

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

## ITCC-P4 International Workshop IMPROVING PEDIATRIC ONCOLOGY DRUG DEVELOPMENT THROUGH PRECLINICAL RESEARCH 2018

Louis Stancato, Lilly

On behalf of the ITCC-P4 Leadership Team:

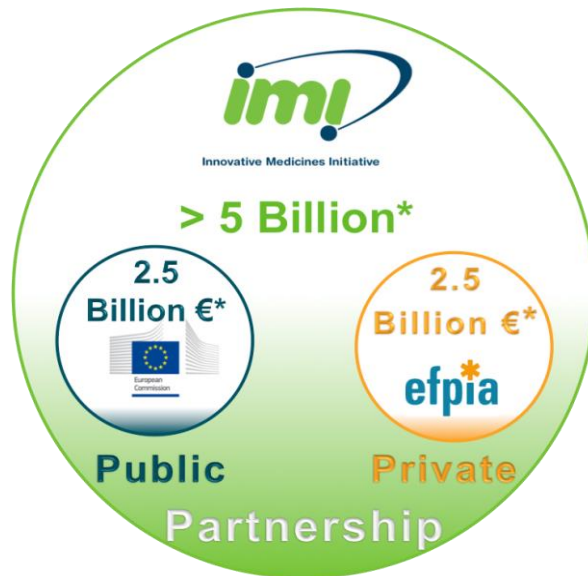
G. Vassal (IGR), H. Caron (Roche), S. Pfister (DKFZ/KiTZ)



# Innovative Medicines Initiative – A Public-Private Partnership



Innovative Medicines Initiative:  
*Joining Forces in the Healthcare Sector*



\* IMI 1+2  
2008-2020

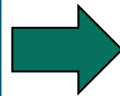
**EU's largest public/private  
partnership in life science:**

- **Speed** development of medicines
- Make drug R&D processes in EU more **innovative** and **efficient**
- Academic-industry **partnerships**
- **Industry**-defined research projects
- Enhance Europe's **competitiveness**



Budget – *EFPIA* budget €9 mio  
(IMI adds 7.5M) → €16.5 mio total

# ITCC-P4: the developing platform



## ITCC-P<sup>4</sup> Workflow

WP 1: Consortium management



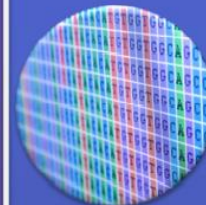
Systematic target prioritization/ actionability in pediatric solid tumors

WP2



Model development including alternative models

WP3A



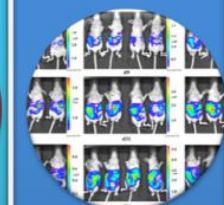
Model characterization including cross-species

WP3B



Regulatory preclinical consensus

WP4



Preclinical drug testing *in vitro* and *in vivo*

WP5

WP 6: Information management and data analysis

WP 7: Sustainability and contractual management

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

# After IMI2 – Sustainability

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

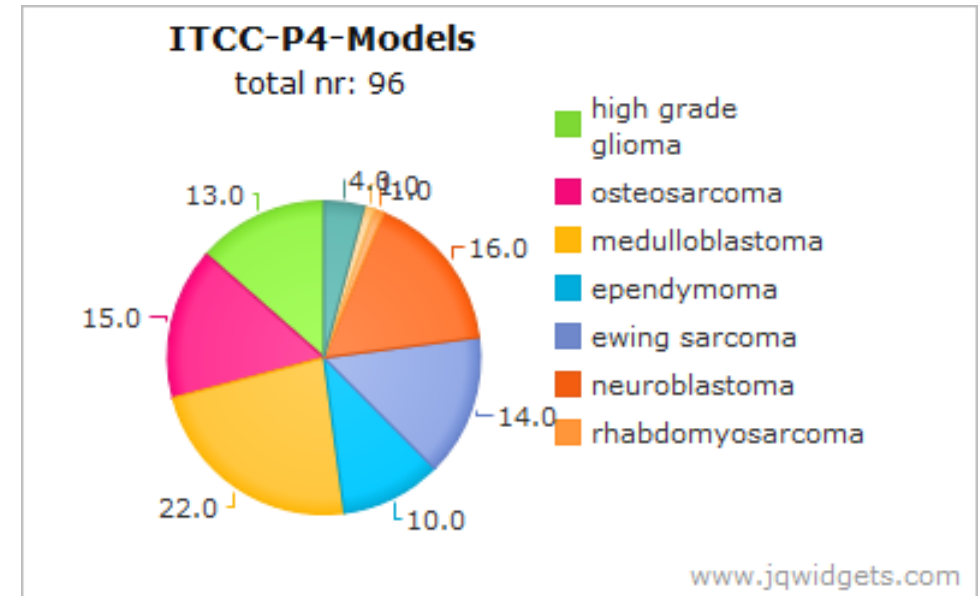
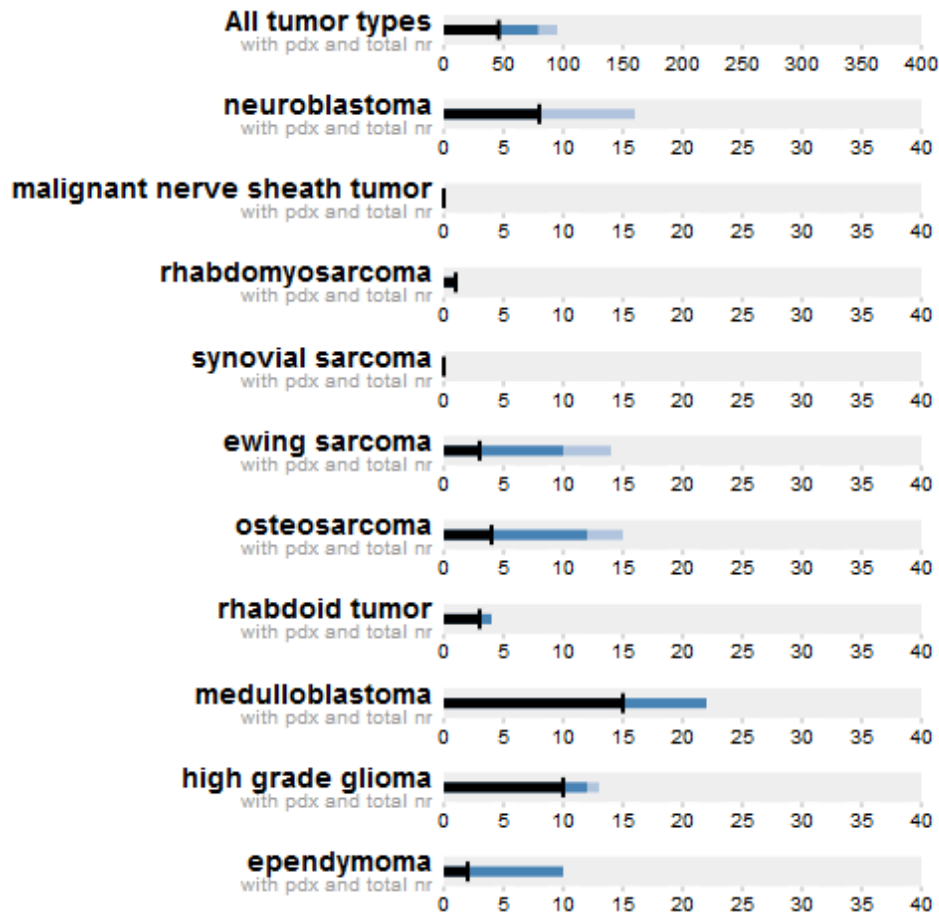
## Principles:

- Address entire paediatric community needs: commercial activities for industry and accessibility for academia
- Focus on *in vivo* testing in preclinical models
- Secured access to data and models, providing fee-for-service and generation of data

# Progress to Date

- Model development underway (~100 by Q1 '19)
- Target Actionability methodology developed (first consortium manuscript)
- Compounds identified for Q1/'19 efficacy testing
- This symposium (and growing relationship w/PPTC)

# The Growing PDX Library – Models entered in R2



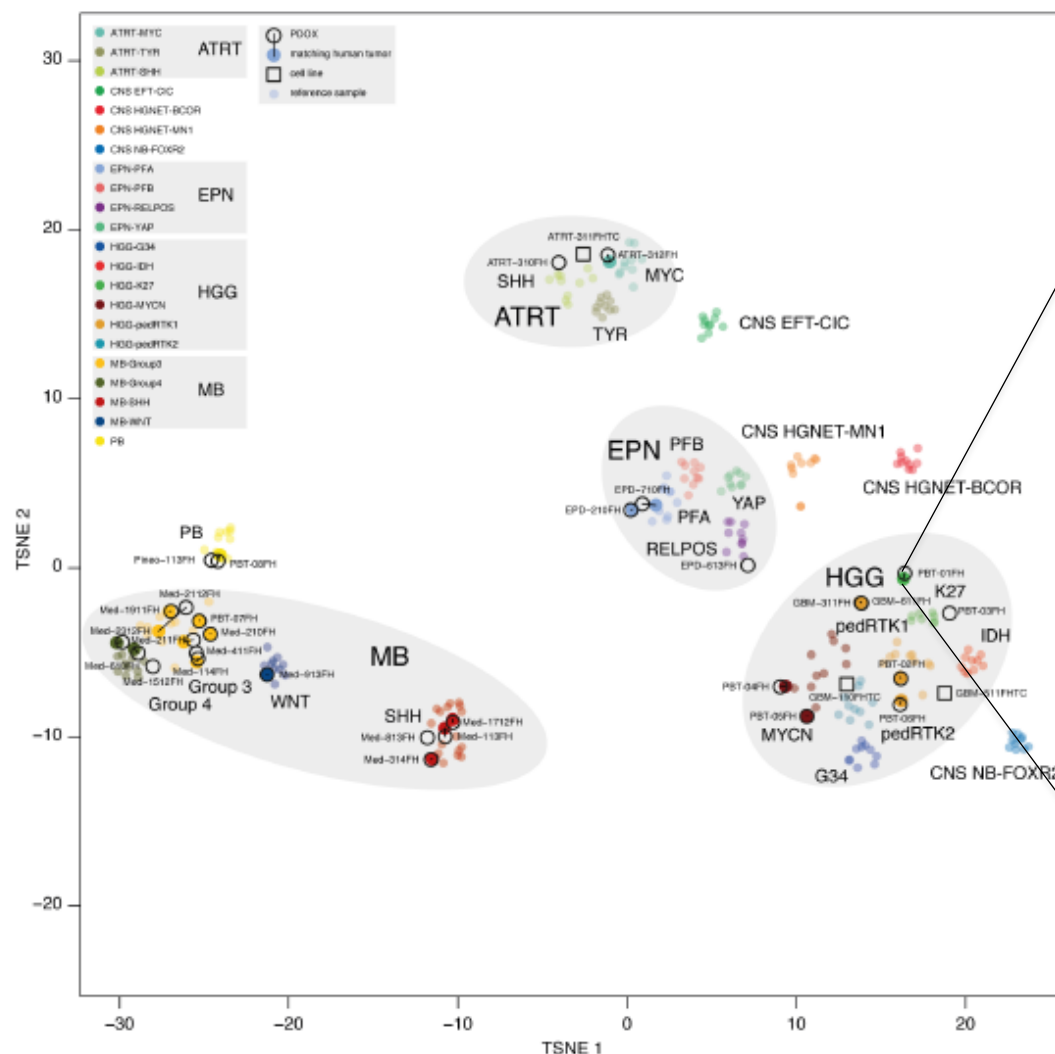
Total **96 entries** in database,  
including **80 PDX** entries,  
**46** of these are established PDX  
models

# Current overview of models established

Established models	Total	Internal	Not yet in R2 database					
		R2 barcoding	Seattle	Australia	IGR	Curie*	Barcelona*	Zurich*
<b>All</b>	<b>168</b>	<b>46</b>	<b>6</b>	<b>31</b>	<b>27</b>	<b>31</b>	<b>22</b>	<b>5</b>
Neuroblastoma	21	8	1	7	3	3	4	0
Malignant Nerve Sheath Tumor	4	0	0	0	0	3	1	0
Rhabdomyosarcoma	22	1	0	2	10	6	4	3
Synovial Sarcoma	0	0	0	0	0	0	0	0
Ewing Sarcoma	16	3	0	2	3	7	10	0
Osteosarcoma	22	4	0	2	5	6	2	2
Rhabdoid Tumor	8	3	0	0	1	3	1	0
Medulloblastoma	20	15	3	2	0	0	0	0
High-Grade Glioma	27	10	0	13	4	0	0	0
Ependymoma	7	2	1	1	1	2	0	0
Unknown (e.g. just "sarcoma")	3	0	1	2	0	0	0	0

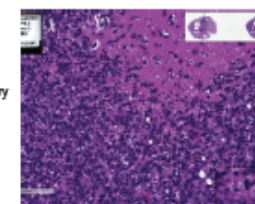


# R2 data sharing, analysis and visualization platform



**PBT-01FH**  
Altamira IDs: Astro-110FH

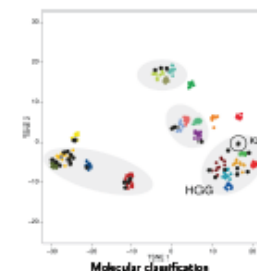
**Clinical annotation:**  
Age: 5  
Gender: Female  
Location: Cortex, bilateral thalamic  
Diagnosis: Anaplastic Astrocytoma (WHO Grade III) at autopsy, Fibrillary Astrocytoma (WHO Grade II) at initial biopsy  
Pre-treatment: Radiation and chemotherapy  
Source: Recurrent, autopsy  
Stage: Localized  
EFS (months): 2.4 from diagnosis  
OS (months): 14.4 from diagnosis



**Pathology of human tumor.** From autopsy: The numerous mitotic figures and hypercellularity of the astrocytes seen at autopsy help to reclassify this tumor as a WHO grade III lesion. Some areas appear similar to the biopsy specimen, and have lower cellularity and only rare mitoses, but the majority of the lesion is higher grade. Areas of necrosis are present, which are possibly related to the patient's therapy. Definite vascular proliferation, which could indicate a higher grade neoplasm, is not identified. From initial diagnosis: Sections demonstrate a moderately cellular tumor composed of uniform fibrillary astrocytes with long cell processes which infiltrate around neurons. The tumor cells have irregular hyperchromatic nuclei without mitotic activity. They stain intensely for GFAP. The stroma is microcystic with scattered normal neurons, highlighted by Huch Immunostain. Necrosis or vascular proliferation is not present. Ki67 stains ~2% of the tumor cells.

**Model information:**  
Mouse strain: NOD scid gamma (NSG)  
Site of transplantation: Cortex  
Protocol: Olson lab POX protocol  
Days to P0/P1/P2: 116/89/89  
PI: James M. Olson  
Contact: <http://www.bcrf.org>

**Molecular information:**  
Entity: High-grade glioma  
Subgroup: K27  
Curated lesions: HIST1H3B K27M mutation  
Detailed information: [r2.amc.nl](http://r2.amc.nl)



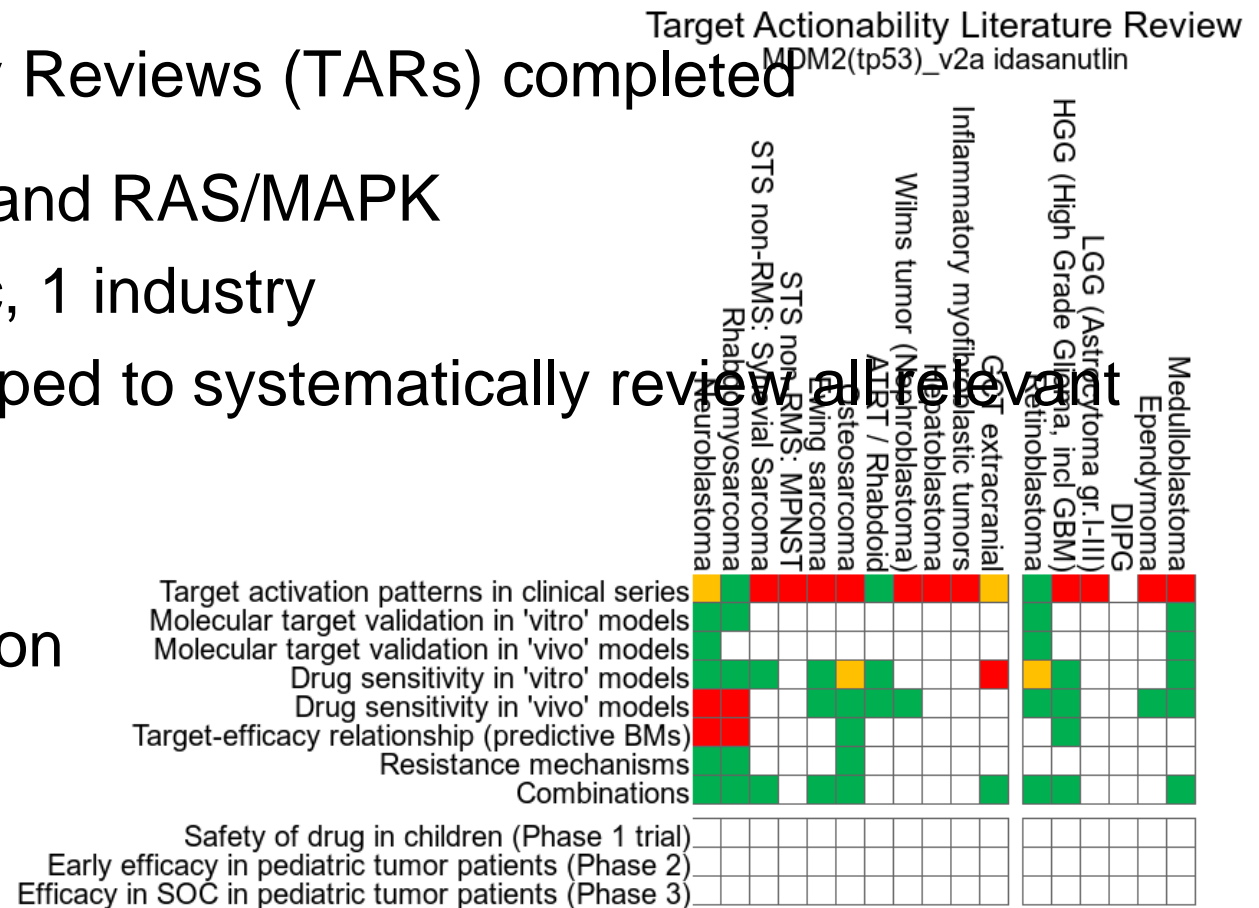
Brabetz et al. *Nature Medicine* 2018, in press



# Target Actionability in pediatric cancers

## Two pilot Target Actionability Reviews (TARs) completed

- Pathways: p53/MDM2 and RAS/MAPK
- Reviewers: 2 academic, 1 industry
- Scoring method developed to systematically review all relevant literature
- Uploaded to R2
- Manuscript in preparation



Schubert, Bergthold, Eleveld, Rodriguez, Koster, Molenaar, Caron  
Roche, Lilly, AMC, Prinses Maxima Centrum

# Drug Testing – Pool of test agents

platform tumor indications	SoC 1	SoC 2	SoC 3	two-SoC combination	ID 1	ID 2	ID 3	ID 4	ID 5	ID 6
Medulloblastoma (MB)	E	CPA	L	CP + E	Src-I	BET/Brd4	CHK1	CDK4/6	Akt-I	TGFBi
High Grade Glioma (HGG) (including DIPG)	TZ	L	RT	TZ + RT	MEK-I	PI3K-I	BET/Brd4	AKT-I	ERK1	CHK1
Ependymoma (EPN)	RT	CPA	AD	RT + CP	MDM2-I	PI3K-I #1	AKT-I	CDK4/6	FGFRi	PI3K-I #2
Atypical Teratoid / Rhabdoid Tumor (ATRT)	DR	CP	E	DR + CPA	CDK4/6i	SMOi	FGFR-I	MKI1	AKT-I	MKI2
Neuroblastoma (NB)	CPA	E	TT	CPA + CP	MDM2-I	BET/BRD4	CHK1	MEK-I	ALK	PI3K
Rhabdomyosarcoma (RMS)	VC	TF	ID	AD + VC	MEK-I	FGFR-I	Regorafenib	ALK-I	CDK4/6	AKT-I
Non-RMS soft tissue sarcoma	E	ID	TF	AD + VC	MEK-I	FGFR1	BET/Brd4	MTOR	ALKi	CDK4/6
Osteosarcoma (OS)	DR	RT	CIP	DR + M	FGFR-I	MDM2-I	Regorafenib	CDK4/6	Bevacizumab	
Ewing sarcoma (EWS)	DR	VC	AD	DR + CPA	Regorafenib	BET/Brd4	PI3K-I	CDK4/6	MDM2	FGFR-I
all GEMMs	entity-specific SoC drugs				Immune checkpoint inhibitor					

- “Unshielded” targeted agents matched with genomically appropriate tumors (utilizing e.g., target actionability reviews)
- Cytotoxics, radiotherapy and combinations thereof represent current histology-specific SOC