials were AYA-specific. The proportion of academic trials was higher for transitional (69%; 298 of 421) than for adult trials (49%; 832 of 1,719) (p < .001). The total number of new trials increased over the years (156 in 2007; 228 in 2017); however, the number of transitional trials remained stable. The availability of trials increased with age, with a major increase at age 18 years: at age 17 years, 20% (442 of 2176) of trials were potentially accessible vs 95% (207 of 2176) at 18 years. For trials investigating targeted therapies, this increase was 46% (197 trials available at age 17 years; 101 at 18 years) and for immunotherapies, 120% (55 at age 17 years; 658 at 18 years).

Conclusions: AYAs have limited access to cancer trials and innovative therapies, with no improvement over the last decade. The 18-years-old age limit continues to be a major hurdle. Our findings are consistent with the internationally supported idea that age inclusion criteria in oncological trials should be changed.
As part of the responsibility to provide better medicines for children, the EFGCP strongly recommends:

- That researchers, regulators, and members of ethics committees weigh the totality of physiologic, pathologic, and other disease specific evidence to consider adolescent inclusion in adult research and vice versa – young adults as an extension population in paediatric/adolescent studies - when relevant as a trial methodology to facilitate earlier access to investigational and approved medicines for adolescent patients.

Analyses for publication:

1. Defining pre-requisites/minimum requirements/key criteria for risk-benefit evaluation in support of AI

2. Analysis of EU/US regulatory guidance
   - Permission (P), Exclusion (E) or Silence (S) on the role for AI
   - Guidance stated basis for P or E

3. Retrospective analysis and experience in EU/US of adult registration programs which incorporated AI → How was the data generated then utilized in product registration(s)
Within the new Accelerate brand identity, Fair Trials is building:

- Fresh set of web resources (established)
  - Media release (imminent)
- Roll-up conference posters (in development)
- Set of flyers (in development)
Objective 3
Resource Tools

Raising Awareness

Redesign of the web site

ACCELERATE front page
SUPPORTS to the FAIR trial initiative

INTERACTIVE MAP of national FAIR trial initiative

Contact with paediatric oncologists involved in early drug development and AYA friendly

Paediatric and Medical Oncologists

Fostering Age Inclusive Research (FAIR) Trials for Adolescents & Young Adults

Paediatric and medical oncologists in Europe are transforming the ACCELERATE FAIR Trials initiative into a country by country action plan. They are working together to break the 18 years dogma, despite the fact that countries have different health care structures, early drug development programmes and approaches to AYA population care. Here are a few sentences about each country on what is being done and why it is important. Contact details are given, should you wish to promote the initiative.

ACCELERATE FAIR initiative – country by country Action Plan

What does this mean represent for your country?

Pediatric Oncologist(s) and Medical Oncologist(s):
France have been pioneer in favoring age inclusive research for adolescent and young adults in oncology from early drug development. All the actors of the drug development are involved. Pediatric and medical oncologists have started to work together from early drug development helped by the national cancer institute (INCa) within the frame of the CLIP2 (https://www.e-cancer.fr/Professionnels-de-la-recherche/Recherche-clinique/Structuration-de-la-recherche-clinique/Les-CLIP2).

French authorities such as ANSM (Agence nationale de sécurité du médicament et des produits de santé) are willing to push the initiative, along with the ethics committees. The pharma implicated in the LEEM (les entreprises du médicament; https://www.leem.org/) support the initiative.

Patient and parent advocates have been very active in promoting and disseminating the idea of including adolescents in adult trials from early drug development. Although all the perceived breaks have not fully disappeared, a positive dynamics has started that we try to push forward for the benefit of adolescents and young adults with cancer.
RESOURCES to implement the FAIR trial initiative

FAIR Investigations/ Sponsor Toolkit

Fostering Age Inclusive Research (FAIR) Trials for Adolescents & Young Adults

Colleagues from Pharma and Academia, involved in paediatric drug development, have put together a set of practical resources to assist in designing age inclusive clinical trials.

Table of contents:

- FDA Draft Guidance for Industry
- eCRF and Standard Analyses
- Patient Reported Outcomes (PROs)
- Assent templates for adolescents
- Protocol Elements
- Examples of HA/EC considerations on AYA
- List of AYA-clinical sites
- List of approved protocols including adolescents in adult trials

Fostering Age Inclusive Research Group
FAIR for AYA Stamp

Fostering Age Inclusive Research (FAIR) Trials for Adolescents & Young Adults

Aim

The FAIR Trials initiative aims to accelerate innovation in drug development for young people with cancer, through the removal of arbitrary age limits in clinical trials. To facilitate this, ACCELERATE is offering a ‘Stamp’ for trials which actively avoid unnecessary barriers based on the age of participants. Applications are invited from sponsors of multinational trials compatible with our six proposals – specifically, adult early phase trials offering adolescent accrual or paediatric trials with accrual for young adults.

Benefits

The FAIR for AYA Stamp can be used for publicity purposes and can feature on trial protocols, clinical trial applications or other associated documents, as well as academic publications. Trials which have received the Stamp will appear on the ACCELERATE website and may be used in other ACCELERATE media as exemplars for the research community.
AYA and parent representative support of the FAIR trial initiative

Patient and Parent advocates

Fostering Age Inclusive Research (FAIR) Trials for Adolescents & Young Adults

Patient and parent advocates play a fundamental role for the success of the FAIR trials initiative. Please find below some useful links.

- The patient voice – Clinical trials for adolescents and young adults – video (Institut Gustave Roussy)
- The power of the personal story in spreading our message – article by Debbie Binner
- Mixed media: Childhood and Adolescent Cancer in the UK Press by Max Williamson (09-07-2018)
- Unite2cure fully supports the ACCELERATE FAIR trials initiative – article by Patricia Blanc (Unite2Cure)
Industry support of the FAIR trial initiative

Why FAIR trials?

What you can do

Paediatric and Medical Oncologists

Patient and Parent advocates

Industry

Regulatory

Early Drug Development for Adolescents: Oncology Protocols Survey

Resources

Publications

Who we are

Industry

Fostering Age Inclusive Research (FAIR) Trials for Adolescents & Young Adults

From an industry perspective, the inclusion of adolescent and young adults is an important initiative that allows this patient population access to experimental therapies in a more timely manner than traditional paediatric trials. It is well recognised that adolescent and young adults are often underrepresented in clinical trials and hopefully this is one important step in overcoming this issue.

The inclusion of this patient population can also be important in helping guide paediatric patients most likely to respond to new experimental agents by obtaining early evidence of activity in these children, improving the design and focus of subsequent trials in paediatrics.

Expanding inclusion of these patients into adult trials may also help reduce the economic burden of developing novel treatments by identifying drugs that are not likely to be effective in children, or with toxicity profiles that may be contraindicated in children at a much earlier stage than has been traditionally achieved.

As we expand our knowledge of the important molecular differences between most adult and paediatric tumours, these changes with inclusion of adolescent and young adults into adult trials and comparison of the resultant biology may also provide critical improvement in our underlying understanding of paediatric tumours.
Regulatory entities’ support of the FAIR trial initiative

Objective 4
Endorsement of the adolescent strategy

To go further by integrating it in the EMA regulation As done by FDA

Regulatory
Fostering Age Inclusive Research (FAIR) Trials for Adolescents & Young Adults
Spring 2019 has brought statements of support for age inclusive research from three major international health forums.

The European Medicines Agency (EMA) and its Paediatric Committee (PDCO) follow closely and with great interest the Accelerate’s FAIR (Fostering Age Inclusive Research) initiative. We sincerely appreciate your efforts and hope we can all continue to work together to improve the development of medicines for children with cancer.

Read the full letter from the EMA (April 2019)

The US Food and Drugs Administration recommends the inclusion of adolescent patients in disease- and target-appropriate adult oncology clinical trials to enable earlier access to investigational and approved drugs for adolescent patients with cancer.

FDA (March 2019)

As part of the responsibility to provide better medicines for children, the European Forum for Good Clinical Practice strongly recommends:

That researchers, regulators, and members of ethics committees weigh the totality of physiologic, pathologic, and other disease specific evidence to consider adolescent inclusion in adult research and vice versa – young adults as an extension population in paediatric/adolescent studies – when relevant as a trial methodology to facilitate earlier access to investigational and approved medicines for adolescent patients.

EFGC Children’s Medicines Working Party (March 2019)

Advancing Medicines Development for Adolescents: The EFGC Children’s Medicines Working Party Adolescent Initiative by Christine Bacci-Rechweg on behalf of the EFGC CMWP Adolescent Initiative

Read the article
FAIR Trials achievements 2019

- Redesign of the web site with accessibility to
  - Practical tools:
    - survey
    - Stamp for AYA
    - interactive map of national representative of the FAIR group and centers
    - investigators/sponsor tool kit
  - Endorsement of key stakeholders:
    - AYA and parent representatives
    - industry
    - EFGC,
    - EMA
  - Engagement with societies: SIOPE ... EMSO, EORTC?
To develop a communication plan in accordance with ACCELERATE policy: public press release

To engage more effectively with different stakeholders:
- ethics committees: EFGCP, European Network of Research Ethics Committees (EUREC), country by country action
- Pharma: EFPIA, EUCOPE, EuropaBIO, BIO, PhARMA
  - Endorsement
  - Practical actions: age inclusion as part of the standard trial planning process
- health authorities/regulators: Clinical Trial Facilitation Group (CTFG), paper journal for regulatory authorities (Evi); ask EMA to provide guidance as FDA did, country by country action
- medical oncologists

Analysis of enrollment on current adult trials open to adolescents
- Using publically available data
- Using survey of investigators

To submit abstracts to ESMO 2020, ASCO 2021
ACCELERATE FAIR trial group

We are ready to jump
What about you?
Fit for Filing Working Group

Pam Kearns, University of Birmingham
Elly Barry, Pfizer, Inc.
Working Group Membership

Academia:
- Pam Kearns (University of Birmingham)
- Bram De Wilde (Ghent University Hospital)
- Beth Fox (Children’s Hospital Philadelphia)

Industry:
- Elly Barry (Pfizer)
- Kathleen Neville (Johnson & Johnson)
- Mark Kieran (BMS)

Regulatory:
- Greg Reaman (FDA)
- Dominik Karres (EMA)

Patient Advocacy
- Carol Ludwinski
Aims

To develop best principles on how the design and deliver a trial with a dataset that can be included in a package for filing

• Define the barriers and propose solutions to ensure academic trial datasets are usable for regulatory submissions?

• Define how industry can pharma support academic/healthcare institutions to deliver fit for filing trials?
Deliverables

• 2019: Survey of industry experience and academic experiences
  • Successes, challenges, lessons learned

• 2019/20: Produce best principles guidelines
  • Defining elements of a data package for filing
  • Defining roles and responsibilities in collaborative studies
  • Define the resource needs to operationalise and deliver these types of trials

• 2020: Develop an Education Programme
  • to disseminate the guidelines and support investigators and academic sponsors and industry collaborators to understand the needs for ‘fit for filing’ trials
Work Plan

• May 2019: Pam and Elly to meet via TC to start to develop framework

• June 2019: Pam and Elly to meet F2F in Chicago

• August 2019: convene virtual Working Group (WG)

• October 2019 (SIOP): F2F meeting of WG
  • Organized into 4 subgroups
  • Actions led by the 4 sub-groups

• December 2019 /January 2020:
  • Information gathering by each of the 4 subgroups
Two initial Surveys to establish experience of academic FFF trials

• Survey of Academic Sponsors’ (ITCC and COG) experience/perceptions of FFF trials

• Survey of Industry Collaborators’ experience/perceptions of FFF trials
Survey of Academic Sponsors (ITCC and COG)

Aim:
• To determine:
  • The current experience and capabilities of academic sponsors to deliver ITCC paediatric clinical trials according to the requirements of the ICH E6 guideline.
  • The current experience and capabilities to deliver an E3 compliant Clinical Study Report

Method:
• 2 checklists provided and institutions asked to comment on whether they could meet each of the listed requirements in accordance with the guidelines
Conclusions from Survey of Academic Sponsors

• Academic sponsors have well prepared systems to conduct trials (multi-centre, multi-country) compliant with GCP and associated regulations

• The QMS and SOPs are not written specifically to comply with ICH E6

• Not possible to assess in this survey whether or not the current SOPs would generate data that could be readily submitted as part of a filing package

• End of Study Reports standard but not experienced in writing E3 CSR (usually outsourced)
FFF Industry Survey

• Q1: In the past, have you utilized clinical trial data from an investigator-sponsored trial conducted by a cooperative group/academic research center to support regulatory submissions?
• Q2: If yes, what type of regulatory submissions were the data used to support? (Check all applicable)
• Q3: Was the regulatory filing ultimately successful/accepted by Regulators?
• Q4: Was the use of this data for regulatory submission anticipated from the start of the study?
• Q5: Were there any issues/difficulties experienced in submission of these data to a regulatory agency?
• Q6: In what form were the data submitted to regulators?
• Q7a: Was there a formal data or database transfer from the academic sponsor to industry partner?
• Q7b: If so, did you re-analyze/re-interpret the data?
• Q8: What support for the study did you provide as the industry partner?
• Q9: What do you see are the pros/cons of this approach vs. an industry-sponsored trial?
• Q10: What the key issues/problems that, if addressed, would make these types of studies better suited for regulatory submissions?
• Q11: Is there anything else that you would like to share?
FFF Industry Survey

• AMGEN X1
• ABBVIE X2
• NOVARTIS X2
• ROCHE X1
• GRITSTONE X1
• ELI LILLY X1
• BMS X2
Conclusions from Survey of Industry Sponsors

• Most **companies are/will be involved in these types of collaborations**
  • Work to be done in alignment between protocol & regulatory obligations/expectations

• **Experiences:**
  • Data collection – incomplete
  • Data monitoring/cleaning – not comprehensive
  • Database/data format issues
  • Incomplete documentation
  • CSR: Usually Industry-generated

• **Funding model**
  • You get what you pay for
Four Key topics identified

1. **Essential Documents** (Elly and Dominik)
   - **Aim:** Provide a checklist of the required documents for a filing package
     - Build from what is already required by ICH guidelines
     - Identify additional documents required for filing and **provide the rationale**

2. **CRF Essential Data** (*Rosanna*, Beth and Greg)
   - **Aim:** Identify critical data items that should be collected in trials aiming for a filing package
     - Review of standardised CRFs from Industry and Academia
     - Identify commonalities and differences
Four Key topics identified

3. **Data Management** (Pam, Bram, Elly and John)
   • **Aim:** Provide guidance of the data management plan to support a filing package
     • Identify the critical steps in data management processes that enable a FFF trial
     • Review industry DM standards and translate to recommendations/guidance for academic sponsors

4. **Operational Resources** (Kathleen, Pam, Donna, Greg)
   • **Aim:** Identify the additional budget requirements to move an IIT to a FFF trial
     • Gather data from academic sponsors and industry re: cost of resourcing for FFF trials
     • Provide guidance on the level of investment needed to support an academic sponsor in delivering a FFF trial
Next Steps

• **Best Principles Guidelines**
  - Finish collecting data (CRF essential data, study budgets)
  - Connect with CRO(s) for additional data
  - Develop outline of a consensus paper: Spring 2020
  - Engage wider group of stakeholders in finalising consensus recommendations
  - Publish consensus paper: Late 2020

• **Develop Education Programme**
  - Define elements and mechanism of a dissemination and education plan
Readdressing the need for long-term follow up

Danielle Horton Taylor, *PORT/PanCare/Unite2Cure*
Mark Kieran, *Bristol-Myers Squibb*
Long-Term Follow-Up Working Group

• Increasing number of survivors of targeted and immunotherapy
• Current clinical focus has been collection of acute and semi-acute toxicities
• Increasing requirement by the regulatory agencies to have a better understanding of the late effects of biologic therapies
• Needs of clinicians and families to be informed of the long term effects of treatment in order to guide their decision making
• Opportunity to improve the survivorship care of patients with a more comprehensive understanding of late effects
Vision

Create an international data repository with ACCELERATE to collect information on long-term health in children who have received new modalities of anticancer treatment to facilitate an open sustainable resource to allow for the evaluation and optimization of follow up care.
Proposal for a Long-Term Follow-Up Working Group

Proposed development of 4 initiatives within the working group (see notes from the LTFU meeting at SIOP 2019 in Lyon France)

1) Infrastructure – What types of databases are compatible with academic LTF centers, can be used internationally, can be expanded

2) Data elements – What data elements are required, preferred

3) Governance – Location and management of the information

4) Sustainability – How to support this initiative going forward (finances, personnel)
Infrastructure – What types of databases are compatible with academic LTF centers, can be used internationally, can be expanded

Working sub-group leaders: Riccardo Haupt and Jeanette Falck Winter
Working sub-group members: Michael Hawkins, Leontien Kremer, Peter Manley, Carina Schneider, Monica Terenziani

Issues:
• Access to existing academic or pharma databases unsuccessful to date

Moving forward:
Reviewed multiple potential data structures presented by members of the committee
• Conference call to ensure alignment on major structural issues of database
  • Then Q2W calls
• F2F meeting at SIOPe in Valencia, Spain
Data Elements

Data – What data elements are required, preferred

Working sub-group leaders: Lars Hjorth*, Leontien Kremer, Roderick Skinner
Working sub-group members: Greg Armstrong, Eric Chow, Manuel Diezi, Francis Donaldson, Marc Fellous, Michael Hawkins, Holger Lode, Peter Manley, Yousif Matloub, Carina Schneider, Monica Terenziani, Azzeddine Zemam, Michel Zwaan

Issues:
• Access to existing academic or pharma data elements unsuccessful to date

Moving forward:
Reviewed multiple potential data sources presented by members of the committee
• Conference call to ensure alignment on major data elements Q2W
• F2F meeting at SIOPe in Valencia, Spain
Governance

Governance – Location and management of the information

Working sub-group leaders: Helena van der Pal, Susan Weiner
Working sub-group members: Riccardo Haupt, Delphine Heenen, Lars Hjorth, Carina Schneider

Issues:
• Dependent on database, scope of data
• Need for budget

Moving forward:
• Conference call to ensure alignment
• F2F meeting at SIOPe in Valencia, Spain
Sustainability

Sustainability – How to support this initiative going forward (finances, personnel)

Working sub-group leaders: Hubert Caron, Marc Fellous, Helena van der Pal
Working sub-group members: Carina Schneider

Issues:
• General support from pharma to finance (depending on final costs)
• Need to support efforts of Working Group pending final proposal

Moving forward:
• Danielle and Mark will prepare 1 page white paper on justifying a working group budget (project manager, unaffiliated participants, meeting support)
How to strengthen international collaboration

Greg Reaman, *US Food and Drug Administration*
Nicole Scobie, *Zoe4Life*
### Working Group Committee

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Name</th>
<th>Title/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academia</td>
<td>Steve Hunger</td>
<td>Director of the Center for Childhood Cancer Research, Children’s Hospital of Philadelphia, PA</td>
</tr>
<tr>
<td></td>
<td>Martin Schrappe</td>
<td>University Hospital Kiel, Germany</td>
</tr>
<tr>
<td></td>
<td>Andrea Biondi</td>
<td>Scientific Director of the “M.Tettamanti” Research Center for leukaemic and haematological diseases of children and of “S. Verri” Cellular and Gene Therapy Laboratory</td>
</tr>
<tr>
<td></td>
<td>Tom Gross</td>
<td>Associate Professor of Clinical Pediatrics, Gordon Teter Chair of Pediatric Cancer, The Ohio State University</td>
</tr>
<tr>
<td></td>
<td>Alberto Pappo</td>
<td>Director, Division of Solid Tumor Malignancies, St. Jude Children’s Research Hospital</td>
</tr>
<tr>
<td></td>
<td>Maryam Fouladi</td>
<td>Medical Director, Brain Tumor Center, Marjory J. Johnson Chair, Brain Tumor Translational Research</td>
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<tr>
<td></td>
<td>Brenda Weigel</td>
<td>Director of the Division of Pediatric Hematology/Oncology at the University of Minnesota, Children’s Oncology Group (COG) Phase 1 and Pilot Consortium</td>
</tr>
<tr>
<td></td>
<td>Jim Whitlock</td>
<td>Division Head of Haematology/Oncology, Hospital for Sick Children, Toronto, Canada</td>
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<tr>
<td></td>
<td>Kathy Brodeur Robb</td>
<td>Executive Director at C17 Council, Canada</td>
</tr>
<tr>
<td></td>
<td>Maria Grazia Valsecchi</td>
<td>Professor of Medical Statistics at University of Milano-Bicocca</td>
</tr>
<tr>
<td></td>
<td>Todd Alonzo</td>
<td>Professor of Research Preventive Medicine Group Statistician for Children’s Oncology Group</td>
</tr>
<tr>
<td></td>
<td>Peter Wejbora</td>
<td>Director Research Development and Partnerships at Children’s Cancer Institute, Children’s Cancer Institute, Australia</td>
</tr>
<tr>
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<tr>
<td>Regulators</td>
<td>Dominik Karres</td>
<td>Scientific Officer at European Medicines Agency, EMA</td>
</tr>
<tr>
<td></td>
<td>Gregory Reaman</td>
<td>Associate Director for Pediatric Oncology Oncology Center of Excellence, Office of the Commissioner, U.S. Food and Drug Administration</td>
</tr>
<tr>
<td></td>
<td>Geoff McCowage</td>
<td>CEO, Australasian Children’s Clinical Cancer Trials</td>
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<tr>
<td>Advocacy</td>
<td>Leona Knox</td>
<td>Research Coordinator, Solving Kids’ Cancer Europe</td>
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<td></td>
<td>Nicole Scobie</td>
<td>Présidente, Zoé4life, Board Member, Childhood Cancer International</td>
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<td></td>
<td>Vicki Beugner</td>
<td>President, Coalition Against Childhood Cancer</td>
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<tr>
<td></td>
<td>Donna Ludwinski</td>
<td>Director of Research Programs at Solving Kids’ Cancer</td>
</tr>
<tr>
<td>Industry</td>
<td>Darshan Wariabharaj</td>
<td>Director, Global Regulatory Leader, Oncology, Janssen</td>
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<tr>
<td></td>
<td>Elly Barry</td>
<td>Senior Director</td>
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<td></td>
<td>Anjali Sharma</td>
<td>Amgen</td>
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<tr>
<td></td>
<td>Kathleen Neville</td>
<td>Sr. Director, Pediatric Drug Development, Child Health Innovation Leadership Department, Johnson &amp; Johnson</td>
</tr>
</tbody>
</table>
Working Group Goals and Deliverables

Endorsement of position paper by ACCELERATE Steering Committee to provide impetus for increased and more effective collaboration.

Position paper that:

- Makes case for collaboration and cooperation.
- Addresses negative perceptions, regulatory differences, and logistical obstacles.

Identify obstacles and challenges to international collaboration and propose potential solutions.
Work plan

• Identify multi-center trials and networks (including disease-focused). US, Canada, EU, Australia

• Identify/quantitate logistical obstacles:
  • Study sponsor responsibilities
  • Multiple sponsors (geographically determined)
  • Data management, data center responsibilities/capabilities
  • Role of funding agencies for publicly and privately supported networks
  • Distribution (internationally) of investigational drugs
  • Central pathology and/or response assessment review
  • Centralized vs. regional validation of IVDs for study eligibility and response assessment
  • Biologic sample collection and submission internationally
  • Regional differences in disease-specific strategies vis à vis control arms and add-on study designs
  • Others

• Regulatory obstacles:
  • Responsibility for clinical trial approval: U.S. vs. EU vs. Canada vs. Australia vs. South/Latin America
  • EU General Patient Data Regulation- impact on international clinical trials
  • EU Clinical Trials Regulations - Pending changes and timelines, consideration for collaboration outside of EU
## Working Plan Timeline

<table>
<thead>
<tr>
<th>Month</th>
<th>Event Details</th>
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<tbody>
<tr>
<td>Jan 2020</td>
<td>First TC with all WG members: overview of Accelerate, WG plan and deliverables, discussion</td>
</tr>
<tr>
<td>Feb 2020</td>
<td>First F2F meeting of WG in Brussels. Review issues, work plan and assign tasks</td>
</tr>
<tr>
<td>April, June, Sept, Dec 2020</td>
<td>Follow up TCs</td>
</tr>
<tr>
<td>Dec 2020</td>
<td>Report back to Steering Committee</td>
</tr>
<tr>
<td>October 2020</td>
<td>F2F meeting at SIOP Ottawa</td>
</tr>
</tbody>
</table>
Thank You!
ACCELERATE-AACR Pediatric Cancer Working Group Meeting (April 2, 2019) (Action Item)

- Peter Adamson, Chair, Children's Oncology Group
- Greg Reaman, Associate Director for Pediatric Oncology, OCE, FDA
- Darshan Wariabharaj, Janssen Pharmaceuticals “a Johnson & Johnson company”

1 Currently under negotiation with AACR
2 Acknowledgements: ACCELERATE Steering Committee (particularly Gilles Vassal, Andy Pearson, Raphaël Rousseau)
Disclaimer

The views and opinions expressed in this presentation do not necessarily reflect the views or policies of any company in the Johnson & Johnson Family of Companies.
"Think-Tank Meeting": What and Why?

• ACCELERATE:
  • Provided transparent forum to discuss + address overarching issues in development of innovative anticancer medicines for children and adolescents.
  • Significant stakeholder time & effort:
    • Pediatric strategy forums (PSFs)
    • Working Groups (WGs)
  • However, opportunities to identify and address drug/disease agnostic bottlenecks and hurdles
    • Outside of scope of PSFs and WGs

• ACCELERATE multi-stakeholder “Think-Tank” meeting proposed:
  • Reach “trans-atlantic” consensus on bottlenecks and identify opportunities to address.
Multi-stakeholder\textsuperscript{1} “Think Tank Meeting”

• Goal(s):
  • Identify top challenges and recommended solutions which could lead to tangible improvements in delivery of informative pediatric data.
  • Develop a set of action plans/potential solutions for the top challenges.

• Objectives:
  • Define "“best practice” for innovative drug development from pre-clinical (\textit{when necessary}) to early pediatric clinical evaluation to registration (\textit{when warranted}).
  • “Best practice” identified following discussion and analyses of case studies of anticancer drugs in pediatric and adolescent populations.

\textsuperscript{1} FDA/EMA (including Academia representatives on PDCO and FDA’s Pediatric ODAC and EMA pediatric coordinators) and diversity of academia from broader pediatric oncology community
F2F Meeting\textsuperscript{1} Multi-stakeholder engagement

- Multi-stakeholder engagement (70 to 80 participants) beneficial:
  - Different views/perspectives on whether something is issue.
  - Industry:
    - Pediatric oncologists “embedded in industry” helpful (thought-leader perspective)
    - Corporate leadership and regulatory leads can provide broader perspective
  - Regulators:
    - FDA (including Academia representatives on Pediatric ODAC)
    - EMA (including Academia representatives on PDCO and EMA pediatric coordinators).
  - Academia: Representation from broader pediatric oncology community
  - Advocacy: Patient’s perspective

- Opportunity for break-out sessions (\textit{similar to ACCELERATE Annual Conference})?

- Discussion/analyses of case studies (ideally 4). Case studies:
  - At least one case study would showcase rapid development (parallel/minimal lag in adult and pediatric development).
  - Would demonstrate the top challenges and recommended solutions which could lead to tangible improvements in delivery of informative pediatric data.

\textsuperscript{1} Opportunity for “remote” participation
“Think-Tank Meeting” Like PSFs

- Invitation to participate via submission of expressions of interest
  - Industry provide valuable perspective to meeting **BUT:**
    - Must include provision of proposed case study (relates to anticancer drug in development or planned for development in pediatric and adolescent populations)
    - Case study should:
      - Include to extent applicable “milestone data”
      - Identify where pediatric development has worked smoothly and where it has not

- “Think-Tank Meeting” Steering Committee
  - Members - TBD
  - Final selection of case studies
  - Agree on significant issues to focus on at “Think-Tank Meeting”
  - Limit discussion and strategy to address these key topics
  - Agenda development facilitated via stakeholder consultation (including EMA pediatric coordinators, PDCO members and FDA reviewers)
Case Studies

• Case studies identified:
  • Via direct solicitation (companies who attended prior ACCELERATE conferences)
  • Advertisement on ACCELERATE website
  • Outreach to trade associations (PhRMA and EFPIA) via:
    • ACCELERATE Pediatric Strategy Forum Oversight Committee (Trade association representatives)
    • Industry Advisory Committee to AACR
  • Request up-to 4 representative examples

• Case studies should:
  • Include “milestone data” and ideally represent a diversity of challenges or provide the most frustrating experiences due to bottlenecks and hurdles.
  • Identify where development has worked smoothly and where development has not.
<table>
<thead>
<tr>
<th>Case Study Milestone Data (1)</th>
<th>Case Study Milestone Data (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND/CTA submission</td>
<td>Feedback from PDCO (Day 30; Day 60); FDA (iPSP or PPSR)</td>
</tr>
<tr>
<td>First in human study initiated (i.e. adult phase 1 trial)</td>
<td>Meetings with external advisors (academia) to review FDA/PDCO feedback</td>
</tr>
<tr>
<td>Proof of Concept (POC) for adult indication initiated</td>
<td>Interim meetings with PDCO/FDA</td>
</tr>
<tr>
<td>Start of pivotal adult study</td>
<td>Submission of modified PIP; iPSP (initial Pediatric Study Plan)</td>
</tr>
<tr>
<td>Initiation of pediatric development activities to satisfy FDA &amp;</td>
<td>FDA approved iPSP; EMA approved PIP</td>
</tr>
<tr>
<td>EMA regulatory requirements</td>
<td></td>
</tr>
<tr>
<td>Internal pediatric team assembled/pediatric development planning initiated</td>
<td>Company approval of pediatric plan</td>
</tr>
<tr>
<td>Contract/Clinical Trial Agreement negotiations between sponsors and academic clinical trial groups/networks initiated</td>
<td></td>
</tr>
<tr>
<td>External pediatric oncology advisors (academia) (if any) initial meeting</td>
<td>Contract/Clinical Trial Agreement(s) finalized Initiation of pediatric preclinical studies</td>
</tr>
<tr>
<td>Initial meeting with PDCO/EMA; Initial meeting with FDA</td>
<td>1st pediatric study: Protocol finalized; First patient enrolled; Protocol completed (if available); Preparation of CSR and data packages to be submitted to regulatory agencies</td>
</tr>
<tr>
<td>Submission of proposed PIP; iPSP; PPSR (Written Request)</td>
<td>Timing of pediatric formulation development (if needed)? Approval of pediatric indication by FDA, EMA</td>
</tr>
</tbody>
</table>
Advancing New Therapies For Childhood Cancer

Cesare Spadoni PhD, MBA – Chief Operating Officer & Founder
Mission-Driven

Parents - Entrepreneurs
Marc Goldberg, JD, MBA, Founder, BoD
Seasoned Life Sciences VC
BioVentures Investors, MBRI, MassBio co-founder

Marco Muñoz, Founder, BoD
Senior Fundraiser
Senior Director Strategic Initiatives Office of the MIT Chairman
Corporate Goals

- **Worldwide Leader** in pediatric oncology
- **Partner of Choice** for pharma/biotech industry
- **First Investment Choice** for foundations and patient associations
Creating Value for investors and patients

- Incentives
- Sales
- Sub-License
Senior Leaders with Strong Drug Development, Commercial Track Records

Michel Janicot, PhD
Chief Scientific Officer
Janssen, Rhone-Poulenc Rorer

Eva Méndez, PhD
Head of Drug Discovery
+20 years in drug discovery
Ferrer, Inst. Of Research in Biomedicine (Barcelona)

Evie Mengou, MSc
Head of Regulatory
20+ years in drug dev. (biothecs and CROs)

Jeffrey Skolnik, MD
Senior Board Advisor
Pediatric oncologist, GSK, AZ, Inovio Pharmaceuticals

Kirk G. Tanner PhD
Senior Board Advisor
Vertex Pharmaceuticals

Marta Princep, PhD
Senior Strategy Advisor
+20 years in drug dev.
Ferrer, Biocat BoD
**Bench-to-bedside**

**IP generation**
- Target identification
- Hit identification
- Hit to Lead
- Pre-clinical Studies
- Clinical Studies
- Regulatory Approval
- Patient

**In-licensing opportunities from academia or industry**

**DISCOVERY Phase**

**CLINICAL DEVELOPMENT Phase**

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volasertib
Development
Background

- Polo-Like-Kinase 1 (PLK1) Inhibitor
- Developed by BI for acute myelogenous leukemia (AML) for adults
- Program stopped after unsatisfactory Phase III
- Phase I pediatric clinical trial completed
PLK1 link to RMS

Thalhammer V. et al Cancer Res. 2015 Jan 1;75(1):98-110
Mechanism: Degradation of Fusion Protein

Volasertib Rationale - 2

Thalhammer V. et al Cancer Res. 2015 Jan 1;75(1):98-110
Preclinical efficacy

Patient derived xenograft model

* Standard of care

Volasertib Road Map

August 2019
Licensing agreement with BI

2021
Volasertib Phase Ib/II trial begins

2023
Volasertib Phase II trial begins

2025
Phase II completion
NDA/MAA submission

2026
FDA/EMA regulatory approval. PRV granted

These timings are estimations based on discussions with KOLs
and analogies to similar development projects
volasertib
additional indications

Pediatric Indications
• Diffuse Intrinsic Pontine Glioma (DIPG)
• Hepatoblastoma

Adult Indications
• Breast Cancer
• Others
Criteria for new asset identification and pipeline building

1. Unmet Medical Need
2. Strong Science
3. De-risked approach
4. Clear Go/No-Go decision points
Drug Discovery project for Medulloblastoma

- Novel drug combinations – New IP
- AI, Systems Biology partnerships (external collaborations)
- Preclinical candidate expected by Q4 2021
n-myc
Drug Discovery Project

“Test-then-build” Prototyping

In silico screening – up to 1B compounds

Iterative Med. Chem. rounds

Lead compound identification
Building a robust pipeline

- **volasertib**: Evaluating Asset #2
- **2Hit**: Evaluating medulloblastoma Asset #3
- **n-myc inhibitor**: multiple pediatric cancers
Leadership
Opportunity

Mission-driven

Risk-contained
Strategy

Robust Ecosystem
“Be the change that you want to see in the world”
Mahatma Gandhi
The Time Has Come, Oncoheroes Is Ready

cspadoni@oncoheroes.com
Y-mAbs

Lene Worsaae Dalby
8th Accelerate Meeting

February 2020
Observations from 7th Accelerate Meeting in 2019

Drug development in paediatric oncology is frequently deemed not profitable

- Too long!
- Complex with different age groups
- Expensive and not profitable
- Regulatory issues and uncertainties on reimbursement
- Small population...
Why YmAbs?
It all started with a child

- Years of searching for options
- Treatment at MSKCC in NY
- High Risk Neuroblastoma survivor
- The Father envisioned helping other families get access to the same treatments that made a difference for his daughter
Our mission is to become the world leader in developing better and safer antibody-based pediatric oncology products addressing clear unmet needs.
## Strong Clinical Pipeline

<table>
<thead>
<tr>
<th>Programs</th>
<th>Phase 1</th>
<th>Phase 2/Pivotal Study</th>
<th>Next Anticipated Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lead Development Candidates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naxitamab (GD2)</td>
<td></td>
<td></td>
<td>Rolling BLA submission initiated Nov 2019</td>
</tr>
<tr>
<td>Omburtamab (B7-H3)</td>
<td></td>
<td></td>
<td>BLA submission expected to be completed end Q1 2020</td>
</tr>
<tr>
<td><strong>Vaccine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GD2-GD3 Vaccine</td>
<td></td>
<td></td>
<td>Ongoing Phase 2 study at MSK</td>
</tr>
<tr>
<td><strong>Bispecific/Early Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GD2xCD3 - BsAb</td>
<td></td>
<td></td>
<td>In Phase 1/2 study since Q1 2019</td>
</tr>
<tr>
<td>Omburtamab-DTPA</td>
<td></td>
<td></td>
<td>IND filed Dec 2019</td>
</tr>
</tbody>
</table>
Naxitamab

**Target?**
- Proven target (GD2)
- Competitors

**Clinical Data?**
- Yes - Phase 2
- Safety population +250 patients

**Differentiator?**
- Another antibody (CDR - 77% different)
- 10-fold higher binding affinity → slower off rates
- Promising clinical data
| Target? | • Indication: CNS/LM neuroblastoma  
|        | • Very high unmet medical need and no SDT |
| Clinical Data? | • Yes - Phase 2  
|               | • Safety population: 130 patients |
| Differentiator? | • Promising clinical data |
Strong Financial Position with Blue Chip Investors

Y-mAbs Has Completed a Series of Successful Financing Rounds, with $374 Million Raised to Date

2017
$95 Million

2018
$110 Million

2019
$144 Million

IPO – September 2018
$110 Million

Follow on: November 2019
$144 Million

$374 Million
Raised to Date

$233 Million
of cash and cash equivalents pro forma (cash balance as of September 30, 2019 and net proceeds from follow-on offering)
Global company with three locations

Agern Alle 11, Copenhagen
Development

230 Park Avenue, NY
Headquarter

Nutley
Y-mAbs Laboratories
Research
Organizational growth

<table>
<thead>
<tr>
<th>Year</th>
<th>US</th>
<th>Denmark</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>2016</td>
<td>1.5</td>
<td>5.5</td>
<td>7.0</td>
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<tr>
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<td>1.5</td>
<td>10.5</td>
<td>12.0</td>
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<tr>
<td>2018</td>
<td>7.5</td>
<td>25.5</td>
<td>33.0</td>
</tr>
<tr>
<td>2019</td>
<td>21.5</td>
<td>47.5</td>
<td>69.0</td>
</tr>
</tbody>
</table>
Company Highlights

Two ongoing global multicenter studies – naxitamab & omburtamab

Two BLA submission planned for 2020 - naxitamab & omburtamab

First BsAb product candidate in Phase 1/2

2nd gen radioconjugate - Omburtomab-DTPA-Lu177
• starting Phase 1/2 in Q2 2020

GD2-GD3 Vaccine
• ongoing Phase 2 Study at MSK in high-risk NB

Financial strength – secured through the end of 2022
“....address the topic of accelerating pediatric oncology drug development.”
THANK YOU
Developing therapeutic innovations for children with cancer in Australasia

Peter Wejbor, Children’s Cancer Institute
*Sydney Australia*
Content

• Regional Context
• Brief snap shot of the medical research eco system
• Zero Childhood Cancer program
• Therapeutic Innovation initiatives
Paediatric cancer – the regional context

- Both Australia and New Zealand have relatively small patient populations – 800/150 per annum in A/NZ
- Similar overall 5-year relative survival rate of 84%* across the two countries
- Contrast to the Asia region – high density populations with large numbers of patients (China alone has in excess of 27,000 new cases each year) and relatively poor outcomes
- Collaborative efforts within the paediatric cancer field largely focused on Europe and North America, but
- Growing efforts and links into China with significant further growth opportunities

The Australian medical innovation eco system

- Highly supportive governments – both Federal and State (NSW) efforts to develop precision medicine capabilities, both diagnostic and therapeutic innovation
- Medical Research Futures Fund – doubling investment in medical research – focus on translational research
- National investment priorities into rare cancers, clinical genomics, clinical trials support, drug repurposing – focus on childhood cancers
- Review of National Medicines Policy
- Establishment of 1st Comprehensive Cancer Centre for Children
- Established national research and clinical trials networks and infrastructure with strong international links
The Clinical Trials Landscape - ANZCHOG

- Dedicated Clinical Trials Group for Children’s Cancer: Australian New Zealand Children’s Haematology Oncology Group – ANZCHOG
- Working with all children’s cancer centres in Australasia
- Australasian sponsor and National Coordinating Centre for a wide spectrum of international groups in the US, Canada, Europe and the UK
- National sponsor of PRISM trial as part of the - National Precision Medicine Platform – Zero Childhood Cancer
- Robust and efficient multi-site approval process
Clinical Trials Regulatory Process (Australia)

- **HREC Review**
  - HREC Submission for multiple sites via National Mutual Acceptance Scheme (NMA)
  - HREC review: trial protocol, scientific validity, Risk vs Harm, Ethical acceptability
  - Multi-site National HREC Approval

- **Site-specific Governance Review**
  - Site specific Governance Submission
  - Site Specific Governance Review
  - Site Specific Governance Approval

- **National regulatory approval**
  - Notification only to the Therapeutic Goods Administration (TGA) via CTN Scheme.
  - Sponsor must be an Australian Entity
  - TGA acknowledgment

- **Site Activation**
  - Site training and initiation visit
  - Sponsor review of site essential documents
  - Site activation → Recruitment commences
NZ Clinical Trial Regulatory Process

- Population of 4.8 million, 160 cases of childhood cancer/year
- 25-30 active paediatric and AYA trials at any one time
- Participate by entering into clinical trials agreement with relevant study groups
- ANZCHOG hold insurance to cover conduct of ANZCHOG sponsored trials in Australia and NZ
- Supportive legislative environment to allow paediatric drug assess through clinical trials, and outside of clinical trials

- Clinical trial approval takes 4 simple steps:

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDEC Review</td>
<td>Approval allows conduct anywhere in NZ</td>
</tr>
<tr>
<td>Local Review</td>
<td>Health institution and formal cultural review</td>
</tr>
<tr>
<td>National Regulatory Review</td>
<td>Medsafe approval for trials that include drugs not currently registered in NZ</td>
</tr>
<tr>
<td>Site Activation</td>
<td>Site training and initiation visit</td>
</tr>
</tbody>
</table>
Zero Childhood Cancer Program

- National precision medicine research platform – hub and spoke model
- Comprehensive analytical framework, incorporating whole genome, RNA sequencing, methylation profiling, in-vitro and in-vivo testing as well as immune profiling
- Liquid Biopsy program currently under development in collaboration with University of Cambridge
- Established first Paediatric Cancer Immunology group in Australia (at PeterMac)
- Advanced pre-clinical modelling capability (building on PPTC)
- Computational Biology group linked to international efforts – data sharing
- PRISM study enrolling nation wide ~ 400 patients/limited to most difficult cases of less than 30% survival
- Next iteration of ZCC – expansion of cohort and intervention trials
- Diagnostic capabilities not yet matched by therapeutic options
ZCC - Therapeutic Innovations Group

Paediatric Cancer Drug development incubator aligned with biotech start up company

• collaborating with industry to contribute to and fast-track the creation of an evidence base for efficacy, safety and dosing for novel agents, in order to make them accessible for paediatric clinical trials

• driving drug development efforts through international collaborations to address some of the most intractable challenges in childhood cancer that remain without a therapeutic solution
Drug Access Challenges

- Drugs are licenced in Australasia for disease not molecular indication
- Currently no legislative/regulatory provision to encourage early access to novel drugs for paediatric cancer patients (both regulatory and reimbursement)
- Significant lag times between approval (Therapeutic Goods Administration) and reimbursement (Pharmaceutical Benefits Scheme)
- Children are disadvantaged because there are no specific PBS criteria for paediatric cancers.
- Small population and rare nature of paediatric cancer means we never get numbers sufficient to power clinical trials
- Age restrictions on drugs coming to market (is it time to define a child<12y similar to FDA push and EU
- Getting access to drugs – who pays?
- Pharma companies in Australasia mostly subsidiaries of global enterprises – limited decision making authority in Australia
- Appetite for risk of off label use of drugs differs at different centres
- Equity/access issue for patients national
- Use of compassionate access means no central collection for response to therapy.
How can we improve drug access for children with cancer in Australia?

- Collaboration with Medicines Australia – industry drug access survey
  
  Key learnings:
  - High levels of willingness, low levels of awareness
  - Surprising extent of variability across companies in terms of preferred access routes, and sometimes within companies (ISR, Compassionate Access, EA)
  - Preferred pathways (transfer to existing trial) are not routinely possible
  - Decision-making is multi-factorial, but there are common influences
  - Time is of the essence
  - High commitment to do better
Decision making factors

- Existing confidence in data or biological rationale, clinical risk assessment
- Global processes and flexibility in same
- Expected timing – ability to deliver; ISRs in particular take some time to enact, and for some companies, the only option for ZCC trial
- Stage of therapy & co-existence of other programs or trials
- Design of the trial
- Clarity regarding access to data, including adverse effects
- Supply – availability, ease of supply and assuring quality - Stock and supply carries internal challenges and competition for access
- Compassionate access does not always allow for learning through case studies – sponsors do not expect data (x/c AEs)
- Costs, pricing
- Other ethical considerations
Next Steps

- Establishment of Oncology Industry Taskforce subcommittee for ZCC
- Framework for easier access – pre-approval process where possible
- Drug Access Navigator position established
Summary

- Australia/NZ have a sophisticated medical research and clinical service/trials environment
- Globally linked precision medicine platform and advanced diagnostic capabilities
- Drug access challenges but a number of initiatives in train to address issues
- We welcome and seek new partnerships to accelerate both research and clinical programs
Acknowledgements

• Medicines Australia
• Liz DeSomers
• Michelle Burke
• Industry Oncology Task Force
Passionate Childhood Cancer Advocate

Patrick Sullivan, Chair, Childhood Cancer Canada
You Have To Recognize A Problem To Address It
The Access Problem In Canada

- Proportion of pediatric trials in oncology has been decreasing over time, especially for those which are investigator-led (rather than industry-sponsored)

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2014</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # of CTAs</td>
<td>827</td>
<td>806</td>
<td>791</td>
</tr>
<tr>
<td>Total pediatric CTAs</td>
<td>136</td>
<td>109</td>
<td>134</td>
</tr>
<tr>
<td>% oncology</td>
<td>19.9%</td>
<td>16.5%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Academic-sponsored oncology</td>
<td>14.0%</td>
<td>12.8%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Industry-sponsored oncology</td>
<td>6.6%</td>
<td>3.7%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>
We Are Collectively Working Hard to Address The Access Problem

• Excellent working relationship with Clinicians & C17
• Excellent working relationship with Health Canada
  • Efforts to modernize Clinical Trial regulatory structure
  • Change in approach to off-label drugs in Clinical Trials
  • Continue to meet with informally
• Reminding everyone that we need to start with Why and then move to what and how
• $30 Million Federal Government Commitment To Pediatric Cancer
• Continuing to diagnose the problem
Way(s) Forward to Further Address What An Access Gap That I Believe Will Get Worse

- Embed patients in the international regulatory cooperative efforts that Alysha spoke to
  - Keep the focus on Why
  - Drive a respectful sense of urgency
  - Think the problem differently
- Use the Accelerate forum to combat the Law of Unintended Consequences
- Develop relationships with Payors
- Understand both the problems and the opportunities from the perspective of Industry
- Play to our strengths and embrace the possibilities inherent in an International Pediatric Oncology Regulatory Sandbox
Thank You!
Updates on Health Canada’s Regulatory Initiatives

Alysha Croker, PhD
*Health Canada*
About Health Canada

• Under the *Food and Drugs Act*, Health Canada regulates, evaluates and monitors the safety, efficacy, and quality of therapeutic products
  — ~14 000 drugs, 36 000 medical devices

• Includes oversight at all stages of a product’s life cycle, from early testing through clinical trials, to post-market surveillance of adverse drug reactions, and compliance monitoring

• Canadian model
  — Federal role
  — Provincial / Territorial roles
Getting products to patients in a lengthy, complex process...

Drug Development, Clinical Trials – ACADEMIA / INDUSTRY
(years)

Regulatory Review – HEALTH CANADA
(~1 year)

Health Technology Assessments / Funding Recommendations
(6 - 9 months)

Provincial / Territorial purchasing review and price negotiations
(2 - 12+ months)
Health Canada’s Ongoing Regulatory Updates

Clinical Trial Modernization Initiative:
• To have better, safer, and more trials in Canada

Regulatory Review of Drugs and Devices Initiative (R2D2):
• To create an agile regulatory system that supports better access to therapeutic products based on healthcare system needs

Paediatric Lens to Health Canada’s Regulatory Processes:
• To increase access to safe and effective medicines for children in Canada
Clinical Trial (CT) Modernization

Legislative changes enable Health Canada to make regulations going forward that will allow for:

- **Risk-based approach to clinical trial regulation**
  - Flexible, risk-based oversight to better address evolving CT environment and ensure continued protection for participants

- **Clinical trial regulations streamlined across product lines (as appropriate)**
  - Greater alignment across CT product lines and internationally (where appropriate) to reduce burden

- **New authorization scheme for the conduct of clinical trials over the trial lifecycle**
  - Tailor authorization / oversight based on the risk of the trial / product, while maintaining protection for participants (ability to add terms / conditions, specific requirements for studies involving new uses for approved products)

- **New transparency requirements on registration and publishing of results**
  - Require that trials be publically registered and disclose results
Health Canada’s Regulatory Review of Drugs and Devices Initiative (R2D2)

Objective: An agile regulatory system that supports better access to therapeutic products based on healthcare system needs

1. Expanded collaboration with health partners
   - Alignment of Health Technology Assessment Review with Health Canada Review
   - Implementing a Mechanism for Early Parallel Scientific Advice
   - Use of Foreign Reviews / Decisions
   - International Collaboration and Work Sharing in Reviews

2. More timely access to drugs and devices
   - Expansion of Priority Review Pathways
   - Improving Access to Biosimilars and Biologics
   - Improving Access to Generic Drugs
   - Building Better Access to Digital Health Technologies
   - Pre-Submission Scientific Advice for Medical Devices
   - Special Access Programme (SAP) Renewal

3. Enhanced use of real world evidence
   - Leveraging data for assessing drug safety and effectiveness
   - Strengthening the use of real world evidence and regulations for medical devices

Modern and Flexible Operations:
- Common Submission Intake
- Appropriate cost recovery framework
- Public Release of Clinical Information
Australia, Canada, Singapore, Switzerland (ACSS) Consortium

• A cooperation of medium-sized regulatory authorities facing similar challenges focused on concrete information and work sharing initiatives
  – 4 sub-groups focusing on new active substances, generics, complementary health products, and IT architecture

• Goal of maximising international cooperation, reducing duplication, and increasing the capacity of regulatory authorities to ensure consumers have timely access to high quality, safe and effective therapeutic products

• Recent results (New Active Substance Working Group; Australia – Canada worksharing):
  – ERLEADA (apalutamide) - treatment of prostate cancer – NOC July 3, 2018
  – VERZENIO (abemaciclib) - treatment of metastatic breast cancer – NOC April 05, 2019
  – ZEJULA (niraparib) - maintenance treatment for ovarian cancer – NOC June 27, 2019
Project ORBIS

- FDA Oncology Center of Excellence (OCE) initiative that allows for the concurrent submission and review of oncology drugs between international partners

- Enables regulatory agencies to share information, expertise and analysis, to allow for the more effective review of submissions and identification of any regulatory divergence across jurisdictions
  - Concurrent submissions are filed in each jurisdiction
  - Each jurisdiction reviews the applications independently, but shares data, questions, and conclusions
  - Each jurisdiction comes to a decision independently and is responsible for the development of its own drug labelling (approaches may differ across jurisdictions)

- Results to date:
  - **LENVIMA** (lenvatinib) in combination with **KEYTRUDA** (pembrolizumab) - treatment of certain advanced endometrial carcinomas – NOC September 20, 2019
  - **CALQUENCE** (acalabrutinib) – treatment of adult chronic lymphocytic leukemia – NOC November 28, 2019

NOC = Notice of Compliance (drug is authorized / approved)
Ecosystem of International Collaboration

• WHO – Paediatric Regulatory Network Task Force
  – *(DRAFT)* Provides a global paediatric working network as a platform for exchange of regulatory information on paediatric medical products and to support the availability of quality-assured medical products for children through facilitation of communication, collaboration, training, and regulatory harmonization across the lifecycle of paediatric medical products

• ICH Guidances
  – Regulators across jurisdictions and the pharmaceutical industry come together to discuss scientific and technical aspects of drug registration / approval
  – Mission is to achieve greater harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed and registered / approved in the most resource-efficient manner
  – Health Canada director general (Celia Lourenco) recently re-elected as ICH Assembly Vice-Chair

• Discussions Between Regulators (e.g., EMA-FDA Pediatric Cluster)
  – Canada, Japan, and Australia are also active members
  – Monthly teleconferences between regulators to discuss product-specific pediatric topics
  – Objective to enhance the science of pediatric trials and to avoid exposing children to unnecessary trials; provides a robust ethical and scientific framework for pediatric studies
Paediatric Lens to Health Canada’s Regulatory Activities

• Health Canada is working to develop and implement approaches to address issues around paediatric medicines, for example:

  — Investigating regulatory changes that would support the submission of paediatric data and / or paediatric submissions

  — Exploring alternative pathways to bring paediatric medicines to Canada (e.g., Use of Foreign Decisions, Real World Evidence, etc.)

  — Investigating additional incentive models to support paediatric data submissions (current model is 6 month data protection extension for sponsors who submit useful* paediatric data for a drug within 5 years of the first NOC)

* Useful = data gets reflected in the drug’s label
Moving Forward on Paediatric Activities…

• Health Canada is engaging across the Health portfolio, with our health system partners, and international regulators to support aligned approaches to issues around paediatric medicines

• Improving work in this area will require an international approach from all stakeholders

• We look forward to working with you to improve our regulatory processes to support accelerated access (through accelerated evaluation) to important cancer therapies for children and adolescents
Thank You!

Please Contact Us!

Office of Paediatrics and Patient Involvement
100 Eglantine Driveway, Tunney’s Pasture
Ottawa, ON K1A 0K9
Mail Stop 0603C
hc.oppi-bppp.sc@canada.ca
Implementation of the Race for Children ACT

Greg Reaman, *US Food and Drug Administration*
RACE for Children Act, FDARA Sec 504: The Evolving Landscape for Pediatric Cancer Drug Development

Gregory Reaman, M.D.
Associate Director for Pediatric Oncology
Oncology Center of Excellence, Office of the Commissioner
Associate Director, Pediatrics, Office of Oncologic Diseases,
Office of New Drugs, Center for Drug Evaluation and Research
RACE for Children Act:

- Incorporated as Title V Sec. 504 of the FDA Reauthorization Act (FDARA), enacted August 18, 2017
- Amends Pediatric Research Equity Act PREA (Sec. 505B of the FD&C Act)
- 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.”
  - Substantially relevant based on evidence deemed adequate by the Secretary of HHS: no pre-clinical evidence required.
- Molecularly targeted pediatric cancer investigation: clinically meaningful study data, “using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling.” [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)].
- Elimination of orphan exemption for pediatric studies for cancer drugs directed at relevant molecular targets.
Sponsor Requirements

• Sec 505B(e) of the FD&C Act requires sponsors have an Agreed initial Pediatric Study Plan (iPSP) prior to submission of a NDA/BLA.

• After Aug. 18, 2020, the PREA requirements for applications of NEW active ingredients will no longer be based on indication, rather the molecular MOA of an investigational product (including orphan-designated); impact on automatic waivers

• The iPSP must include details of the “molecularly targeted pediatric cancer investigation”: non-hypothesis testing, dose finding, signal of activity-seeking study or justification for waiver or deferral plan

• Early communication between Industry and Investigator community encouraged

• Statute provides for early meeting with FDA to discuss development of iPSP (Sec. 503 FDARA)
Statutory Requirements for FDA

• Establish with NCI, update regularly, and post on FDA website a list of “relevant” targets (1 year)
• Establish and post a list of targets (non-relevant) leading to waivers of pediatric studies (1 year)
• Work with NCI, Pediatric Subcommittee of ODAC, PeRC, investigators, sponsors, experts, and advocates on implementation and required studies
• Convene an open public meeting (1 year)
• Issue guidance on implementation (2 years)

https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

• Focus on accelerating appropriate initial pediatric evaluations early in development timeline not increasing number of pediatric phase 1 studies
Target Lists

- Statutory requirement to purportedly address regulatory uncertainty for Industry and **guide (not dictate)** decision-making re. early evaluation plans and iPSP submission for a specific agent in accordance with the amended PREA requirement
- Lists subject to change due to emerging science
- **Designation as relevant neither an absolute nor exclusive requirement for decisions related to pediatric evaluation:** studies of new products may be required if directed at a target **not** on the list and waivers may be justified for products directed at targets considered relevant
- **Not envisioned to restrict authority or flexibility**
- **Candidate** Target List constructed by OCE with NCI and input from international content experts in open public meetings
- Association of a target with one or more pediatric cancers as reported in published, peer-reviewed literature, abstracts, public databases
- No pre-specified **evidence base**
Relevant Target Lists

• Targets associated with specific gene abnormalities

• Targets associated with cell lineage determinants

• Targets on normal immune cells and cells within the Tumor Microenvironment

• Other Targets: Pathways and Functional Mechanisms

• Plans to regularly review and update lists: open Federal register docket for recommendations

• Lists posted on FDA’s OCE website Pediatric OncologyProgram(https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/default.htm)
Deferral Considerations for Agents Directed at Relevant Molecular Targets

• Pending sufficient evidence of pre-clinical/clinical activity observed in response to target inhibition
• Uncertainty regarding the single agent activity of a drug until such time that one or more biologically rational combinations demonstrate an effect (pre-clinical or clinical)
• Absence of an appropriate formulation for investigational purposes provided there has been due diligence in development and establishing bioequivalence
Waiver Considerations for Agents Directed at Relevant Targets

- Serious known or expected developmental toxicity—consideration for **full or age dependent partial waiver**
- Multiple “in class” product (single agent) without compelling evidence of substantial differences in efficacy, safety, PK profiles, or formulation to warrant additional pediatric studies
- Feasibility and practicability due to small study populations potentially addressed by limited study requirements and innovative study design and conduct: embedded pediatric trials, expansion cohorts, histology-agnostic development
- Age-dependent waivers based on available formulations for specific age groups
Considerations for Target and Product Prioritization

- Likely variable by target class and disease
- Prevalence of target expression in a single disease or across histologies
- Level of evidence that target inhibition modulates specific tumor growth: **Pediatric pre-clinical data**
- Extent of unmet clinical need (disease-specific) and potential public health impact
- Availability of and access to agent; formulation
- Availability of predictive or response biomarkers
- Collaboration between Industry and clinical investigator community: **External multi-stakeholder input** to inform FDA decision-making
Sec. 503 Early Advice Meetings

• Focus on clarifying iPSP requirements for original NDA/BLAs to be submitted on/after Aug. 18, 2020 resulting from PREA amendments
• Scheduled and held within 30 days of request
• Briefing Document and Questions required
• Meeting request to Review Division; scheduled with and by OCE Pediatric Oncology Program at OCEperc@fda.hhs.gov
• Internal meeting scheduled
• Written responses to questions prior to meeting
• Meeting management and minutes responsibility of OCE Pediatric Oncology Program
Closing

- Amendments to PREA by the RACE for Children Act finally bring equity to children with cancer globally.
- FDARA Sec. 504 will dramatically alter the landscape for pediatric cancer drug development.
- Earlier consideration of pre-clinical assessment of new assets using pediatric-specific models will be critical.
- Innovation in study design and coordination/conduct on a global scale is essential.
- **Multi-stakeholder input** to rational decision-making is required.
- RACE for Children Act will not solve all the obstacles to pediatric cancer drug development.
- Improvement in cancer outcomes for children through timely assessment of appropriate novel drugs requires successful implementation.
- Regulatory agency coordination/collaboration is essential.
Perspectives for the European Regulatory Environment

Fabio D’Atri, *European Commission, DG SANTE*
Evaluation of the Orphans and Paediatric Regulations

- Paediatric study/report on Reg. 1901/2006
  - Public health impact
  - Economic impact

- Incentives study
  - Impact on innovation, availability accessibility

- Gap Analysis study for evaluation of orphans

ACCELERATE
Innovation for Children and Adolescents with Cancer
Timeline of the evaluation

December 2017

Roadmap

4-week public consultation

April 2018 – October 2019

Study on orphans

Public consultation: 12 October – 4 January 2018
Targeted consultations: October – November 2018

2020

Evaluation of orphans and paediatrics
Staff Working Document

17 June 2019 Conference
What are we looking at?

Orphan & Paediatric Regulations

- EU policy context
- EU initiatives
- National policies and initiatives

Source: Technopolis Group
Patients with rare diseases without cures in the EU

Pharma industry not willing to develop OMP under normal market conditions

Only a few MS developed measures for rare diseases

Orphan Regulation

Tools

EU procedure for orphan designation
EU authorisation
EMA Committee
Protocol assistance
Aid for R&D
EMA fee waiver

Involvement of patients groups
10-year market exclusivity +2 PIP
Children without cures in the EU

Pharma industry not willing to develop paediatric medicines

Off-label use of adult medicines for children

Paediatric Regulation

Involvement of young patients

12-year market exclusivity Or 6 months SPC

Paediatric Investigation Plans

Scientific advice

PUMA

EMA Committee

EMA fee waiver
Challenges

- High prices
- Are MS reviewing the market exclusivity after 5 years?
- Crowded areas
- Paediatric only areas neglected
- Almost no applications based on "insufficient return on investment"
- Unmet medical need
- Paediatric development is adult driven
- PIP system too strict/"inflexible"?
Problems identified still existing

Orphans: More products, available faster and to more MS

Paediatrics: More products, more clinical paediatric research and improved information on the paediatric use of medicines

Development for the rarest diseases

Increased use of orphan incentives = important for the development of orphan products

For most orphan medicines the market exclusivity reward has helped to increase profitability, without giving the sponsor an unbalanced or unfair compensation

Both Paediatric and Orphan Regulation appear to work coherently with related EU and national legislation and initiatives

Impossible to achieve similar results without EU level action
PROBLEMS IDENTIFIED
(preliminary)

- Unequal access to authorised orphans
- **Ready for the scientific developments?**
- **Large unmet medical need (95% of rare disease patients without treatment, off label use in neonates, paediatric oncology)**
- **Paediatric development linked to adult development**
- **ROI never used in orphan applications**
- Risk of overcompensation for some orphans (multiple indications, small R&D costs)
- **Paediatric Regulation perceived burdensome, SPC complex and inefficient**
- Various incentives do not fully interact -> gaming the protection period
- **Efficient interactions between EMA committees, procedures?**
What's next?
Thank you for your attention!

*Disclaimer:* The views and opinions expressed in these PowerPoint slides are those of the presenter; they do not necessarily reflect the opinion of the European Commission.
The IMI2 ITCC-P4 Paediatric Preclinical Proof-of-Concept Platform

Louis Stancato, Eli Lilly and Company

On behalf of the ITCC-P4 Leadership Team
G Vassal (GR), H Caron (Roche), S Pfister (DKFZ)

www.itccp4.eu Grant Agreement No 116064 ITCC-P4
A reminder of why we are here

- Pediatric Cancer: ~51,000/year (US & EU, 2018 est.; 175,000 worldwide) \(\rightarrow\) the leading cause of death by disease in children >19
  - Solid tumors >50%
  - CNS tumors: ~20%
    - 2\textsuperscript{nd} most common pediatric cancer
    - 1\textsuperscript{st} cause of morbidity/mortality
- 1 in 5 patients will succumb to their treatment or their disease
- 3 in 5 survivors will experience significant late effects:
  - 2\textsuperscript{nd} cancers
  - Mental/developmental delays; physical disabilities; endocrine dysreg; infertility
Why the Paediatric Community Needs Public-Private Partnerships

- >20% of all paediatric cancer remains incurable

- Paediatric cancer is a complex, multi-stakeholder problem

- Lack of and/or limited access to well-characterized paediatric cancer research tools limits the availability & predictability of preclinical testing

- A close academia – industry partnership is essential
  - Brings all needed pieces together in a precompetitive platform

A PPP would be opening doors to paediatric development in a concerted and rigorous fashion
Innovative Medicines Initiative – A Public-Private Partnership

Innovative Medicines Initiative: Joining Forces in the Healthcare Sector

Europe’s largest public-private life sciences initiative
- Address key societal challenges
- Enhance Europe’s competitiveness
- Speed development of medicines
- Academic-industry partnerships (industry defined)

Our Budget – EFPIA budget €9 mio (IMI adds 7.5M) → €16.5 mio total (plus a little more ... 😊)
The ITCC-P4 platform

- ~150 models fully validated and characterized; data now being uploaded into R2
- 400 PDX models/5yrs; GEMMs: expanding into liquids
- Standard-of-care and targeted compound testing
- POC for immunotherapies in humanized models
- POC for organoids

ITCC-P4 Workflow

WP 1: Consortium management
WP 2: Systematic target prioritization/ actionability in pediatric solid tumors
WP 3A: Model development including alternative models
WP 3B: Model characterization including cross-species
WP 4: Regulatory preclinical consensus
WP 5: Preclinical drug testing in vitro and in vivo
WP 6: Information management and data analysis
WP 7: Sustainability and contractual management
Tumor types we are targeting

**Most common solid tumors**

- **Brain tumors** are orthotopic; all others flank
- Ependymoma supratentorial (EPD_ST)
- Atypical teratoid/rhabdoid tumor (ATRT)
- High grade glioma other (HGG_other)
- High grade glioma K27Mmut (HGG_K27M)
- Ependymoma infratentorial (EPD_IT)
- Medulloblastoma WNT (WNT)
- Medulloblastoma SHH (SHH)
- Medulloblastoma Group3 (G3)
- Medulloblastoma Group4 (G4)
- Neuroblastoma (NB)
- Synovial Sarcoma (SS)
- Ewing Sarcoma (ES)
- Osteosarcoma (OS)
- Rhabdomyosarcoma (RMS)
- Malignant Peripheral Nerve Sheath Tumor

**Comming soon:**
- Liquid Tumors
- AML
- ALL
- Lymphoma

**Rarer entities**

- ETMR
- Desmoplastic small round cell tumor
- HGNETH-BCOR
- CNS neuroblastoma (FOXRI2)
- Inflammatory myofibroblastic tumor
- Renal cell carcinoma
- Hepatocellular carcinoma
Consortium progress

• A highly functioning consortium
• Methodology accepted, four new TARS underway
• ~150 validated; overall a bit behind
• White paper submitted in Q1’20
• Testing did not begin Q4/19; Q1/20
• R2 evolving to become even more powerful
• Well in advance of typical IMI projects
IMI interim review of ITCC-P4:
“Showcase project for what IMI can do.”

• Team gathered in Brussels last November for mid project review
• IMI scientific officer and project reviewers from across the EU
• High marks overall (except for our website 😞)
  • “Ability to set the standard for the field … high achieving … might change the paradigm … showcase project for what IMI can do.”
• Impressed with the depth of sustainability discussions
• We passed!
Helping shape the preclinical paediatric research landscape

**WP2 Deliverable**: Target Actionability Review Methodology

Systematic target actionability reviews of preclinical proof-of-concept papers to match targeted drugs to paediatric cancers

Nil A Schubert†, Caitlin D Lowery†, Guillaume Bergthold†, Jan Koster, Thomas F Eleveld, Ana Rodríguez, David T W Jones, Gilles Vassal, Louis F Stancato, Stefan M Pfister, Hubert N Caron*, Jan J Molenaar*

**WP4 Deliverable**: Preclinical Consensus on Data Requirements

International consensus on minimum preclinical testing requirements for the development of innovative therapies for children and adolescents with cancer

G Vassal, PJ Houghton, SM Pfister, M Smith, H Caron, X Li, DJ Shields, O Witt, J Molenaar, S Colombetti, J Schueler, L Stancato
The growing PDX library – models entered in R2 portal
Unshielded Drug testing – pool of test agents

<table>
<thead>
<tr>
<th>platform tumor indications</th>
<th>SoC 1</th>
<th>SoC 2</th>
<th>SoC 3</th>
<th>two-SoC combination</th>
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<td>Medulloblastoma (MB)</td>
<td>E</td>
<td>CPA</td>
<td>L</td>
<td>CP + E</td>
<td>Sec-I</td>
<td>BET/Brd4</td>
<td>CHK1</td>
<td>CDK4/6</td>
<td>Akt-I</td>
<td>TGFB1</td>
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<td>High Grade Glioma (HGG)</td>
<td>TZ</td>
<td>L</td>
<td>RT</td>
<td>TZ + RT</td>
<td>MEK-I</td>
<td>PI3K-I</td>
<td>BET/Brd4</td>
<td>AKT-I</td>
<td>Regorafenib</td>
<td>CHK1</td>
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<td>Ependymoma (EPN)</td>
<td>RT</td>
<td>CPA</td>
<td>AD</td>
<td>RT + CP</td>
<td>PI3K-I #1</td>
<td>AKT-I</td>
<td>CDK4/6</td>
<td>FGFR1</td>
<td>PI3K-I #2</td>
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<td>Atypical Teratoid /</td>
<td>DR</td>
<td>CP</td>
<td>E</td>
<td>DR + CPA</td>
<td>CDK4/6i</td>
<td>SMOI</td>
<td>FGFR-I</td>
<td>MK11</td>
<td>AKT-I</td>
<td>MK22</td>
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<td>Rhabdoid Tumor (ATRT)</td>
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<tr>
<td>Neuroblastoma (NB)</td>
<td>CPA</td>
<td>E</td>
<td>TT</td>
<td>CPA + CP</td>
<td>MDM2-1</td>
<td>BET/Brd4</td>
<td>CHK1</td>
<td>MEK-I</td>
<td>ALK</td>
<td>PI3K</td>
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<td>Rhabdomyosarcoma (RMS)</td>
<td>VC</td>
<td>TF</td>
<td>ID</td>
<td>AD + VC</td>
<td>MEK-I</td>
<td>FGFR-I</td>
<td>Regorafenib</td>
<td>ALK-I</td>
<td>CDK4/6</td>
<td>AKT-I</td>
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<tr>
<td>Non-RMS soft tissue</td>
<td>E</td>
<td>ID</td>
<td>TF</td>
<td>AD + VC</td>
<td>MEK-I</td>
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<td>BET/Brd4</td>
<td>MTR</td>
<td>ALK</td>
<td>CDK4/6</td>
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<td>sarcoma</td>
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<tr>
<td>Osteosarcoma (OS)</td>
<td>DR</td>
<td>RT</td>
<td>CIP</td>
<td>DR + M</td>
<td>MDM2-I</td>
<td>Regorafenib</td>
<td>CDK4/6</td>
<td>Bevacizumab</td>
<td>open</td>
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<tr>
<td>Ewing sarcoma (EWS)</td>
<td>DR</td>
<td>VC</td>
<td>AD</td>
<td>DR + CPA</td>
<td>Regorafenib</td>
<td>BET/Brd4</td>
<td>PI3K-I</td>
<td>CDK4/6</td>
<td>MDM2</td>
<td>FGFR-I</td>
</tr>
</tbody>
</table>

**all GEMMs**

- MTAs nearly in place (tougher than drug testing …)
- Histology-specific SOC

**immune checkpoint inhibitor**
Progress towards sustainability

Build a sustainable post-IMI2 infrastructure that will provide the biological and preclinical data to identify new oncology drugs for pediatric populations.

Progress

- GR taking the lead, building the business case
- Multiple scenarios identified & under consideration
- Will serve the needs of both academic and industrial customers
- Plan to ensure the platform and the science carries on
ITCC-P4’s visibility is increasing

Education Session: Crossing Oceans: Preclinical Collaboration to Improve Pediatric Drug Development
Track(s): Pediatric Oncology; Developmental Therapeutics—Molecularly Targeted Agents and Tumor Biology

FNIH has been approached to develop a PPP for a centralized resource for pediatric preclinical testing

- Initial approach and support for partnership generated through PhRMA; partnership concept has been formally vetted by FNIH with NIH and FDA leadership
- Compliance with the Research to Accelerate Cures for Children (RACE) Act is the compelling ‘impending event,’ but a comprehensive approach to the public health challenges of providing robust, scientifically valid preclinical testing is the goal
- Partnership should involve both NIH funding (NCI PPTC, due to be recompetited in 2020) as well as private sector funding...
- …but the need for a global solution is well-recognized, and should complement established initiatives such as the IMI2 ITCC-P4 and ACCELERATE efforts in the EU
What ITCC-P4 will deliver in 2020

- Drug testing!
- Development of liquid tumor models
- Target actionability reviews (up to four)
- Significant progress towards EMA Qualification Process
- Shielded compound testing
- Continued exposure at international paediatric forums (ASCO, CureSearch Pediatric Early Development Symposium)
- Sustainable business model
Pediatric Cancer Preclinical Testing Partnership

David Wholley, FNIH
Stacey Adam, FNIH
About the FNIH

The mission of the Foundation for the National Institutes of Health (FNIH) is to support the mission of the NIH. The FNIH creates and leads alliances and public-private partnerships that advance breakthrough biomedical discoveries and improve the quality of people’s lives.

The FNIH was created by Congress in 1990 as a not-for-profit charitable organization. The Foundation began its work in 1996 to facilitate groundbreaking research at the U.S. National Institutes of Health (NIH) and worldwide.

Why Collaborate?
• Attract and share resources
• Enable insight and innovation
• Establish standards
• Distribute expertise
• Create consensus
• Drive competitiveness in marketplace
• Disseminate knowledge
• Enhance credibility
• Reduce costs
• Support training & education
• Manage complexity
FNIH
By the Numbers

- $1B+ raised to date
- $0.86 of every dollar spent directly supports programs
- 600+ programs supported since inception
- 120 active research partnerships, scientific education/training, conferences/events, capital programs
- 16 years of outstanding Charity Navigator ratings
Public-Private Partnerships—the Role of the FNIH

Facilitate Collaboration:
- Convene stakeholders
- Provide a “safe harbor” or “neutral forum” for interactions between and among government agencies, industry, foundations, not-for-profits, academic entities
- Establish and manage a variety of governance structures appropriate to each partnership

Relationship Management and Fundraising:
- Directly solicit contributions
- Steward and manage donor funds

Policy Management:
- Create and implement policies that support NIH ethical and policy standards
- Intellectual Property Management: provide “pre-competitive” structures for handling intellectual property

Program Management:
- Drive consensus across all stakeholders about appropriate scientific selection and execution of projects

Project Management:
- Ensure projects meet established deliverables and “go/no go” milestones
FNIH partnerships currently managed by the Research Partnerships team

- **Accelerating Medicines Partnership**
  NIH (OD), NIA, NIAMS, NIDDK, NINDS, 12 companies, 10 not-for-profit organizations
  $360+ million

- **Partnership for Accelerating Cancer Therapies**
  NCI, PhRMA, 12 pharmaceutical companies
  $220 million

- **Alzheimer’s Disease Neuroimaging Initiative (ADNI)**
  NIA, NIBIB, 25+ companies, 3 not-for-profit organizations
  $148 million

- **The Biomarkers Consortium**
  FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations
  $95 million

- **LungMAP: Master Lung Protocol Trial**
  NCI (SWOG), FDA, Friends of Cancer Research, 5 companies to date
  $42 million

- **Helping End Addiction Long-Term (HEAL) Partnership Committee**
  NIH contract
  $0.4 million
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centralized resource for pediatric preclinical testing

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- ...but the need for a global solution is well-recognized, and should complement established initiatives such as the IMI2 ITCC-P4 and ACCELERATE efforts in the EU

- FNIH will establish a partnership framework research agenda with all interested parties using a well-tested consensus-building and planning methodology it has used to establish other PPPs such as AMP and PACT; goal is early 1Q 2020 for initial plan

- As a first step, FNIH has gathered initial perspectives via individual calls with NCI, FDA, PhRMA, BIO, 15 companies, and several major patient advocates
Program Design Process

- Design Phase ~7 months
  - Concept Evaluation
    - NIH RFC and FNIH Board Review
  - Initial Research Outline ("White Paper")
    - NIH
    - Companies
    - Academic KOLs
    - Non-Profits and Patient Advocates
  - Preliminary Support Commitments
    - Companies
    - Non-Profits
  - Detailed Research Plan
    - NIH
    - Private Sector Partners
  - Funding Agreements
  - NIH Grants Solicitation and Awards Processes

- FNIH Project Leadership and Support

- Early to Mid-2020
  - PROGRAM LAUNCH

- Today
Where we have been and where we are going

Timeline

1. 1 month before F2F Meeting
   - 6 Focused Topic Area Calls
     - Mouse Models - Aug 2, 2019 – 9:00 – 10:30 a.m. ET
     - Operating Structure - Aug 8 – 9 – 10:30 a.m. ET
     - Data Standards/IT - Aug 8 – 10:30 a.m. – noon ET
     - Scale and Regulatory - Aug 9 – 10:00 – 11:30 a.m. ET
     - Regulatory Needs - Aug 12 – 12 – 1:30 p.m. ET
     - Standards, Cost Model, and other Needs – Aug 15 – 8:30-10 am ET

2. 2-3 weeks
   - Whitepaper Outline Drafted – Aug 15-31, 2019

3. A few days prior F2F
   - Whitepaper Outline Distributed – Sep 3, 2019

4. F2F Meeting
   - Discuss/Develop Partnership Aspects – Sep 5-6, 2019
     - North Bethesda Marriott – Bethesda, MD
     - 8 a.m. – 6 p.m. ET – Sep 5th and 8 a.m. – 3 p.m. ET – Sep 6th

5. Post-conference
   - Finalize Whitepaper for Stakeholder Review – Sep 7 – Feb 10, 2020
Proposed scale and scope

1. Create, publish, and continuously update a catalogue of existing preclinical pediatric cancer models and facilitate research community access to these models
2. Establish and validate a high-throughput in vitro testing platform (e.g., cell lines and potentially organoids as well), and make it broadly available to stakeholders
3. Harmonize existing standards across models, data, response criteria, and informed consent
4. Develop new murine models through collaborative pilot studies to address the key current gaps in the field,
5. Invest in enhanced and expanded “data commons” capabilities to enable aggregation and comparison of existing and new testing data to support enhanced decision-making
6. Establish an ongoing forum for tracking progress and allocating new investments, the Strategic Advisory Committee (SAC)

7. Conduct joint target and agent feasibility analyses, similar in nature and process to the Target Actionability Reviews currently undertaken by the ITCC-P4, but encompassing data from publicly available repositories that is unpublished as well as the data generated by the testing conducted within the PPP (once appropriate exclusivity periods are met)

8. Conduct testing of agents at sites established by the PPP, either CRO or academic, depending on the needs of the company providing the agent in consultation with the SAC. Make results available to the broader research community (once appropriate exclusivity periods are met)
Creating a Centralized Data Commons

- Require at appropriate US federal compliance for data protection and security
- Need to have a role-based access instituted to protect patient associated and company proprietary data
- Need to be compliant [NCI Cancer Research Data Commons (CRDC)](https://cancercommons.cancer.gov/) guidelines
- Able to federate data from other preclinical testing initiatives
IP, Data Sharing, and Publication Guidance

• CTEP IP Option for Collaborators will be the foundation for the PPP IP approach for company agents

• Still discussing IP for preclinical models generated with private sector funds, but joint ownership between the group that creates and the group that characterizes is being considered. Models generated with public sector funds will follow NCI guidelines.

• Data Sharing Guidelines outline two paths for sharing:
  • One track would allow for a 3 tiered release of the data, allowing for appropriate exclusivity periods for company regulatory filing and publication
  • One track would allow for quicker sharing within the partnership and the broader community, but still allow for data publication

• Group agreed that International Medical Journal Editors Consortium guidelines for authorship would be the easiest for publication. Companies would have set time to review any publications and request a delay if necessary for filing. If data not published in 18 months, it could be made broadly available to the community.
## Current Estimated Baseline Budget (as of 2/2020)

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Total Costs</th>
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<tbody>
<tr>
<td>1. Create, publish, and continuously update a catalogue of preclinical pediatric cancer models and facilitating research community access to these models</td>
<td>$525,000</td>
<td>$325,000</td>
<td>$325,000</td>
<td>$325,000</td>
<td>$325,000</td>
<td>$1,825,000</td>
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<tr>
<td>2. Establish and validate a high-throughput <em>in vitro</em> testing platform (e.g., cell lines and potentially organoids as well), and making it broadly available to stakeholders</td>
<td>$2,125,000/ $1,000,000</td>
<td>$2,125,000/ $1,000,000</td>
<td>$250,000/ $1,000,000</td>
<td>$250,000/ $1,000,000</td>
<td>$250,000/ $1,000,000</td>
<td>$5,000,000/ $5,000,000</td>
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<tr>
<td>3. Harmonize existing standards among models, data, response criteria, and (where possible) informed consent</td>
<td>$500,000</td>
<td>$500,000</td>
<td>$500,000</td>
<td>$500,000</td>
<td>$500,000</td>
<td>$2,500,000</td>
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<tr>
<td>4. Conduct joint target and agent feasibility analyses and assemble data into preclinical data package target assessments for PPP and company review</td>
<td>Up to $1,250,000</td>
<td>Up to $1,250,000</td>
<td>Up to $1,250,000</td>
<td>Up to $1,250,000</td>
<td>Up to $1,250,000</td>
<td>$6,250,000</td>
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<td>5. Develop new murine models through collaborative pilot studies in order to address the key current gaps in the field</td>
<td>$1,750,000</td>
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<td>6. Create an enhanced data commons to aggregate, store, and compare both existing and new testing data, in order to support enhanced decision-making</td>
<td>$7,088,500</td>
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<td>$2,500,000</td>
<td>$2,500,000</td>
<td>$17,088,500</td>
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<td>7. Establish a Scientific Advisory Committee (SAC) to assist with evaluation of preclinical data packages, consult with companies on data generated by the PPP, and act as scientific advisors for PPP</td>
<td>$50,000</td>
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<td>8. Conduct testing of agents at sites established by the PPP (Assumes 2 testing vouchers for standard PDX non-IO testing for each company partner, assumes 10 partners)</td>
<td>$60,000</td>
<td>$60,000</td>
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<td>$1,000,000</td>
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<td>(Support of 10% discount of testing through membership support)</td>
<td>New Compound Profiling</td>
<td>$1,300,000/ $9,000,000</td>
<td>$1,300,000/ $9,000,000</td>
<td>$1,300,000/ $9,000,000</td>
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<td>(Assumes 200 non-IO agents/year in PDX testing at n=10 strategy)</td>
<td>$120,000 (Design of Agent Review Process)</td>
<td>$5,000,000 (Coordinating Center)</td>
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<td>(Assumes 40 IO agents/year in IO relevant models n=10 strategy)</td>
<td>FNIH Program Management Funds</td>
<td>$1,720,000</td>
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**Base Investment Total**

**Fee-for-Service**

$111,858,500

($61,858,500/
$50,000,000)
Back Up Slides
Payment Structures for Funds from FNIH

1. Supplement NIH Grants (NIH Recognized Indirects Rate)

2. FNIH RFPs/Contracts (Capped Indirects 15%)

3. Direct in-kind contributions (e.g., data, sequencing, etc.)

Industry and Non-profit Commitments

NIH Commitments

PPP Project A
• Grantees

PPP Project A
• (Additional/Optional) Contractees

NCI RFAs

[Future FOAs: Content TBD]
Joint Steering Committee: Proposed Function

- Review recommendations of the Scientific Advisory Committee and use these recommendations to set operational research priorities for the PPP.
- Review progress of projects on an ongoing basis and adjust project plans to ensure appropriate tradeoffs between the timely achievement of key project milestones and production of quality results.
- Conduct assessments of key project milestones, including critical go/no-go milestones, and communicate these assessments to the EC.
- Determine how private sector funds provided to FNIH are distributed (consistent with the final research plan).
- Work with Strategic Communications Committee to review the results of the research efforts and make recommendations regarding how they are disseminated and publicized, consistent with NIH publication rules.
- Oversee active outreach to, and coordination with, other related preclinical pediatric research efforts.
Joint Steering Committee: Proposed Membership

- 5 NIH members (voting), including program officials for the relevant NIH grants
- 5 FDA members (non-voting)
- One voting representative from each funding industry partner; additional industry representatives may attend as alternates but will be nonvoting
- One voting representative from each nonprofit/patient advocate organization
- At least one representative from FNIH (ex-officio, nonvoting)
Scientific Advisory Committee (SAC): Function

- Overseeing preclinical data package development for each high priority target from FDA
- Reviewing the preclinical data package for each target and providing recommendations of what agents need to be tested preclinically, prioritizing which agents should be tested with PPP financial resources
  - A sub-committee will be formed within the SAC to review each agent application and provide recommendations to the overall SAC
  - Membership of the sub-committee can be broad and engage ad hoc members as required to ensure the appropriate expertise for review of each agent
  - All SAC members will be under confidentiality during application review
- Overseeing relevant murine model development, selection, standardization, and deployment
- Encouraging the use of standard models, SOPs, and best practices where necessary
- Enabling and encouraging submission of the data to the “centralized” repository for PPP use
- Enforcing the required data standards for any data submitted to the partnership
Scientific Advisory Committee (SAC): Proposed Membership

- NCI scientists with expertise in pediatric oncology, model and cell line characterization experience, and data science. This may include one or more members of the SC who can act as liaisons.

- Academic researchers with relevant pediatric, preclinical, clinical and translational research expertise. These members, while they serve on the panel, will not be able to serve as principal investigators on studies associated with the PPP.

- Scientists with industry experience in pediatric oncology drug development who do not have current employment with or active ties to individual companies in the areas of interest for the PPP, to avoid conflicts of interest.

- One or more representatives from nonprofit/patient organizations with an interest in pediatric oncology.

- FDA, EMA, or other regulatory scientists – *In strictly advisory capacity*
Strategic Communications Committee (SCC): Proposed Function and Membership – Working Group of the JSC

- SCC will be responsible for crafting and overseeing a comprehensive communications plan for the PPP. This group will also function as the primary outreach point from the PPP to the broader pediatric oncology community with key research findings, initiatives, and messaging.

- The membership of the SCC should include the following:
  - 3 representatives from pediatric oncology related patient advocacy organizations
  - 2 scientific representatives from the SAC
  - 1-2 communications representative from participating companies
  - 1 communications representative from NIH/NCI
  - 1 communications representative from EU efforts
Governance: Executive Committee

• Provide general guidance for the overall strategy of the PPP.
• Review progress of PPP on a regular basis and ensure its effective and timely execution. This includes review and approval of major go/no-go milestones and funding changes.
• Communicate progress of PPP and any related challenges to the partners and pediatric oncology community and manage the relationships among the partners.
• Establish policies that govern PPP and ensure they are adhered to.
• Oversee the operation of SC and resolve any conflicts or questions that they may not be able to resolve on their own.
• Consider new initiatives or partners that may be added to PPP over time.
Executive Committee: Proposed Membership

• 3 senior-level NCI officials, including the Director of the National Cancer Institute and two others of his choosing
• 2 representatives from FDA (non-voting)
• A patient advocate representative
• 3 senior-level executives from three different biopharmaceutical company partners
The European Agenda for children and adolescents with cancer

Professor Pam Kearns, President SIOP-E
What is SIOP Europe?

Society with over 2000 members from > 30 countries across Europe
SIOP Europe has pan-European Representation

> 30 National Paediatric Haemato-oncology Societies

www.siope.eu
SIOP Europe is a highly Collaborative Community

19 Clinical Trial Groups
Working Groups

• Young SIOPE

• SIOP Europe AYA Committee

• SIOP Europe Radiation Oncology Working Group

• SIOPE Host Genome Working Group
Cancer remains the first cause of death by disease in Europe in children older than 1 year

In Europe:
more than **35,000** new cases are diagnosed every year

over than **6,000** young patients die every year

There are nearly **500,000** childhood cancer survivors
the majority experience adverse long-term effects

There are substantial **inequalities in access** to the best available care and expertise

**20%** differences in survival rates between EU countries
The SIOPE Strategic Plan

Seven Medical and Scientific Objectives

- **Innovative treatments**: to introduce safe and effective innovative treatments (i.e. new drugs, new technologies) into standard care
- **Precision cancer medicine**: to improve risk classification as well as biological characteristics of both the tumour and patient (such as molecular and immunological factors) to help guide decisions on which therapies to use
- **Tumour biology**: to increase knowledge of tumour biology and speed up translation from basic research to clinical care to benefit patients
- **Equal access**: to bring about equal access across Europe to standard care (in both diagnosis and treatment), expertise and clinical research
- **Teenagers and Young Adults**: to address the specific needs of teenagers and young adults (TYA), in cooperation with adult oncology
- **Quality of survivorship**: to address the consequences of cancer treatment such as long-term side effects, to better understand the genetic background/risk of an individual, and to improve quality of life of survivors of childhood cancer
- **Causes of cancer**: to understand the causes of paediatric cancers and to address prevention wherever possible
The SIOPE Strategic Plan

Seven Medical and Scientific Objectives

- **Innovative treatments**: to introduce safe and effective innovative treatments (i.e. new drugs, new technologies) into standard care

- **Precision cancer medicine**: to improve risk classification as well as biological characteristics of both the tumour and patient (such as molecular and immunological factors) to help guide decisions on which therapies to use

- **Tumour biology**: to increase knowledge of tumour biology and speed up translation from basic research to clinical care to benefit patients
THE EUROPEAN CANCER DRUG DEVELOPMENT NETWORK FOR CHILDHOOD CANCER

57 Paediatric Oncology Centres

International Sponsoring Centre
National Co-ordinating Centres

ITCC P4 PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM
Quality of survivorship: to address the consequences of cancer treatment such as long-term side effects, to better understand the genetic background/risk of an individual, and to improve quality of life of survivors of childhood cancer

- 500,000 survivors of childhood cancer in Europe
- > 2/3 live with significant long term side effects of their disease and/or treatment

Need to ensure life–long multi-professional and multidisciplinary care pathways for cancer survivors

- What matters for patients (and families) – impacts on well-being and quality of life
- Secondary prevention
A document to be given to the individual patient after the elective end of therapies

- Paper and/or electronic based
- Containing cancer history and therapy information
- Providing advice and guidance on survivor-specific long-term follow-up of possible late effects
- Written and translatable in all languages of the EU
Equal access: to bring about equal access across Europe to standard care (in both diagnosis and treatment), expertise and clinical research
Equal access: to bring about equal access across Europe to standard care (in both diagnosis and treatment), expertise and clinical research

Standardisation of best clinical practice
Radiotherapy: Mapped over 250 paediatric radiotherapy centres treating children with cancer in 34 countries

Access to medicines:
Reduce drug shortages, ensure accessibility to newly approved expensive medicine and foster availability of safe age-appropriate oral formulations.

Innovation:
Facilitate cross-border access to ensure equal access to both specialist treatments and innovation

Very Rare Tumours:
The ‘Rare Cancer Agenda 2030’ Booklet

- 10 Recommendations / Chapters

- Dedicated section on childhood cancer in each

JARC has received funding from the European Union’s Health Programme (2014-2020)
Equal and best paediatric cancer care and outcomes for all children and young people in Europe.
ERN PaedCan

Network that facilitates sharing of disease specific expertise, knowledge and access to ‘state of the art’ care for all

- **Access to Virtual Expert Tumour Boards**
  - Medical expertise and knowledge travels rather than patients
  - Use of the EU- Clinical Patient Management System (CPMS) as an important health-care tool

- **Proportionate & Appropriate Cross-Border Healthcare**
  - Unites the best experts across Europe to tackle complex Paediatric Cancer Conditions that require highly specialized interventions and a concentration of knowledge and resources

- **ERN PaedCan: defining Standard Care Pathways**
  - Collaborative Work with the SIOP-E Clinical trial Groups defining current treatment standards
BEATING CANCER IN EUROPE:
BEATING CANCER IN EUROPE:
LET’S NOT FORGET OUR CHILDREN AND ADOLESCENTS

1. Improve access to anti-cancer medicines & innovation for children & adolescents
2. Enable research progress in an area of ‘market failure’
3. Exploit the Artificial Intelligence potential for paediatric cancers
4. Commit to counter inequalities in childhood cancer survival
5. Ensure best possible follow-up care, research, empowerment of childhood cancer survivors
6. Support to families with severely ill children with cancer by facilitating the care continuum with special psychosocial and financial support

Europe’s Beating Cancer Plan and the Cancer Mission Area are among the initiatives that hold great promise for children and adolescents with cancer.

EU should ensure that their urgent needs are not overlooked and instead become an integral part of all relevant EU policies and programmes
The critical need to increase EU investment in childhood cancer research

• Funding for childhood cancer research:
  – The ten-fold difference in contributions between the USA and Europe
  – 7.1% EU vs 77.7% US*

*Loucaides et al Lancet Oncol 2019 20:e672–84
‘an ambitious €100 billion research and innovation programme that will succeed Horizon 2020’
• 5 major European research and innovation missions including

• Mission on the topic of cancer

• Important potential for inclusion of childhood cancer as a Mission topic

Evolution of a Horizon Europe Mission

‘Mission-oriented research and innovation initiatives are typically ambitious, exploratory and ground-breaking in nature, often targeting a concrete problem or challenge, with a large impact and a well-defined timeframe. Such initiatives tend to be sizeable, cross-disciplinary, inter-sectoral and involve several types of stakeholders’
Evolution of a Horizon Europe Mission

• In Horizon Europe, a mission .................. intended to

  • achieve, within a set timeframe, a measurable goal that could not be achieved through individual Member States actions
  • have impact on European society and European and national policy- making through science output and technological and digital advancement
  • be relevant for European citizens
A European paediatric cancer mission: aspiration or reality?

Pamela R Kearns • Gilles Vassal • Ruth Ladenstein • Martin Schrappe • Andrea Biondi • Patricia Blanc • Angelika Eggert • Anita Kienesberger • Olga Kozhaeva • Rob Pieters • Kjeld Schmiegelow

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https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30487-5/fulltext
A MISSION TO BEAT CHILDHOOD CANCER

Cure more and Cure better: Half the deaths and half the burden by 2030

Basic Science
- Elucidate the role of the immune system and epigenetics for therapeutic interventions

Medical Sector
- Develop effective and less toxic therapies in standard care

E-Health
- Ensure equal access to innovation and standard treatments across Europe

Social and Human Sciences
- Prevent long-term morbidity and death

Digital Sector
- Develop Artificial Intelligence for diagnosis and treatment

Biopharmaceutical industry
- Systematic use of all available research and healthcare data

Patients, advocates & NGOs
- Understand the causes of childhood cancers for prevention strategies

www.siope.eu
Advocating Policy Priorities for Paediatric Cancer to the EU

EUROPE’S BEATING CANCER PLAN
STRENGTHENING OUR APPROACH AT EVERY STAGE

Prevention

Diagnosis

Treatment

Quality of life of patients & survivors

Ursula Von der Leyen
President, European Commission
Advocating Policy Priorities for Paediatric Cancer to the EU

1. Europe’s Beating Cancer Plan: ‘Roadmap’ open feedback
   Feedback period
   04 February 2020 - 03 March 2020
   https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2020-693786

2. Europe’s Beating Cancer Plan: Public consultation
   Consultation period
   04 February 2020 - 28 April 2020

   (Commission adoption expected: 4th quarter 2020)
Special Policy Meeting: Towards Beating Childhood Cancer in Europe at the European Parliament 28 January 2020
• First-of-a-kind event co-hosted by all political groups
• Co-organized by SIOP Europe – CCI Europe – PanCare
• Discussion with MEPs fully dedicated to childhood cancer
Join us at the annual EU event

International Childhood Cancer Awareness Day (ICCD2020)

18 February 2020
13:00 to 15:00

European Parliament
Brussels, Belgium

European Parliament, Brussels
Together we work towards a brighter future for our children and adolescents with cancer

Clos-Chapelle aux Champs 30 – 1200 Brussels Belgium

office@siope.eu

www.siope.eu
2ND ANNUAL MEETING OF THE EUROPEAN SOCIETY FOR PAEDIATRIC ONCOLOGY

SIOP EUROPE
2020

2ND ANNUAL MEETING

4-8 MAY 2020
VALENCIA, SPAIN

www.siope.eu