Webinar | IMI2 - Call 7
‘A comprehensive ‘paediatric preclinical POC platform’ to enable clinical molecule development for children with cancer ’

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Need for public-private collaboration

- Despite significant advances over the past 20 years in treatment and survival >20% of all paediatric cancer remains incurable

- The underrepresentation of research tools in the fight against paediatric cancer, and the incomplete nature of their characterization, limits the predictability of preclinical testing of potentially promising new agents and is hampering clinical development

- A close Academia-EFPIA partnership is *essential*
  - Academia is well suited to developing relevant tumour models
  - EFPIA molecules must be matched with appropriate tumours

A consortium would open doors to paediatric development in a concerted and rigorous fashion

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Objectives of the Project

- Accelerating targeted paediatric drug development
- Build a comprehensive translational platform of paediatric solid tumor PDX models, matching cell lines/organoïds and GEMMs. (see next slide)
- Support biomarker driven patient tailored paediatric drug development by preclinical POC testing of pharma compounds
- Develop new scientific insights into sensitivity, resistance and synergistic combinations of molecular targeted therapies (marketed or in clinical testing) in the context of the biological diversity of paediatric tumors
- Custom development of informatics tools to enable objectives

Pediatric Preclinical POC Platform

Target Actionability Reviews

In Silico Target Patterns

Preclinical Model Development

10 Diseases
400 PDX
>20 GEMM

Molecule POC Testing

Data Reporting & Molecule Determinations

Regulatory Preclin Consensus

‘Mechanism-of-Action’ ← ‘match’ → ‘Pediatric Tumor Drivers’

in preclinical pediatric models

- **Preclinical POC testing**
- **Informs rational decisions for clinical trials**
- **Potential to clarify regulatory requirements**

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Objectives of the full project, continued

Major solid tumor types in scope:

- Neuroblastoma
- Soft-tissue Sarcoma
  - Rhabdomyosarcoma (RMS)
  - Synovial Sarcoma
  - Malignant Peripheral Nerve Sheath Tumor (MPNST)
  - Ewing's sarcoma
- Osteosarcoma
- Atypical Rhabdoid Tumours
- CNS
  - Medulloblastoma
  - High Grade Glioma (HGG), incl. diffuse intrinsic pontine glioma (DIPG),
  - Ependymoma

Pre-competitive nature

- Academic and EFPIA partners to share in the models & technology including:
  - Testing Platforms
    - PDX models
    - Matching cell lines (1^0 cell lines/organoïds)
    - GEMMs
    - Humanized immuno mouse models (limited subset of disease)
  - Complete molecular characterization data for all models
  - Standard-of-care testing data across models

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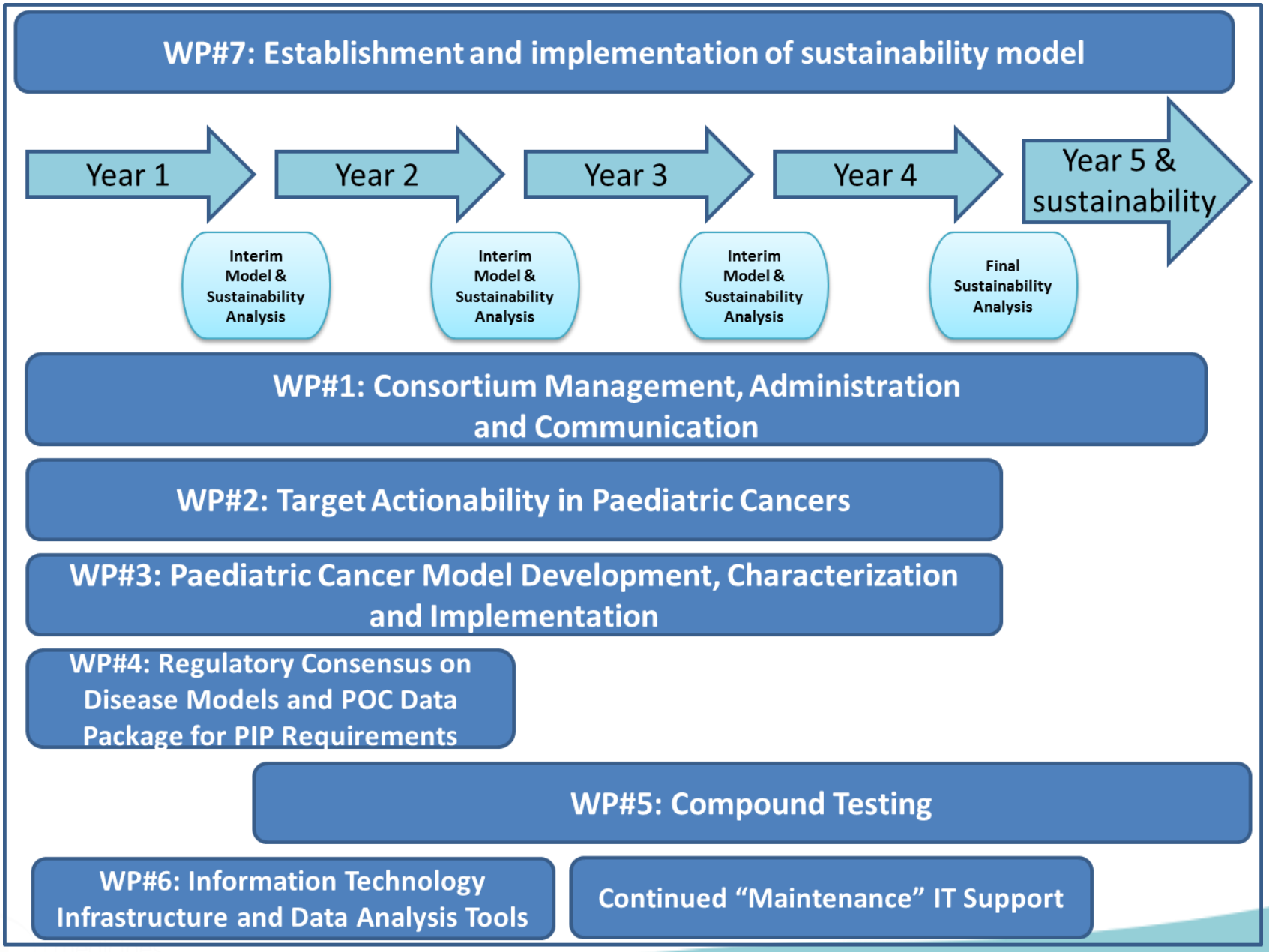
Expected impact on the R&D process

- Speeding the development of the next generation of medicines to combat paediatric cancer
  - Increasing the number of cures
  - Mitigating the long term health effects assoc. w/chemotherapy

- Data-driven, rational decisions on which tumours to treat and with which combination of agents

- Paediatric drug development will be a fully functional research paradigm that rivals approaches created for adult malignancies

Suggested architecture of the project



Key Deliverables for each Work Package

1. Consortium Management → EFPIA-Academia partnership in project oversight (EFPIA overall project lead)
2. Target Actionability → define preclinical POC data packages and perform systematic literature reviews (see backup slides)
3. Model development → comprehensive panels of well-characterized precompetitive preclinical models
4. Regulatory → framework for interaction with PDCO and PIP process, consensus on POC packages
5. Compound testing → testing of compounds from all consortium members incl. SOC, open and shielded cmpds.
   - Pathway evaluation – pilot project to develop common methodology for drug development
6. IT → data repository and data visualization tools
7. Sustainability → plan for continuance post IMI2 phase

Target Actionability and POC data package

Preclinical Target Actionability Data Package	
Module 1	Target Activation Patterns in Clinical Series
Module 2 *	Target Dependence in *'in vitro'* models' (molecular validation)
Module 3 *	Target Dependence in *'in vivo'* models (molecular validation)
Module 4	Molecule 'on target' Efficacy *'in vitro'*
Module 5	Molecule POC Efficacy *'in vivo'*
Module 6	Biomarkers; Predictive and Biological Efficacy (PD) (confirmation)
Module 7	Resistance mechanisms
Module 8	Rational combinations

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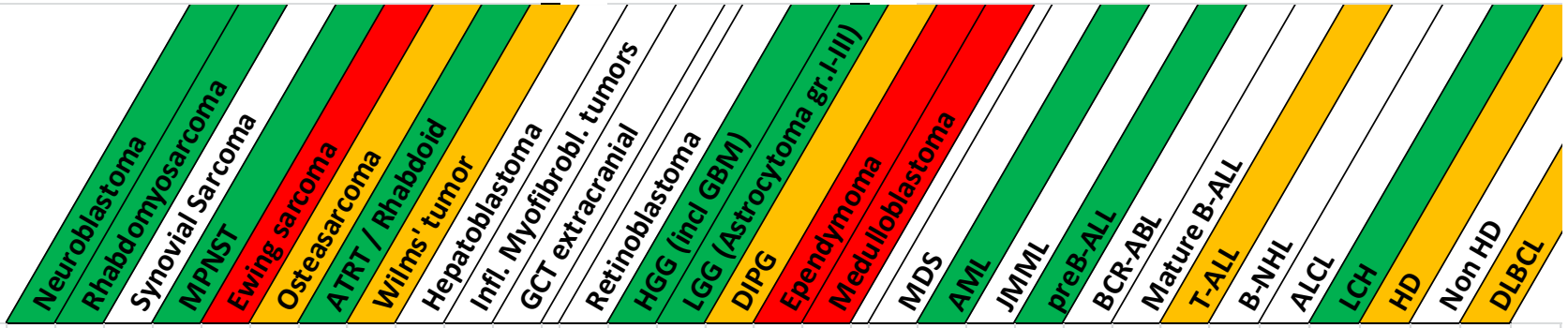
* Considered out-of-scope for this project

MEK, ERK
Target Actionability Review

Target/pathway:	*RAS/RAF/MEK/ERK*
Version Date:	*Cotellic*
Author:	*18Jan2016*
	Simko, Caron,
	Berger



Preclinical

1. Clinical target patterns
2. Molecular Target Validation (vitro)
3. Molecular Target Validation (vivo)
4. Compound Efficacy (vitro)
5. Compound Efficacy (vivo)
6. Biomarker Predictive
7. Resistance Mechanisms
8. Combination

Clinical

7. Safety in children (phase 1 trials)
8. Efficacy in children (phase 2 trials)
9. Efficacy in SOC (phase 3 trials)

Target Review Scores
sufficient
inconclusive ('needs more work')
negative
not tested

Disease scores
suff. POC for clin. development
needs more work
no candidate for clinical dev.
no data

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Expected contributions of the applicants

- In vivo pharmacology expertise
- Proven access to existing PDX models and cell lines
- Proven surgical expertise → for cell line and PDX generation; histopathology; tissue block creation
- Pathology expertise (for tumor histological determination)
- Proven primary cell-line generation
- Informatics expertise incl., data storage, retrieval and visualization
- Medical advice on current best practices for treating paediatric malignancies (advisory role only)
- Centralized testing capabilities
- Regulatory interactions
- Professional Project Management Organization
- Proposal for project sustainability

Expected (in kind) contributions of EFPIA members

- EFPIA partners (Lilly – project lead, Roche – co-lead, Bayer, Pfizer and PharmaMar) will provide:
  - Dedicated researchers (senior scientists, post-docs, overall project leadership, etc.)
  - Cell line testing capabilities (mechanistic follow-up only)
  - Chemotherapy formulation and dosing expertise
  - Available paediatric cell line and PDX models
  - Development and validation of new paediatric models
  - Informatics capabilities – data visualization and analysis tools
  - Regulatory expertise
  - Deep cell line and in vivo model characterization incl. WES, RNA-seq (including fusion analysis), SNP6 array and reverse phase proteomic array
  - Compounds for POC testing, subject to agreement with the contributor on transfer of and access rights to results generated on such compounds in accordance with IMI2 IP Policy

What's in it for you?

- *Academic researchers*: high profile research; expansion of models; molecule testing; clinical testing opportunities based on preclinical results; high impact collaborative opportunities with pharma
- *SMEs*: expanded pool of in vivo models; expanded pool of customers; new business; intangible benefits associated with increased visibility in paediatrics
- *Patients' organisations*: acceleration of potential life-saving medicines into clinical development; line of sight for (guaranteed) paediatric research and drug development
- *Government regulators*: streamlined and standardized preclinical testing process for paediatric indications, potentially linked to PIP process

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Questions?

Contact the IMI Programme Office
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