How to take Genetic Data to Clinical Practice in Oncology

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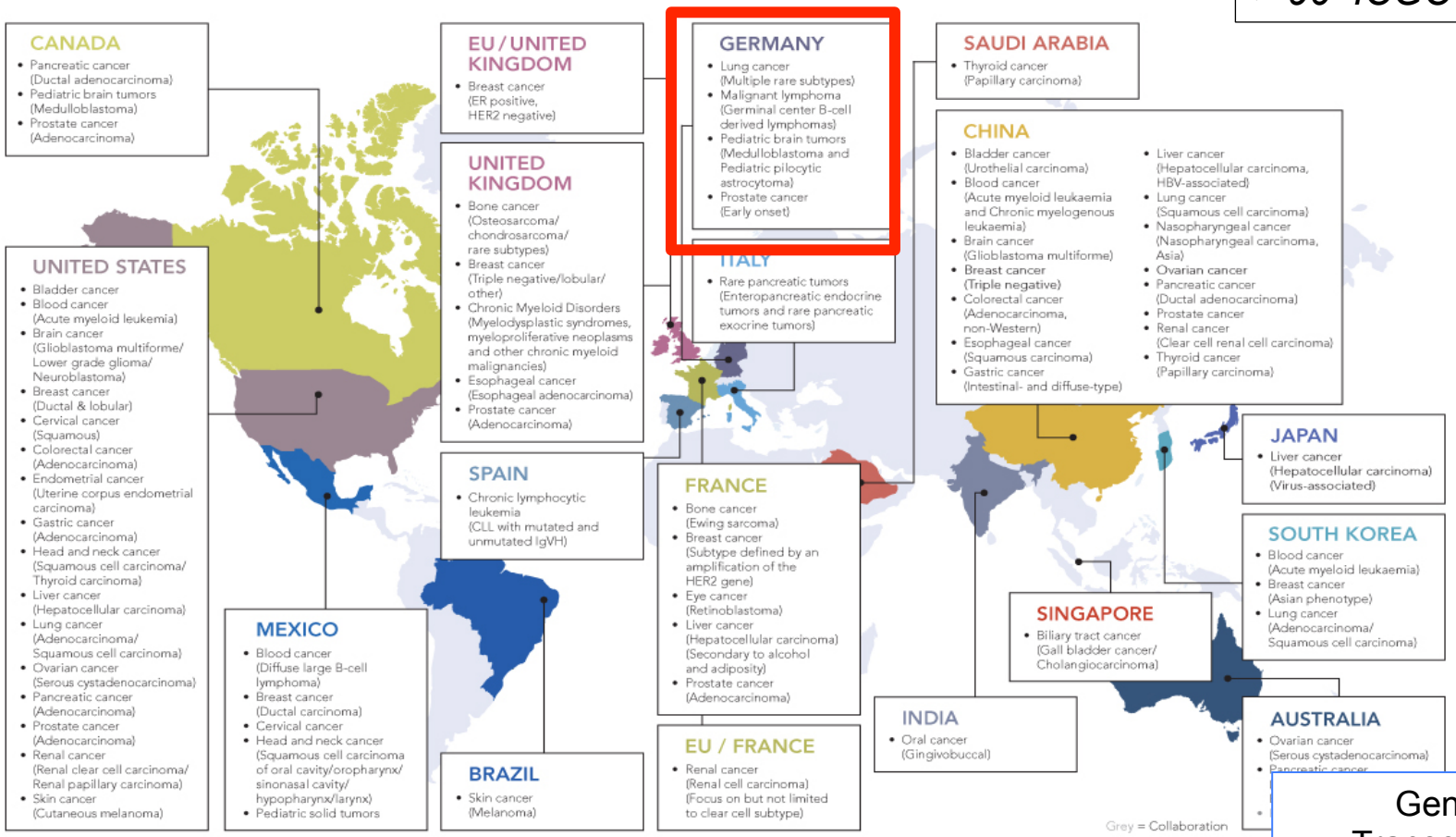
dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

50 Years – Research for A Life Without Cancer

International Cancer Genome Consortium

> 90 ICGC Projects



- PedBrain Tumor (Pediatric Brain Tumors)
- Prostate Cancer ("Early Onset")
- MMML Seq (Molecular Mechanisms in Malignant Lymphoma)

Genome
Transcriptome
Methylome
Clinical Annotation

Tom Hudson et al.
Nature 464
993-998 (2010)

ICGC

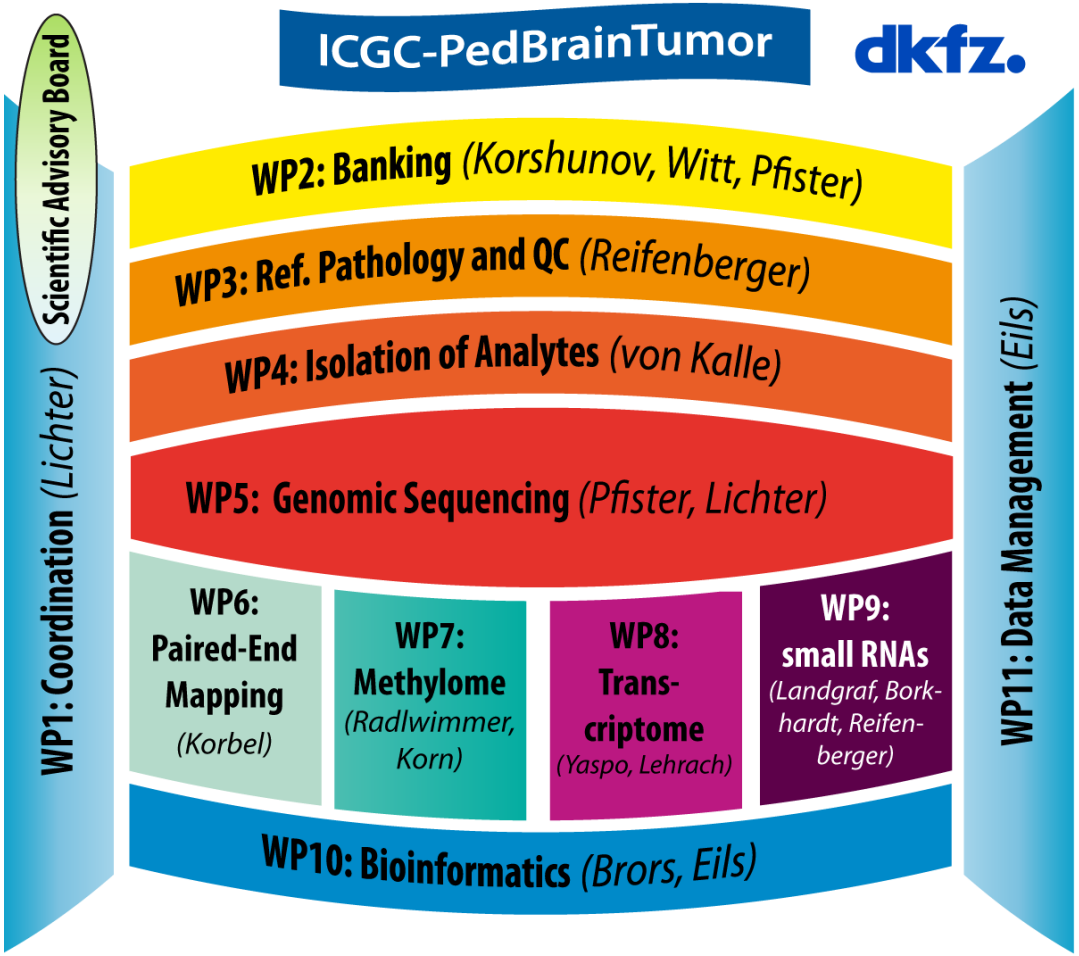
Low-grade Astrocytoma

Medulloblastoma

Glioblastoma

Ependymoma

> 600



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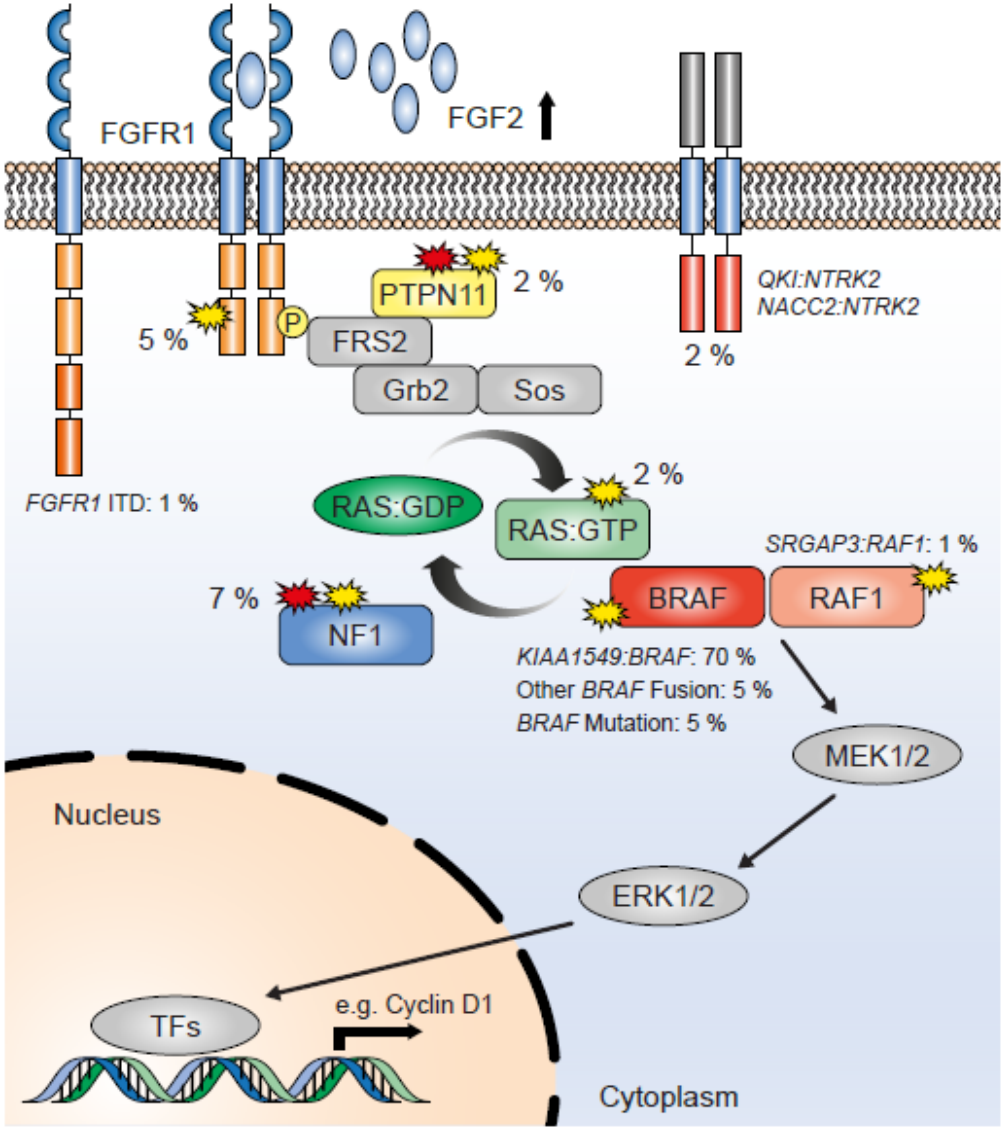
National Center for Tumor Diseases – NCT
University Hospital Heidelberg
European Molecular Biology Laboratory – EMBL
University Düsseldorf
Max-Planck-Institute for Molecular Genetics – MPI-MG

Pilocytic Astrocytoma



n = 96

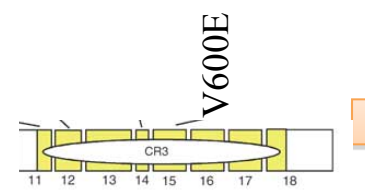
- Novel "actionable" targets
- Alterations in one pathway in 100% of cases
- Pilocytic Astrocytoma: a "single pathway" disease!

=> „Druggable" mutations

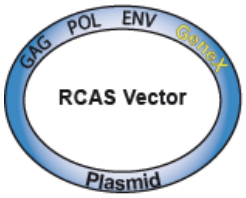
=> Therapy options

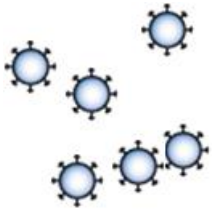
Jones, Hutter, Jäger et al. Nature Genetics 2013

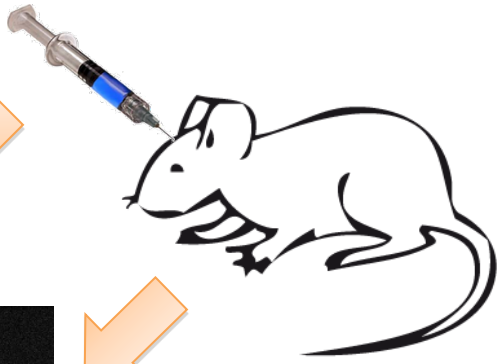
Preclinical model



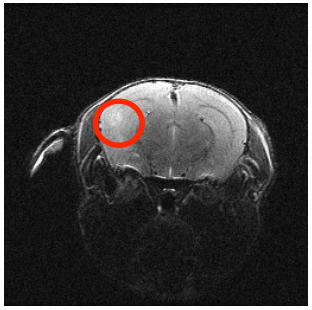
BRAF kinase domain







Construct	Incidence (tumors/dead)
BRAF wt FL	0/10
BRAF V600E FL	0/10
BRAF wt Kin	0/10
BRAF V600E Kin	26/29 (89%)

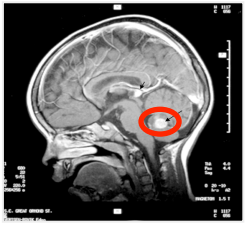


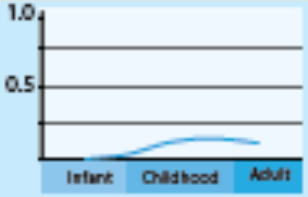
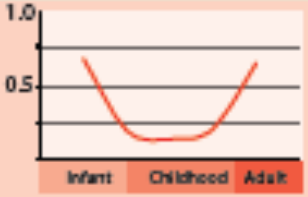
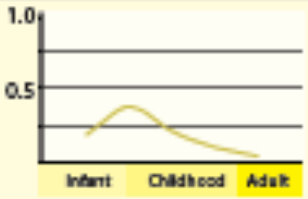
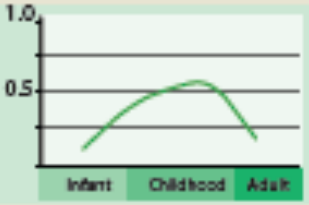
Pilocytic Astrocytoma

Gronych et al., J Clin Invest, 2011

⇒ Currently used to test inhibitors of BRAF and other MAP kinase pathway factors

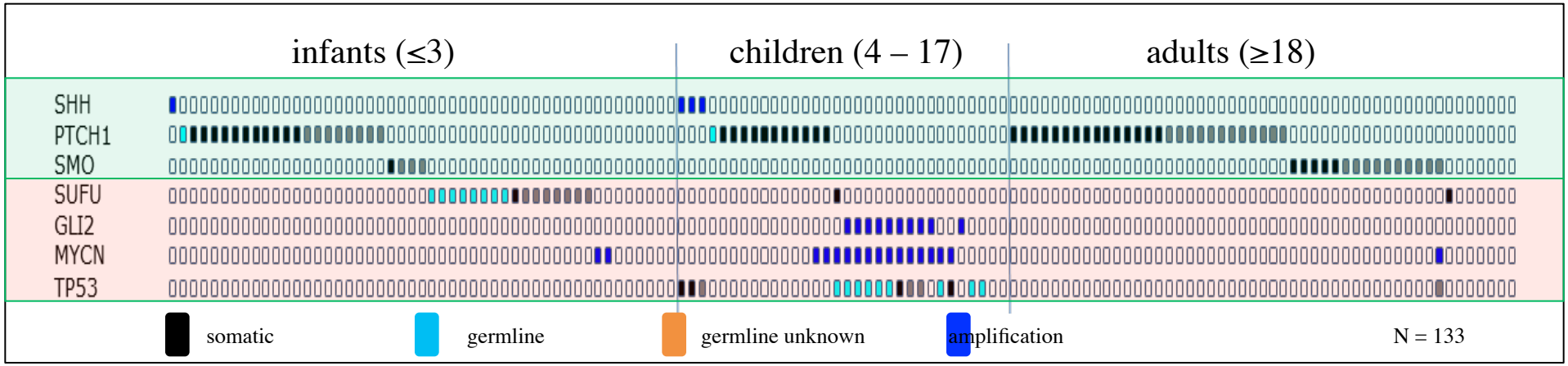
Medulloblastoma: Molecular Classification

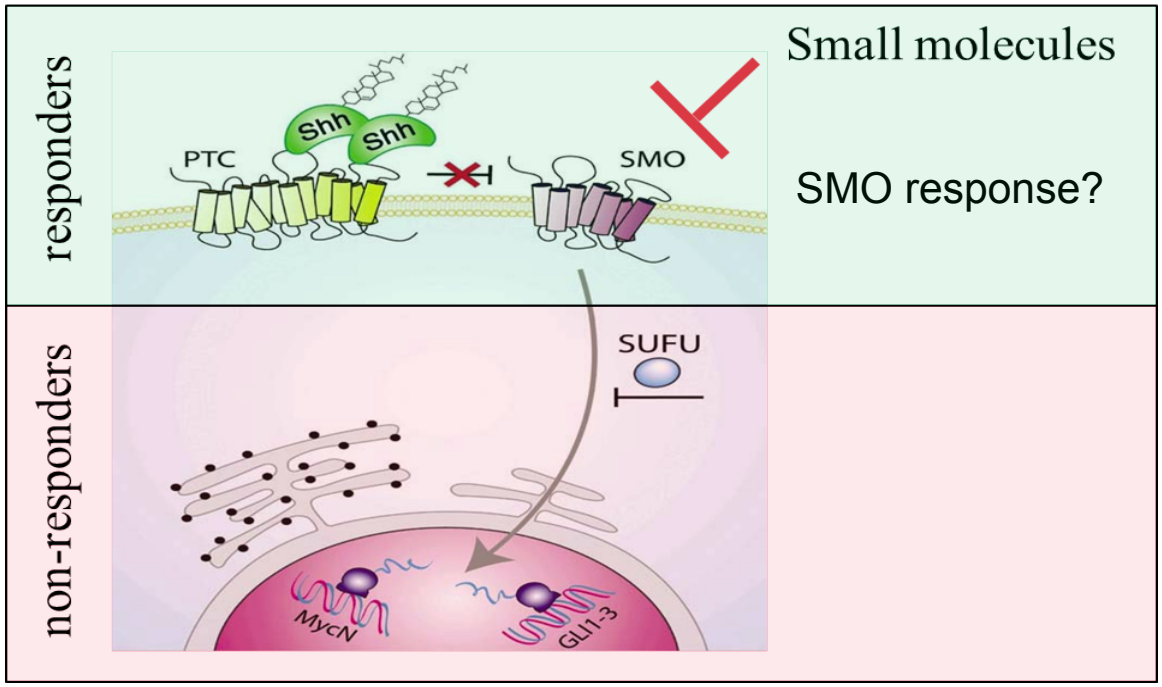


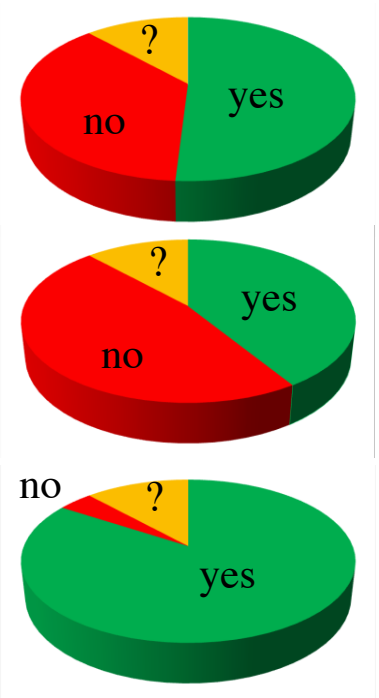
	WNT	SHH	Group 3	Group 4
Subgroup				
Gender ratio				
Age distribution				
Histology	Classic; very rare LCA	Classic> Nodular > LCA >MBEN	Classic > LCA	Classic; rarely LCA
Metastasis @ Dx	~5-10%	~15-20%	~40-45%	~35-40%
Patient Survival	~95% OS	~75% OS	~50% OS	~75% OS
Proposed Cell of origin	Lower rhombic lip progenitor cells	CGNPs of the EGL and cochlear nucleus; neural stem cells of SVZ	Prominin 1(+), lineage(-) neural stem cells; CGNPs of the EGL	Unknown

Northcott et al. Nature Reviews Cancer 2012

Infants, children & adult SHH-MBs: different mutations in pathway





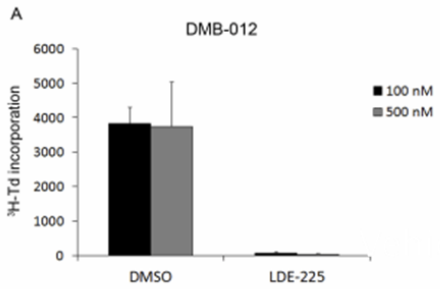


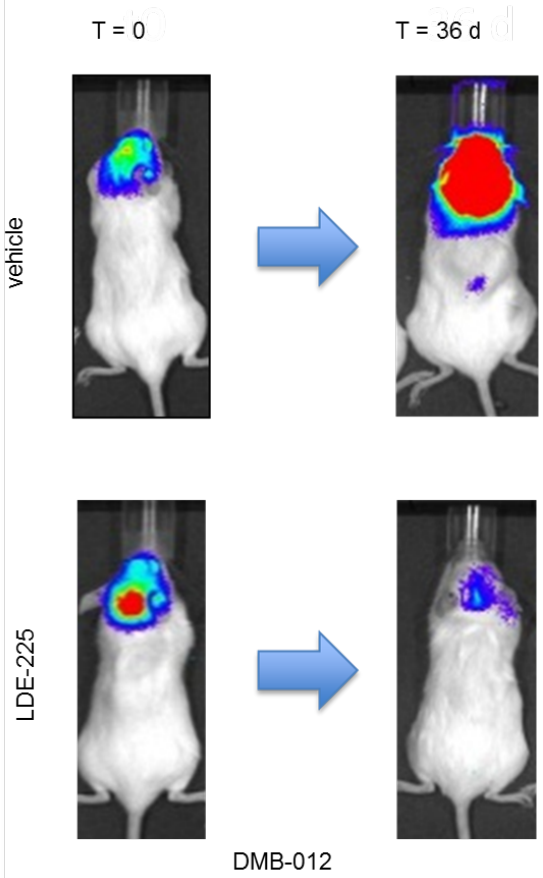
Kool et al., Cancer Cell 2014

SMO inhibition in different SHH models

A

3 yr old female, desmoplastic PTCH1 mutation



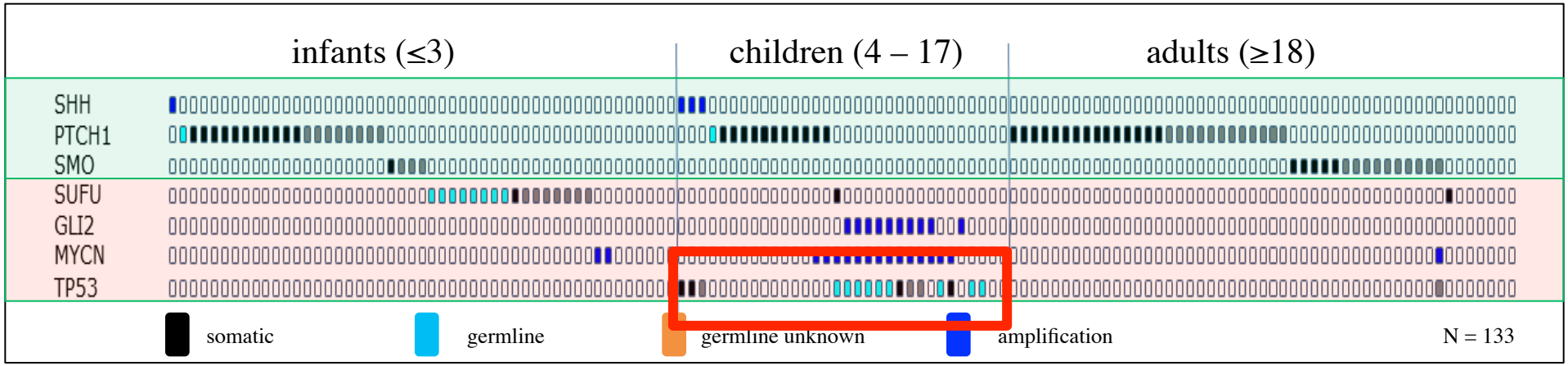


LDE-225, a drug already tested in clinical trials

Rob Wechsler-Reya

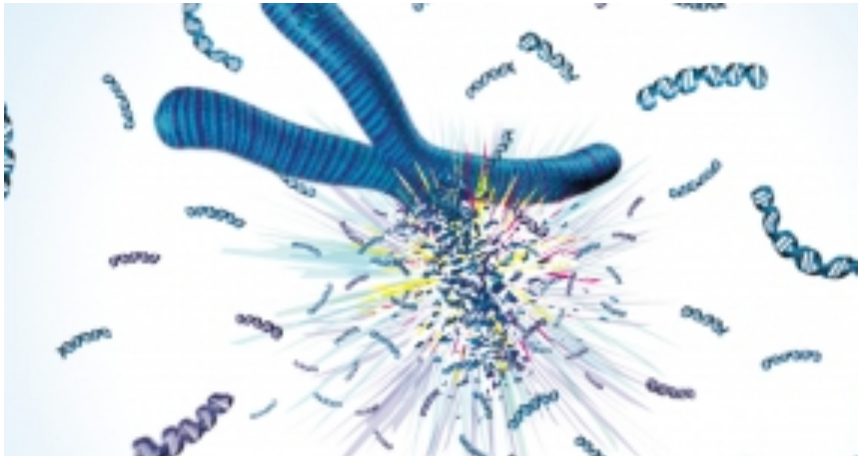
Kool et al., Cancer Cell 2014

Infants, children & adult SHH-MBs: different mutations in pathway



Kool et al., Cancer Cell 2014

TP53 Mutations in SHH-Medulloblastoma are linked to chromothripsis and are germline mutations



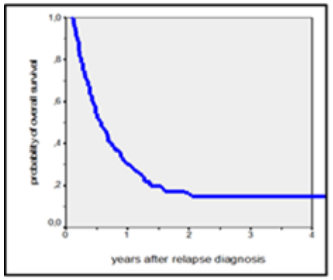
Chromothripsis

Clinical implications:
⇒ no SMO-inhibitors
⇒ minimize radiation
⇒ genetic counseling

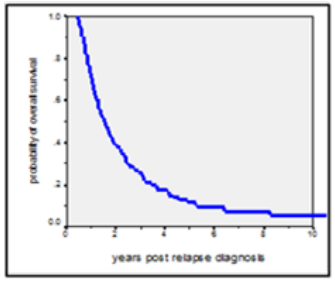
Rausch et. al, Cell 2012

Survival curves for relapsed pediatric patients

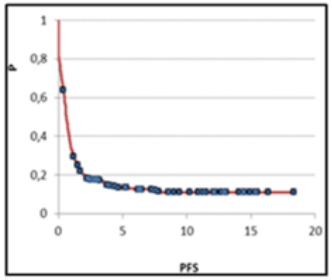
ALL-HR



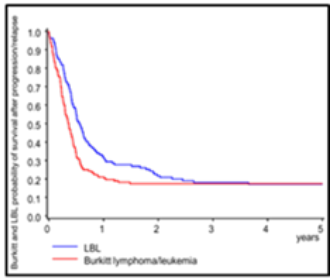
ALL post-SCT



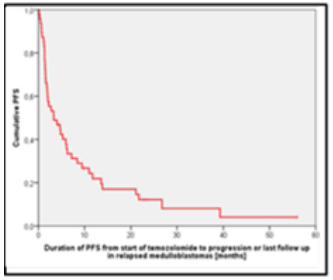
AML



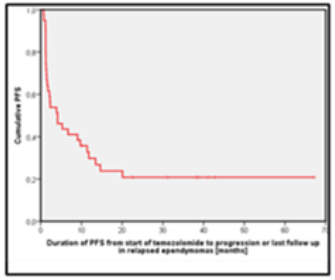
NHL



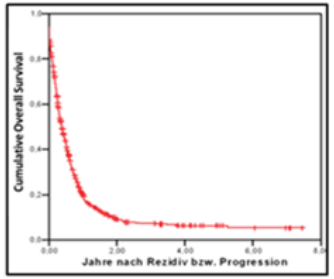
Medulloblastoma



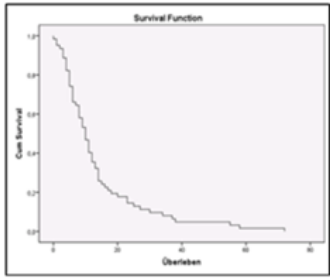
Ependymoma



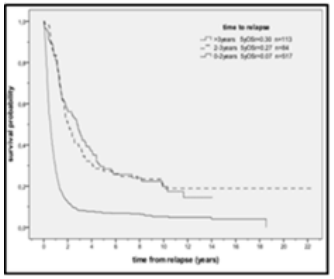
HGG (incl. DIPG)



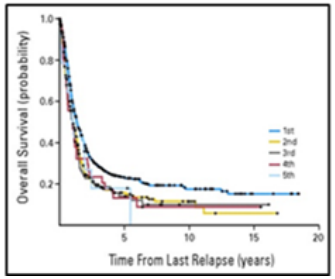
Rhabdoid Tumors



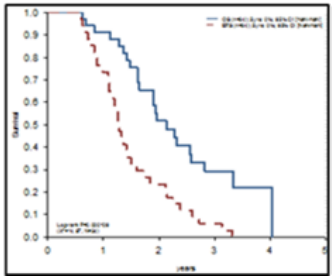
Ewing Sarcoma



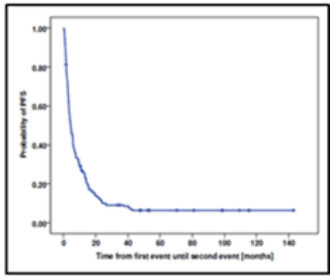
Osteosarcoma



Rhabdomyosarcoma

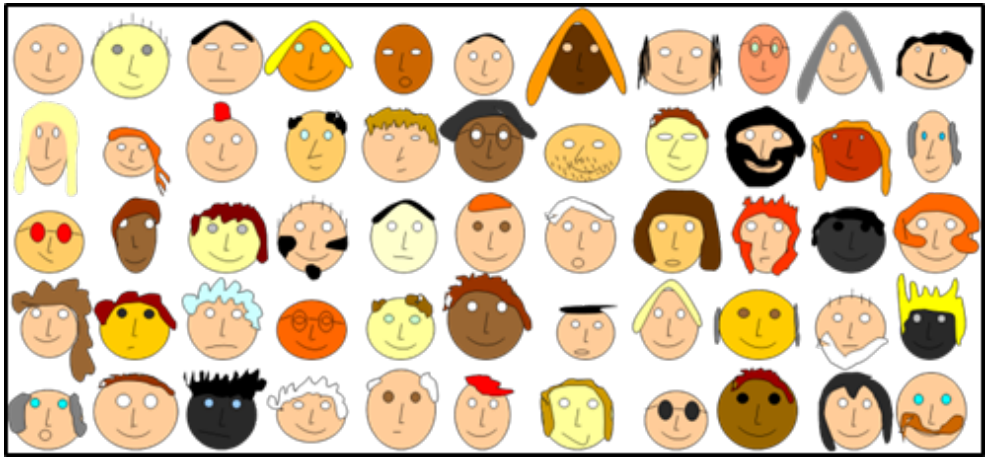


Neuroblastoma



INdividualized therapy FOr Relapsed Malignancies in childhood

INFORM: next-generation diagnostics for children with progressive/relapsed malignancies



German Cancer Consortium

NATIONAL CENTER FOR TUMOR DISEASES HEIDELBERG

Stefan Pfister

Peter Lichter

Angelika Eggert

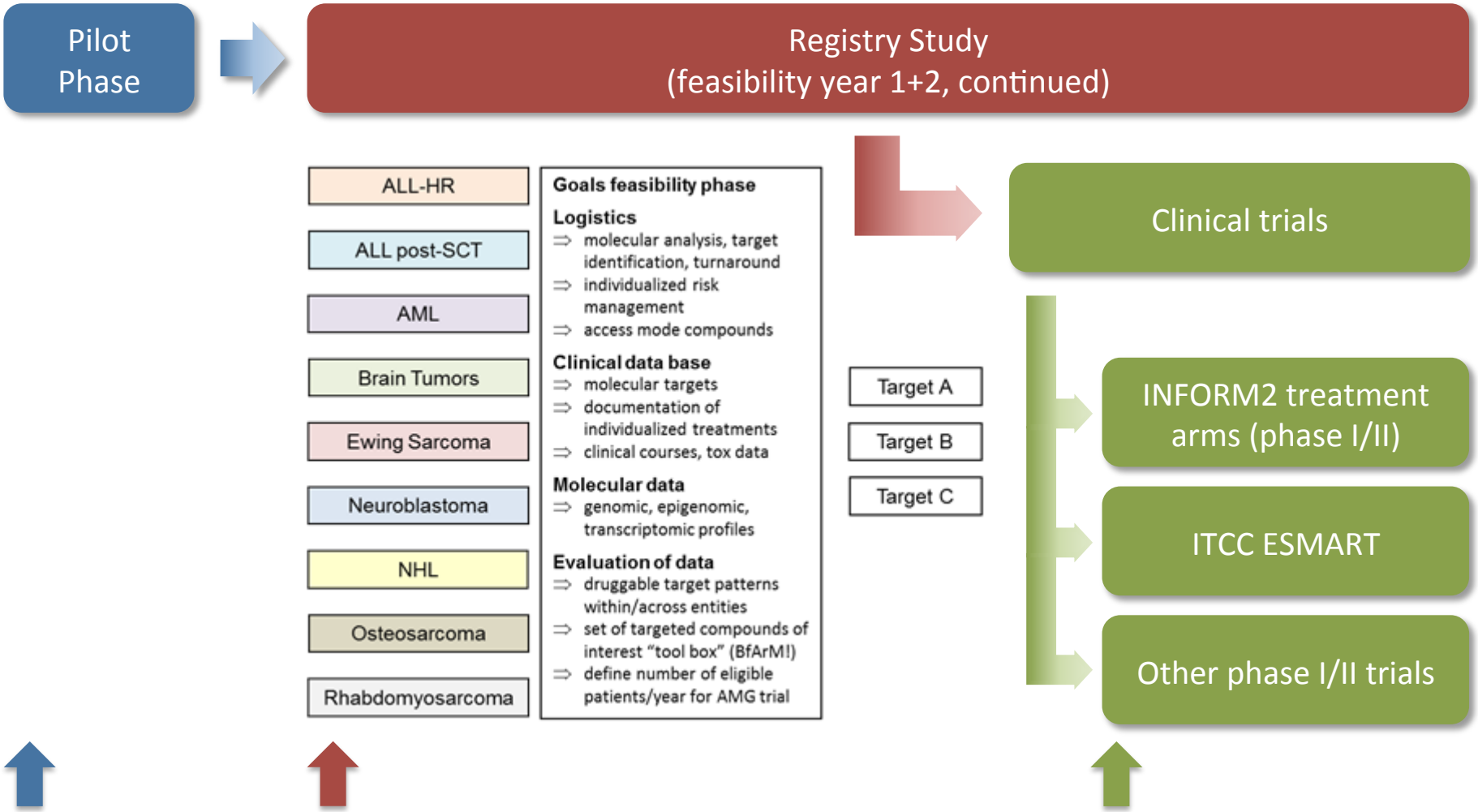
Olaf Witt

UniversityHospital Heidelberg

INFORM

INFORM

Identification of actionable targets by NGS => molecular tumor board => targeted therapy approaches



INFORM: Molecular Analysis

Copy-number changes

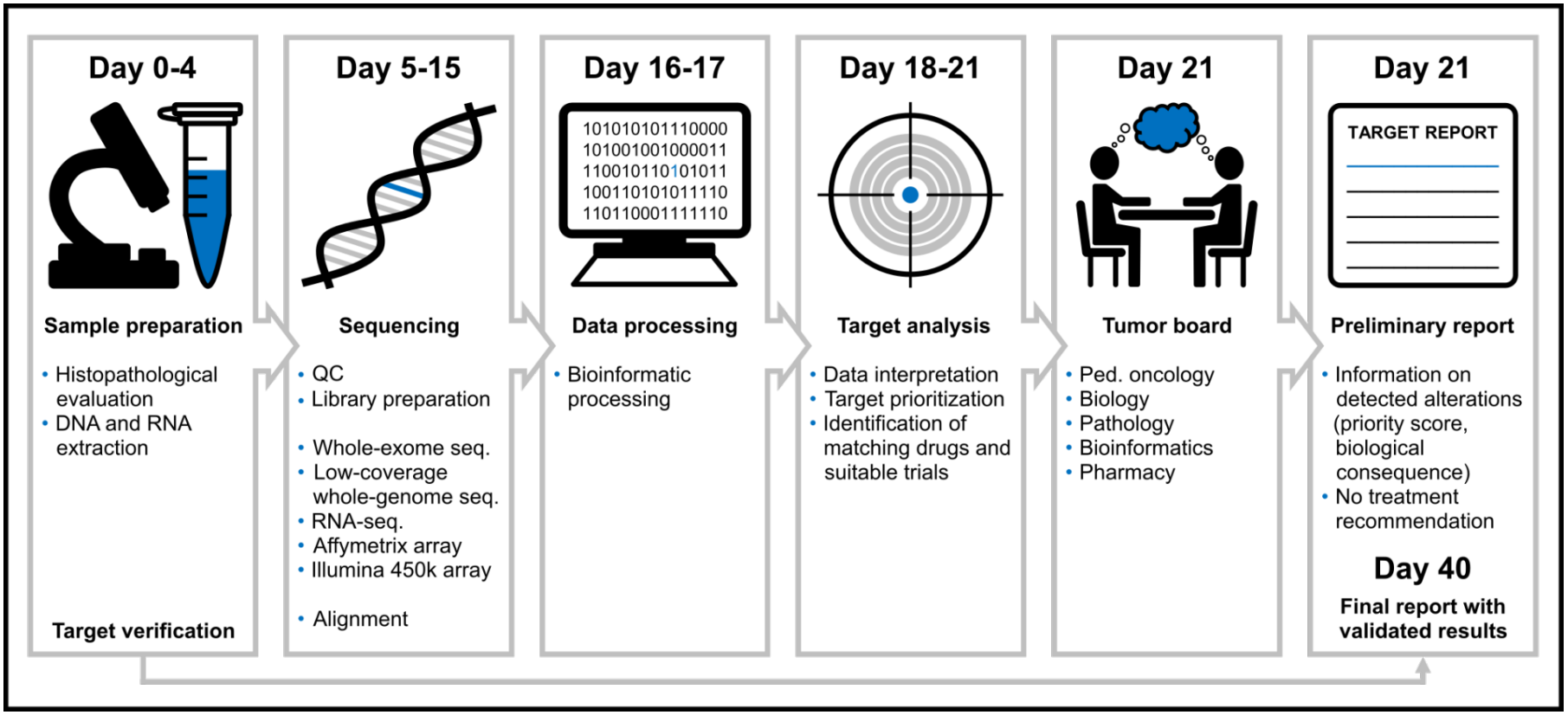
SNVs/InDels
- somatic (drug targets, ADME)
- germline (tumor predisposition, ADME)

- Fusion genes
- Expression of somatic SNVs
- Changes in gene expression

- Changes in gene expression
  (comparison with entity specific reference cohorts)

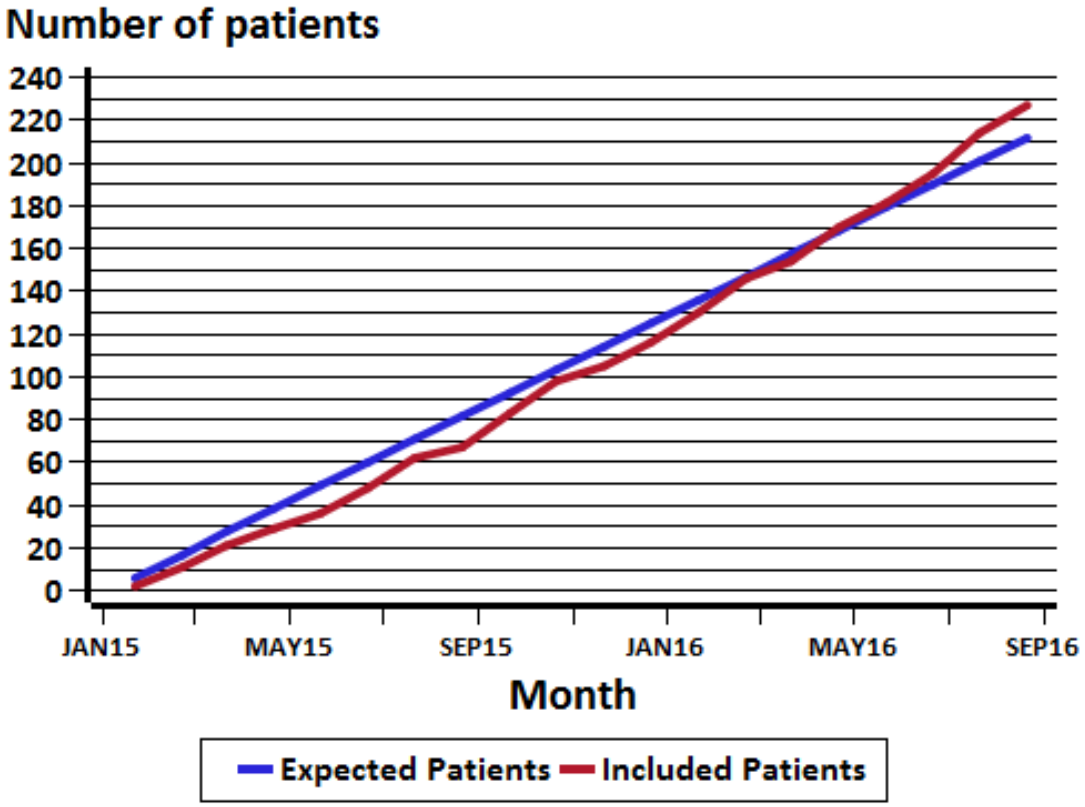
- Classification (e.g. brain tumors)
- Gen-Silencing

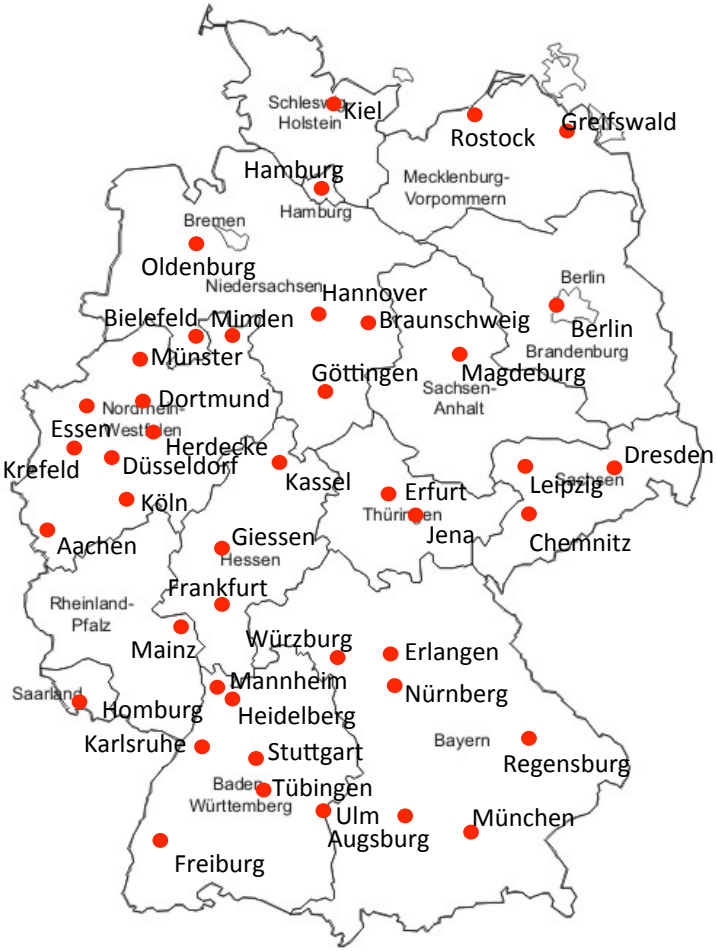
INFORM – Workflow Heidelberg



Worst et. al, Eur J Cancer, 2016

INFORM recruitment Germany (registry phase, 01/2015-09/2016)





INFORM Patients (pilot/registry phase, 10/2013-09/2016)

291 patients approached

sex:	female	130
	male	161
age:	average	13 years
	min	1 year
	max	40 years

→ 34 ineligible

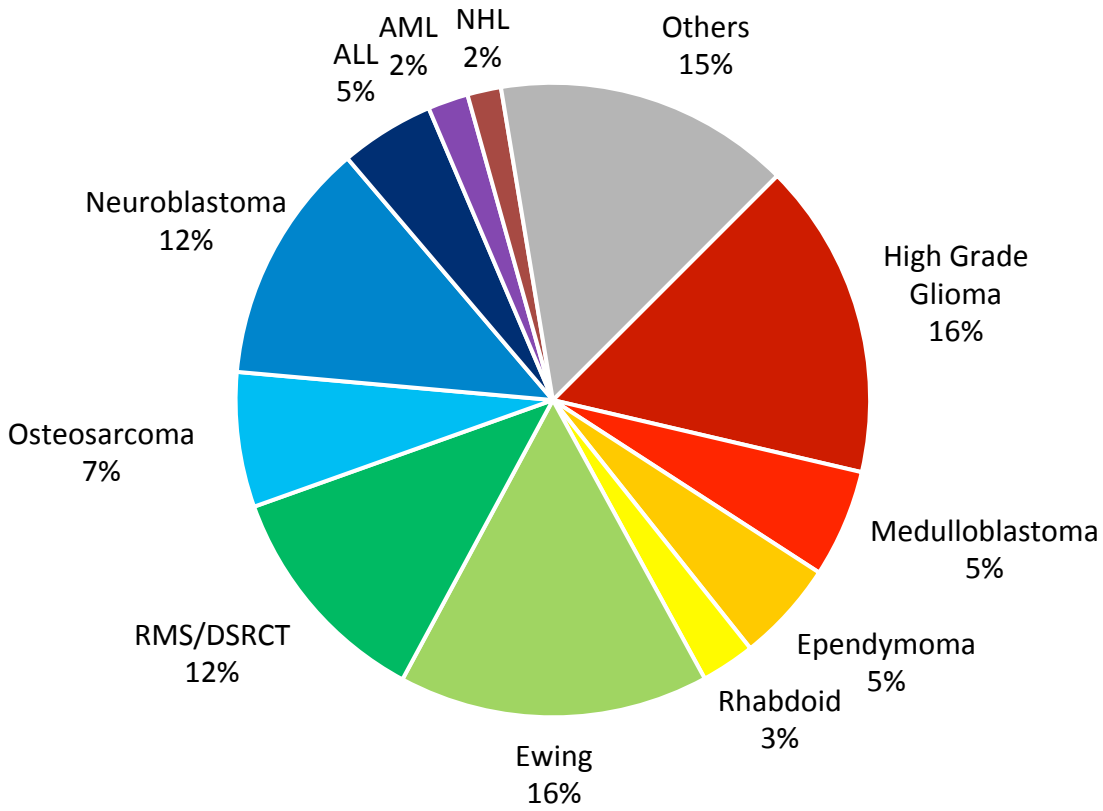
257 patients enrolled

→ 7 insufficient/no tumor

237 patients sequenced

→ 5 no tumor

232 patients analyzed
(13 patients pending)



Target Priorization – stratification for INFORM2

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	Any	Genetic hit
	Overexpressed driver	Specific	Protein/Expression Change
Borderline	Possible driver	Any	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

Algorithm to be tested in INFORM2

Can a higher score predict a better response/outcome?

± 60% of patients:
Target with Score ≥ intermediate

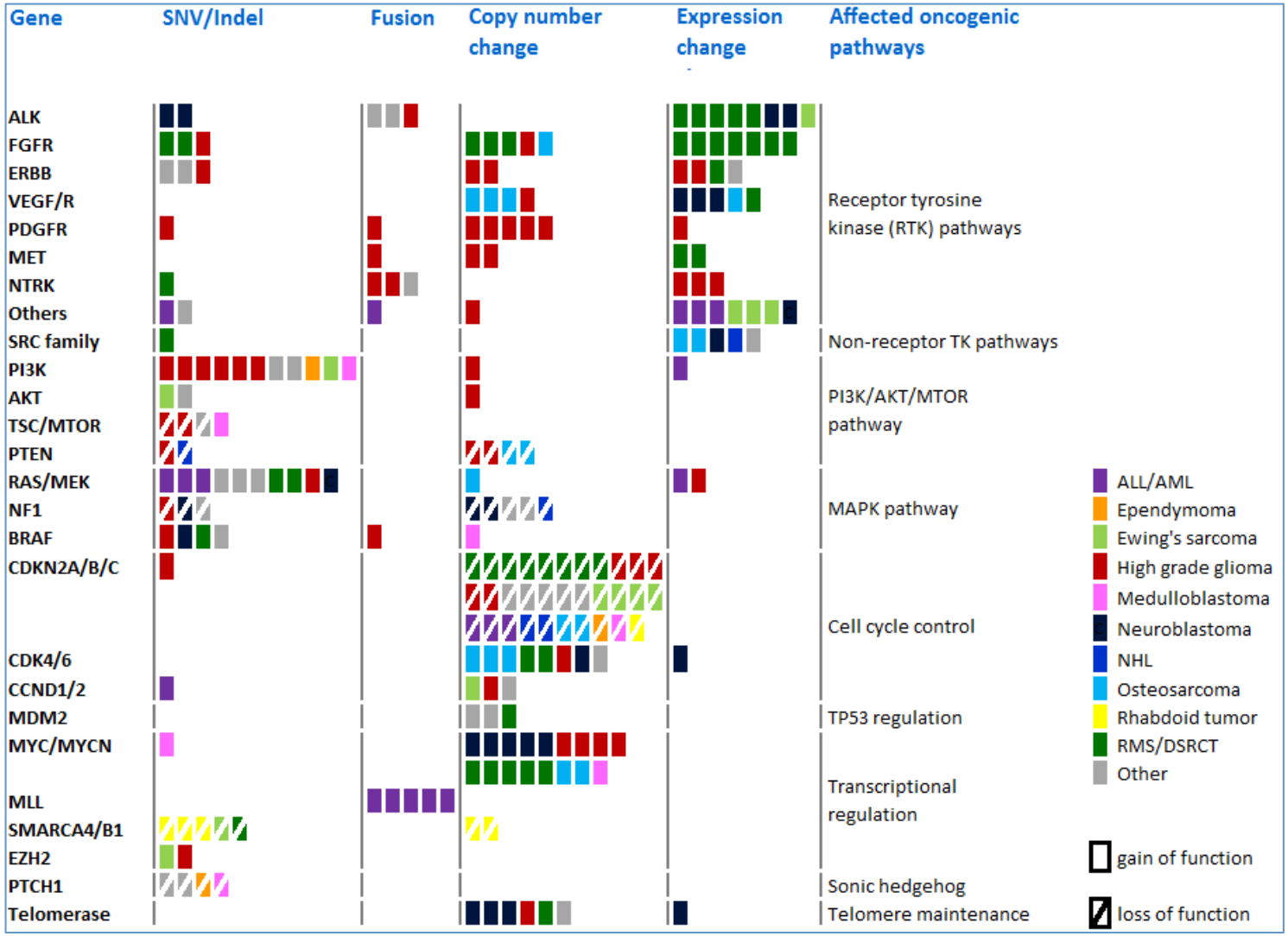
↑

± 85% of patients:
Potentially actionable target

↑

All analyzed patients: 100 %

Targets mit Score ≥ intermediate (198 patients, 10/2013-06/2016)



Worst et. al, Eur J Cancer, 2016

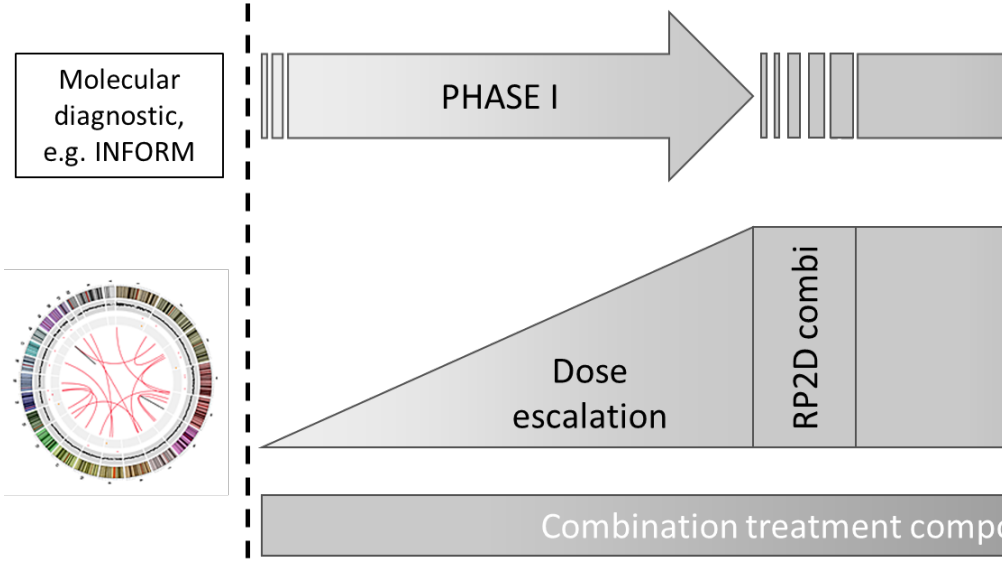
INFORM2 plans – clinical trials

Design principles

- Entity versus **target** driven approach
    - limited number of recurrent actionable alterations
- Mono- versus **combination** therapy
    - but at least one drug with pediatric RP2D (recommended phase II dose)
- Phase I versus phase **I/II**
    - fast escalation phase I (assuming no interactions and known toxicity profile) to max. 100% pediatric RP2D
    - seamless phase II thereafter
- Multi-arm versus **multiple trials**
    - multiple trials in 1 mock-up protocol (medical regulatory body: BfArM)

INFORM2 plans – potential subtrials

Compound class 1	Compound class 2
MET/ALK/ROS1 inhibitor	MEK1/2 inhibitor
RTK inhibitor (e.g. ABL, PDGFR, VEGFR2 Src, RET, FGFR, NTRK)	MEK1/2 inhibitor
PI3K inhibitor	HDAC inhibitor
anti-PD-1 antibody	-



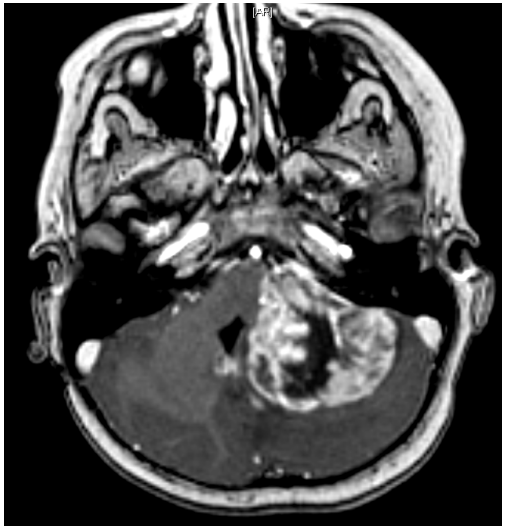
Examples:

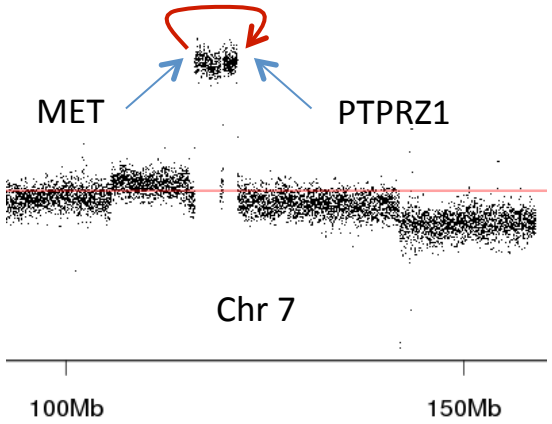
- Stratum A: panTKi + MEKi
- Stratum B: „spec"TKi + MEKi
- Stratum C: EZH2i + DNMTi
- Stratum D: PI3Ki + MEKi
- Stratum E: RAFi + MEKi
- Stratum F(i): HDACi + BETi/AURKi
- Stratum G: METi + MEKi
- Stratum H: ALKi + MEKi
- Stratum I: SMOi + PI3Ki
- Stratum K: CDKi + MEKi
- Stratum L: MDM2i + MEKi

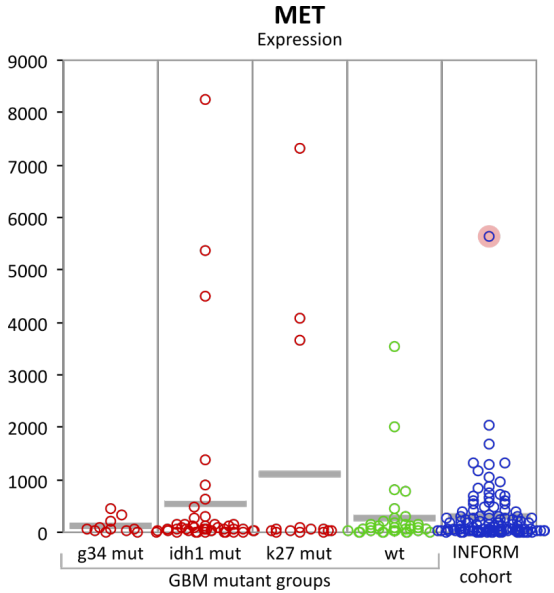
Patient example I

***2006, male**

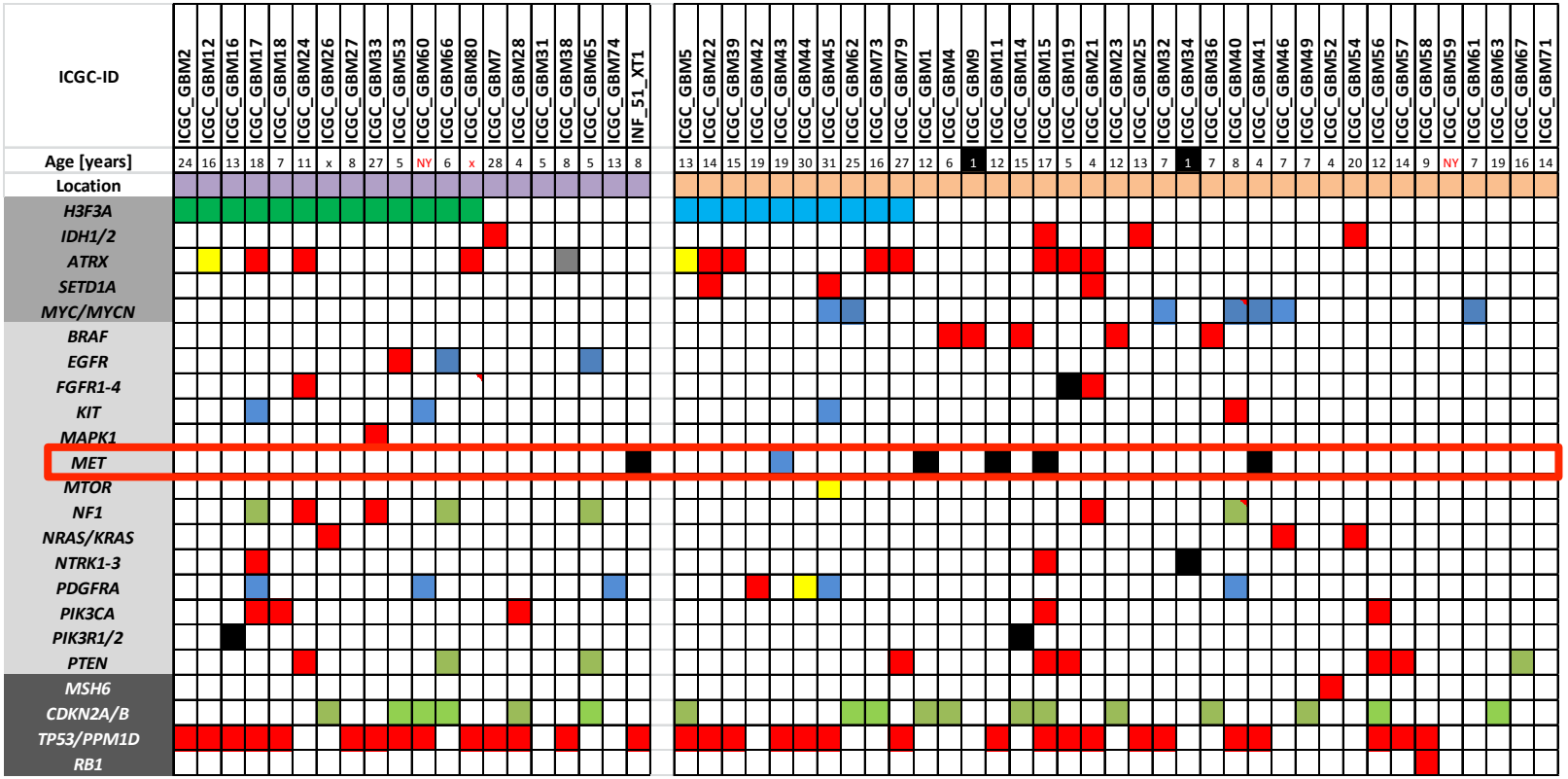
- 04/2011: initial diagnosis of a metastasized group 3 **Medulloblastoma** treatment according to the standard protocol (incl. craniospinal irradiation)
- 09/2014: massive tumor growth
- 10/2014: **INFORM** analysis: **PTPRZ1-MET fusion** with **amplification** and **overexpression** of **MET** + **TP53** mutation (most likely radiation-induced **Glioblastoma**)

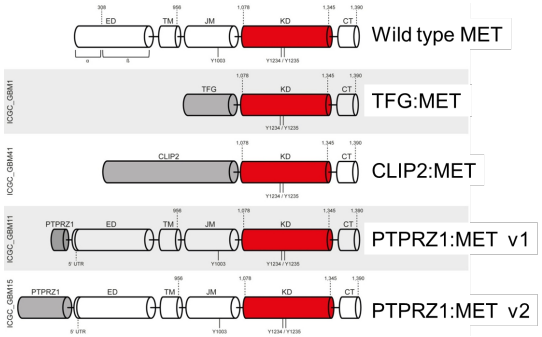






Sequencing of 55 Pediatric Glioblastoma

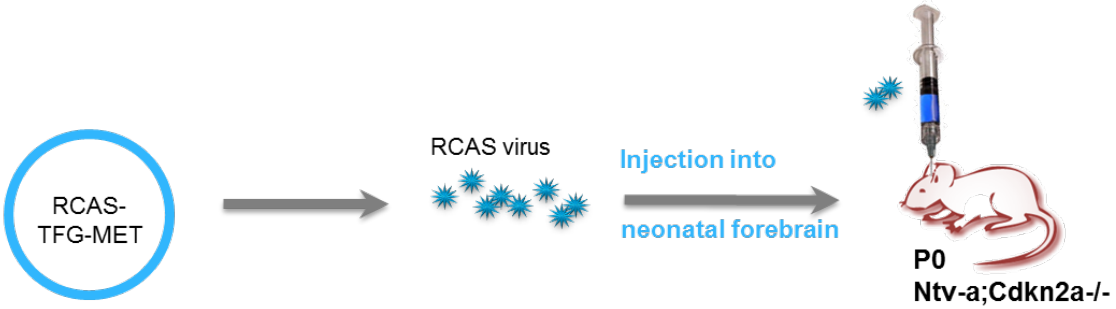


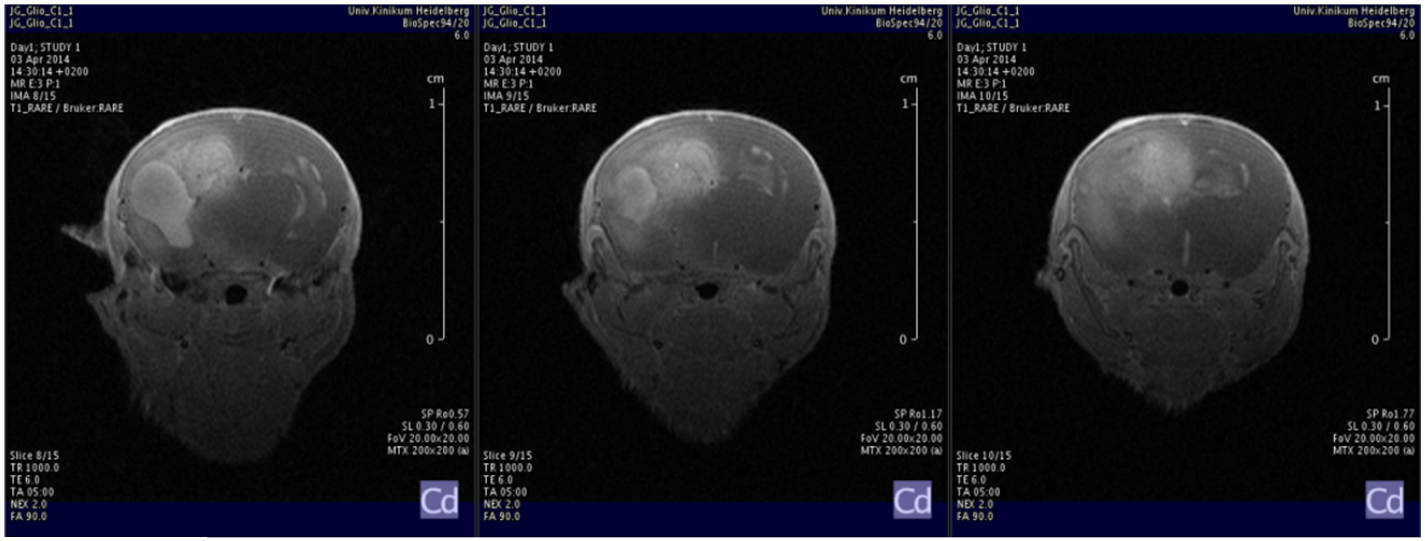


RNAseq showed recurrent fusions involving *MET*

ICGC PedBrain Paper:
Bender et al., *Nature Medicine* (Oct 17, 2016)

Mouse model: MET fusion causative for glioblastoma

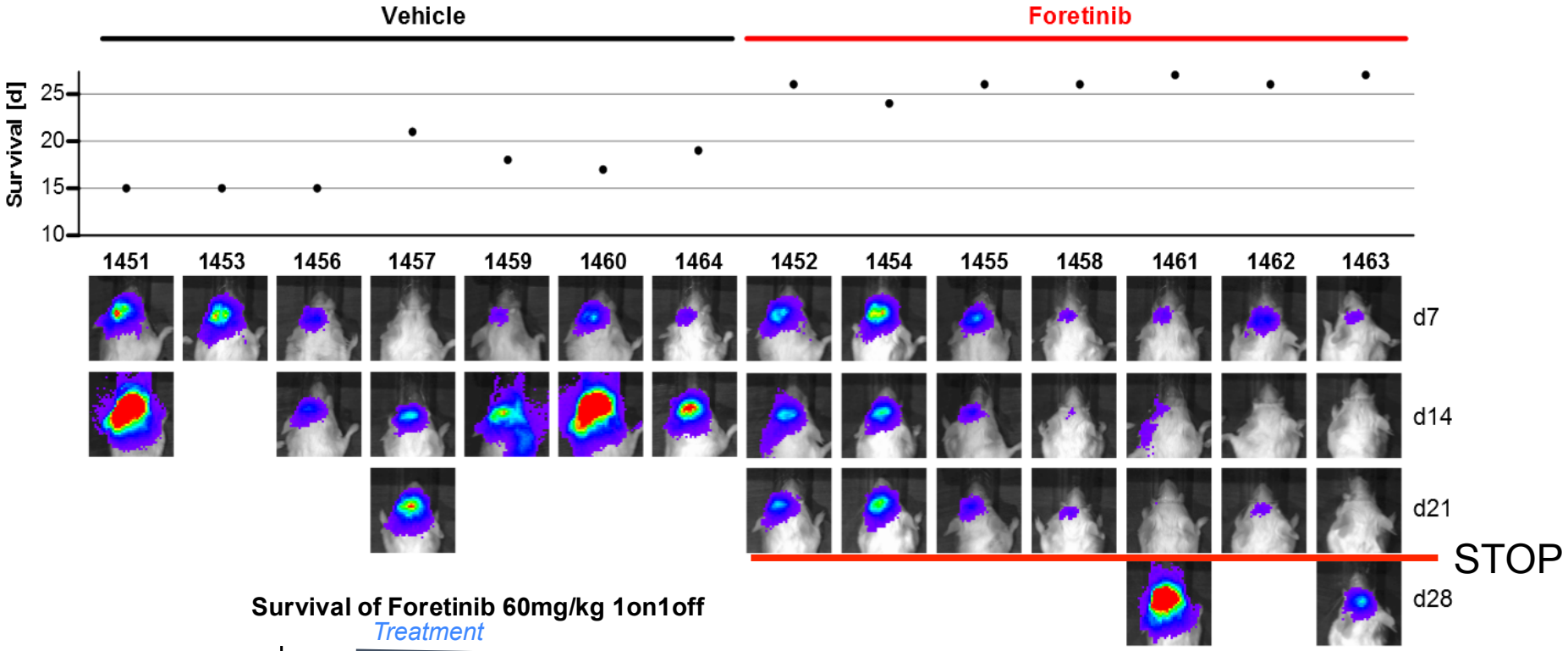


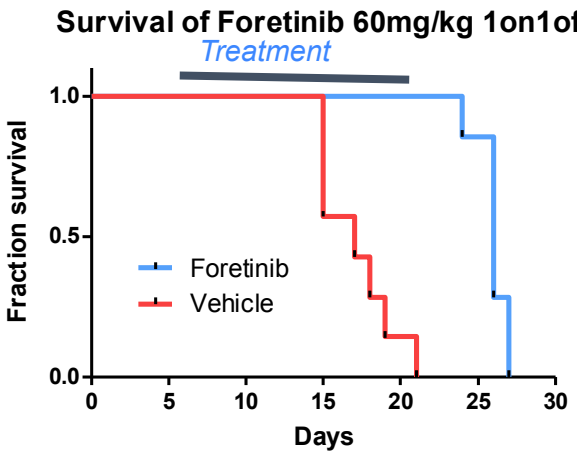


Jan Gronych

ICGC PedBrain Paper:
Bender et al., *Nature Med* (October 17, 2016)

Preclinical testing of targeting inhibitors





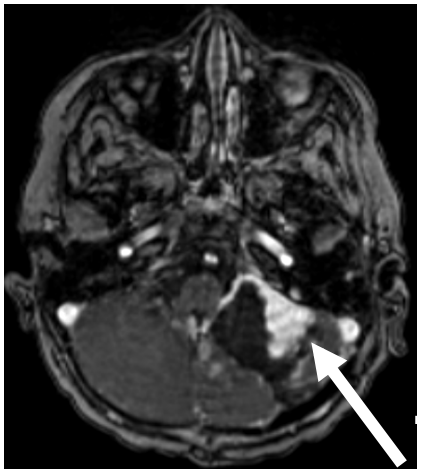
ICGC PedBrain Paper:
Bender et al., *Nature Med* (October 17, 2016)

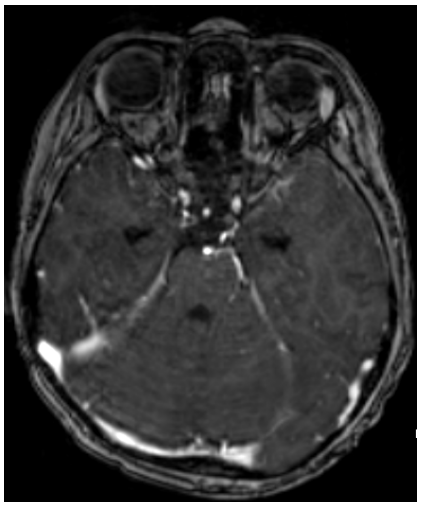
Patient example I: Treatment response ….

…. and resistance?

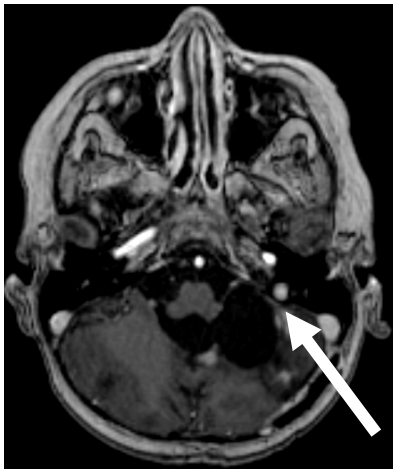
Treatment with a **MET-inhibitor (Crizotinib)**

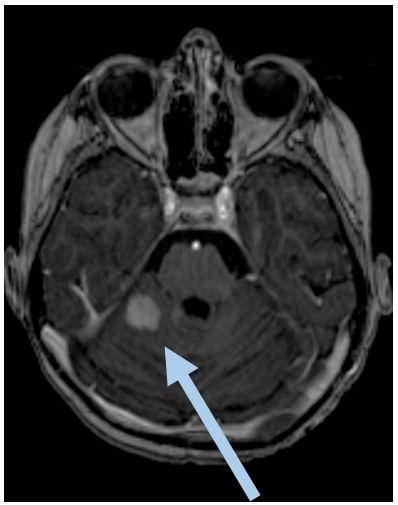
baseline post-OP



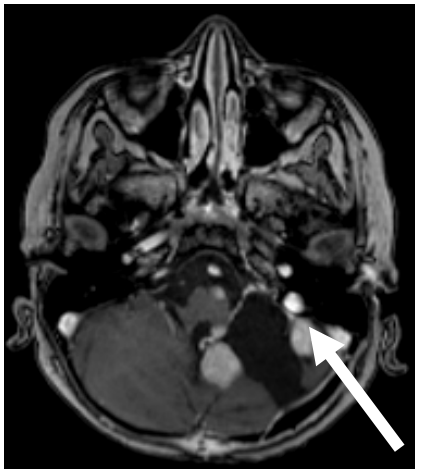


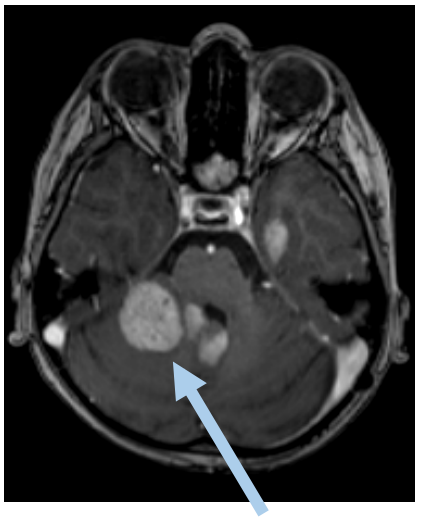
2 months Crizotinib





further 16 days Crizotinib

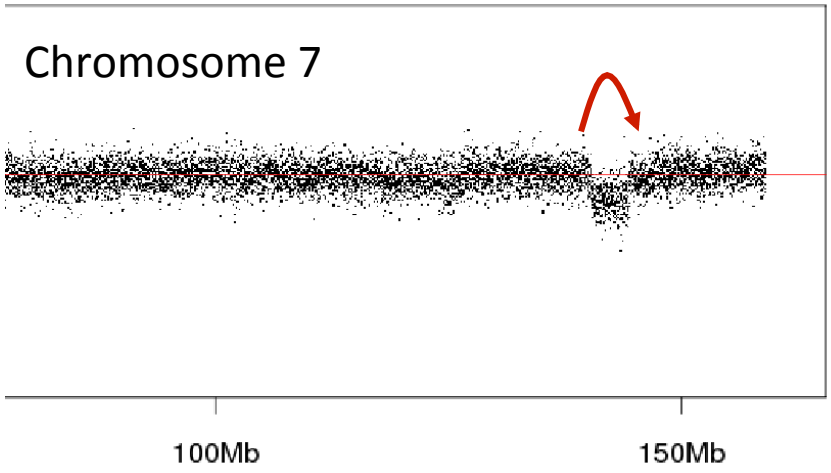


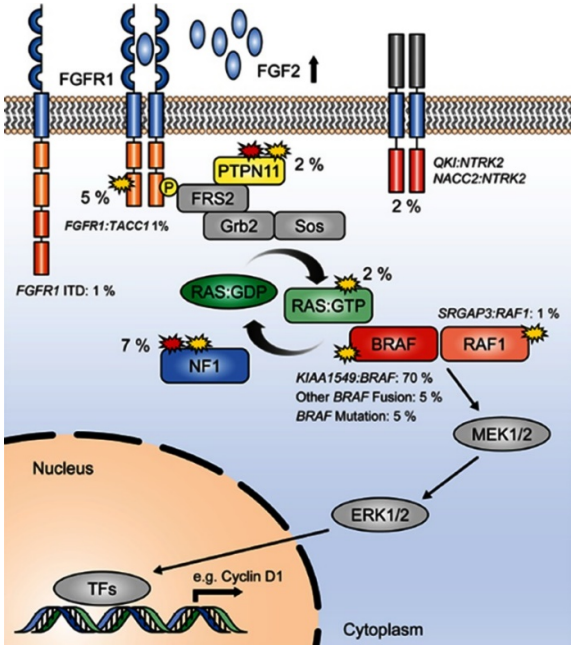


Patient example II

***2008, female**

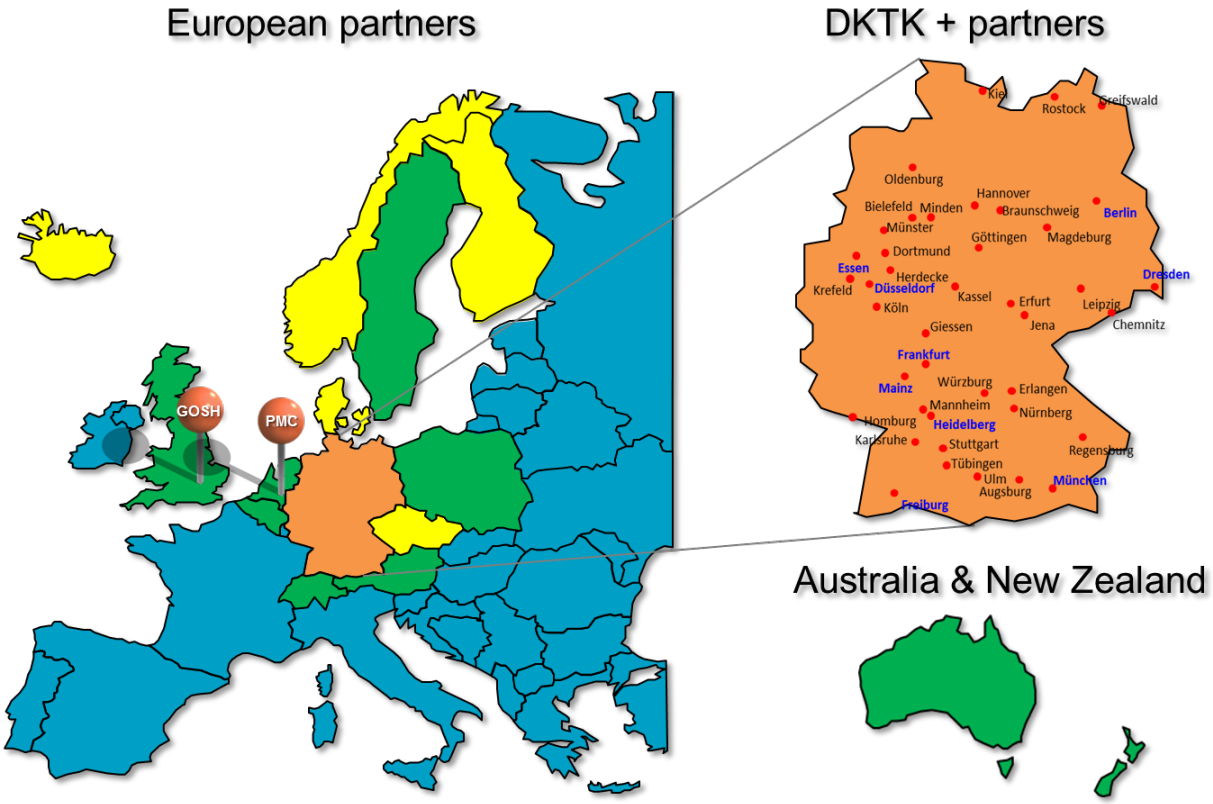
- initial diagnosis of an **Anaplastic Astrocytoma III°** in 11/2013
  treatment according to the standard protocol (HIT-HGG, RTx and TMZ)
- Tumor progress in 11/2014
- 12/2014: **INFORM** analysis: **FAM131B:BRAF fusion** identified, typical for **Pilocytic Astrocytoma I°**
  => MAPK pathway activation
- Patient is now treated with a **MEK-inhibitor (Trametinib)**
  + valproate + low-dose cyclophosphamide + chloroquine
- 10/2015: **stable disease**





ICGC PedBrain Paper: Jones et al., *Nature Genet* 2013

INFORM registry international



Countries that are currently preparing for participation (consent, ethics, logistics, national sponsors).

Countries that are currently considering participation

Strategic cooperation partners: GOSH = Great Ormaond Street Hospital London; PMC= Prinsess Maxima Center Utrecht

Innovative Therapies for Children with Cancer

ITCC European consortium

Integration of national molecular matching trials

1. Generate a tumor molecular portrait for each patient (whole exome and RNA sequencing, immunoprofiling)

MAPPYACTS | INFORM | ITHER | COMETH

2. Match treatment proposal to molecular portrait

Multidisciplinary Molecular Tumor Board

3. Evaluate new drugs and drug combinations

- PHASE 1 Trials
- PHASE 2 Trials
- Genentech / Roche MATRIX trial
- eSMART ITCC trial (multi-agent, multi-company academic trial)

4. Create a large European Well-annotated clinico-biological database

5. Identify new targets, new pathways for specific pediatric drug development

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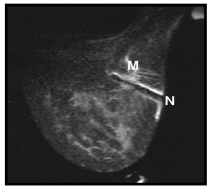
NCT NATIONAL CENTER FOR TUMOR DISEASES HEIDELBERG

Worst et. al, Eur J Cancer, 2016

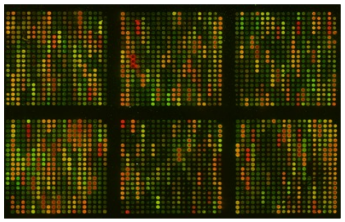
Outlook: Testing for therapy choice in cancer?

Body fluid



Biopsy

Molecular Profiling

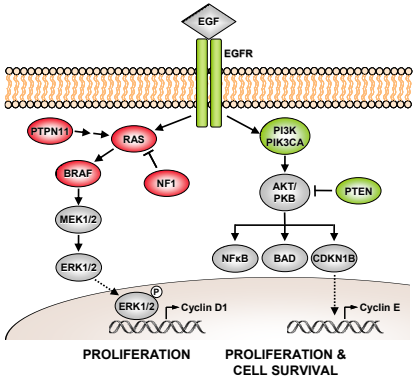


Culture

Xenograft

Treatment

Analysis
of activated
pathways



Selection of drugs (from existing options)

Treatment of respective patient depending on outcome
Monitor patient to detect resistance to therapy

ICGC med

Goal: sequence samples from at least 200,000 cancer patients over the next decade

(One project: 4000 patients, e.g. over five years)

=> collection of adequate clinical information will be of utmost importance!

White paper: http://icgcmed.org/

The added value of ICGCmed:

Development of common databases containing information on

- molecular alterations that can be targeted by drugs
- the prioritization of molecular targets
- the impact of rare molecular variants
- the availability of drugs for respective applications
- clinical response that was observed
- the tumor types, in which clinical response could be expected
- the clinical consequences of treatment combinations
- the impact of ethnic background in this setting
- the association of adverse drug effects with patient's constitution
- the potential familiar background of cancer cases