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

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

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http://www.imi.europa.eu/ - http://www.itccp4.eu

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**

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

ITCC-P4: the developing platform

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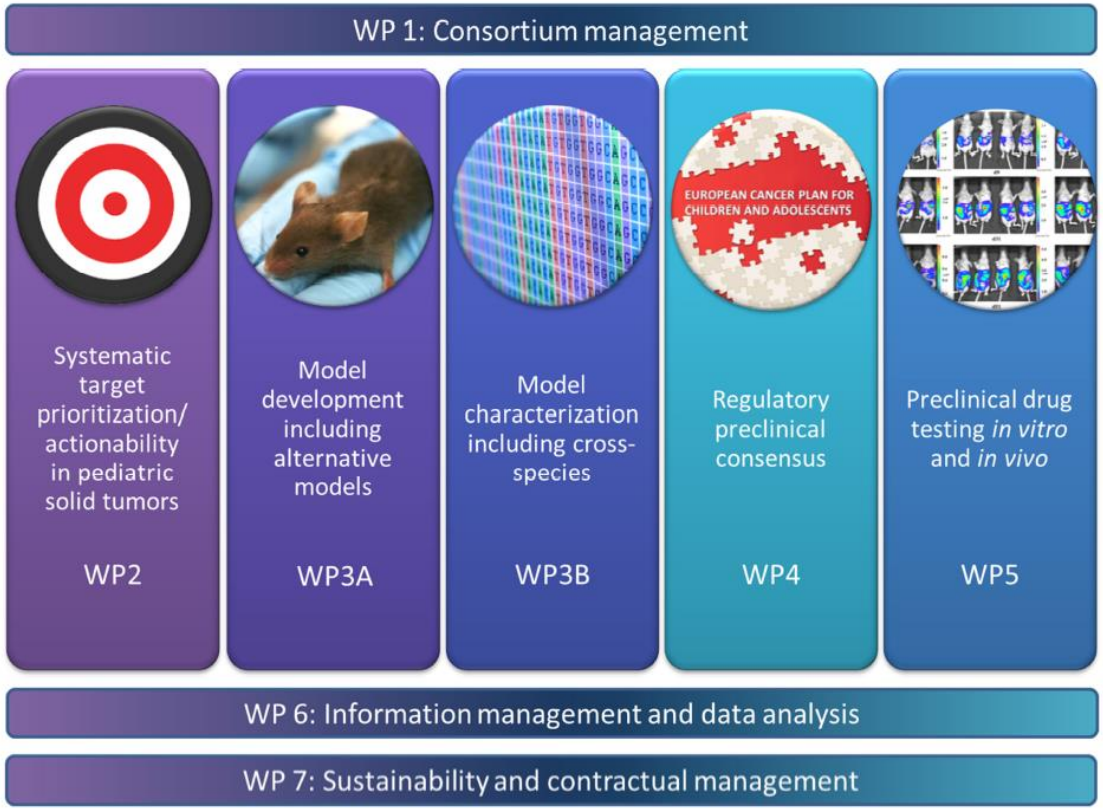
ITCC-P4 Workflow



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

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After IMI2 – Sustainability

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

<u>Principles:</u>

- 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

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Progress to Date

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- 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)

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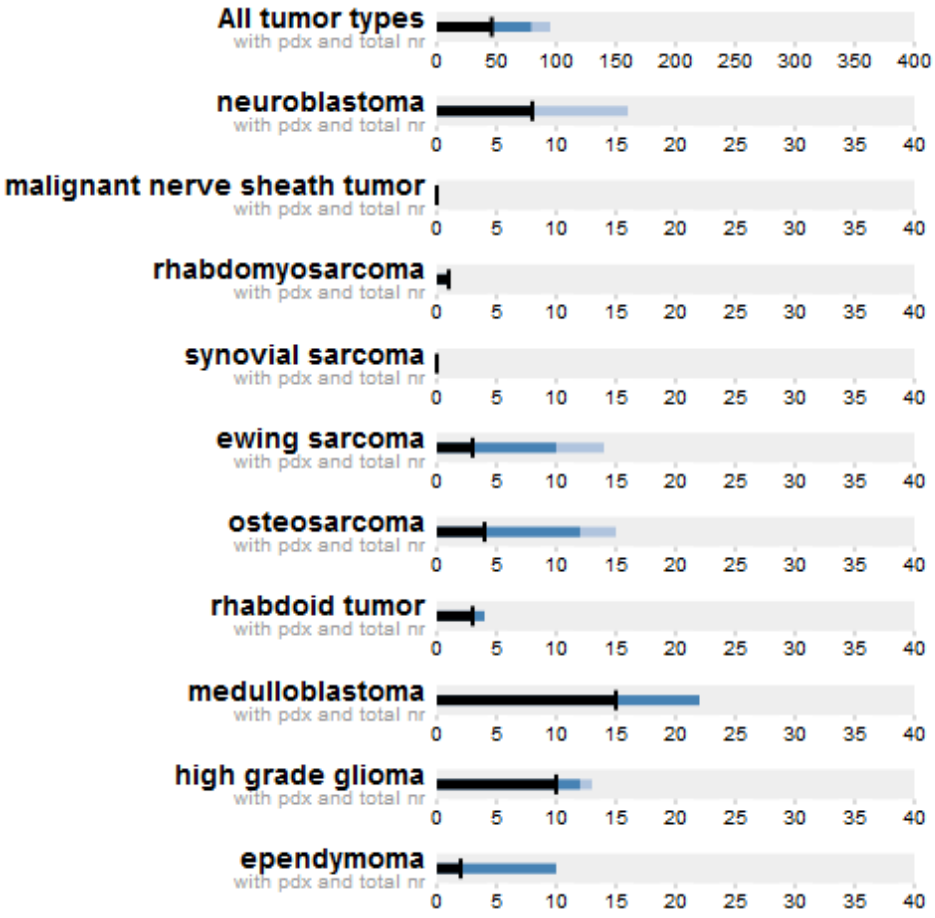
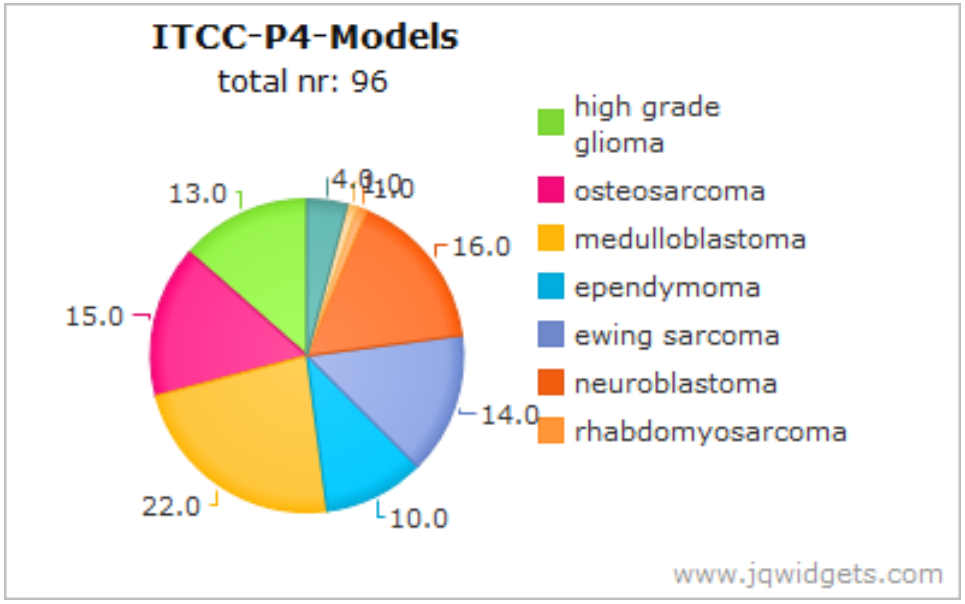
The Growing PDX Library – Models entered in R2





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

Current overview of models established

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Established models	Total	Internal R2 barcoding	Not yet in R2 database					
			Seattle	Australia	IGR	Curie*	Barcelona*	Zurich*
All	**168**	**46**	**6**	**31**	**27**	**31**	**22**	**5**
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

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R2 data sharing, analysis and visualization platform

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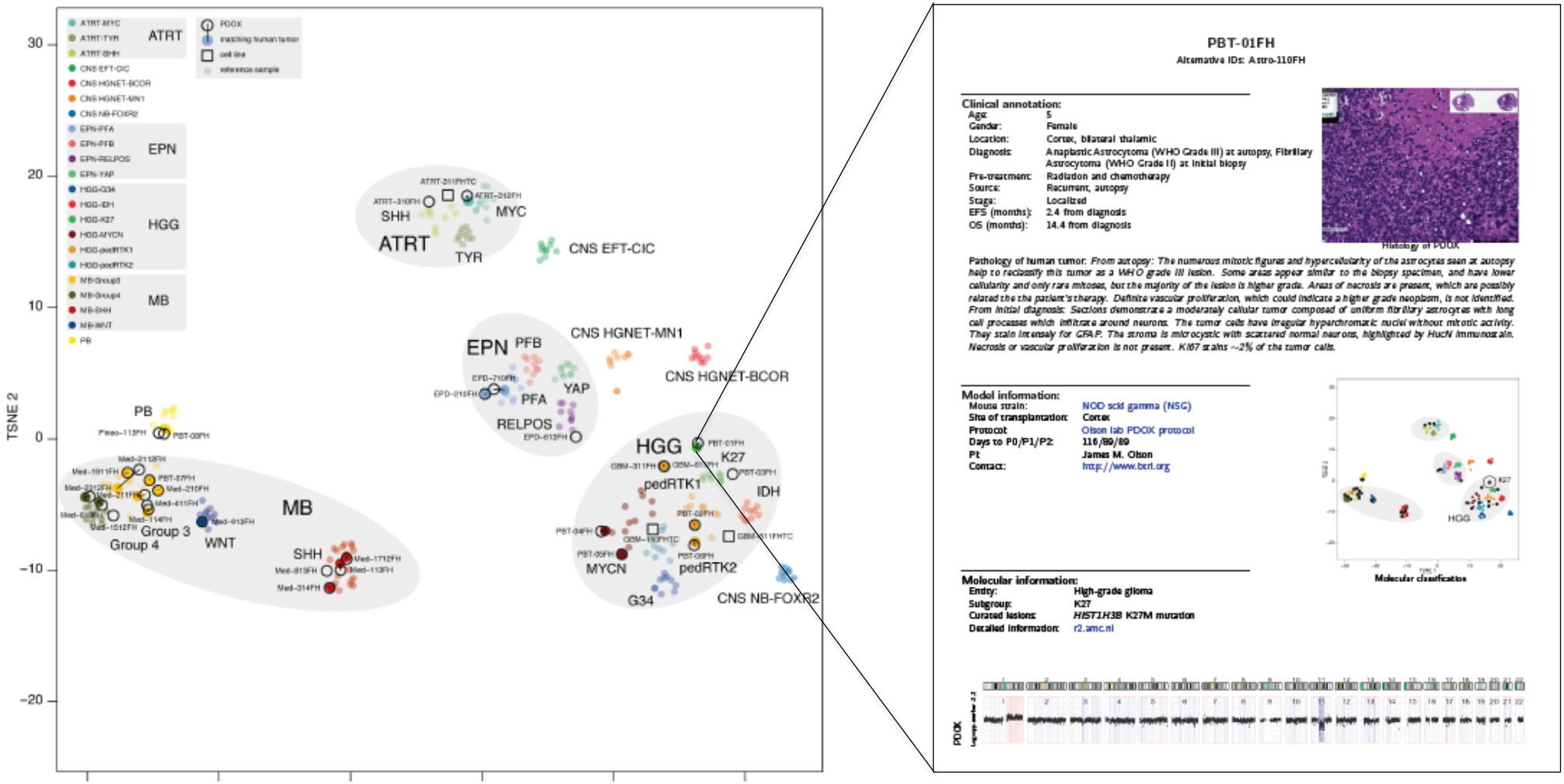

Brabetz et al. *Nature Medicine 2018, in press*

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Target Actionability in pediatric cancers

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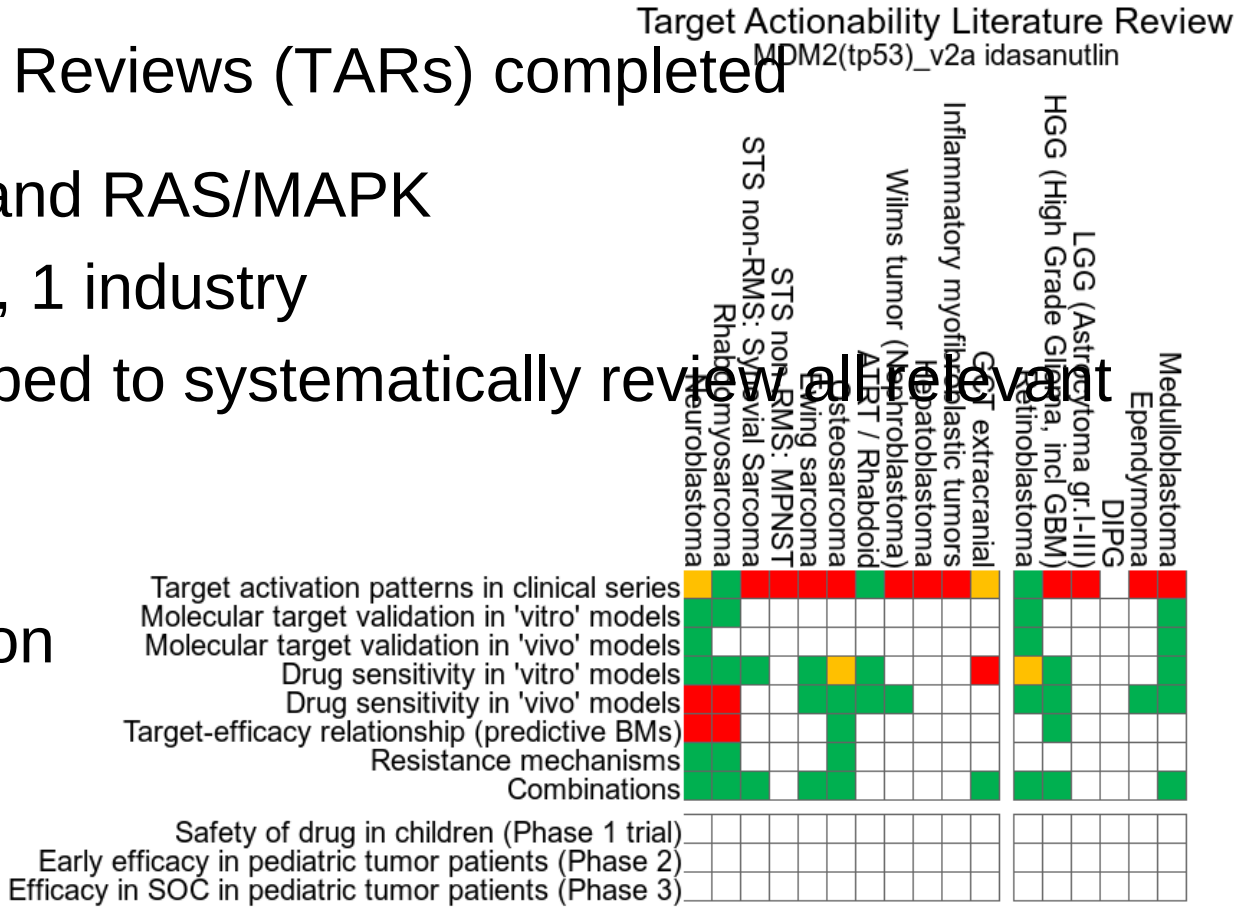
Two pilot Target Actionability Reviews (TARs) completed

- 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

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Drug Testing – Pool of test agents

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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 chekpoint 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

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