Precision Medicine in Pediatric Oncology drug development:

The right time to accelerate innovation for children and adolescents with cancer

Gilles Vassal

Amsterdam, January 27, 2017

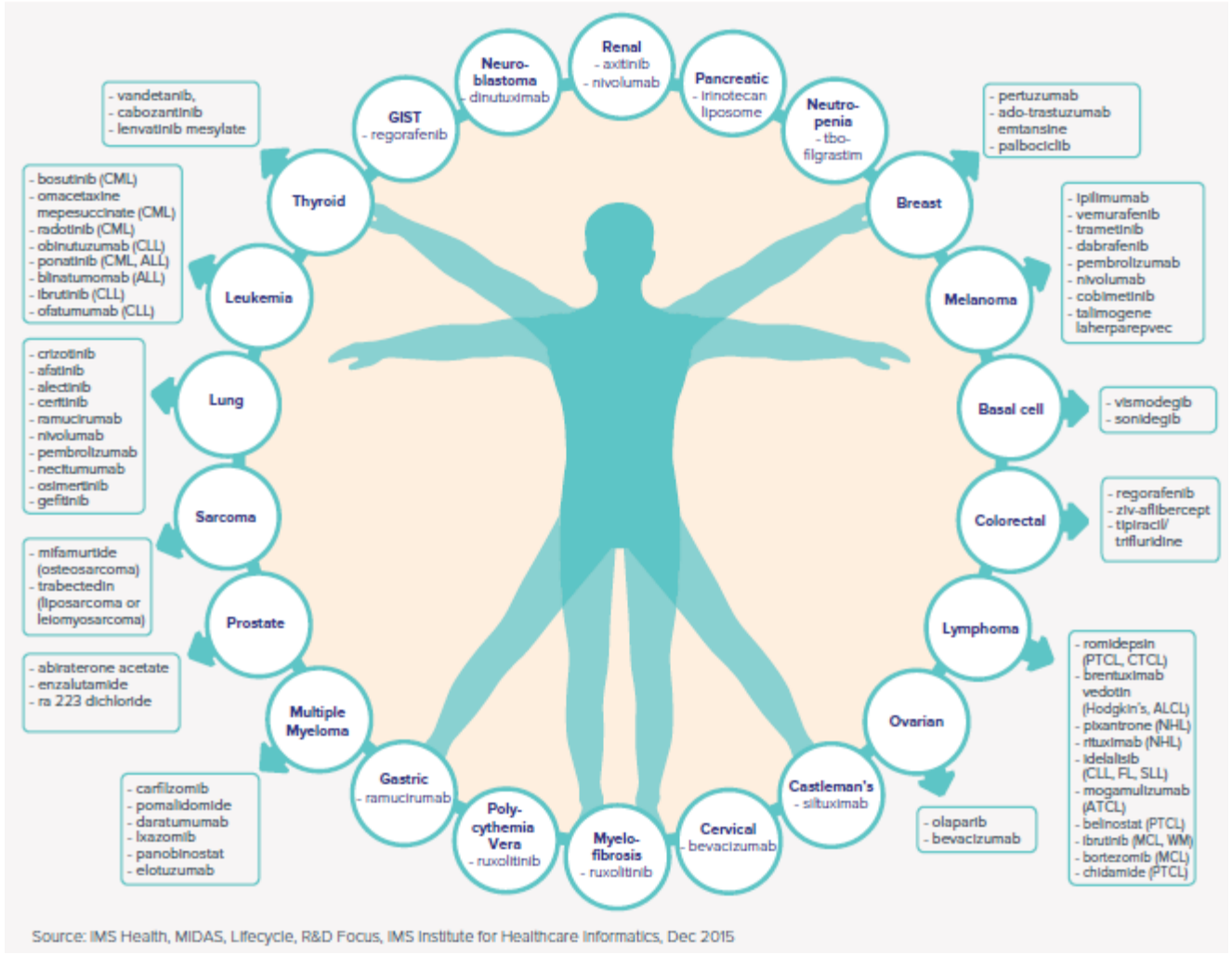
Cancer in Young People in Europe

- 6000 young people die each year of cancer
- Need for safe and effective innovative medicines rapidly introduced in front line

Leading cause of death by disease beyond one year in the EU

http://www.siope.eu/SIOPE_StrategicPlan2015/

From 2011 to 2015, 70 new oncology treatments have been launched for over 20 uses in adults



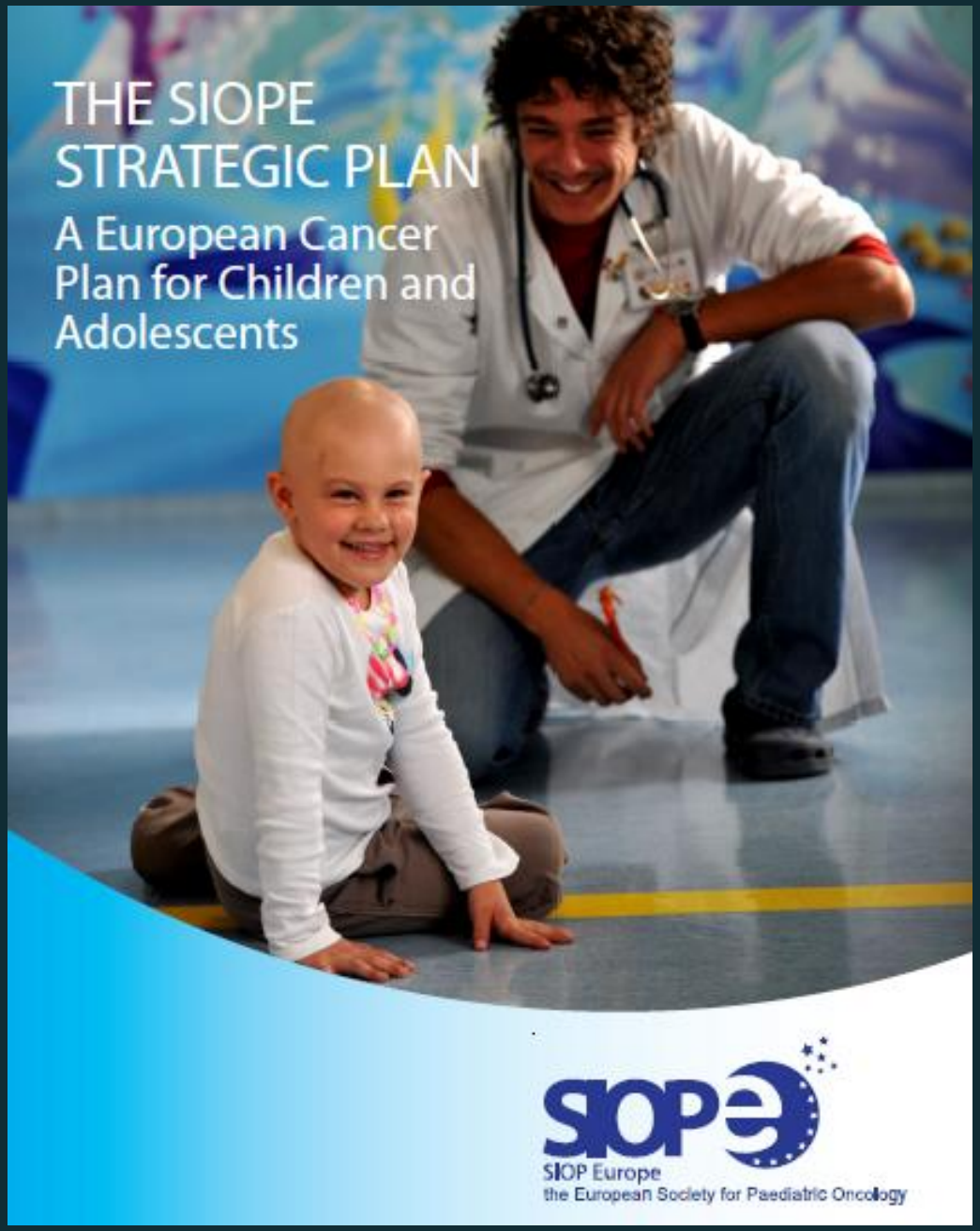
Source: IMS Health, MIDAS, Lifecycle, R&D Focus, IMS Institute for Healthcare Informatics, Dec 2015

2008 – 2016: 4 new anticancer medicines* have been launched for 3 pediatric malignancies through a PIP

- **Unituxin®** (an anti-GD2 monoclonal antibody) for neuroblastoma
- **Votubia®** (mTOR inhibitor) for sub-ependymal giant cell astrocytoma,
- **Spectrila®** (recombinant asparaginase) for ALL*
- **Xaluprine®** (mercaptopurine) for ALL*

* Asparaginase and mercaptopurine have been used for more than 40 years in the treatment of ALL

*1st marketing autorisation after 26 july 2008



http://www.siope.eu/SIOPE_StrategicPlan2015/

SIOPE Strategic Plan; The 7 objectives

1. Innovative therapies
2. Precision medicine
3. Knowledge on biology
4. Equal access
5. Teenager and young adults
6. Quality of survivorship
7. Causes of pediatric cancers

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How to accelerate?

- Science driven pediatric oncology drug development
- Early access to innovative medicines during their adult development
- Investment in developing specific pediatric oncology drugs
- Enlarge the number of drugs in trials through precision medicine
- Increase access to innovative medicines for children in relapse across Europe (goal > 1 in 2 children in 2025)
- Speed up introduction of innovative medicines in front line treatment of high –risk malignancies

Needs

- Science driven pediatric oncology drug development
- Early access to innovative medicines during their adult development
- Investment in developing specific pediatric oncology drugs
- **Enlarge the number of drugs in trials through precision medicine**
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Objective 1

The Innovative Therapies & PCM Programme²

1

A tumor molecular and Immunology portrait at relapse

Molecular Matching Trials

M A T C H

2

Enriched Phase I and II Trials w single agents and combinations

Targeted and immune therapies

All patients are proposed access to new drugs

Innovative Therapies for Children with Cancer

ITCC European consortium

SIOPE SIOP Europe

MERGE

3

New Knowledge

Clinico-Biological Data

Specific Pediatric Drug Development

4

http://www.siope.eu/SIOPE_StrategicPlan2015/

MOlecular Screening for CAncer Treatment Optimization (MOSCATO-01) in pediatric patients:

A prospective molecular stratification trial

PI Birgit Geoerger

- Monocentric, non-randomized, prospective feasibility study (NCT01566019)
- **73 patients (biopsy at relapse) (median age, 11y)**
- **42 (58%) with at least one actionable target**
- **Of whichn 14 (32%) received a matched therapy**

Sponsor : Gustave Roussy, Villejuif, FRANCE

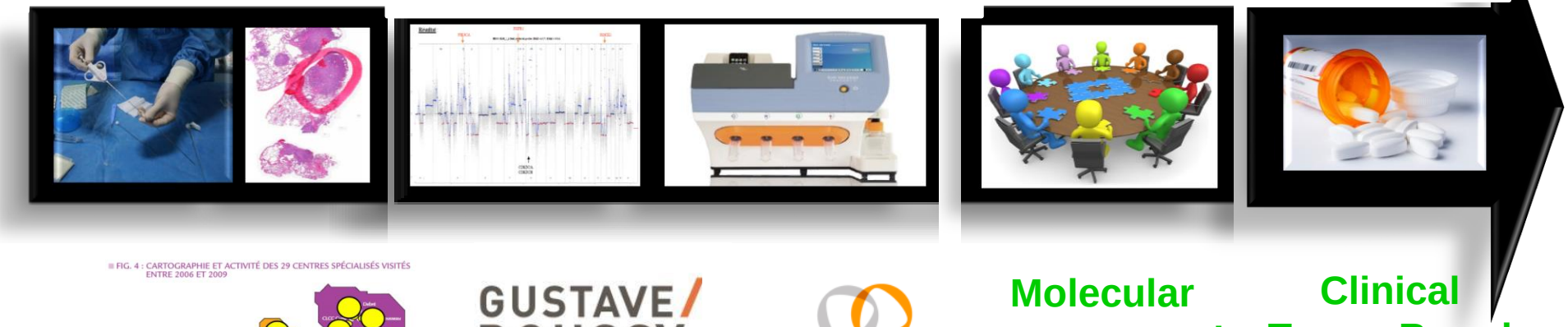
MAPPYACTS

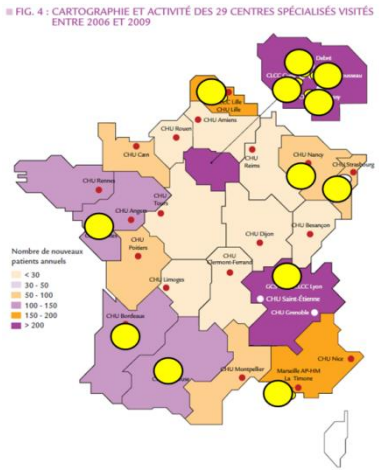
PI: B Geoerger, CoPI: Gudrun Schleiermacher

MoleculAr Profiling for Pediatric and Young Adult Cancer Treatment Stratification

Children and Adolescents, in relapse, solid tumors and leukemias

Biopsy or resection at relapse → **Tumor Molecular Profiling (WES/RNAseq/Immuno)** → **Molecular Report** → **Traitement**





GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

institutCurie Together, let's beat cancer.

Molecular Tumor Board

Clinical Tumor Board

300 children in 3 years
FPI in January 2016
170 patients as of Dec 2016

INSTITUT NATIONAL DU CANCER

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER

INFORM

Pilot Phase → Feasibility-Registry Study (year 1+2)

Lab => bedside

- ALL-HR
- ALL post-SCT
- AML
- NHL
- Neuroblastoma
- Ependymoma
- Medulloblastoma
- High grade glioma
- Soft tissue sarcoma
- Ewing sarcoma
- Osteosarcoma
- Rhabdoid tumors
- Other

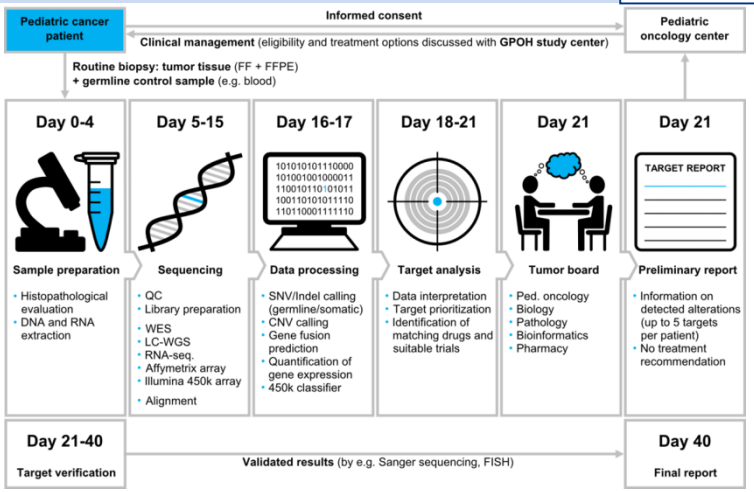
Goals feasibility phase

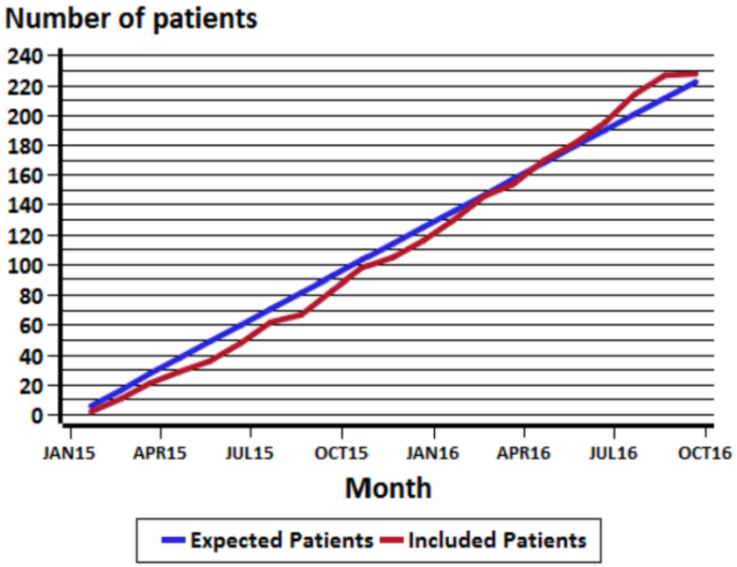
Logistics
⇒ molecular analysis, target identification, turnaround
⇒ individualized risk management
⇒ access mode compounds

Clinical data base
⇒ molecular targets
⇒ documentation of individualized treatments
⇒ clinical courses, tox data

Molecular data
⇒ genomic, epigenomic, transcriptomic profiles

Evaluation of data
⇒ druggable target patterns within/across entities
⇒ set of targeted compounds of interest "tool box"
⇒ define number of eligible patients/year for clinical trial





21.10.2013 — 19.1.2015 — SAB1: 11/2015 — SAB2: 11/2016 — Q2-3 2017 ?

The ITCC Precision Cancer Medicine program

1. Generate molecular profiling for each patient

Molecular Matching Trials at relapse

WES, RNA seq, methylome immunophenotype

- **INFORM** (Germany) — dkfz. German Cancer Consortium
- **MAPPYACTS** (France, Spain, Denmark, Italy) — Institut National du Cancer; Fondation ARC pour la recherche sur le cancer; Gustave Roussy Cancer Campus Grand Paris
- **iTHER** (Netherland)
- **SM- PAED** (UK)

Platform, pipelines and data harmonization

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2. MATCH

3. Evaluate drugs and combinations

Phase 1 & 2 ITCC Trials

(sponsored by industry and ISTs)

MATRIX trial (Genentech/Roche)

eSMART trial

IST multi-agent from multi-company

AcSé; Gustave Roussy Cancer Campus Grand Paris; Imagine for Margo Children without Cancer; Institut National du Cancer; Fondation ARC pour la Recherche sur le Cancer

INFORM2 — dkfz. German Cancer Consortium

4. Create

European clinico – biological database

5. New knowledge

new druggable pathways
for specific pediatric drug development

1000 exomes in relapse

Innovative Therapies for Children with Cancer
ITCC European consortium
AcSé INSTITUT NATIONAL DU CANCER
e★smart
European proof of concept therapeutic stratification trial of molecular anomalies in relapsed or refractory tumors in children
IMAGINE FOR Margo Children without CANCER
FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Patient with tumor molecular profile at relapse (WES, RNAseq, Immuno)

MATCH

MATCH

ITCC #	Agent/Combo
ITCC-021	E
ITCC-024	P
ITCC-025	I
ITCC-027	E
ITCC-011	N
ITCC-015	V
ITCC-037	G
ITCC-033	N C
ITCC-034	I
ITCC-041	L
ITCC-022	V
ITCC-032	T
ITCC-045	V
ITCC-038	A
ITCC-047	R
ITCC-044	D
ITCC-050	L
ITCC-036	P
ITCC-049	A
ITCC-0xx	N
ITCC-0xx	M
ITCC-0xx	M
ITCC-0xx	T

Portfolio of ITCC phase I and phase II trials

AcSé INSTITUT NATIONAL DU CANCER **eSMART** GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

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

IST - phase I/II
single agent and combo

Goal >10 drugs from >3 Companies

Wave 1: 7 treatment arms with 5 drugs from AZD, Novartis, BMS

launched august 2016

Multistakeholder Paediatric Oncology Platform

To improve new oncology drug development for children

December 2013

Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer

Eur J Cancer 2015;51:218.

Gilles Vassal [a,*], Raphaël Rousseau [b], Patricia Blanc [c], Lucas Moreno [d], Gerlind Bode [e], Stefan Schwoch [f], Martin Schrappe [g], Jeffrey Skolnik [h], Lothar Bergman [i], Mary Brigid Bradley-Garelik [j], Vaskar Saha [k], Andy Pearson [l], Heinz Zwierzina [m]

Academia,
Industry,
Parents,
Regulatory Bodies

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

www.accelerate-platform.eu

CDDF - ITCC - SIOPE 4th Paediatric Oncology Conference

ACCELERATING THE DEVELOPMENT OF NEW ONCOLOGY DRUGS FOR CHILDREN AND ADOLESCENTS

20-21 January 2016
Brussels, Belgium

Proposals

1. Pediatric development should be based on drug **mechanism of action** instead of adult indication
2. **Prioritisation** should be set up to choose compounds to be evaluated or not in children
   - Based on MOA, needs, feasibility
   - Using stonger biological and preclinical data
3. **Reduce delay in starting pediatric development**
4. **Break the 18 years dogma**
5. **New incentives and rewards**

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

CDDF ITCC SIOPE

Cause of children with cancer

Champions in the Parliament

Elena Gentile ,Françoise Grossetête,
Alojz Peterle, Glenis Willmott

European Parliament

Resolution of the EU Parliament voted in15 December 2016 (2016/2902(RSP))

Conclusion

- Precision Medicine in Pediatric Oncology drug development:
  The right time to accelerate innovation for children and adolescents with cancer
- Work together and re-invent partnerships

ACCELERATE Multistakeholder Paediatric Platform

5th Annual Paediatric Oncology Conference

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

SAVE THE DATE

2-3 March 2017 | Brussels, Belgium

March 2nd & 3rd, 2017