Where do our therapeutics come from?

ITCC Educational Days
October 15th, 2018

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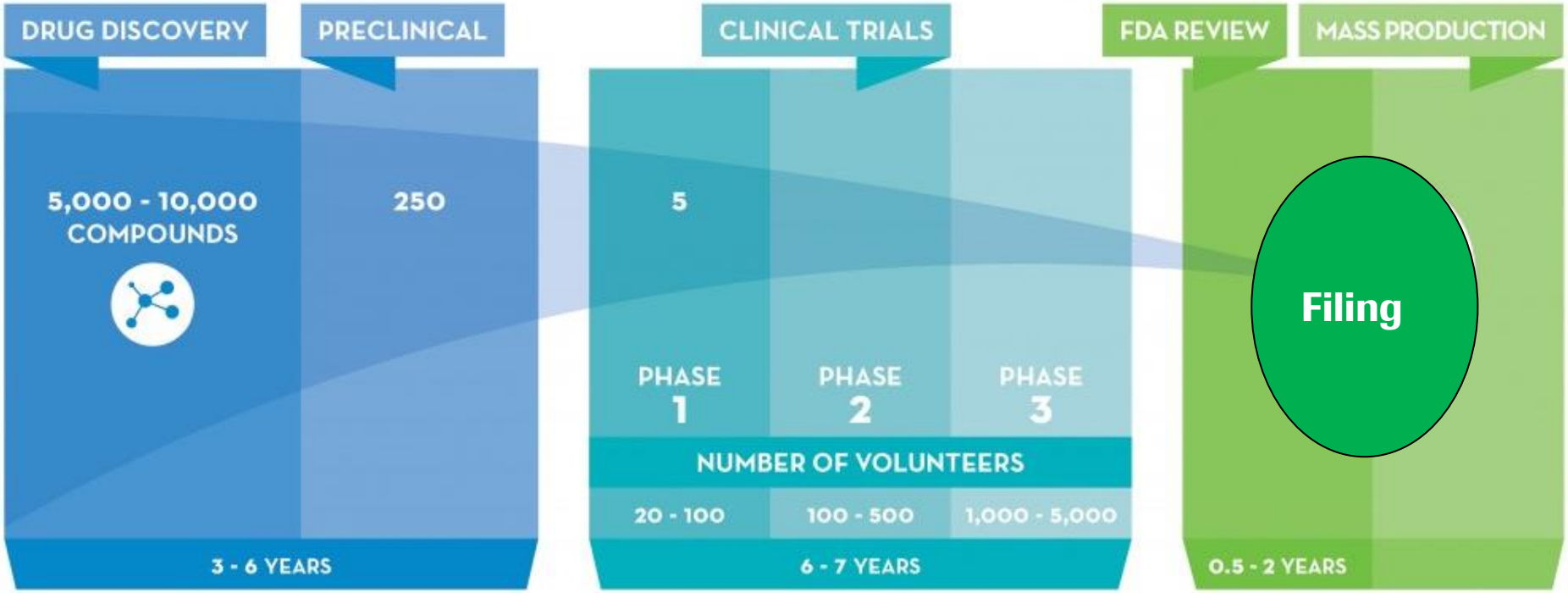
Disclaimer

I am a Roche employee and I will not discuss off-label use of investigational agents.

The views in this presentation are my own and do not necessarily reflect the position of Roche-Genentech

The actors in drug development

The steps of drug development
From discovery to filing



~10-15 years average from discovery to filing

Source: 2015 WFSJ

The classical process of adult drug development and obligations

- Regulations in EU and US oblige pharma companies to have a pediatric development plan agreed by HAs for each drug in adult development before filing a market application authorization
- compliance to the pediatric plan is then checked with EVERY subsequent interaction
- sponsors get waiver to develop in children only if the adult indication has no equivalent in children (*automatic class-waiver list*)
- compliance to an agreed pediatric plan entitles the Sponsor for a 6-month Supplemental Patent Certificate (EU) or Data Exclusivity (US) **even if the results of the pediatric clinical trial are negative**

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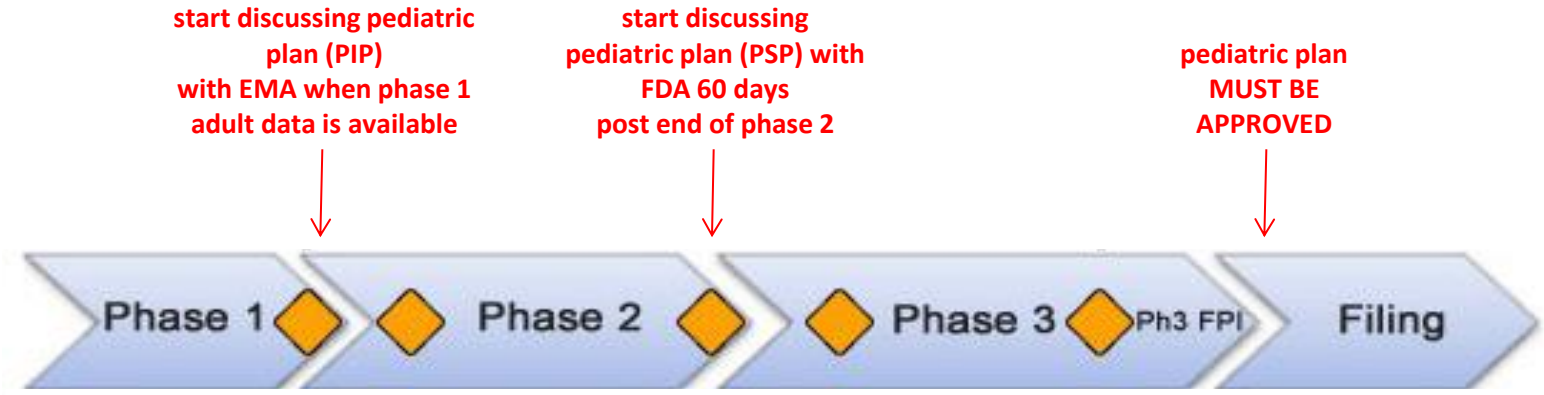

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Children with Cancer Do Not Have Timely Access to Safe and Efficacious Drugs

- **US Experience:** 466 pediatric labeling changes for drugs and biologics (1998-2012)
  - **Only 15 labeling changes (4 approvals) in oncology**[1]
- **EU Experience:** MAA for 28 new oncology drugs (2007-2012)
  - **26 with a potentially relevant pediatric MOA**, **however only 4 drugs are approved for use in children**[2]
- **Ongoing Development Programs**[3]**:** 551 oncology agents in phase 2/3 development globally (May 2014)
  - **Only 53 (<10%) of these agents have ongoing pediatric studies**
- **Key Issues:**
  - Regulations often interpreted as emphasizing **adult indications that also occur in children**
  - Diseases that represent **unmet need in pediatric cancer substantially different than those in adults**
  - **revision of the class-waiver system in EU +/- US will greatly increase the number of pediatric programs, thus the need for prioritization across portfolios**

[1] Pediatric Oncology Subcommittee of ODAC, FDA Briefing Document November 4, 2013
[2] Gilles Vassal, Birgit Geoerger and Bruce Morland, Clin Cancer Res 2013;19:1315-1325. Published OnlineFirst January 17, 2013.
[3] Pharmaceutical Research and Manufacturers of America, NIH (www.clinicaltrials.gov), corporate websites and databases of HemOnc Today

Paradigm shifts are urgently needed in pediatric drug development

Isolated development		**Harmonized across industry**
Reactive, late		**Proactive, early**
“Stick and carrot”		**Pediatric-centric**
Molecule-based		**Mechanistic, biomarker-based in disease and molecule context**

Developing the Roche pipeline for children with cancer

Pediatric-centric, MOA-based

Our Vision

- Provide children with unmet medical needs with innovative, safe, life-saving therapies

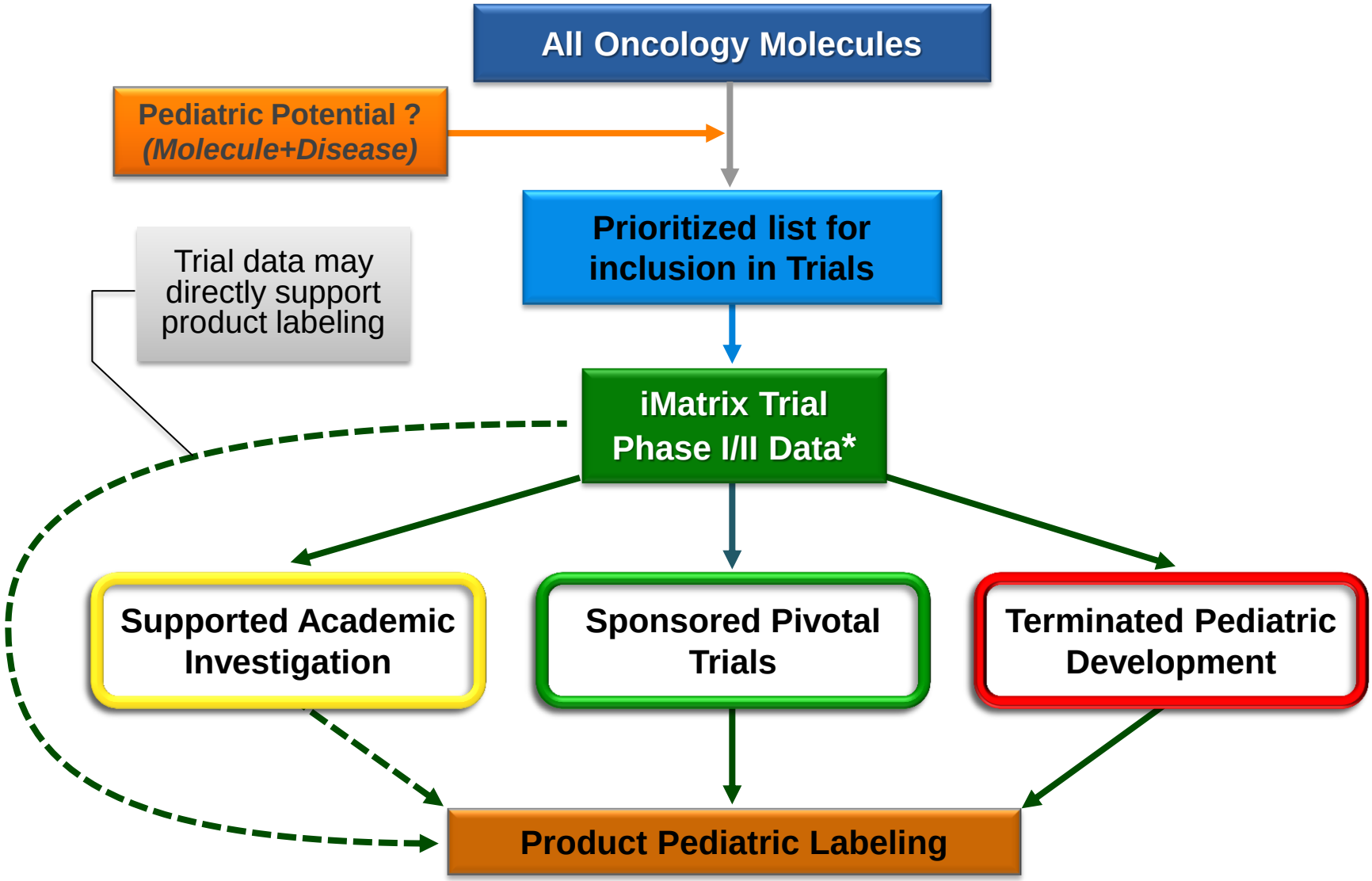
Our Missions

- Ensure **early access** to drugs for children with high unmet medical needs
- Improve pediatric patient care through **pediatric product labeling**
- Fulfill pediatric regulatory obligations to **timely registrations in adults**

Our Actions

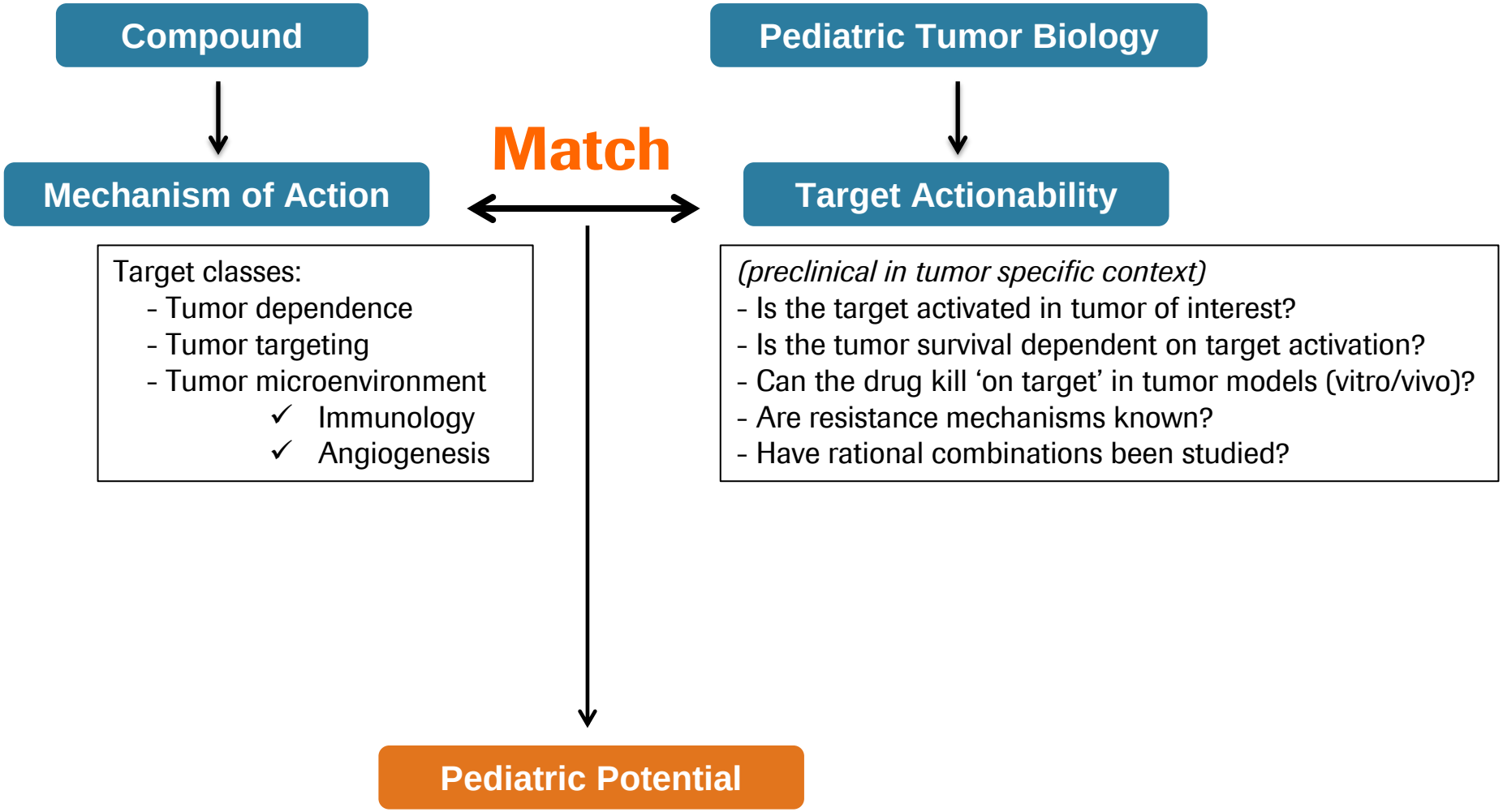
- Voluntary development of the Roche pipeline for children with cancer
- MOA-based, science-driven, multi-stakeholder collaborations

The Roche approach to drug development for children with cancer



*Safety, PK, Preliminary Efficacy

Matching Molecule MOA with Pediatric Tumor Biology



Target actionability assessement
Preclinical proof-of-concept program

- Generate target actionability reviews
- Assess ‘in silico’ target patterns in pediatric clinical series
- Proof-of-concept experiments with academic collaborators

iPODD preclinical proof-of-concept program

- **Generate target actionability reviews**
- Assess ‘in silico’ target patterns in pediatric clinical series
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Target Actionability: Pre-clinical 'Proof-of-Concept'

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Target status in clinical series/subsets	- *DNA mutations, copy numbers* - *(over)expression* - *Tissue arrays*
↓	
Target validation *'tumor-dependence'*	- *gene mutations/transl/amplif* - *RNAi* - *functional assays*
↓	
In vitro efficacy of targeted drug	- *Cell lines (MTT assays)* - *'on target efficacy' (PD assays)*
↓	
In vivo efficacy of targeted drug	- *Xenografts / GEMMs / others* - *'on target' efficacy (PD assays)*
↓	
Biomarkers	- *'predictive': target status, patient selection* - *'efficacy': biological readout of target inhibition*
↓	
Resistance mechanisms	- mutations, pathway switching, - drug pumps
↓	
Rational combinations	- *targeted + targeted* - *targeted + cytotoxic*

Innovative Therapies for Children with Cancer ITCC European Consortium

encca

Systematic Reviews of (pediatric) 'Target Actionability'

- Scientific pediatric literature
- Sensitive search strategies

- Summarize each paper

- Score on completeness
- Score on experimental quality+quantity

- Summarize in graphic heatmap

Target heatmap overview for BETi

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Target/pathway: BRD2,3,4, Version Date: 13/04/2017, Author: H. Caron, G.Bergthold

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

		Solid tumors											Brain tumors							Hematology										
		NEUROBLASTOMA	RMS	Non-RMS sarcomas	NUT-carcinoma	EWING sarcoma	OSTEOSARCOMA	Rhabdoid tumors (extra-cr.)	Wilms tumors	Hepatoblastoma	Inflammatory myof. tumors	GCT extracranial	ATRT	Retinoblastoma	HGG / GBM	LGG (Astrocytoma gr.I-II)	DIPG	Ependymoma	Medulloblastoma	AML	JMML	T-ALL	B-cell precursor ALL	MLL-ALL	Mature B-ALL	BL (Burkitt's)	DLBCL	ALCL	HD (Hodgkin's)	LCH
PRECLINICAL																														
1. Target status / patterns in clinical serie	BRD																													
	MYC(N)																													
	Hh-GLI																													
	BCL2																													
	CCND1/CDK4-6																													
	BRD4-BRD3 targets identified	MYC, BCL2,		Cyclin D1, BIM	NUT-BRD4	EWS-FLI	RUNX2, FOSL1,								hTERT, BCL-2,				MYC, GLI1,GLI2											
2. Molecular target validation (*in vitro*)																														
3. Molecular target validation (*in vivo*)																														
4. Compound efficacy (*in vitro*)																														
5. Compound POC (*in vivo*)																														
6. Biomarker (predictive)																														
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)																														

iPODD preclinical proof-of-concept program

- Generate target actionability reviews
- **Assess ‘in silico’ target patterns in pediatric clinical series**
- Proof-of-concept experiments with academic collaborators

‘In Silico’ Target Patterns in Pediatric Clinical Series

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- **Pediatric only**
  - TARGET (NCI)
  - PCGP (St Jude)
  - Inform (DKFZ)

  Expression, rearrangements, CNV, mutations

- **Adult & Pediatric**
  - Foundation Medicine — *Rearrangements, CNV, mutations*
  - cBioportal (MSKCC) — *Expression, CNV, mutations*
  - R2 (AMC Amsterdam) — *Expression, Methylation*

Francesca Milletti, pRED-Informatics, Roche
Katie Hutchinson, OBD, Genentech
Ana Gonzalez, iPODD, Roche

Exemples of Systematic Target Actionability Reviews and 'in silico' analyses completed

Molecule	Target (Pathway)	Target Review	No. Papers reviewed
Zelboraf	BRAF	Yes	56
Cotellic	MEK		
Atezolizumab	PD1-PDL1/2	Yes	12
Erivedge	Shh-SMO-GLI	Yes	27
Idasanutlin	MDM2-p53	Yes	135
Venetoclax	BCL2	Yes	44
Polatuzumab	CD79b	Yes	8
Taselisib	PI3K	Yes	151
Ipatasertib	AKT		
Alectinib	ALK	Yes	24
LSD1	LSD1	Yes	16
BETi	BRD4	Yes	40
FAP-IL2	CD20	ongoing	72
FAP-4-1BBL	ANG2-VEGFA	ongoing	

iPODD preclinical proof-of-concept program

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Preclinical Proof-of-Concept Molecule Testing in Pediatric Models

Leveraging Roche adult+pediatric knowledge and academic disease expertise

iPODD
(Pediatric Molecule experts)

Adult team
(Molecule experts)

Proof-of-Concept datasets
(disease specific)

Academia
Preclinical Disease Expertise

- Clinical sample series
- Vitro models
- Vivo models
- Resistance mechanisms
- Combinations

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Spanning the Pediatric Tumor Spectrum in Collaboration with Leading Pediatric Academic Centers

Building and maintaining the projects requires dedicated resources & collaborations

iPODD Pediatric Developability Assessment

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Regulatory

- ....
- .....
- .....

- Regulatory Obligations

Obligations	Future Obligation likely
Time to 1st filing	<1 year
Opportunity for US LOE extension	Unknown

Molecule Feasibility

- .....
- .....
- .....
- .....

- Molecule characteristics:
  - Safety
  - PK + Formulation
  - MOA-based rationale for PEDS
  - Biomarkers
  - Single / combo ?

MOA	Well-understood MOA and/or clear target population
Biomarker	BM under evaluation
Safety	Limited safety info available and/or potential pediatric safety concerns
Formulation feasibility	Requires development

Clinical Feasibility

- .....
- .....
- .....

- Clinical feasibility:
  - Unmet need & prevalence
  - Perceived efficacy
  - Other molecules in class

Pediatric incidence & prevalence	Medium
Perceived improvement over SOC	Low
Competing programs in class	2-3 drugs

Business

- .....
- .....

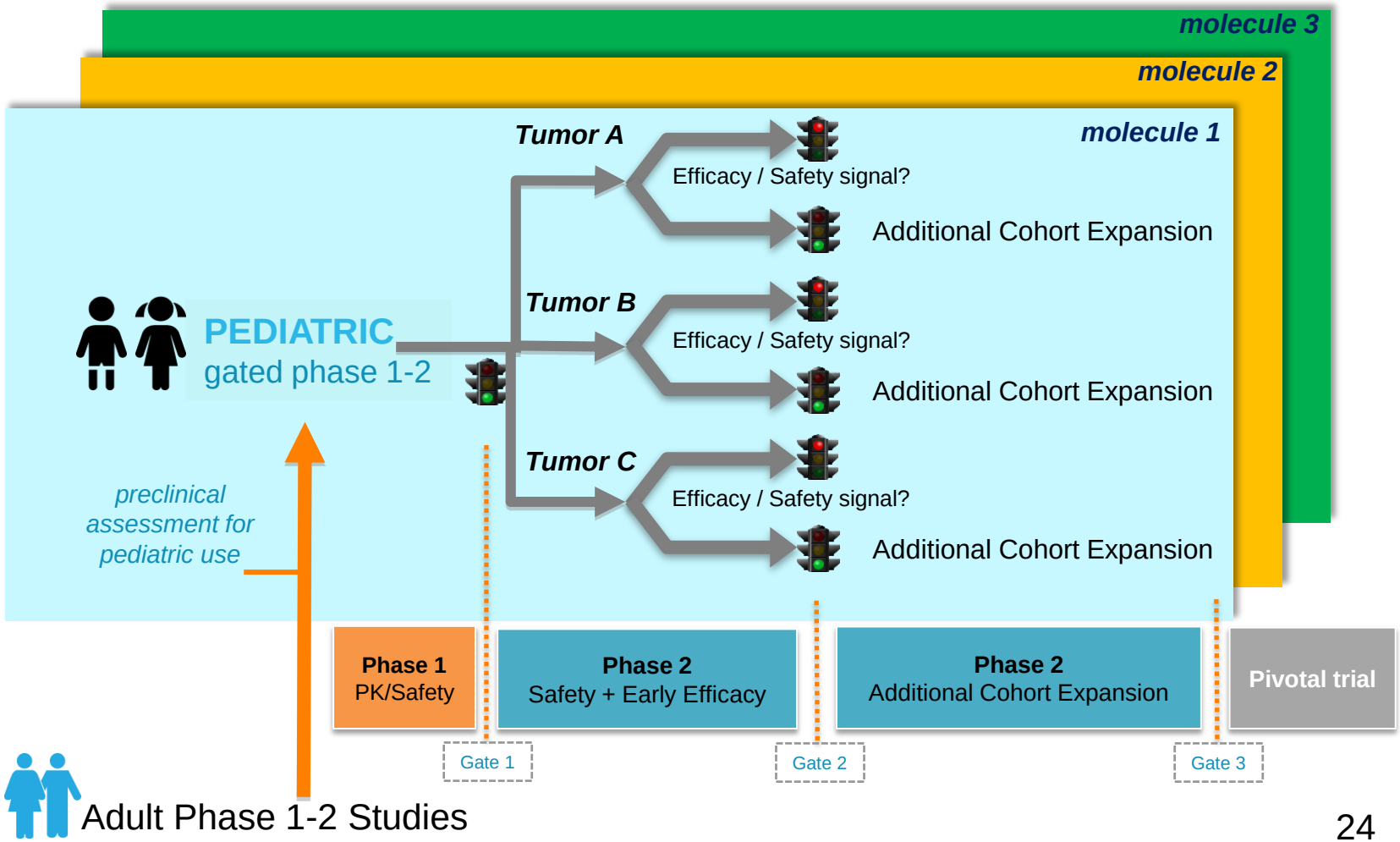
- Regulatory incentives

Estimated value of 6-month LOE extension	

The iMATRIX trial concept

MOA-driven, gated for safety+early efficacy, across diseases, multi-molecule

An innovative **pediatric** oncology clinical trial platform to **investigate several drugs in multiple tumor types**
Parallel molecule arms**, including combinations,** Adolescent+young adults included **age: 0 – 30 yrs**
Endpoints are **safety, dose-finding and early signal seeking**



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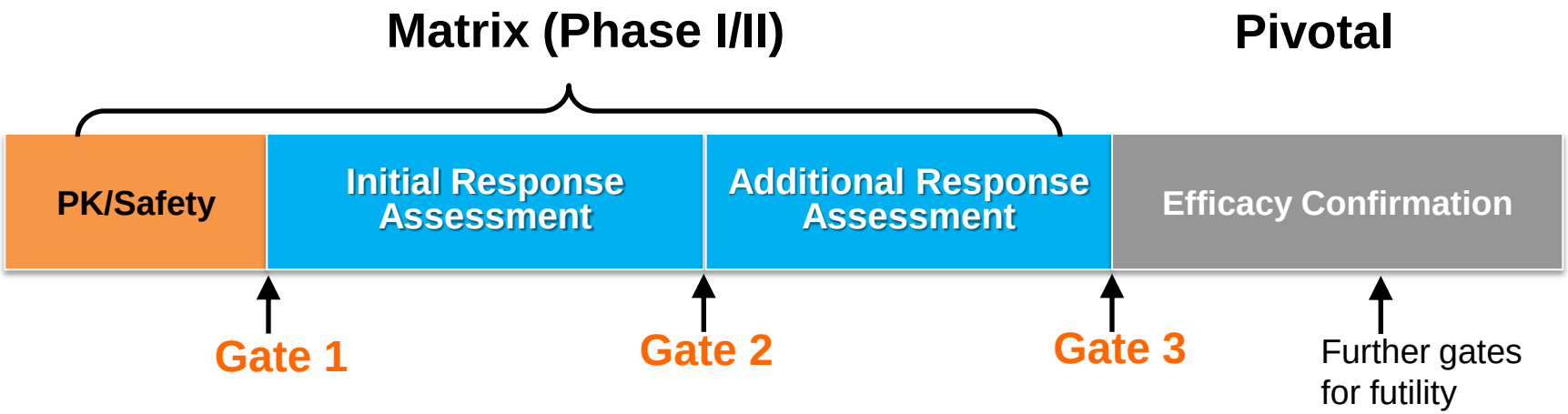
iMATRIX: Current Experience



Investigational sites:	46 sites (ITCC, EU), 10 sites (POETIC, US)
Active molecules:	Atezolizumab FPI Q4 2015, **90 patients recruited, closed for recruitment (LPI Oct 2017)** Cobimetinib FPI Q2 2016, **53 patients recruited** Entrectinib FPI Q2 2016, **28 patients recruited**
In development:	Idasanutlin (MDM2) – FPI – Q2-3 2019
Next Compounds:	Ipatasertib (AKT) Venetoclax (BCL2) (Abbvie), anti-CD20 TCB?, FAP-IL2?, BETi?

iMatrix atezolizumab: Efficacy data review by cohort

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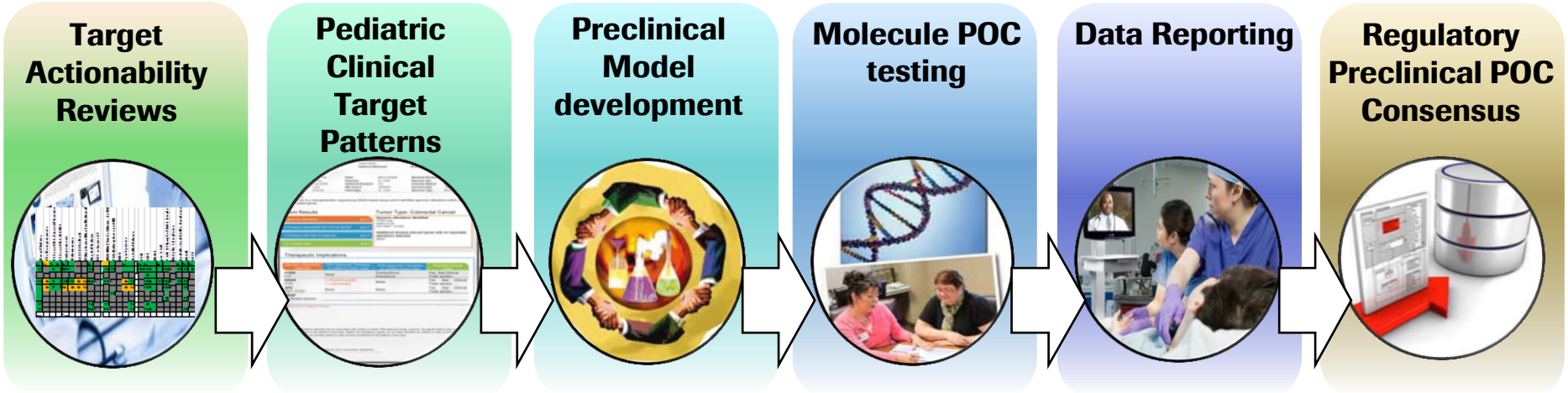
Cohort	Enrolled	Status	Best Overall Response	Gate 2 Criteria
EWS	11	Closed	9 PD - 2 SD	2/10
NB	11	Closed	6 PD - 4 SD – 1 NE	3/10
NRSTS	10	Closed	7 PD - 1 PR - 1 NE 1 Missing*	2/10
OS	12	Closed	10 PD 2 pt. never dosed	3/10
RMS	10	Closed	9 PD 1 Missing*	2/10
WT	10	Closed	7 PD - 1 SD - 2 Missing	2/10
PD-L1+	4	Closed	3 PD 1 Missing*	N/A
PD-L1-	5	Closed	3 PD – 1SD - 1 pt. not dosed	N/A
HL	9	Closed	5 PD - 2 PR - 2 SD	10/14
NHL	3	Closed	1 PR – 1 PD – 1 Missing	6/12
RT	2	Closed	1 PD - 1 Missing*	1/6
ATRT	3	Closed	2 PD – 1 Missing*	1/6

IMI2 ITCC p4 'Pediatric Preclinical POC Platform'

....to Enable Clinical Molecule Development for Children with Cancer



AIM: - preclinical drug evaluation; across pharma; HA-qualified

SET-UP:
- 10 high-risk solid tumors of childhood
- Mouse model platform (>400 PDX + >50 GEMM + Immuno-models)
- Matching organoïd cell cultures and original tumor sample
- Integrated database of 'clinical series'

STRUCTURE: - pre-competitive pharma + academic consortium

PARTNERS:
- Roche, Eli-Lilly (co-leads), Bayer, Pfizer, Pharmamar
- ITCC academic consortium

BUDGET:
- Pharma: €7'500'000 in kind
- Academia: €7'500'000 from IMI2

Where do our therapeutics come from?

- **Pharma in collaboration with academia**
- Assess:

1- Molecule characteristics
- Safety
- PK + Formulation
- MOA match PEDS
- Biomarkers
- Single / combo ?

2- Clinical feasibility
- Unmet need & prevalence
- Perceived efficacy
- Other molecules in class

3- Regulatory Obligations

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Pediatric

"Doing Now What Patients Need Next"