The IMI2 ITCC-P4 Paediatric Preclinical Proof-of-Concept Platform

ACCELERATE 2018
Grant Agreement No 116064 ITCC-P4

Louis Stancato, Eli Lilly and Company
On behalf of the ITCC-P4 Leadership Team
Gilles Vassal (IGR), Hubert Caron (Roche), Stefan Pfister (DKFZ)

www.itccp4.eu
Last year we were a concept driven by patient need

- >20% of all paediatric cancer remains incurable

- ~ 2/3 of childhood cancer survivors will experience significant long-term health consequences

- Lack of well-characterized paediatric cancer research tools limits the predictability of preclinical testing

- A close Academia/SME – EFPIA partnership is essential
  - Will bring all needed pieces together in a precompetitive platform

A public/private consortium would open doors to paediatric development in a concerted and rigorous fashion
This year we are a funded consortium united in meeting that need

- >16.5 million euros in total funding
- Established ITCC-P4 website (itccp4.eu) and LinkedIn account (ITCCP4)
- Informed consent established for majority of centers
- First internal PDX models ready for delivery
- Agreement with external centers for PDX models
- Nearing delivery of first two target actionability profiles
- SOP created for PDX development and testing
- Symposium September, 2018, the Netherlands
- Chairing (along w/PPTC) special topic session at AACR
- Enhanced version of the R2 informatics platform
Innovative Medicines Initiative – A Public-Private Partnership

The biggest public/private partnership in Life Science aiming to:

- Make drug R&D processes in Europe more innovative and efficient
- Enhance Europe’s competitiveness
- Address key societal challenges

Europe’s largest public-private life sciences initiative

- Speed development of medicines
- Academic-industry partnerships
- Industry-defined research projects

Our Budget – EFPIA budget €9 mio (IMI adds 7.5M) → €16.5 mio total
ITCC-P4: the developing platform

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

- 400 PDX models/5yrs; GEMMs
- Standard-of-care and targeted compound testing
- POC for immunotherapies in humanized models
- POC for organoids
Solid tumor types

- Ependymoma supratentorial (EPD_ST)
- Atypical teratoid/rhabdoid tumor (ATRT)
- High grade glioma other (HGGother)
- High grade glioma K27Mmut (HGG_K27M)
- Ependymoma infratentorial (EPD_IT)
- Medullobastoma WNT (WNT)
- Medullobastoma SHH (SHH)
- Medullobastoma Group3 (GR3)
- Medullobastoma Group4 (GR4)
- Synovial Sarcoma (SS)
- Neuroblastoma (NB)
- Ewing Sarcoma (ES)
- Osteosarcoma (OS)
- Malignant Peripheral Nerve Sheath Tumor
- Rhabdomyosarcoma (RMS)

DSRCT as capacity allows
Pilot target actionability review: RAS-MAPK (WP2)

| Target/pathway: RAS/RAF/MEK/ERK | Compound: Cotellic | Version Date: July 2017 | Author: |

Preclinical
1. Target status / patterns in clinical series
2. Tumor dependence on the target in vitro models
3. Tumor Dependence on the Target in vivo models
4. Compound** (Biological) Efficacy in Vitro Models
5. Compound*** (Biological) Efficacy in Vivo Models
6. Target-Efficacy relationship
7. Resistance Mechanisms
8. Combinations

Clinical
9. Safety of compound in children (phase 1 trials)
10. Efficacy in rel/refr. patients (phase 2 trials)
11. Efficacy in Standard-of-Care (phase 3 trials)

Appraisal scores:
- sufficient
- inconclusive ('needs more work')
- negative
- not tested

- Establish unified methodology
- Make extensive use of existing data
- Publish >4 target actionability reviews
PDX data sheet: clinical information (WP3)

Clinical Information

- **Med-211FH**

Model Information

- **Mouse strain**: NOD scid gamma (NSG)
- **Site of transplantation**: Cerebellum
- **Protocol**: Olson lab PDX protocol
- **Days to P0/P1/P2**: 60/60/60
- **PI**: James M. Olson
- **Contact**: Request model at www.litf.org

Molecular Information

- **Entity**: Medulloblastoma
- **Subgroup**: Group 3
- **Curated lesions**: MYC amplification, GFI1B activation [structural rearrangement + overexpression]
- **Detailed information**: Explore molecular data in PDK explorer
  - Explore genomic data of pediatric PDX cohort

Pathology of human tumor: H&E stained sections show a heterogeneous “small round blue cell” neoplasm. In many areas the cells have dense, hyperchromatic, irregularly shaped nuclei with scant amounts of light pink cytoplasm. There is moderate mitotic activity. Finally, the neoplasm is growing in sheets and small nests. Much of the tumor contains a rich neuropil background and ganglion cell differentiation is easily identified; occasionally binucleated ganglion cells are noted. Only very focal frank nodule formation is apparent. Immunoperoxidase staining for TH-1 shows diffuse nuclear expression. Some areas of the tumor have marked neuronal differentiation with easily identified ganglion cells. Neurofil is moderately abundant.
Drug Testing – Pool of potential test agents (WP5)

<table>
<thead>
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<th>Drug</th>
<th>Target</th>
<th>Small / Antibody</th>
<th>SOC (Generic Name)</th>
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<tr>
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<td>B-Raf</td>
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<td>Carboplatin</td>
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<td>Cisplatin</td>
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<td></td>
<td>SMO</td>
<td>small</td>
<td>Cyclophosphamide</td>
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<td></td>
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<td>Doxorubicin</td>
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<td>AKT</td>
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<tr>
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<td>Lomustine/CCNU</td>
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<td></td>
<td>PD-L1</td>
<td>antibody</td>
<td>Methotrexate</td>
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<td>Bayer</td>
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<td>Procarbazine</td>
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<td>Topotecan</td>
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<tr>
<td></td>
<td>FGFR</td>
<td>small</td>
<td>Trofosfamide</td>
<td></td>
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<tr>
<td></td>
<td>Lilly</td>
<td>CHK1</td>
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<td>Vincristine</td>
</tr>
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<td>ERK1</td>
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<tr>
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<tr>
<td></td>
<td>Pfizer</td>
<td>mTOR inhibitor</td>
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“Unshielded” targeted agents to be matched with genomically appropriate tumors

Cytotoxics represent current histology-specific SOC

RAS/MAPK for WPS Objective 3
Disease match (Table 8 DOA)
R2 informatics portal (WP6)

www.r2.amc.nl

R2: Genomics Analysis and Visualization Platform

PDX RECIST

OncoPrint Annotation Overview

N=1 Mouse Trial Data

Gene Expression/IC50 Correlation

J. Koster, AMC
Building a World-class PDX Browser (WP6)

<table>
<thead>
<tr>
<th>Explorer</th>
<th>MB</th>
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### 1. Patient
- **age:** 54
- **gender:** male
- **location:** cerebellum
- **diagnosis:** medulloblastoma, anaplastic large cell
- **presurgical:** none
- **treatment:** surgery
- **staging:** Treanment followed-up
- **wks:** months
- **mos:** months
- **consent:**

<table>
<thead>
<tr>
<th>1. patient</th>
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<tbody>
<tr>
<td><strong>pathology_of_human_tumor:</strong> nd</td>
</tr>
</tbody>
</table>

### 2. Model
- **mouse:** strain med med gamma (map)
- **site:** transplanted: cerebellum
- **protocol:** protocol
- **days:** 1 to 20 days
- **pct:** less:
- **cancer:**
- **contact:** [http://www.imi.org/product/med-113fh](http://www.imi.org/product/med-113fh/)

### 3. Molecular
- **entity:** medulloblastoma
- **subgroup:** sbb xth
- **curated:** lesions

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<tr>
<th>3. molecular</th>
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</table>

**GeneBrowser**
- **view:** [GeneBrowser](http://www.imi.org/product/med-113fh/)
- **plot:** [med-113fh-p1](http://www.imi.org/product/med-113fh-p1)
After IMI2 – Sustainability (WP7)

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

Principles:

- Address paediatric community needs: commercial activities for industry and accessibility for academia.
- Focus on \textit{in vivo} testing in, and \textit{not} the sale of, preclinical models.
- Secured access to data and models, providing fee-for-service and generation of data.
- Need assessment questionnaire – circulated to this audience.
INTERNATIONAL WORKSHOP: IMPROVING PEDIATRIC ONCOLOGY DRUG DEVELOPMENT THROUGH PRECLINICAL RESEARCH (WP4)  UTRECHT, Sept 27-28, 2018

Goal: To reach an international scientific consensus on the role and place of preclinical evaluation on pediatric tumor models to improve prioritisation and effectiveness of drug development for children and adolescents with cancer

Output: Published in a peer-review journal, serving as a basis for a guidance to be submitted to competent authorities for qualification

A multistakeholder meeting by invitation only

- ITCC-P4 members and International Academic experts in science, models and clinical development
- EFPIA experts from companies
- Observers from EMA, PDCO and FDA
- Representatives of parents organisations
Definition of the needs in the field and the specifications of the platform for both private and public research (WP7)

Two Questionnaires (Survey Monkey, <15 minutes):

Q1 to all EFPIA members
• Current activity,
• encountered limitations and hurdles,
• expectations and needs
Sent to Company Research Directors on February 14th

Q2 to the 23 ITCC research laboratories
Sent on February 14th
2018 Pediatric Cancer Working Group Special Scientific Session

Tuesday, April 17, 2018, 1:00 – 3:00 pm CT, Chicago Convention Center

Presentations from the NCI Pediatric Preclinical Testing Consortium and the Innovative Therapies for Children with Cancer (ITCC) Pediatric Preclinical Proof-of-Concept Program

An overview of the NCI Pediatric Preclinical Testing Consortium (PPTC) and the ITCC Pediatric Preclinical Proof-of-Concept Program (P4).

Additionally, leading members from both consortiums will present information on models within their platforms, the various agents being tested, and how these data can lead to potential opportunities for the development of new pediatric cancer therapies.
Strong leadership across academia and industry