Update on Precision Medicine Trials

& the ITCC Portfolio

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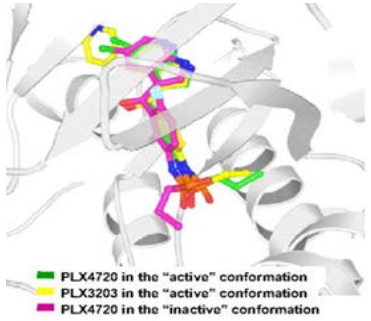
ITCC Introductory Course in Paediatric Drug Development
16 October 2018
Utrecht, NL

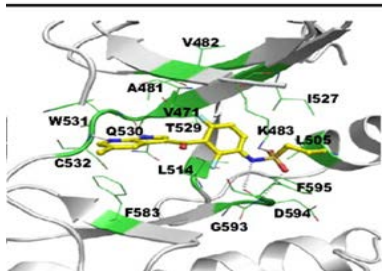
Change of Paradigm in Oncology Drug Development & Era of High-throughput Technologies - When Biology Meets Clinics …..

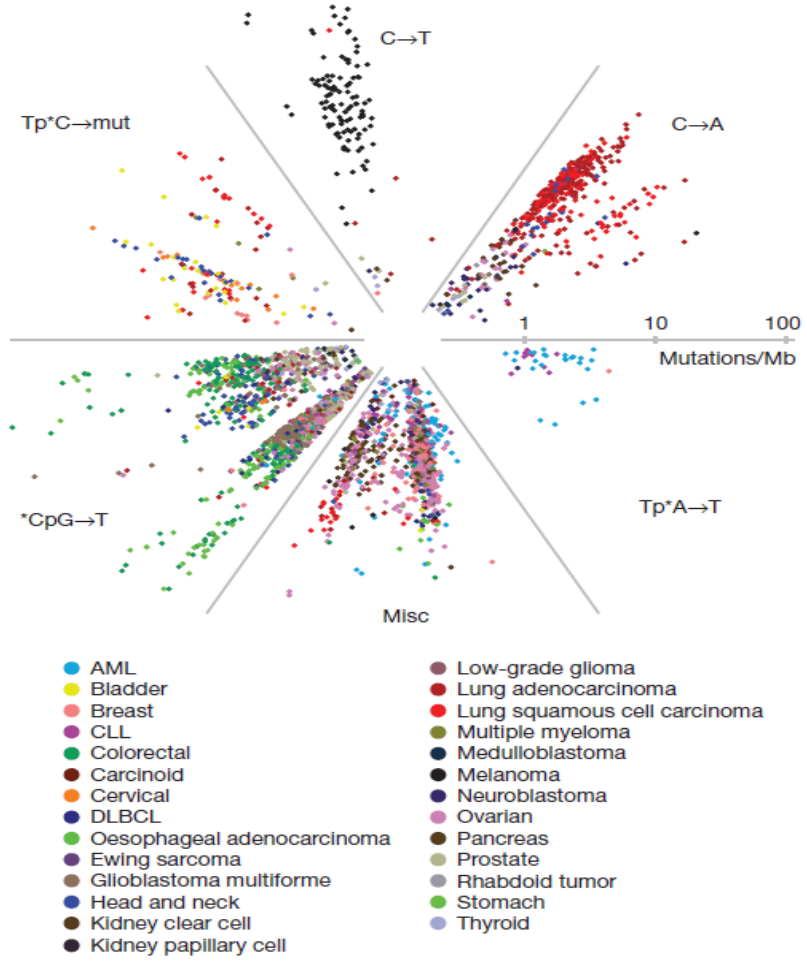
~ 1000 Anticancer compounds yearly under development

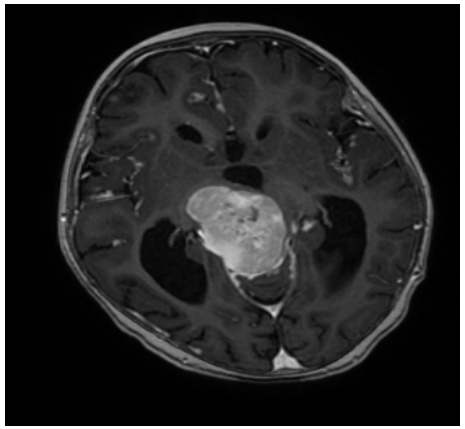
Targeted anticancer compounds

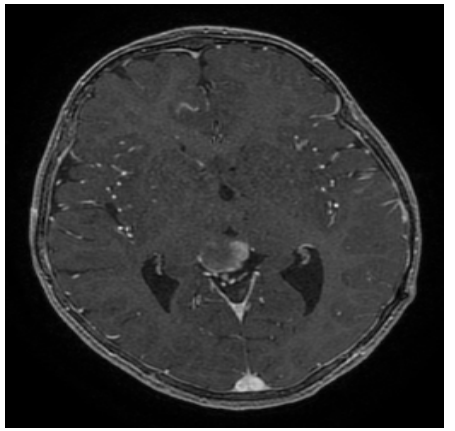
- New mechanisms of action
- New profile of activity
- Distinct profile of toxicity
- Oral and prolonged administration





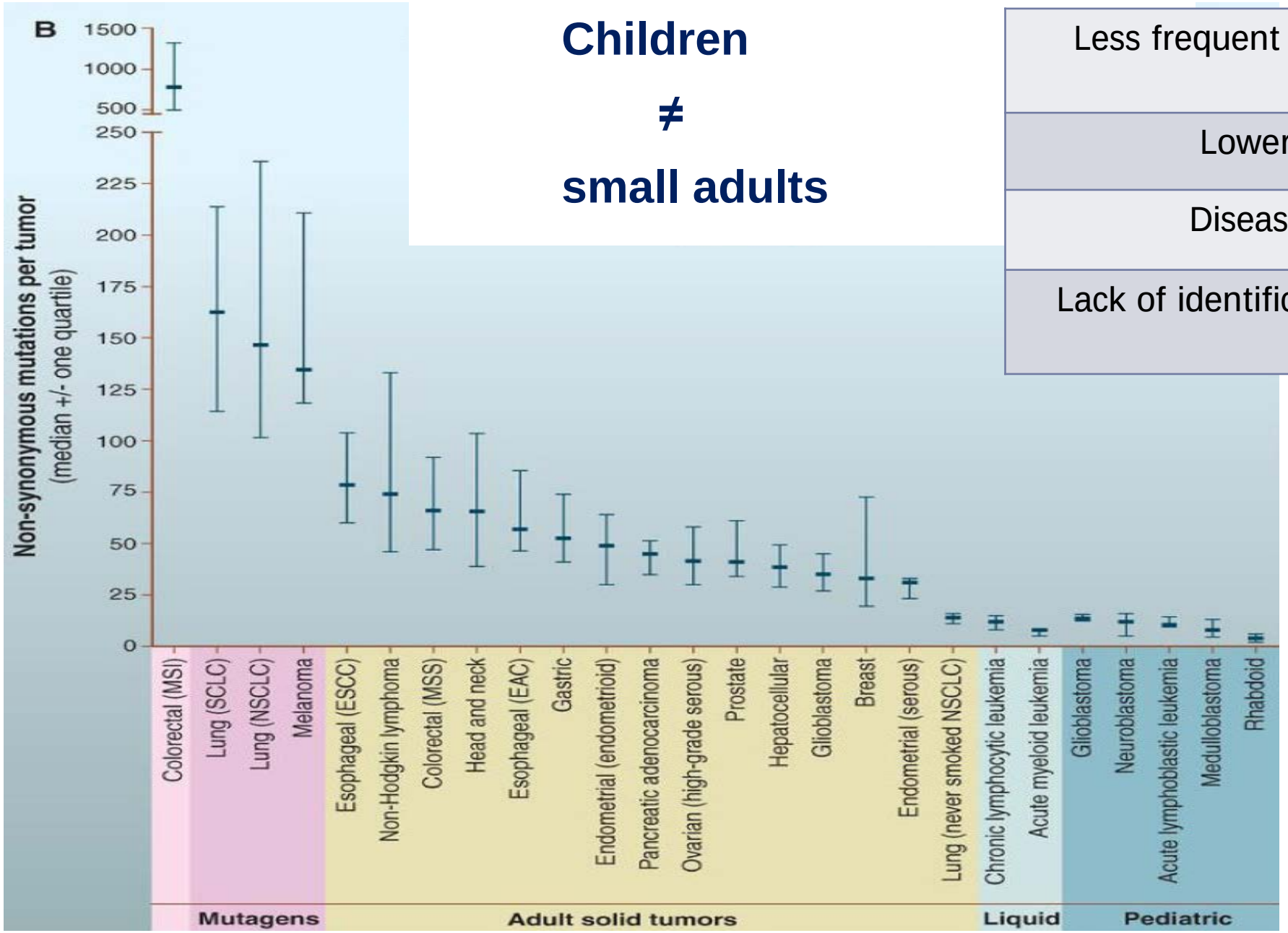






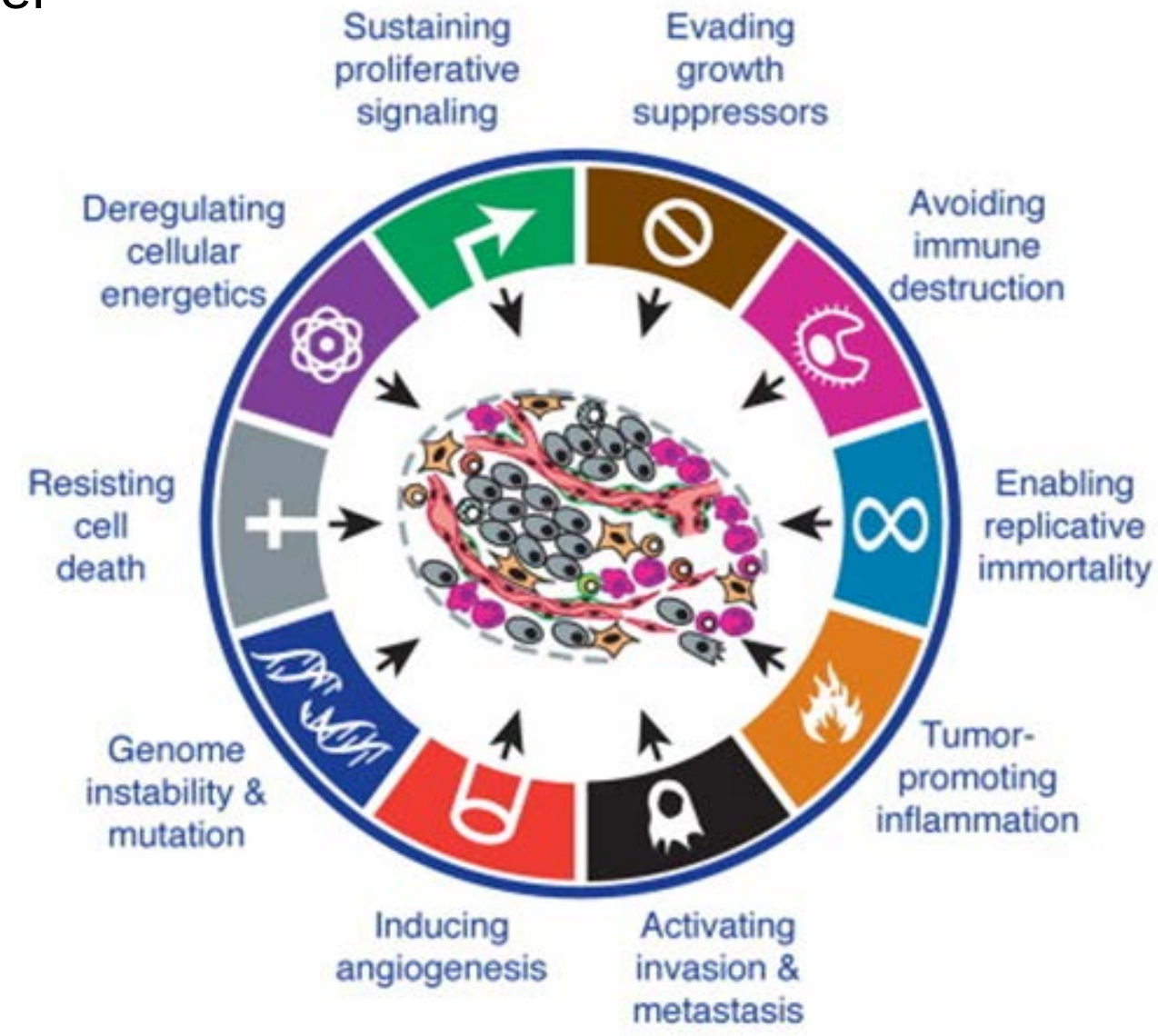
Children ≠ small adults

Less frequent / distinct gene alterations
Lower patient numbers
Disease spectrum differs
Lack of identification of actionable targets



Vogelstein et al., Science 2013

Hallmarks of Cancer



Microbiota

Epigenetic modulation

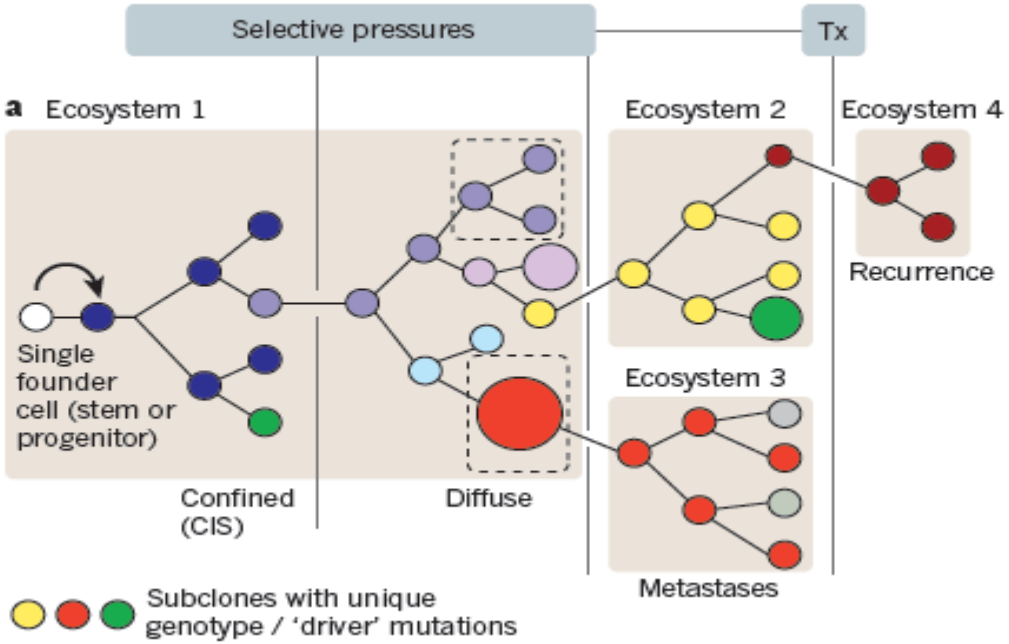
Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]

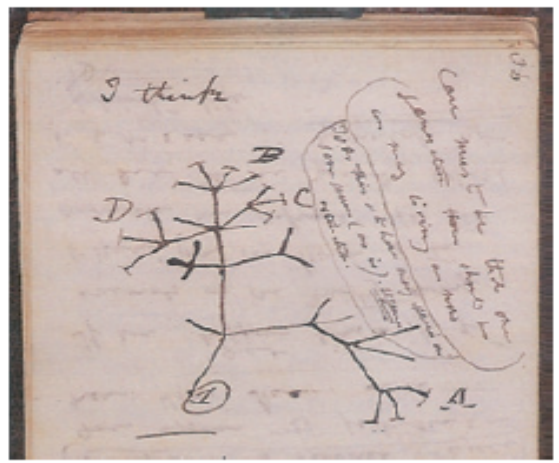
Clonal evolution in cancer

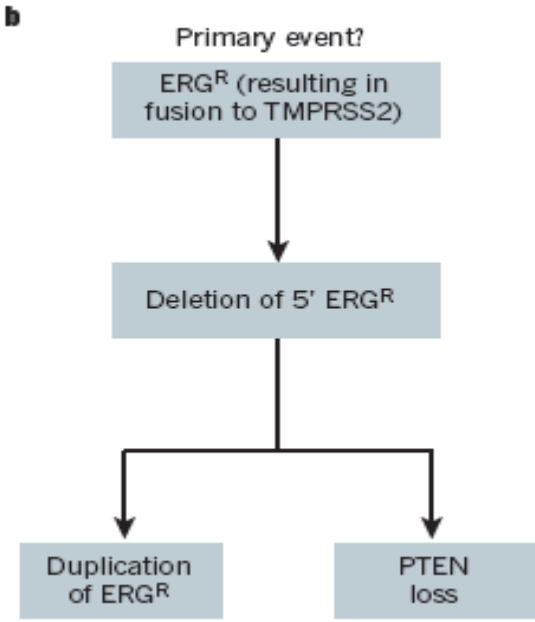
Mel Greaves[1] & Carlo C. Maley[2]

306 | NATURE | VOL 481 | 19 JANUARY 2012

Cancers evolve by a reiterative process of clonal expansion, genetic diversification and clonal selection within the adaptive landscapes of tissue ecosystems. The dynamics are complex, with highly variable patterns of genetic diversity and resulting clonal architecture. Therapeutic intervention may destroy cancer clones and erode their habitats, but it can also inadvertently provide a potent selective pressure for the expansion of resistant variants. The inherently Darwinian character of cancer is the primary reason for this therapeutic failure, but it may also hold the key to more effective control.







European Pediatric Precision Medicine Program in ITCC

1. Generate invididual molecular information at relapse

Molecular Matching Trials

MAPPYACTS
(France, Spain, Italy, Ireland, Israel)

INFORM
(Germany, Austria, Sweden, Switzerland, Belgium)

iTHER (The Netherlands)

SM-PAEDs (UK)

M A T C H

2. Match treatment and tumor profile

3. Evaluate activity of drugs and combinations

Phase 1 Trials (Industry and ISTs)
Phase 2 Trials (Industry and ISTs)

Genentech Roche
Matrix Trial

ESMART Multiarm trial
European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors in children (ESMART)

INFORM2 trial series

SHARE

Princess MÁXIMA center for pediatric oncology
GUSTAVE ROUSSY
institutCurie
ITCC
Great Ormond Street Hospital for Children
THE ROYAL MARSDEN
dkfz. German Cancer Consortium Core center Heidelberg

EU Clinico Biological
(WES/RNAseq
Data Base

Project A
Project B
Project C
Project D
Project E

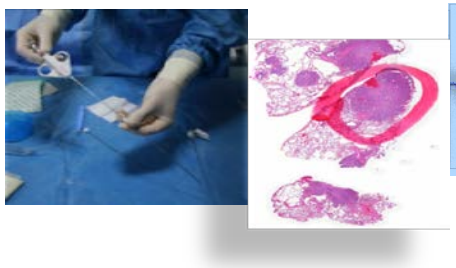
Pediatric
New
Drug
Development

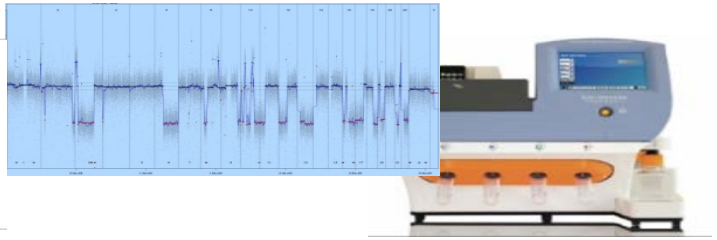
4. Generate new knowledge, new druggable pathways

MAPPYACTS Design & Workflow

A multicentric, prospective proof-of-concept study MoleculAr Profiling for Pediatric and Young Adult Cancer Treatment Stratification

Sample collection → **Molecular analysis** → **Molecular Tumor Board** → **Clinical Molecular Tumor Board** → **Treatment**





On-purpose image-guided biopsy or tumor resection

15-30 centers

Whole Exome & RNA Sequencing
≥ 30% tumor cells

2 platforms

Biologists, bio-informaticians, physician-scientists

Weekly discussion with treating physicians

Early phase clinical trials or off-label or compassionate use

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

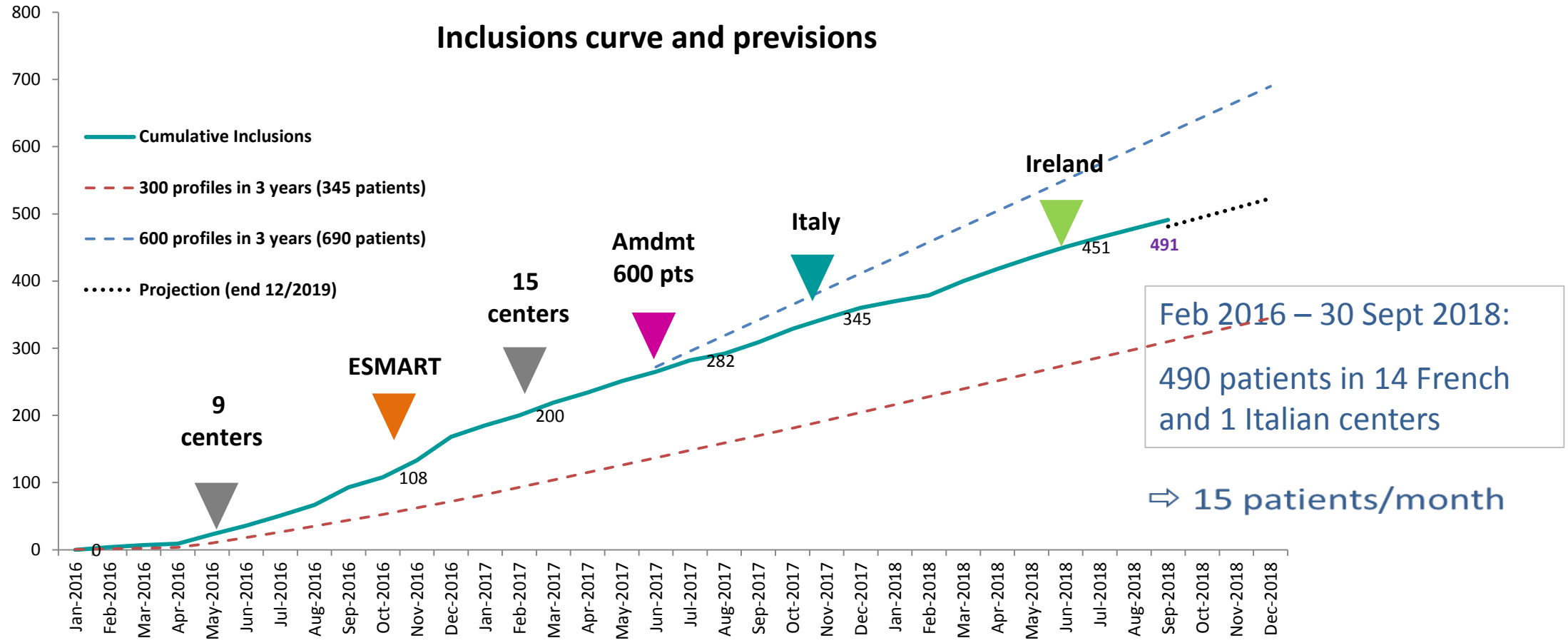
institut Curie Together, let's beat cancer.

Ancillary: cf DNA, Immune atlas, Patient-Derived Xenografts

Aims:

- To screen relapsed or refractory pediatric patients
- To provide them with their individual molecular tumor profile
- Attribute them to matched innovative targeted treatments

MAPPYACTS - Inclusion



Feb 2016 – 30 Sept 2018:

490 patients in 14 French and 1 Italian centers

⇨ 15 patients/month

Main challenges:

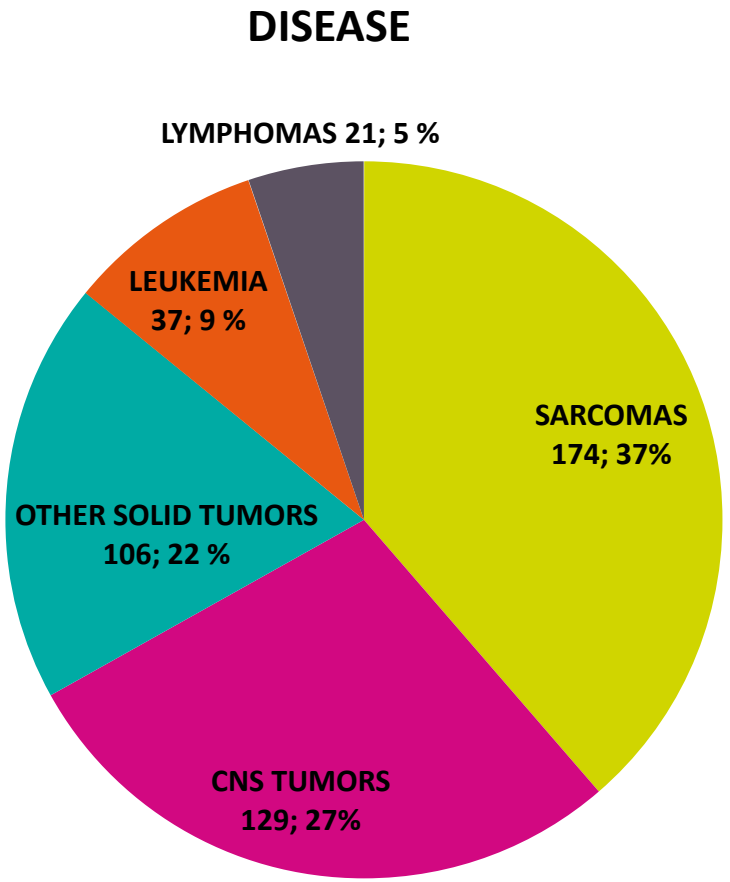
- Critical is waiting time
- Too advanced stage

➢ After biopsy other “standard” treatment

➢ Proposition at earlier stage

MAPPYACTS - Study Population

- Median age: 12 years (range: 1- 33)
- Delay initial diagnosis to registration: 1.8 years (0.1 - 22.6)
- Gender: 291 male (62%)
- Diseases:



Molecular Analysis Whole Exome and RNA sequencing

- Tumor DNA/RNA and paired constitutional DNA (blood or bone marrow during MRD)
  - WES: mean depth of coverage: 100 – 120x in tumor samples, 80-100x in normal tissue, 95% at 20x

- Bioinformatics analysis of WES based on Illumina Pipeline and hg19 human genome:
  - Calling:
    - **SNV (mutations), SV**: following application of filters, modeling of potential functional impact and confrontation with RNAseq data (expression)
    - **CNA**: amplifications > 6 - 8 copies taking into account the ploidy background, and homozygous deletions, only focal events with a size under 1-2 Mb

- Bioinformatic analysis of RNAseq:
  - DeFuse, TopHat 2, Chimera Scan, Fusion Map, …
  - Calling of:
    - Detection of fusion transcripts
    - Detection of splice variants

- Gene alterations were considered ‘actionable’ based on predicted function, taking into account of gain or loss of function and when targetable directly or their pathway upstream or downstream

MAPPYACTS CMTB Report

- Integrated Signatures

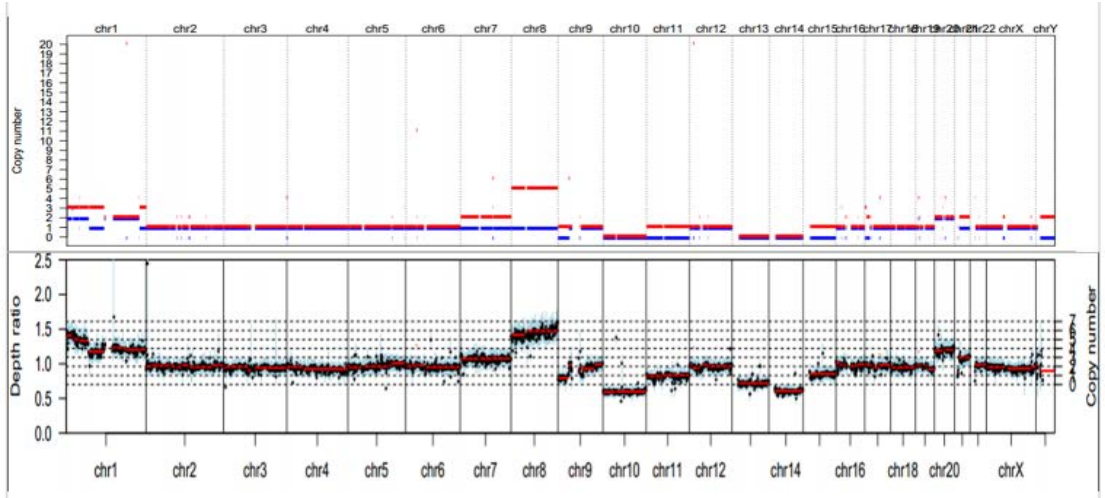
  Exome Tumor and Germline
  RNAseq

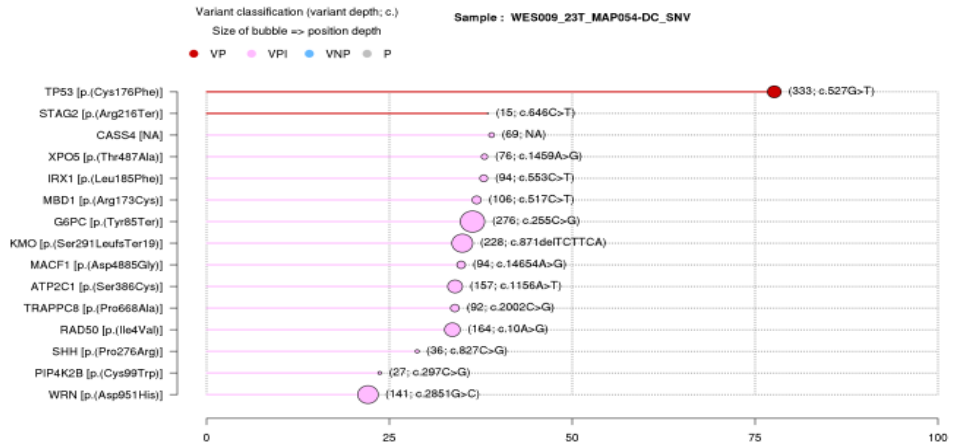
  Copy number Profile

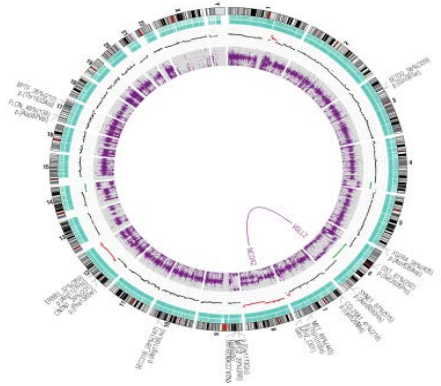
  Mutational Overview

  Translocation identification

  Signature assessment







- A single molecular report for clinical use including
  - Patient's disease history
  - Targeted therapy orientation
  - Germline event: Genetic Counseling Parent/Family

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CANCER CAMPUS GRAND PARIS

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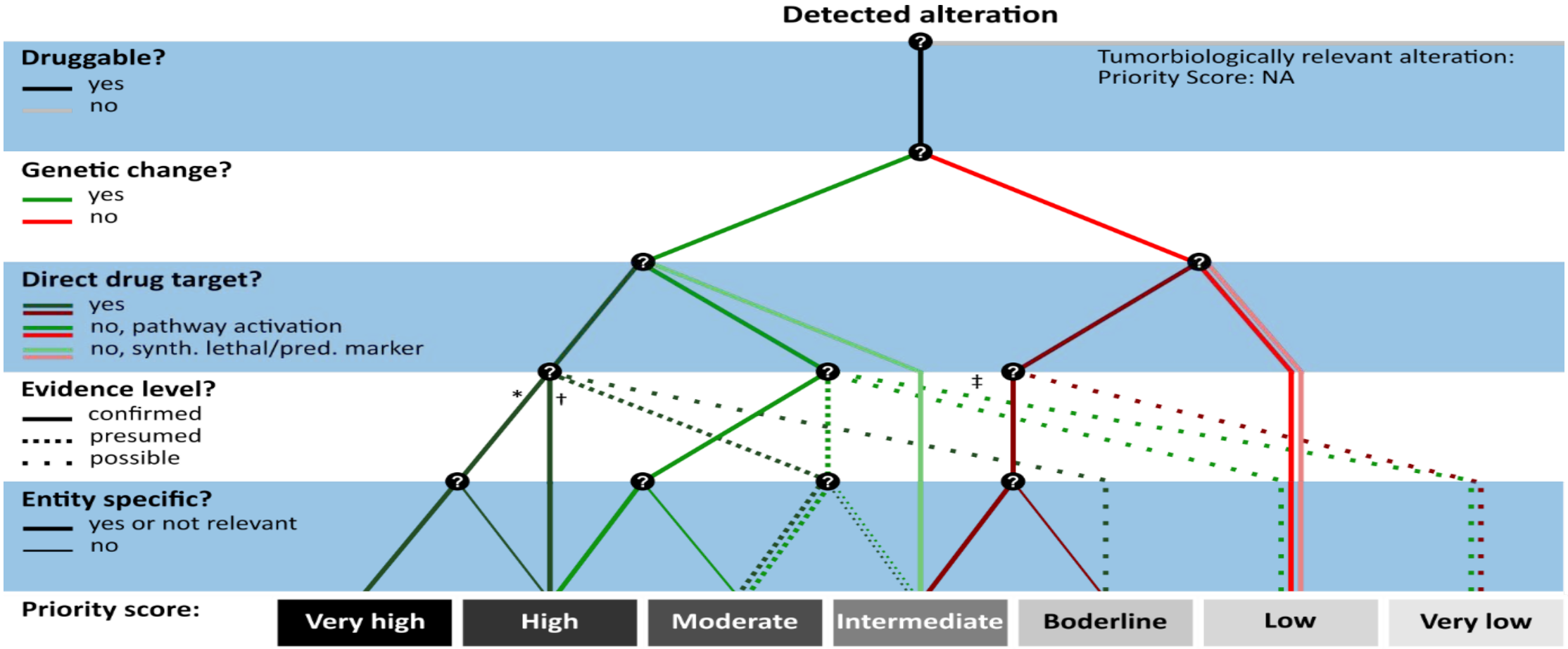
Target prioritization – how to translate “gut feeling“ into a score!?



Drug availability is currently not a criterium in the pediatric setting
(otherwise almost all targets would get a low score)

Target prioritization – stratification

Prioritization table v4

Priority	Target Type	Entity	Target Status
Very high	**Confirmed driver**	**Specific**	**Genetic hit (mutation/rearrangement)**
High	**Confirmed driver**	**Any**	**Genetic hit (focal high-amplitude CNV)**
	Confirmed driver	**Other**	**Genetic hit (mutation/ rearrangement)**
	Confirmed pathway activation, genetic	Specific	Genetic hit (mutation/rearrangement)
Moderate	**Presumed driver**	**Specific**	**Genetic hit (mutation/focal low-amplitude CNV)**
	Presumed pathway activation, genetic	Specific	Genetic hit
	Confirmed pathway activation, genetic	Other	Genetic hit (mutation/rearrangement)
Intermediate	**Presumed driver**	**Other**	**Genetic hit (mutation/focal low-amplitude CNV)**
	Presumed pathway activation, genetic	Other	Genetic hit
	Synthetic lethal / Predictive marker, genetic	Specific	Genetic hit
	Overexpressed driver	**Specific**	**Protein/Expression Change**
Borderline	**Possible driver**	**Any**	**Genetic hit**
	Synthetic lethal / Predictive marker, genetic	Other	Genetic hit
	Overexpressed driver	**Other**	**Protein/Expression Change**
Low	Possible pathway activation, genetic	Any	Genetic hit
	Pathway activation, expression	Any	Protein/Expression Change
	Synthetic lethal / Predictive marker, expression	Any	Protein/Expression Change
Very low	Circumstantial evidence	Any	Genetic/Protein/Expression Change
NA	Biological interest	Any	Genetic hit

INdividualized therapy FOr Relapsed Malignancies in childhood

INFORM

73 patients (61 %)
target with score ≥ intermediate

89 patients (74 %)
target with score ≥ borderline

103 patients (86 %):
actionable alteration

120 patients analyzed
(5 patients pending)

MAPPYACTS CMTB report

LEVEL OF EVIDENCE
Ready for routine use
Investigational
Hypothetical target
Mutation associated to resistance to targeted treatment
Oncogenic without a level of evidence
Oncogenic not targetable

In 318 contributive samples:

Ready for routine use: 16 (5%)

NPM1/ALK , KIAA1549-BRAF, ETV6-NTRK3, KANK2/NTRK2, CCDC6-RET fusions; BRAF p.V600E, PTCH1, NF1 mutations

Investigational: ~40%

CDK4 ampli, CDKN2A/B del, PI3KCA, PTEN loss, FGFR ampli/mut, MYC ampli, ATR, ATM mut, SMARCA1…

Hypothetical target: ~ 20%

Histone mut, CNA gains, TP53 mut?

Resistance mutations:

SMO p.I408V, NTRK3 p.G623R

Oncogenic without level of evidence:

TP53 mut?, VUS, subclonal events

Oncogenic not targetable:

EWS/FLI1, PAX/FOXO1

ECCO / PCM recommendation

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institutCurie

Clinical Molecular Tumor Board (CMTB)

Date CMTB: 27/09/2018

Les perspectives thérapeutiques proposées ci-dessous sont fondées sur des hypothèses précliniques ou cliniques qui n'ont pas systématiquement de preuve évidente d'activité ou d'efficacité.

1. Potential phase I/II clinical trials and treatment recommendations based on genetic alterations identified in the tumor

LEVEL OF EVIDENCE
Ready for routine use
Investigational
Hypothetical target
Mutation associated to resistance to targeted treatment
Oncogenic without a level of evidence
Oncogenic not targetable

Somatic genetic alteration :	Potential treatment :	Level of evidence :
CDKN2A/B focal homozygotic deletion	CDK4/6 inhibiteur : Ribociclib + TOTEM (bras A ESMART ; no slot)	Investigational
ESWR1-FLI-1 fusion	Confirms dg of Ewing	Oncogenic not targetable

2. Potential phase I/II clinical trials based on tumor type available

- Ewing sarcome avec transcrit de fusion ESWR1-FLI-1 = Regobone (slot disponible)
- PARP inhibiteur : Olaparib + Irinotecan (ESMART bras D)

Hiérarchie recommandations: Regobone > ESMART Bras D > ESMART Bras A

Clinical Molecular Tumor Board (CMTB)

Date CMTB: 27/09/18

Les perspectives thérapeutiques proposées ci-dessous sont fondées sur des hypothèses précliniques ou cliniques qui n'ont pas systématiquement de preuve évidente d'activité ou d'efficacité.

1. Potential phase I/II clinical trials and treatment recommendations based on genetic alterations identified in the tumor

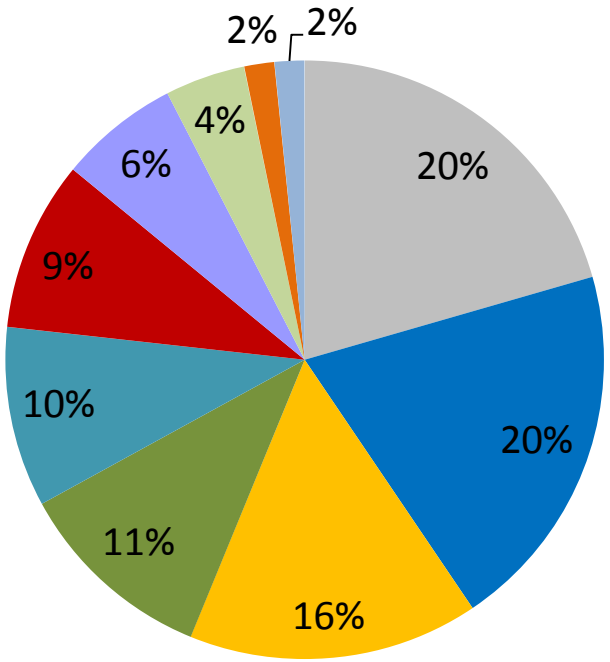
LEVEL OF EVIDENCE
Ready for routine use
Investigational
Hypothetical target
Mutation associated to resistance to targeted treatment
Oncogenic without a level of evidence
Oncogenic not targetable

Somatic genetic alteration :	Potential treatment :	Level of evidence
PBRM1 p.(Asp632GlufsTer11) VP homozygote (LOH) (95,35%)	Epigenetic modulator: EZH2 or HDAC inhibiteurs or depakine (no inclusion criteria for EZH-102 ; off label/ATU)	Hypothetical target
C11orf95/RELA fusion	Confirms dg of supratentorial ependymoma	Oncogenic not targetable

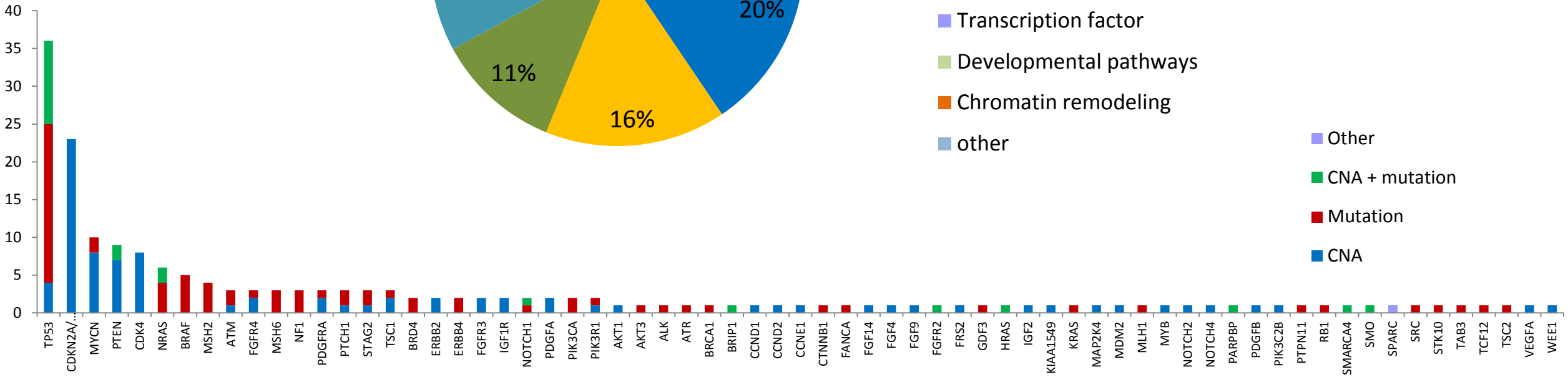
2. Potential phase I/II clinical trials based on tumor type available
   Aucune

Hiérarchie recommandations: Traitement standard > EZH2 ou HDACi (ATU) or depakine

‘Actionable’ Molecular Alterations



- Cell cycle
- Apoptosis
- RTK
- PTEN/PI3K/AKT/mTOR
- MAPK
- DNA damage repair
- Transcription factor
- Developmental pathways
- Chromatin remodeling
- other



Geoerger et al AACR 2017

European Precision Medicine Program: Pediatric Oncology-Hematology 2018

Children and adolescents with refractory or recurrent tumors or leukemia

MAPPYACTS
in F, SP, I, Ir, Is
D: INFORM; NL: iTHER;
UK: SM-PAEDS

Signed informed consent

BIOPSY/ Surgery

Bioinformatics

Molecular analysis:
- WES
- RNAseq (RT-PCR confirmatory)
- IHC, FISH (confirmatory)

Exploratory:
- Methylation array
- miRNA
- Immunmarker/modulators
- CtDNA
- Preclincial models

INCa-NGS Platforms: IGR, IC

Data interpretation & Therapy suggestion

Multidisciplinary Therapeutic Molecular Tumor Board (MTB)
(with signed report from biologists)

Clinical Molecular Tumor Board (CMTB)

INDividualized therapy FOr Relapsed Malignancies in childhood

INFORM

Clinical Trials

If actionable targets:

Ongoing targeted Phase I/II trials or Acse program

Registered targeted agents in pediatric/adult cancer with pediatric dose recommendation

ESMART prospective PoC trial (AcSé):
IST multi-agent from pluri-company
European Proof–of-Concept Therapeutic **S**tratification Trial of **M**olecular **A**nomalies in **R**elapsed or Refractory **T**umors in children

Matrix Trial
Genentech Roche

INFORM2 Trial series
DKFZ

If no actionable targets:

Ongoing non-targeted Phase I/II trials or "non-targeted" arms of ESMART

Ongoing Early Clinical Trials, France October 2018

Phase 1:

- **Leukemia:**
  - ITCC-015 VIDAZA *pending*
  - ITCC-052 Carfilzomib + R3
  - ITCC-054 Bosutinib
  - ITCC-059 Inotuzumab Ozogamycin
  - ITCC-070 Daratumumab CD-38
  - ITCC-067 AC-220 quizartinib Flt-3
- **Leukemia + solid:**
  - ITCC-057 AcSe-ESMART A-J
  - ITCC-062 Arginase BCT-100 (Leuk + solid)
  - ITCC-068 Venetoclax BCL2
- **Solid:**
  - Talimogene Laherparepvec
  - ITCC-037 Dabrafenib (BRAFv600) (Phase 2)
  - ITCC-047 Regorafenib + VI
  - Trametinib (MEK) +/- dabrafenib (Phase 2)
  - ITCC-049 Afatinib (Expansion)
  - Pembrolizumab (HD, MSI)
  - ITCC-061 EPZ 6438 Tamezetostat (pending)
  - ITCC-055 Cobimetinib
  - Fluvabrex 12-08
  - ITCC-066 LOXO-101
  - LOXO-195
- **Molecular Profiling:**
  - MAPPYACTS
- > 18 years one may also consider adult phase I/II trials in adult centers

Phase 2:

- **Leukemia/Lymphoma:**
  - RIALTO 20130320
  - Nivolumab-brentuximab CA209744
  - ITCC-065 Ibrutinib + Rice
  - ITCC-063 Selumetinib +dexa (Dec 2018)
- **Multiple:**
  - Tamezetostat: Rhaboid and INI-neg >16 yr
  - ITCC-053 CRISP (Nov 2018)
- **Sarcoma:**
  - ITCC-050. Lenvatinib + ifo-VP-16 osteo
  - Regobone: Ewing > 10yrs
  - Pembrosarc >18yrs
  - Cabone > 12 yrs
  - Metzolimos
  - Pazopanib GW786034
- **Neuroblastoma:**
  - ITCC-032 BEACON
  - ITCC-077 3F8 (anti-GD2)Naxitamab
  - Lorlatinib NANT (Nov 2018)
- **Brain Tumors:**
  - ITCC-022 VINILO Ph2 Randomization
  - ITCC-051 BIOMEDE
  - Ipilumab-Nivolumab CNS
  - Pomalidomide (CC-4047)
  - ITCC-064 ABT-414 *>12yrs*

Therapeutic Suggestions and Treatments

MAPPYACTS
367 contributive analysis in 359 patients
(AACR: 122)

SUGGESTED THERAPEUTIC PERSPECTIVES per patient

No specific suggestion: 27%
N=33
Specific suggestion: 73%
1: N=32
2: N=31
3+: N=26

Genetic counseling:
N=459 patients

Recommended (ACMG) : N = 31 (6.7%)
Further discussion with geneticists:
N = 105 (23%)
No: N = 323 (70%)

Received Therapies for patients with targets:
N=89
83 pats included in ESMART

Trial with matched targeted agent: N=20
ESMART: N=16
Other phase 1 trial: N=4

Off-label matched targeted treatment: N=3

Trial with non-matched targeted agent:
ESMART: N=8

Off-label non-matched targeted treatment: N=2

Chemotherapy: N=4

Disease controlled under ongoing treatment: N=34

Died early due to PD: N=18

Geoerger et al AACR 2017

AcSé INSTITUT NATIONAL DU CANCER

e★smart
European proof of concept therapeutic stratification trial of molecular anomalies in relapsed or refractory tumors in children

Main Inclusion Criteria:

- Patients < 18 years with a relapsed or refractory malignancy (solid tumor or leukemia)
- Evaluable disease
- Lansky/Karnofsky ≥70%
- No toxicity ≥ G2
- Deep tumor molecular analysis available is mandatory

WAVE 1 of Treatments

ARM	Pathway	Target	Treatment	Enrichment	Pharma
Arm A	Cell Cycle	CDK4/6	Ribociclib + TOTEM*	50%	NOVARTIS
Arm B			Ribociclib + Everolimus	50%	
Arm C	DNA repair	WEE1	AZD1775 + Carboplatin	50%	AstraZeneca
Arm D		PARP	Olaparib + Irinotecan	50%	
Arm E	PI3K/AKT/mTOR	mTORC1/ TORC2	AZD2014	100%	
Arm F			AZD2014 + TOTEM*	50%	
Arm G	Immune checkpoints	PD1	Nivolumab + CyclophoP** +/-RT***	NA	Bristol-Myers Squibb

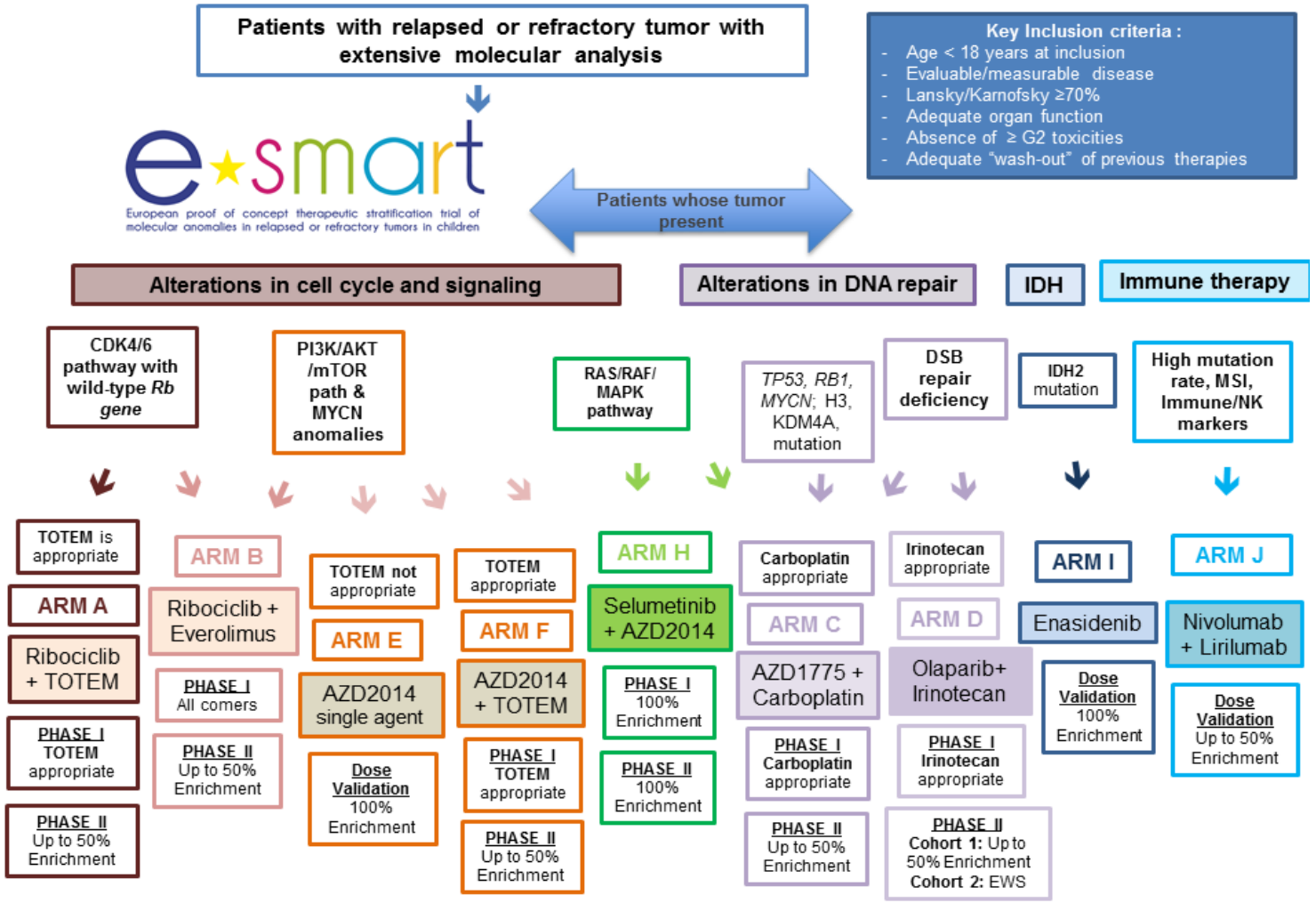
* topotecan + temozolomide; ** cyclophosphamide; ***radiotherapy

Arms Summary protocol v2.0

Protocol v1.3
Protocol v2.0
Arm removed from the protocol

ARM	Pathway	Target	Treatment	Enrichment	Pharma	Investigator
Arm A	Cell Cycle	CDK4/6	Ribociclib + TOTEM*	50%	NOVARTIS	Francisco Bautista
Arm B			Ribociclib + Everolimus	50%		Francisco Bautista
Arm C	DNA repair	WEE1	AZD1775 + Carboplatin	50%	AstraZeneca	Francisco Bautista
Arm D		PARP	Olaparib + Irinotecan	50%		Susanne Gatz
Arm E	PI3K/AKT/mTOR	mTORC1/TORC2	Vistusertib	100%		Lynley Marshall
Arm F			Vistusertib + TOTEM*	50%		Lynley Marshall
Arm G	Immune checkpoints	PD1	Nivolumab + CyclophoP** +/-RT***	NA	Bristol-Myers Squibb	Claudia Pasqualini
Arm H	PI3K/AKT/mTOR Ras-Raf-MEK-ERK	MEK + mTOR	Selumetinib + Vistusertib	100%	AstraZeneca	Pablo Berlanga
Arm I	Metabolic pathway	IDH2	AG-221 (Enasidenib)	100%	Celgene	Stephane Ducassou
Arm J	Immune checkpoints	PD1 + KIR	Nivolumab + Lirilumab	NA	Bristol-Myers Squibb	Nicolas Andre

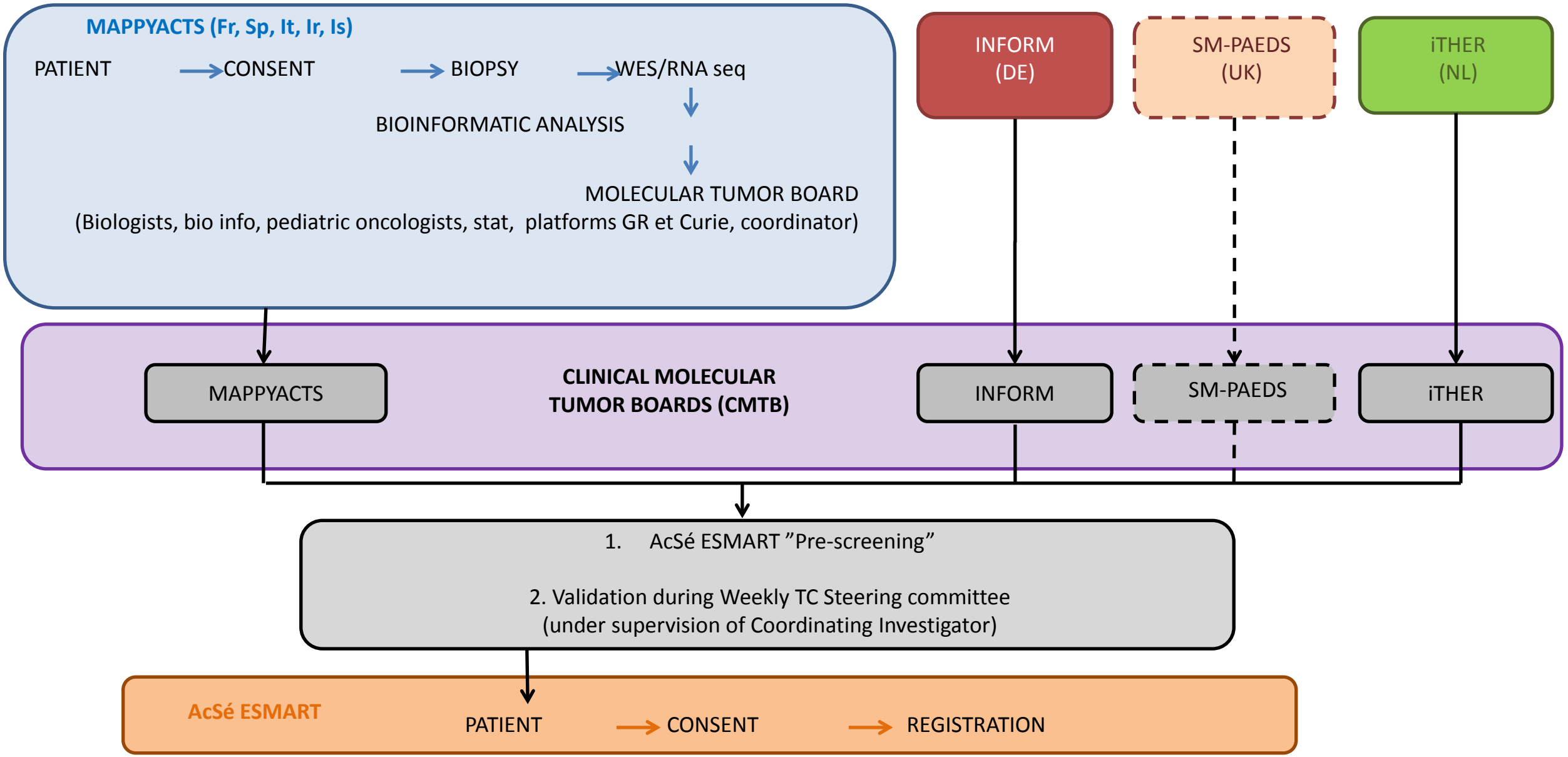
Complexity of Hypothesis Driven Enrichment Strategy & Proof-of-Concept for the Clinical Roles of Molecular Alterations



- ➢ Molecular alterations:
  - Variable level of biological evidence
  - Fusions – CNA – VP/VUS/VNP
  - Homozygotic vs heterozgotic events
  - Subclonal events
- ❑ Hierarchy of multiple alterations
- ❑ Lack of gene methylation, protein expression and functional data

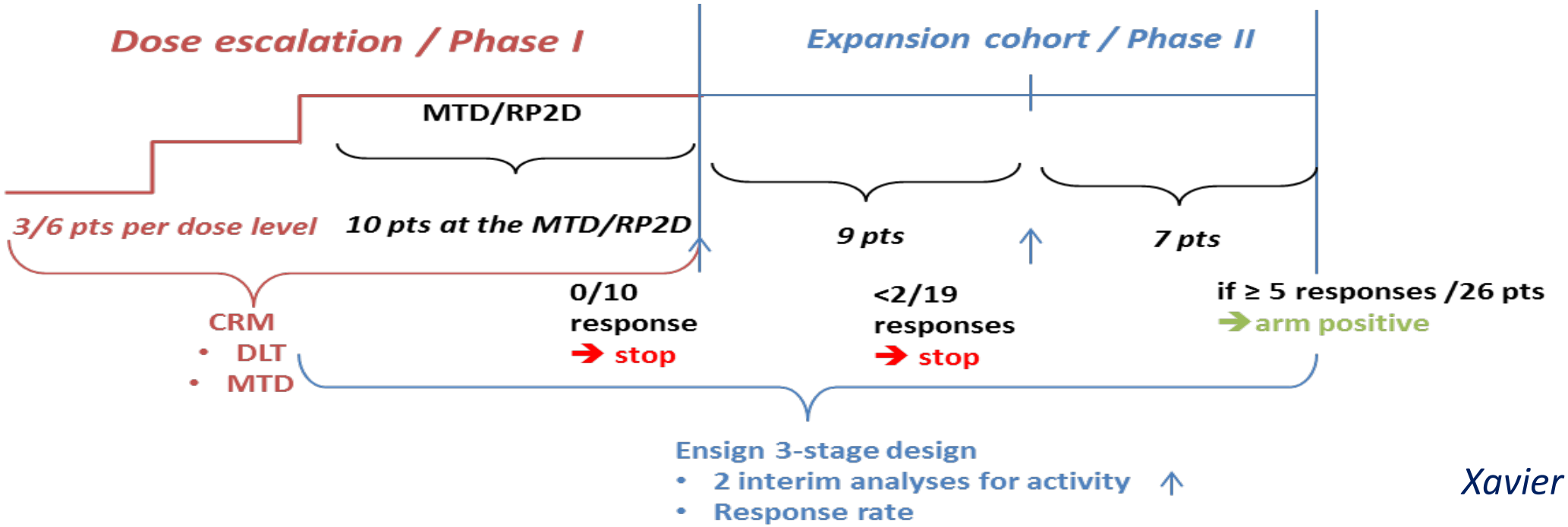
- ➢ Profiles of patients in each arm are currently further explored

Interaction between European molecular profiling programs and inclusion in AcSé- ESMART



AcSé-ESMART Statistical Design

- Each arm is run independently (6-38 patients/arm)
- 2 parts : Phase I et Phase II
  - Evaluation of safety (DLT, MTD, RP2D) AND activity
  - 200 à 285 evaluable patients in 3 years
  - IDMC (1 pediatric oncologist, 1 medical oncologist, 1 pharmacovigilant, 1 statisticien)

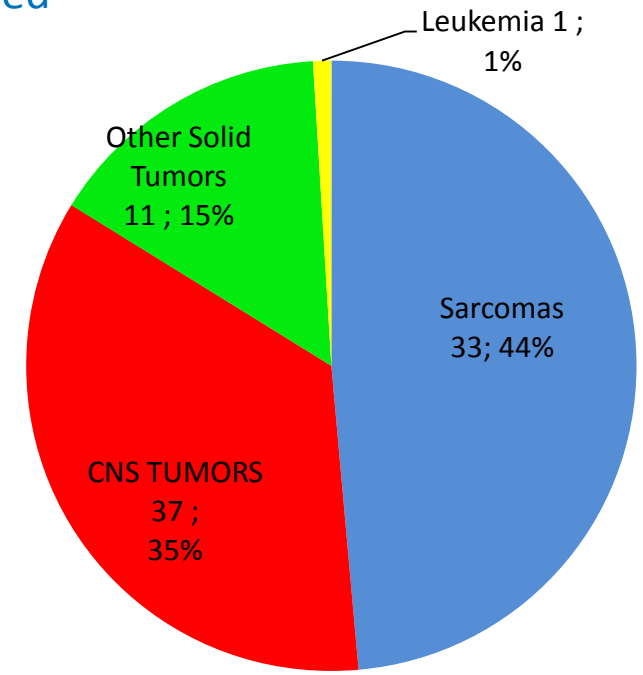


Xavier Paoletti

ESMART Inclusions

August 2016 to 30 September 2018:

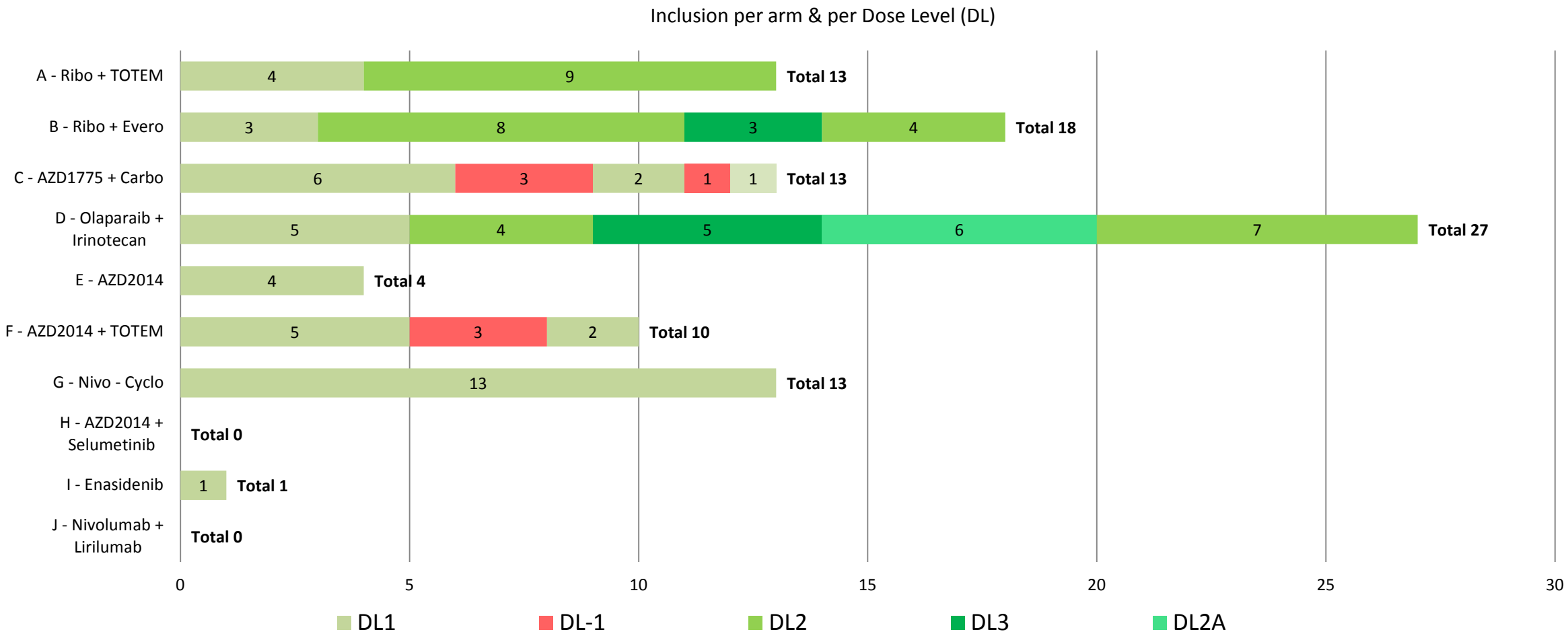
- 106 patients included (~4.2 per month)
- Median age: 14 years (1 – 23 years)
- 11 patients were enrolled in a second AcSé-ESMART arm
- More than 50% were ‘enriched’



Advanced Molecular Profiling:

- MAPPYACTS: 83 inclusions
- MOSCATO-01 7
- BIOMEDE 5
- Other 11
  - ITHER 4
  - Inform 2
  - Curie 2
  - Rare 1
  - Copenhagen 1
  - Sweden 1

ESMART Inclusions per Treatment Arm



To define relevant pathways & combinations

ONCOGENE/TRANSFUSION PRODUCTS

MYCN or C

EWS/ETS

APOPTOSIS & AUTOPHAGY MODULATORS

Bcl2, IAP

Survivin, TRAIL

2018 CTC workshop

EPIGENETICS

HDACi

BET Domain/BRd4

LSD1

EZH2

2017 CTC workshop

DNA REPAIR MODULATORS

2017 workshop

PARP-1

CHK-1

ATR

SIGNAL TRANSDUCTION

FGFR1-4

ALK/ROSi in NB and IMT

MEKi combinations

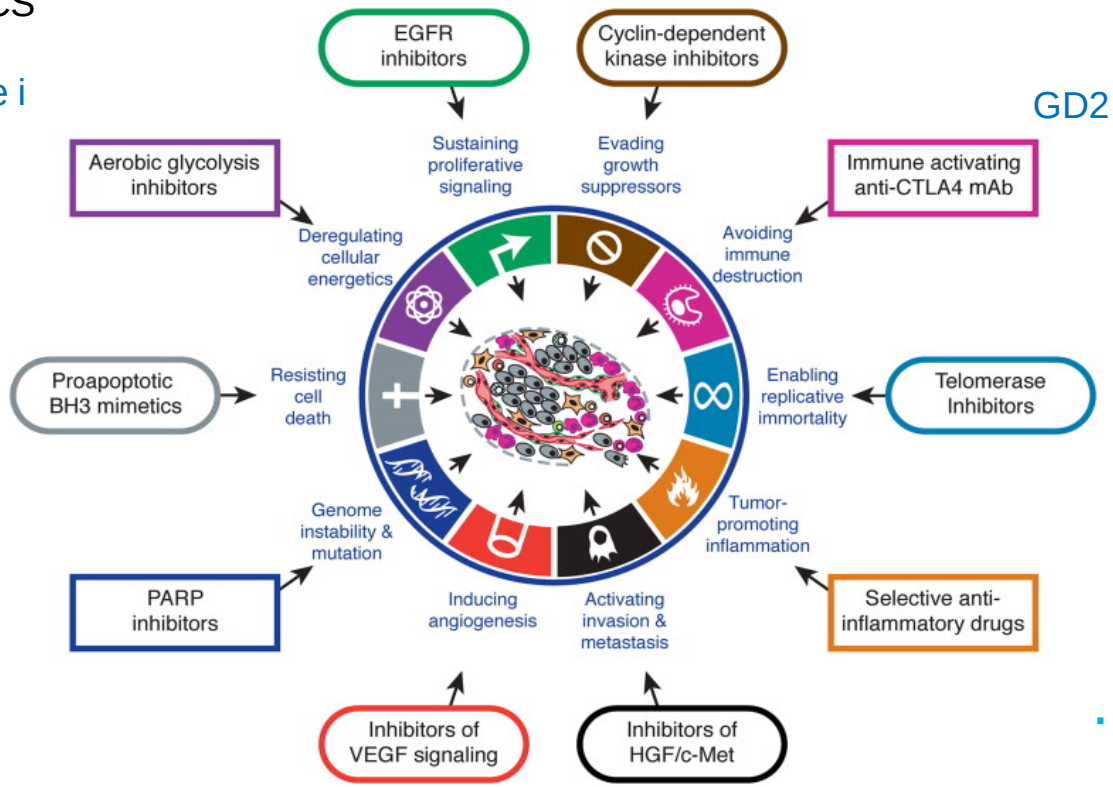
2018 CTC workshop

METABOLICS

IDH1/2i

Proteasome i

Arginase



IMMUNE-RELATED TARGETS

CAR

Vaccine

Cell Therapy

GD2 / PD1 combinations

Telomerase

Imetelstat

.....

ANTI-ANGIOGENIC

Regorafenib in RMS

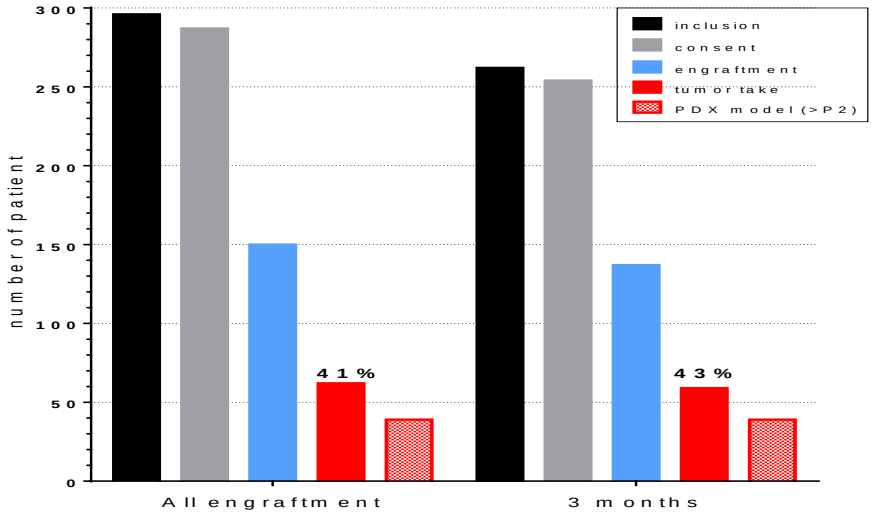
In ESMART – INFORM2 – Pharma – other ISTs

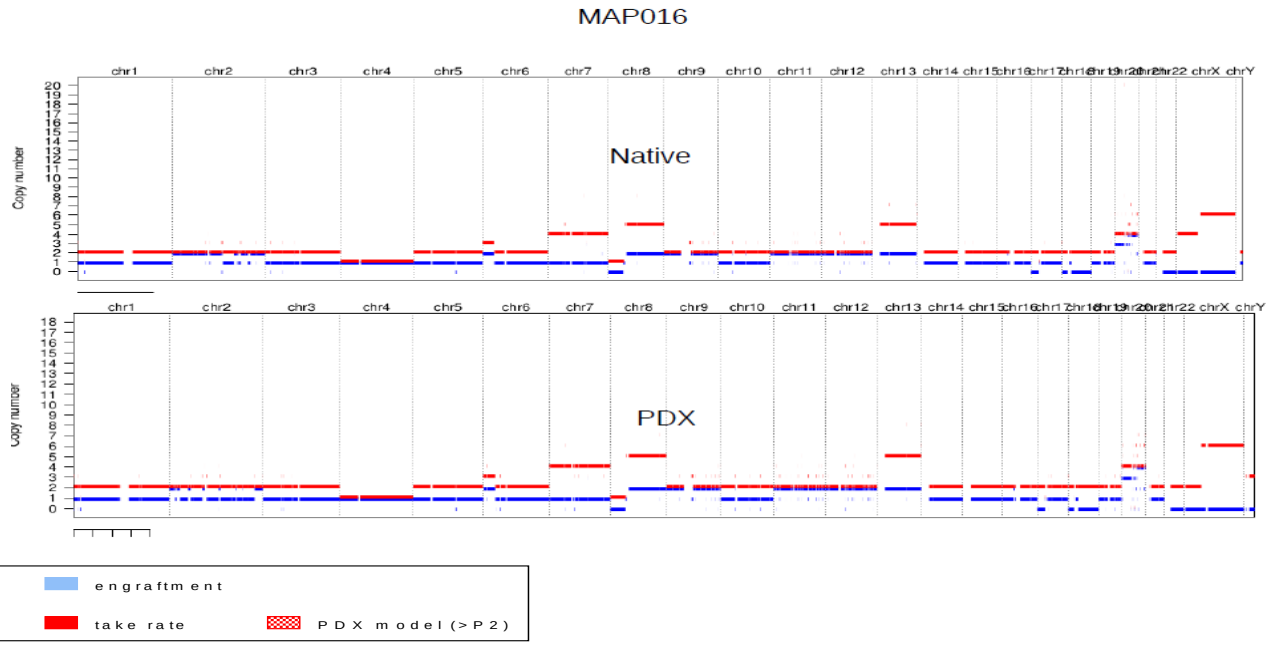
Cell

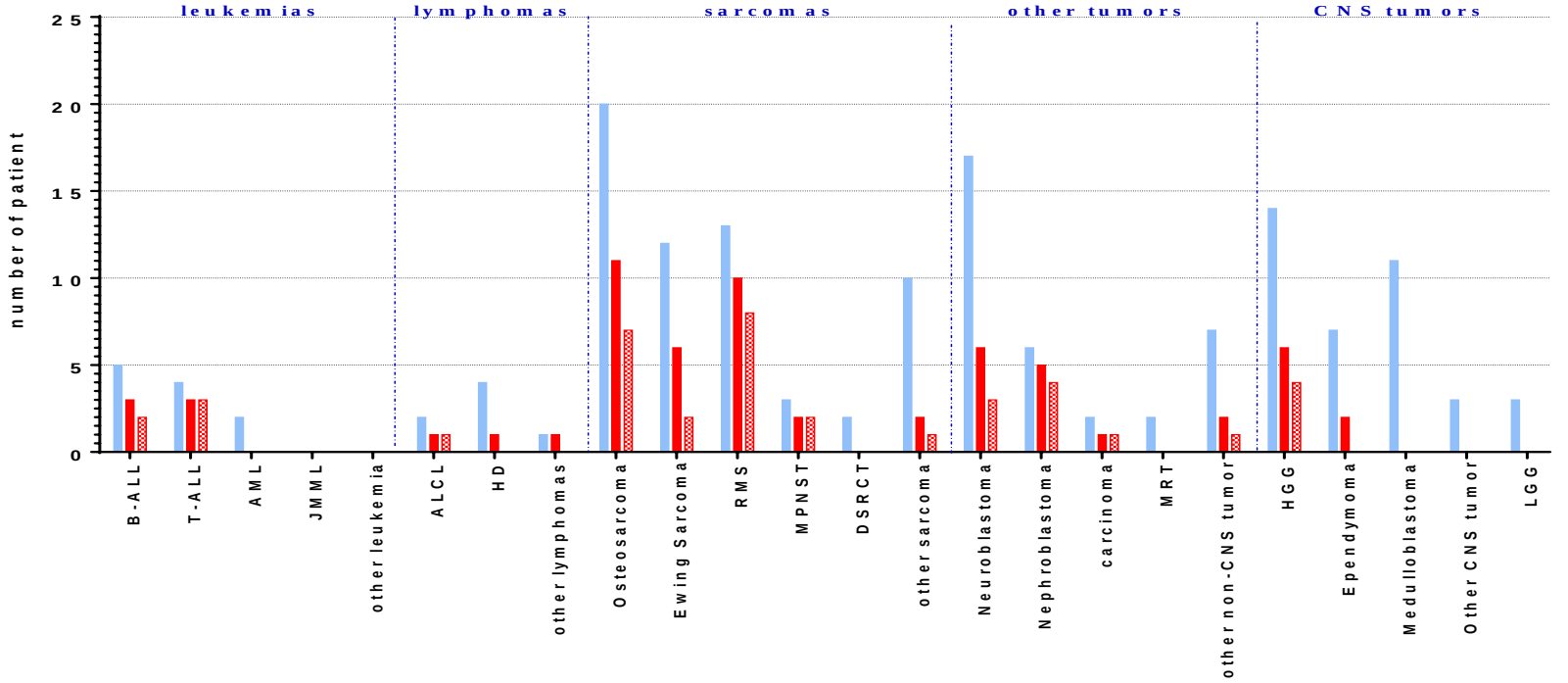
Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]

MAPPYACTS - PDX

more than 65 growing

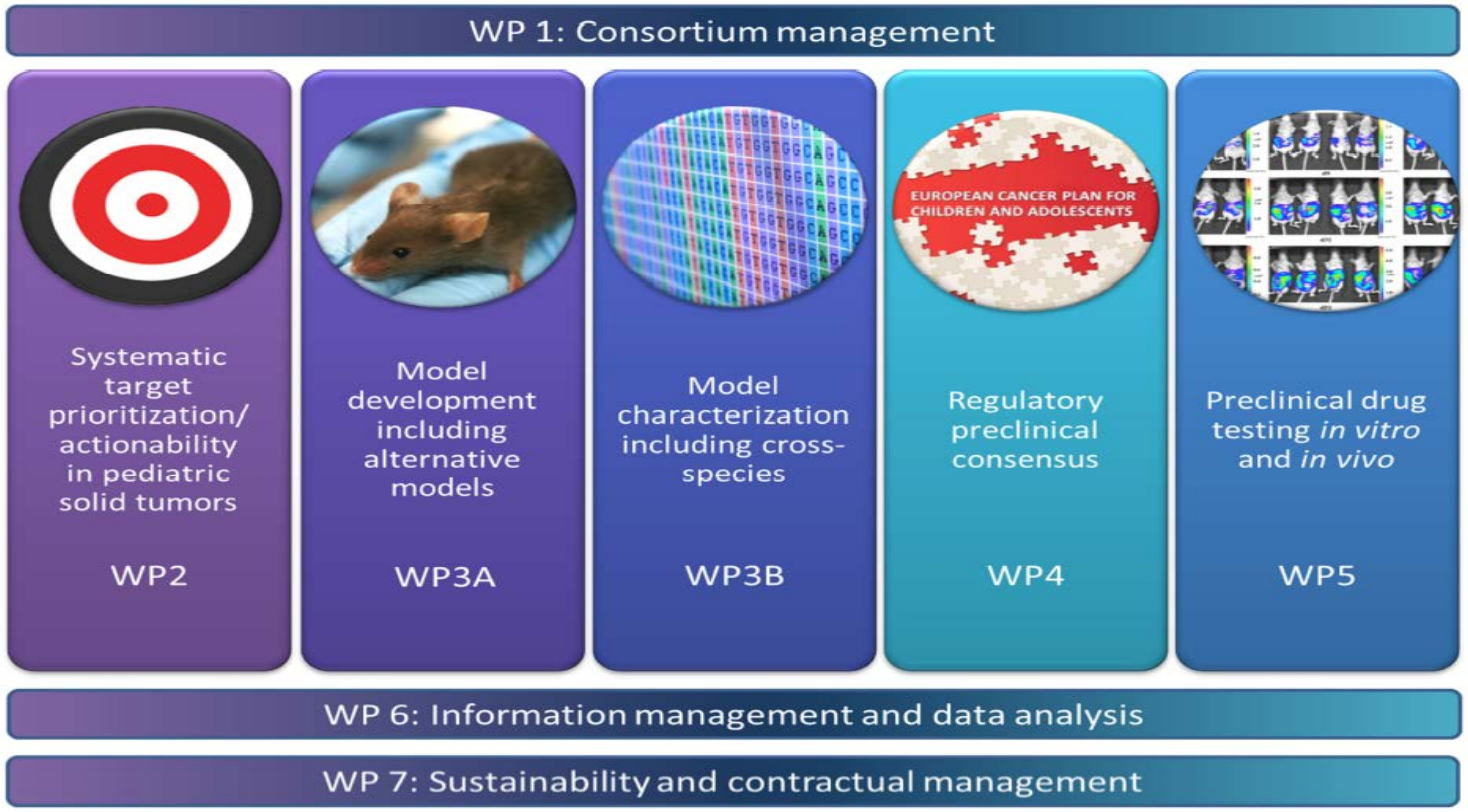






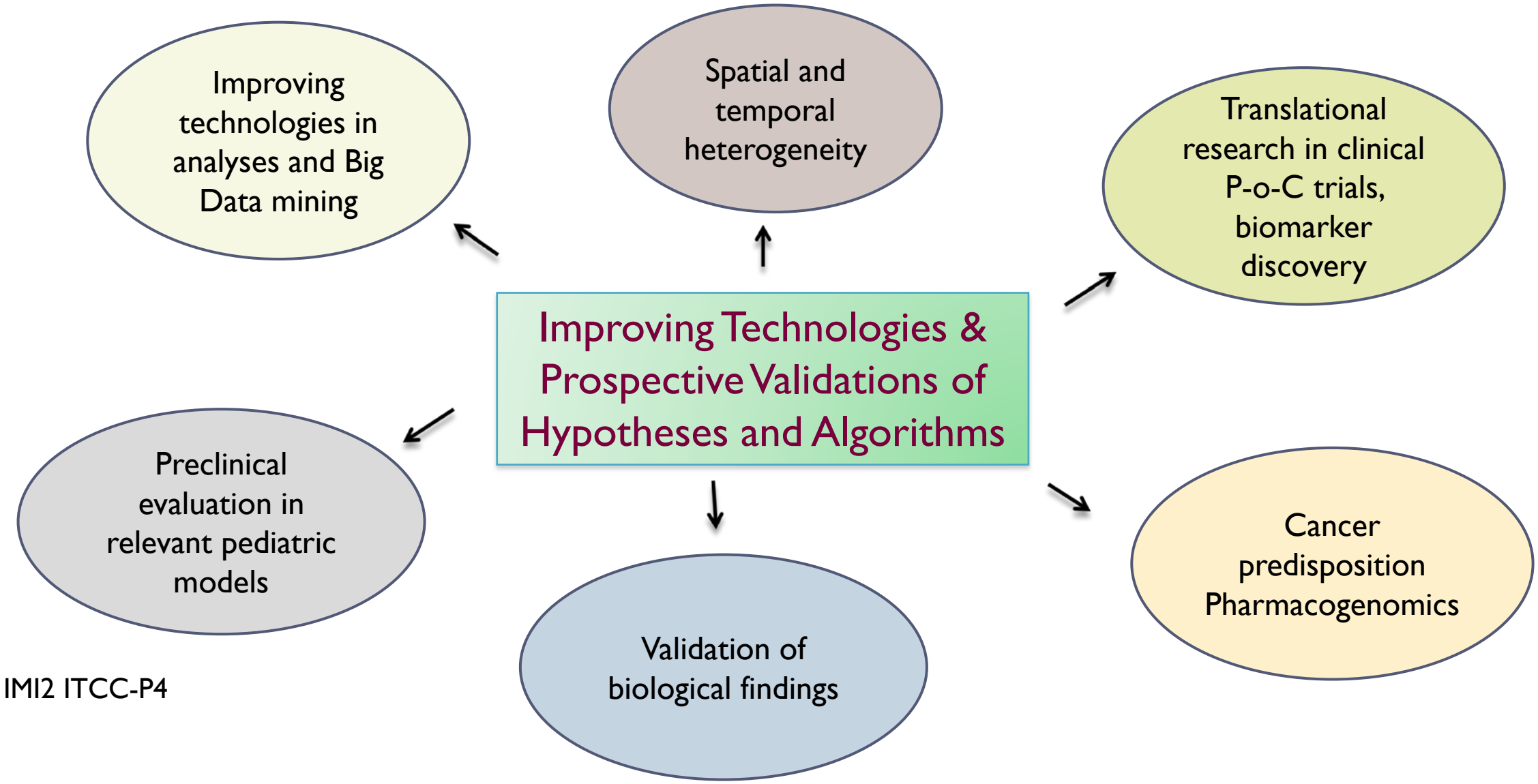
ITCC Pediatric Preclinical Proof-of-concept Platform (**ITCC-P^4**)

ITCC-P^4 Workflow



- 400 PDX models/5 years, 2 GEMMs per entity
- 3 standard-of-care drugs and > 5 compounds
- Proof-of concept for immunotherapies in humanized models

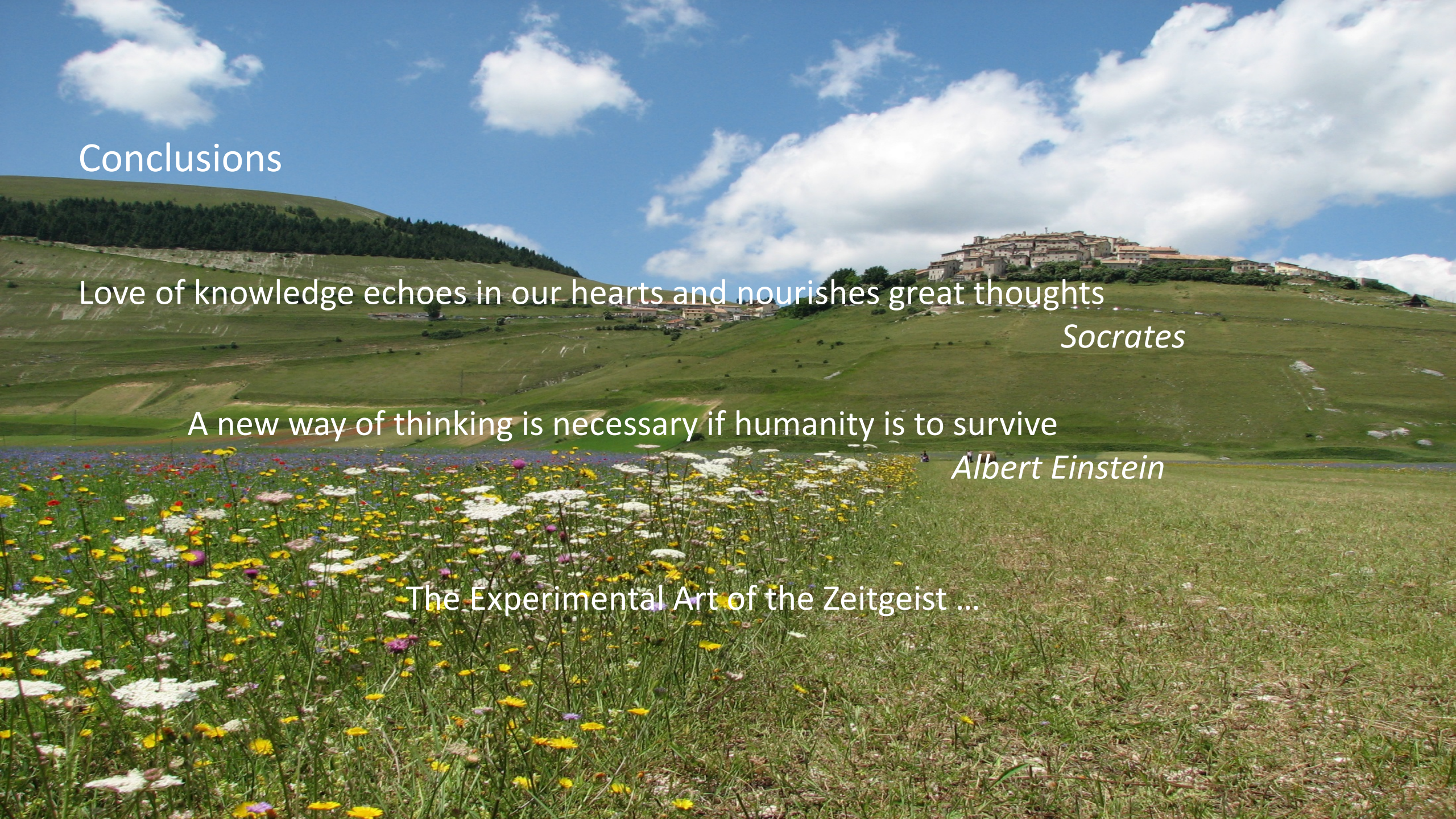
2018/2019 - The End of the Beginning …



IMI2 ITCC-P4

Conclusions

- MAPPYACTS, INFORM, and iTHER show the feasibility of advanced molecular profiling at relapse in a multicentric setting
- Confirm that ‘actionable’ molecular alterations are frequently found in recurrent pediatric cancers
- Few tumors have unique and known targetable driver events
- Proof-of-concept trials are crucial to explore innovate strategies in an enriched setting => from Bedside back to Bench
- Multitude of ancillary research projects
- Only the End of the Beginning …



Conclusions

Love of knowledge echoes in our hearts and nourishes great thoughts

Socrates

A new way of thinking is necessary if humanity is to survive

Albert Einstein

The Experimental Art of the Zeitgeist …

Many thanks to

All patients and parents

Our teams

Pharmaceutical companies

Regulatory bodies

Funders