Personalized Pediatric Oncology: What are the Targets?

Synergy Satellite: Targeted Drugs - scattered goals
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dkfz.
50 Years – Research for
A Life Without Cancer

Disclosure:

Consultant Novartis
Consultant Astra Zeneca
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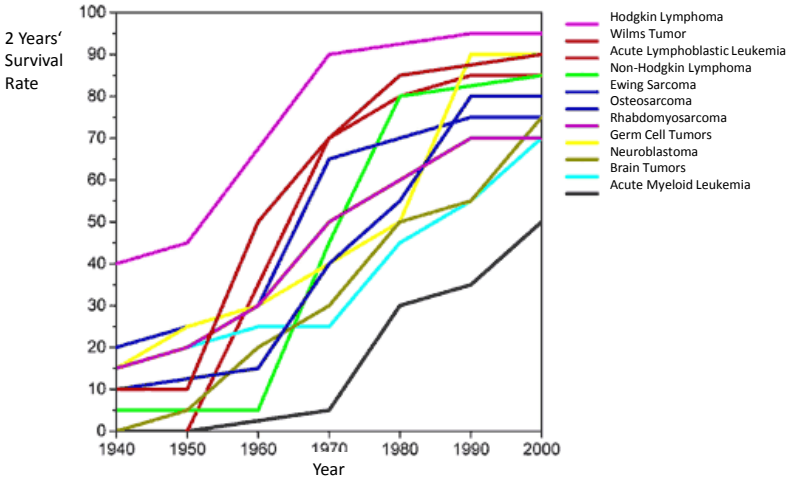
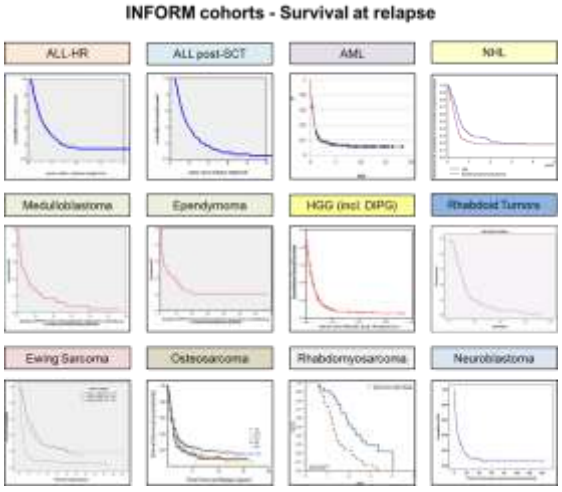
Pediatric Oncology – a success story in firstline treatment

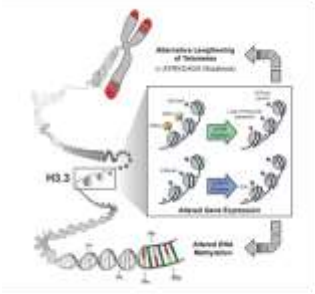


Relapse - Clinical challenge



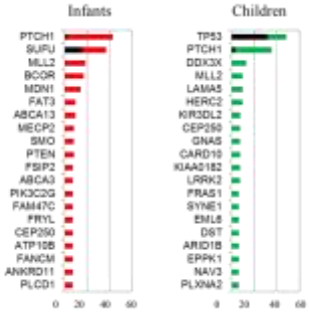
NGS: New drug targets

High-grade glioma



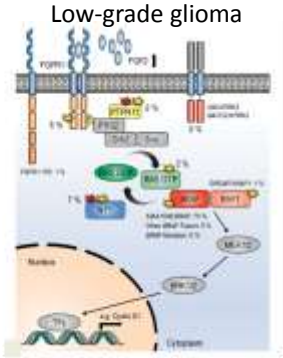
Schwartzentruber et al. Nature 2012
Sturm et al. Cancer Cell 2012
Bender et al. Cancer Cell 2013
Fontebasso et al. Nature Genetics 2014

Medulloblastoma



Rausch et al. Cell 2012
Jones et al. Nature 2012
Paugh et al. Nature 2012
Kool et al. Cancer Cell 2014
Hovestadt et al., Nature 2014
Northcott et al. Nature 2014

Low-grade glioma



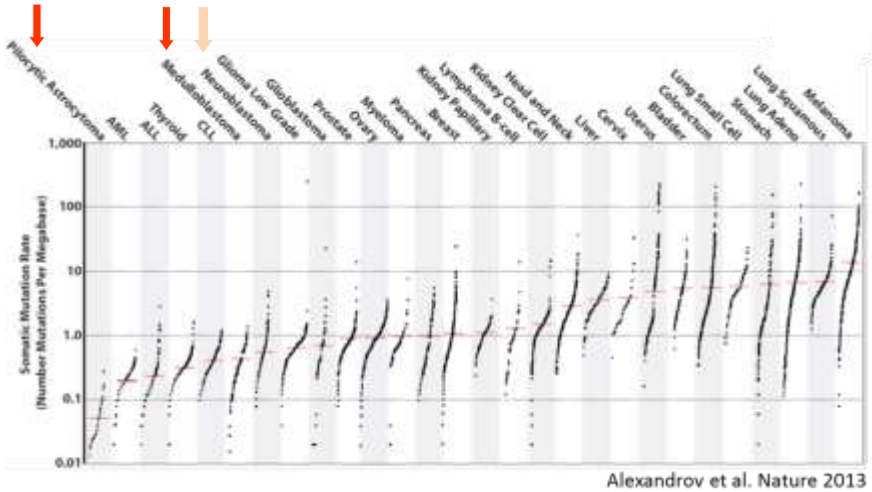
Jones et al. Nature Genetics 2013

+ Ependymoma

Witt & Mack et al. Cancer Cell 2011
Mack & Witt et al. Nature 2014
Pajtler et al. Cancer Cell 2015

→ In addition to brain tumors: PNET, Wilms, ALL, etc.

Pediatric tumor genomes are „simple“



Alexandrov et al. Nature 2013

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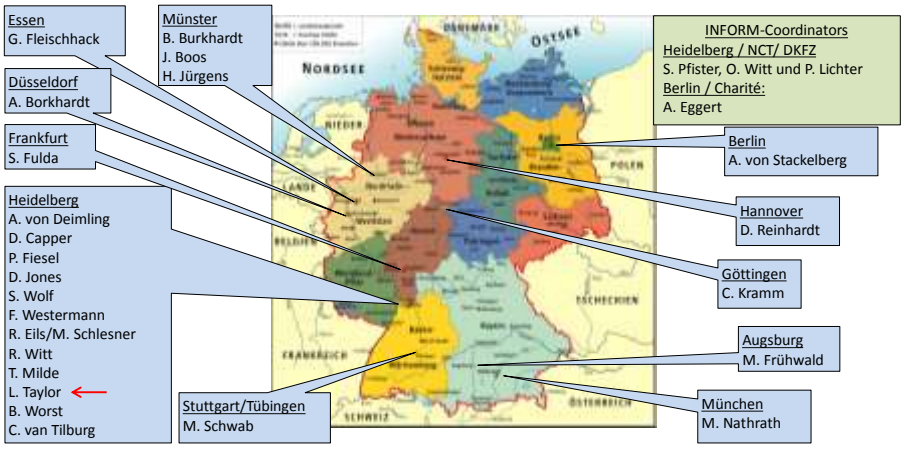

INdividualized therapy FOr
Relapsed Malignancies in childhood

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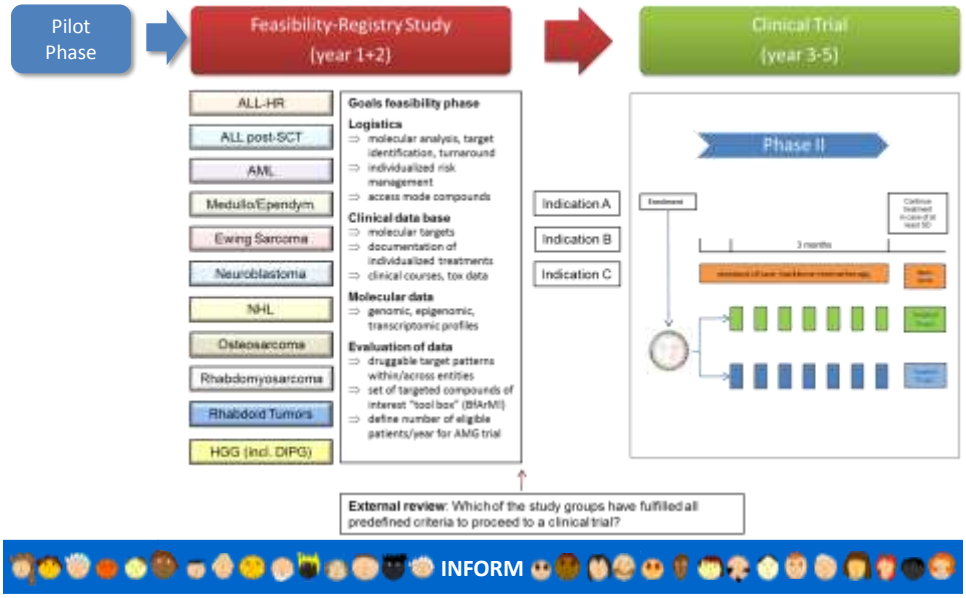
INFORM program: 3 steps



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Key Inclusion Criteria

- Children, adolescents, young adults, 1-40 years
- **Refractory/relapsed/progressive oncological disease**
  - (Exception: some primary rhabdomyosarcoma indications and DIPG)
- **No established treatment option** available

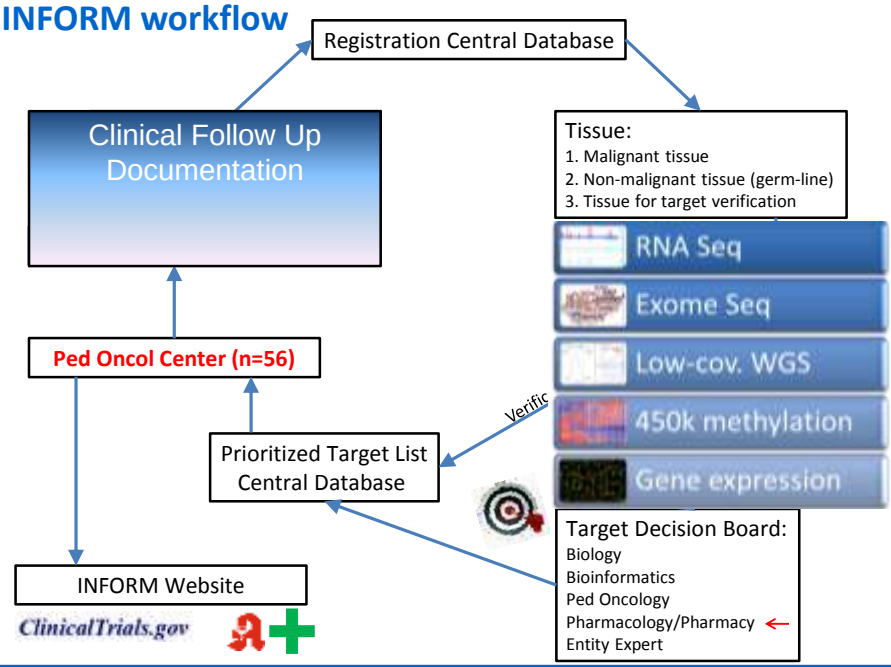
- **Life expectancy > 3 months & Lansky /Karnofsky ≥ 50**
- First-line treatment in GPOH trial protocol
- Inclusion discussed with respective GPOH Study group

- **Current** and **routine** re-biopsy performed (i.e. not part of the study)
  - (Note: non-interventional study, EC approved)

- Solid tumors: **measurable disease activity**

- **Fresh frozen tissue**, matching normal tissue and formalin fixed paraffin embedded (FFPE) mandatory
- Informed consent

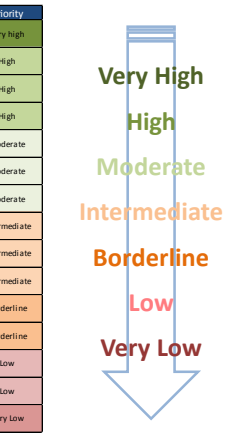
INFORM workflow



Target Selection and Prioritization

Criteria harmonized with Scientific Advisory Board (Jan Molenaar & Huib Caron, NKOC-iTHER project, Holland and Birgit Geoerger, MOSCATO project, France)

Target Type	Entity	Target Status	Description	Priority
Confirmed driver	Specific	Genetic hit (mutation/ rearrangement)	Specific alteration in actionable target confirmed as driving in specific entity	Very high
Confirmed driver	Specific	Genetic hit (focal high-amplitude CNV)	Specific alteration in actionable target confirmed as driving in specific entity	High
Confirmed driver	Other	Genetic hit (mutation/ rearrangement/ focal high-amplitude CNV)	Specific alteration in actionable target confirmed as driving in another entity	High
Presumed driver	Specific	Genetic hit (mutation/ rearrangement/ focal high-amplitude CNV)	Actionable gene known to be a driver in specific entity, function of this mutation likely activating but not proven	High
Presumed driver	Other	Genetic hit (mutation/ rearrangement/ focal high-amplitude CNV)	Actionable gene known to be a driver in another entity, function of this mutation likely activating but not proven	Moderate
Pathway activation, genetic	Specific	Genetic hit incl. focal CNV	Genetic alteration indicating activation of an actionable pathway known to be involved in specific entity; potential drug acting elsewhere in pathway	Moderate
Synthetic lethal / Predictive marker, genetic	Specific	Genetic hit incl. focal CNV	Genetic alteration in a gene known to induce susceptibility to inhibition of another gene in specific entity	Moderate
Pathway activation, genetic	Other	Genetic hit incl. focal CNV	Genetic alteration indicating activation of an actionable pathway known to be involved in another entity; potential drug acting elsewhere in pathway	Intermediate
Synthetic lethal / Predictive marker, genetic	Other	Genetic hit incl. focal CNV	Genetic alteration in a gene known to induce susceptibility to inhibition of another gene in another entity	Intermediate
Overexpressed driver	Specific	Protein/Expression Change	Overexpression of a directly actionable gene known to be a driver in specific entity	Intermediate
Pathway activation, expression	Specific	Protein/Expression Change	Expression changes clearly indicating activation of a potentially actionable pathway linked to specific entity	Borderline
Synthetic lethal / Predictive marker, expression	Specific	Protein/Expression Change	Altered expression of a gene/pathway known to induce susceptibility to inhibition of another gene in specific entity	Borderline
Pathway activation, expression	Other	Protein/Expression Change	Expression changes clearly indicating activation of a potentially actionable pathway known from another entity	Low
Synthetic lethal / Predictive marker, expression	Other	Protein/Expression Change	Altered expression of a gene known to induce susceptibility to inhibition of another gene in another entity	Low
Circumstantial evidence	Other	Genetic/Protein/Expression Change	Alterations with some modest literature evidence of possible pathway activation	Very Low



INFORM – Pilotphase

52 patients screened

sex:	female	24
	male	28
age:	mean	13 years
	min	2 years
	max	40 years

→ 7 ineligible

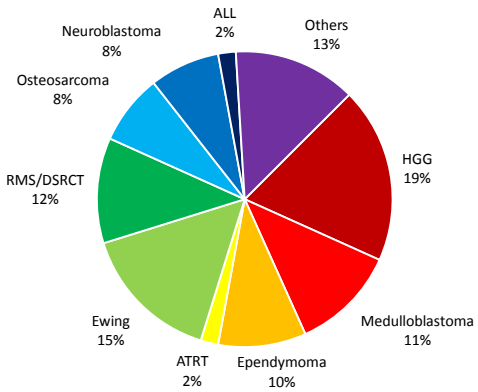
45 patients enrolled

→ 3 insuffient/no tumor

42 patients sequenced
(1 patient twice)

→ 1 no tumor (450k)

41 patients analyzed → 21 patients actionable alteration identified



B. Worst & C. van Tilburg et al., in preparation

Targets identified

	Amplification	Deletion	SNV/Indel	Fusion	Overexpression
ALK				2	2
CCND1/2	2				1
CDKN2A/B		2			
CDK4	1				
EGFR			1		
EWSR1				4	
FGFR4			1		1
HSP90AB1					1
KRAS			1		
MET	1			1	2
MLL				1	
MYCN	1				
PDGFRA	1				
PIK3CA			3		
PTCH1			2		
TSC2			1		
VEGFA					1
VEGFR1	1				
total	**7**	**2**	**9**	**8**	**8**

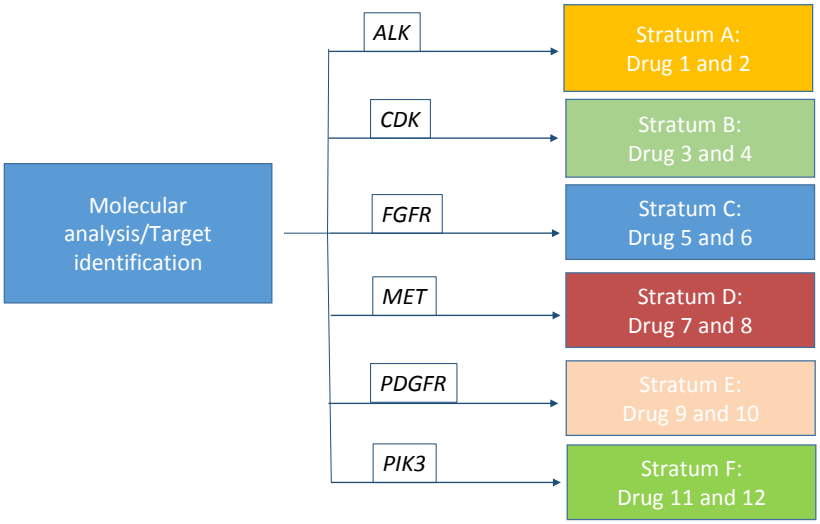
41 patients fully sequenced and analyzed so far, 21 had ≥ 1 alteration with at least "borderline" evidence

B. Worst & C. van Tilburg et al., in preparation

Drug "wish list"

Target	Compound #1	+ Compound #2
ALK	Crizotinib (Pfizer) Ceritinib (Novartis)	?
CDK4/6	LEE011 (Novartis) Palbociclib (Pfizer)	?
FGFR	Regorafenib (Bayer Healthcare) Ponatinib (Ariad)	MEKi
MET	Cabozatinib (Exelixis) Crizotinib (Pfizer)	MEKi
PDGFR	Dasatinib (Bristol Myers Squibb)	?
PIK3	**Everolimus (Novartis)**	Trametinib (GSK)
BRAFV600E	Vemurafenib (Hoffmann-La Roche) Dabrafenib (GSK)	MEKi
Smo+PTCH	LDE225 (Novartis) Vismodegib (Roche)	-
MYC	Panobinostat (Novartis) CUDC-907 (Curis)	BETi Alisertib (Takeda) Pi3Ki EZH2i

Outlook INFORM^2: Basket trial design



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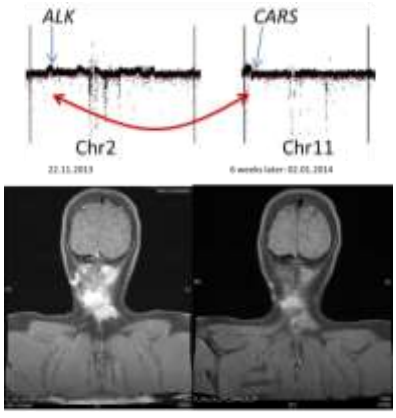
Some preliminary examples...

Pilot – ES-XXX
Very large myofibroblastic sarcoma

INFORM analysis
- ALK fusion identified by sequencing

Clinical consequence
- Recruited to Phase I/II ALKi trial
- PR after 2 months
- CR after 1 year (2nd look surgery)



Courtesy of J. Schulte & G. Fleischhack (Essen)

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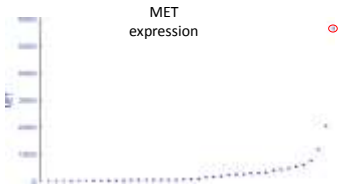
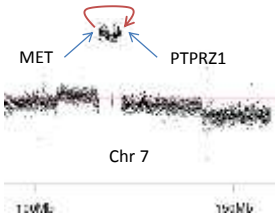
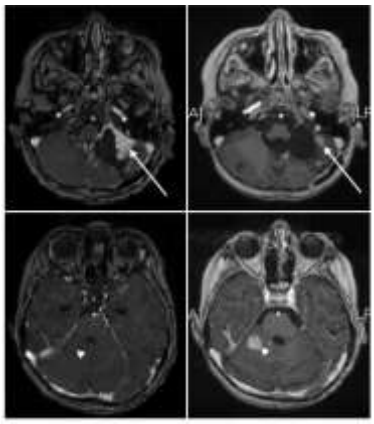
Pilot – HD-XXX
2011: Metastasized group 3 medulloblastoma
2014: Relapse? + meningeosis

INFORM Analysis:
- Secondary malignancy: glioblastoma!
- PTPRZ1-MET fusion with amplification and corresponding overexpression of MET

Clinical consequence:
- Off labe compassionate use: Crizotinib
- Local Partial response, but new metastatic lesions







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Summary & Challenges

✓ High unmet medical need
✓ Personalized moelcular diagnostics: clinically feasible
✓ Targets (being) identified

➢ **Access** to targeted drugs for children very **limited**
➢ Almost **no approved** targeted drugs for children
➢ Limited number of **phase I** data in ped onc
➢ **Combination therapy**: different companies

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- German Childhood Cancer Foundation (DKS)

dkfz. German Cancer Consortium

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