KiTZ
Hopp Children's Cancer Center
Heidelberg

German Cancer Research Center (DKFZ)
Heidelberg University Hospital
Heidelberg University

INFORM:
Präzisionsmedizin für Kinder mit Krebs

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BKK Innovativ

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dkfz.
GERMAN CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

HEIDELBERG UNIVERSITY HOSPITAL

UNIVERSITÄT HEIDELBERG
ZUKUNFT SEIT 1386

Interessenskonflikte

Advisory board member or research grants

- Day One Bio
- Biomede Valley Discovery
- Novartis
- Janssen
- Bayer

Hintergrund: Krebs bei Kindern

- In Deutschland treten jährlich etwa **2.000 neue Krebsfälle** bei Kindern im Alter von unter 18 Jahren auf.
- Krebs ist die **zweithäufigste Todesursache** bei Kindern & Jugendlichen unter 18 Jahren.
- **20%** der an Krebs erkrankten Kinder **sterben**. Rückfälle sind sehr schwer zu behandeln.

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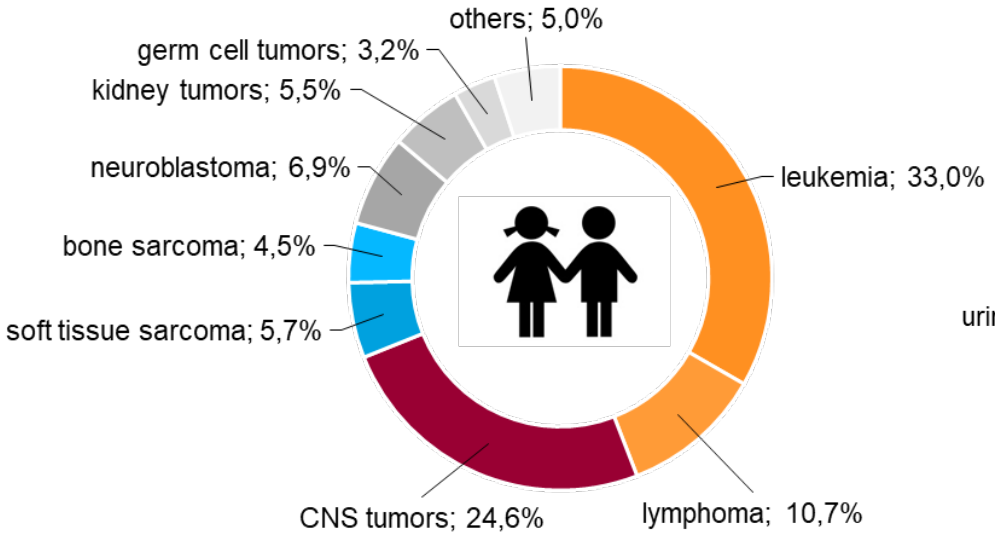
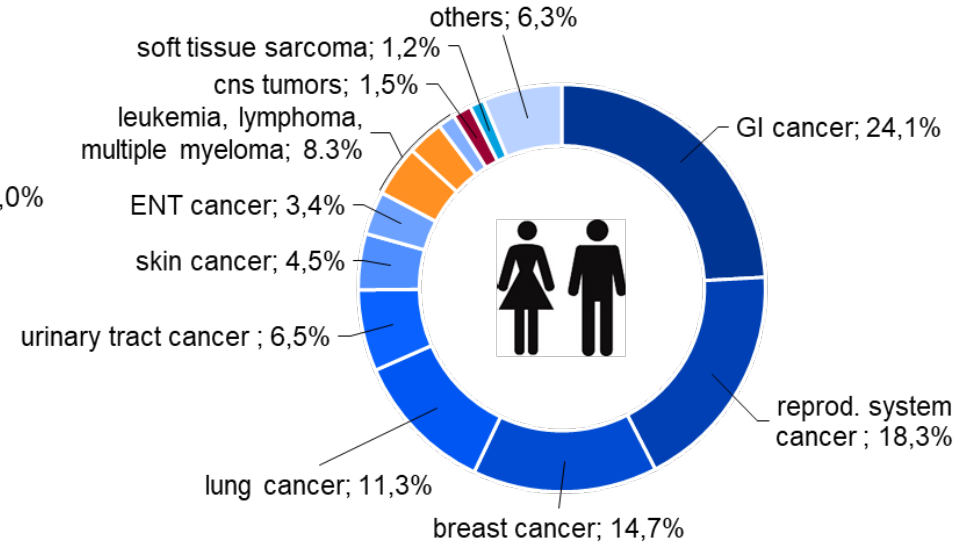
Krebs bei Kindern ist anders



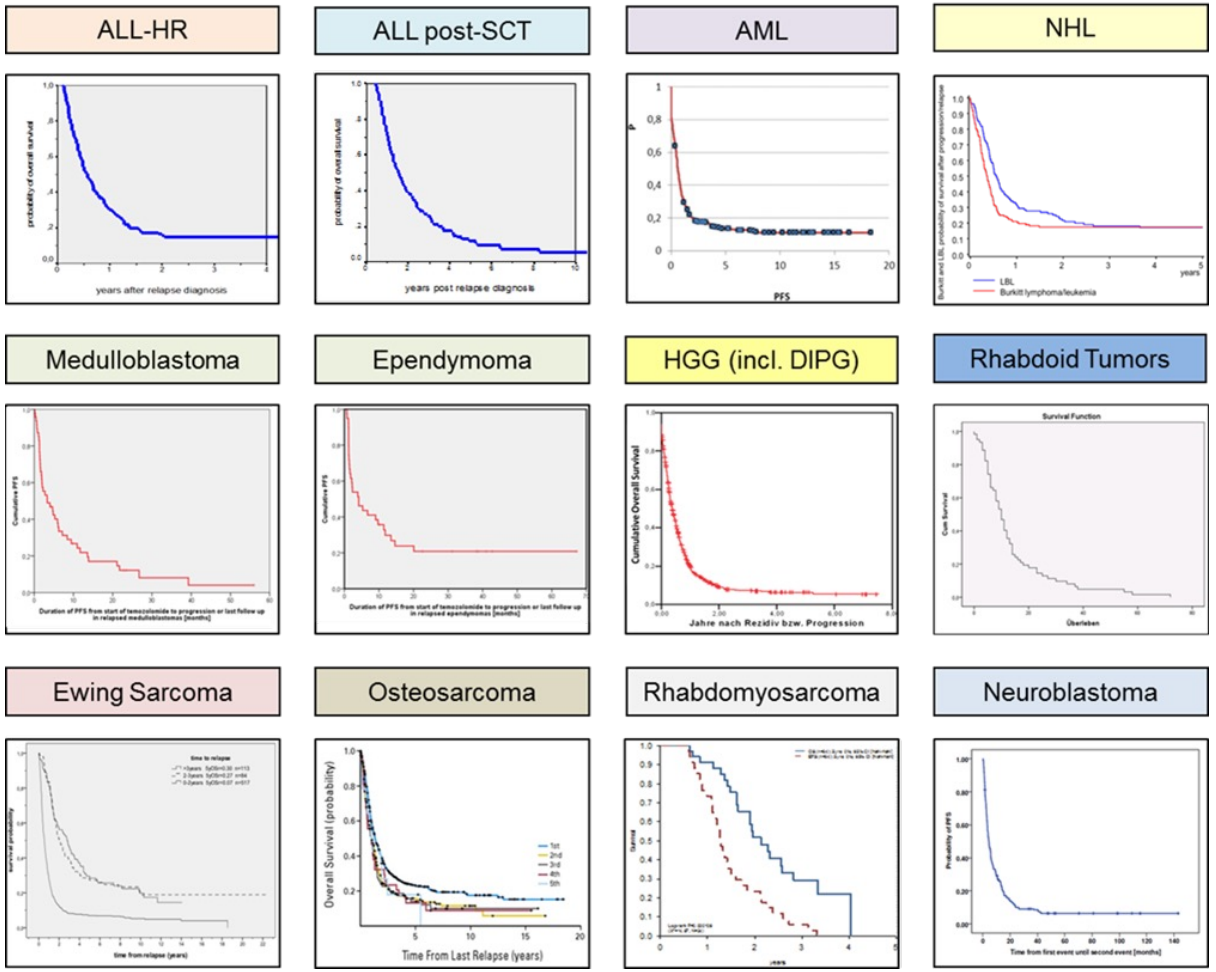
~1%



~99%

- Ganz andere Tumorarten als bei Erwachsenen
- Kleine Zahlen und sehr viele verschiedene Tumorarten
- ~50% aller gewonnenen Lebensjahre (!)

Rezidive verlaufen in der Regel tödlich



- Überleben von Krebserkrankungen bei Kindern im Falle eines Rezidivs
- …neue Ansätze für Rückfälle von Tumorerkrankungen erforderlich !

Molekulare Tumoranalyse in Heidelberg

- DKFZ: Größte Sequenziereinheit in Europa (nach dem Sanger Center)
- Starke bioinformatische Expertise
- International führende Gruppen in translationaler pädiatrischer Onkologie
- Starke Vernetzung in Deutschland (GPOH), Europa (SIOPE) and global

Wie funktioniert die Tumorsequenzierung von INFORM?

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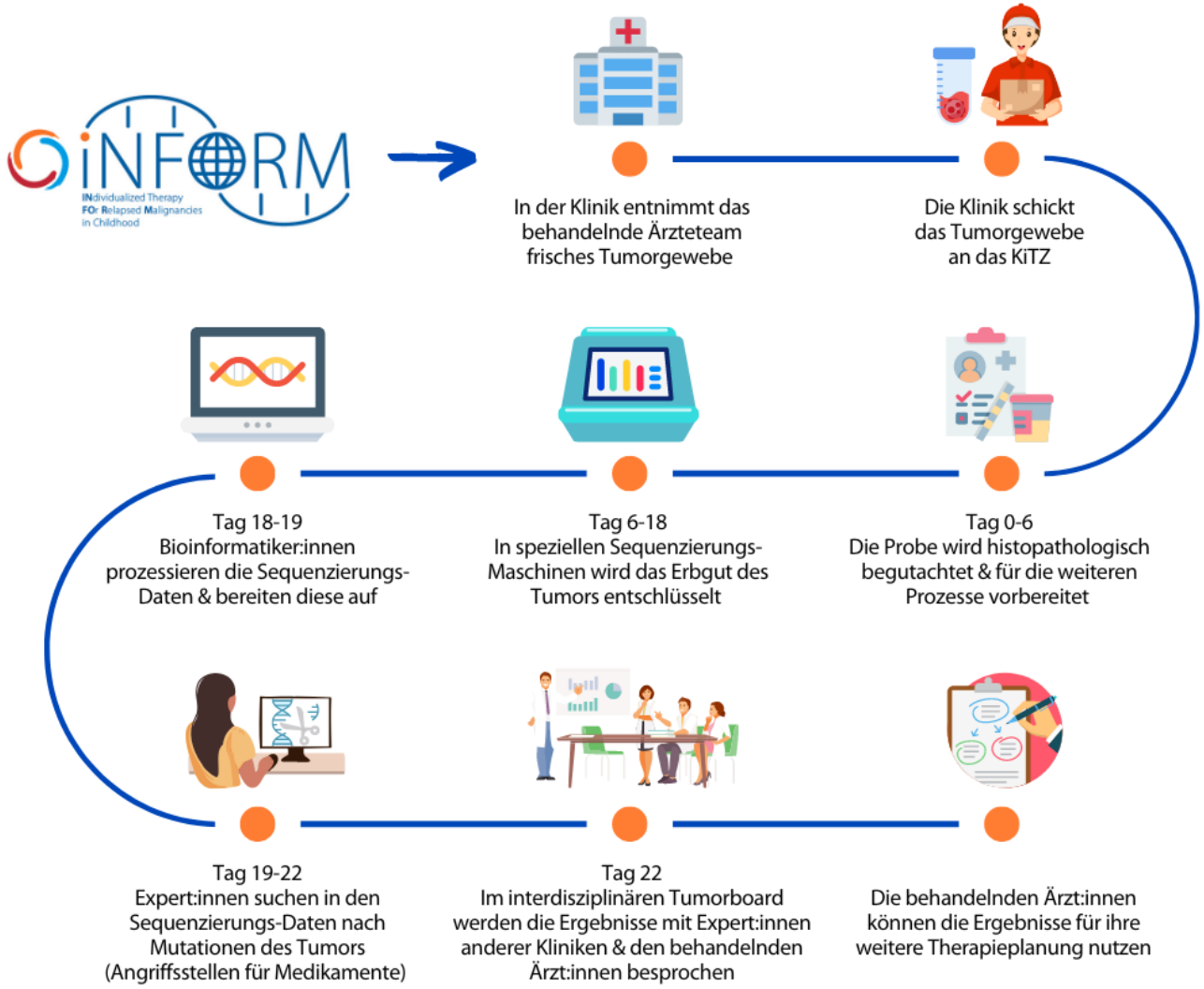
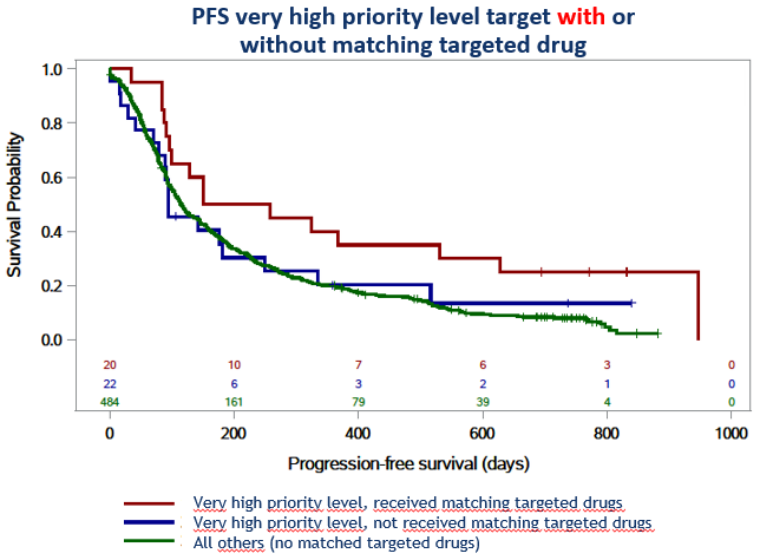


Wichtigsten Ergebnisse

- > **3000 Patienten** in Deutschland und Europa aus 100 kinderonkologischen Zentren eingeschlossen
- Sarkome, Hirntumore, Neuroblastome und seltene embryonale Tumore
- **Kurze Rücklaufzeit** von Tumorgewebe-Eingang bis Tumorboard
- **Detektion ALLER** potentiellen Angriffspunkte für zielgerichtete Therapieansätze
- **Erbliche Formen der Tumorerkrankung** werden **in 10%** der Fälle gefunden
- **Klinische relevante „Korrektur" der Diagnose in 10%** der Fälle
- **Verdoppelung des krankheitsfreien- und Gesamtüberlebens** bei Identifizierung einer Zielstruktur mit hohem Evidenzgrad und passender Therapie



Van Tilburg*, Pfaff*, Pajtler* *et al.*, Cancer Discovery 2021
Heipertz et al., JCO Prec Oncol 2023

Das molekulare INFORM Tumorboard

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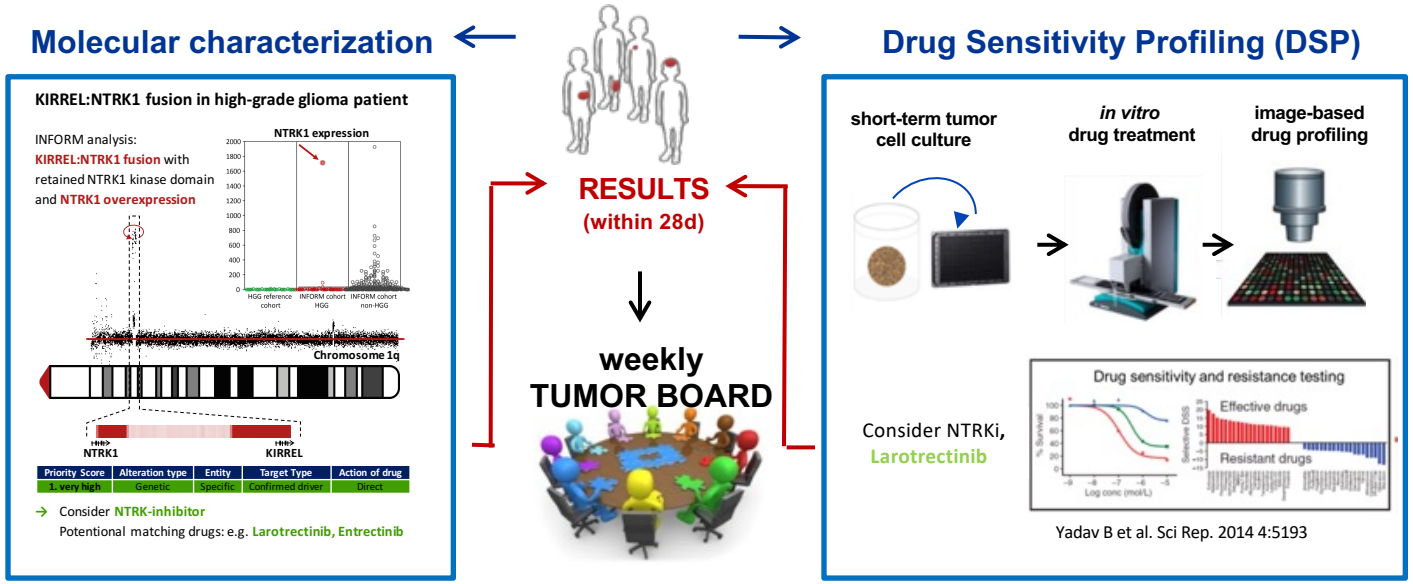
Schlüsselfrage des multidisziplinären INFORM-Boards:
„von welchen gefundenen Veränderungen profitiert der Patient und von welchen nicht?“



Behandelndem:r Ärzt:in,
Molekularbiologe:in
Humangenetik
(Neuro)Pathologie
Pädiatrische Präzisionsonkologie
GPOH-Studiengruppe
Bioinformatiker:in,

Beispiel INFORM-Tumorboard: 11j Mädchen
Target mit hoher Priorität

Gefundenes Target

Beschreibung der biologischen Funktion & klinischen Studien

Verfügbare Medikamente
i) zugelassen
ii) Klinische Studien
iii) Off-Label

Evidenzlevel

Illustration der Alteration

Registry patient I014_059

relapse of I014_012

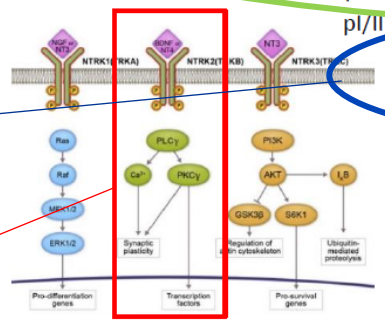
SPECC1L:NTRK2 fusion

NTRK2 (TrkB) is a member of the neurotrophic tyrosine kinase receptor family which is involved in activation of the MAPK pathway. NTRK fusions, including the fusion found here, were described as oncogenic alterations in different adult and pediatric tumor entities, especially non-brainstem HGG (PMID: 24705251, 32238360, 33144287).
Already reported for I014_012. No additional NTRK resistance mutation could be identified.
In recent clinical trials, Larotrectinib demonstrated rapid and durable responses, high disease control rate, and a favorable safety profile in pediatric and adult patients with TRK fusion-positive CNS tumors, including low- and high-grade gliomas as well as non-gliomas (PMID: 34850167), as well as in other solid tumors (PMID: 30624546, 35333737). Also Entrectinib (FDA approved for patients >12 years) showed durable and systemic and intracranial responses in patients with NTRK fusion-positive solid tumors (PMID: 31838007, 35144967).
Note: The TRIDENT-1 (Repotrectinib) also includes patients previously treated with TRKi.

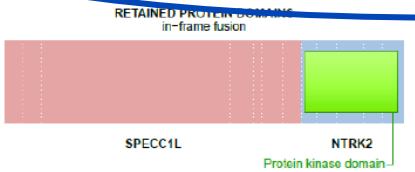
→ consider **TRKi (fusions)**

potential matching drugs: approved: [Larotrectinib/LOXO-101], **Entrectinib** [Ponatinib, Cabozantinib, Lorlatinib]
in dev.: **Selitrectinib/LOXO-195, Repotrectinib** [Sitravatinib, TPX-0005, Milciclib]

open clinical trials: [pI/II **Larotrectinib** (NCT02637687) NTRK1-3 fusion CNS (SCOUT) (DE(B,HD,Stg),NL,FR,CH,DK,SE,ES,IT,UK,PL) ≤21y]
pII **Entrectinib** (NCT04589845) solid/CNS NTRK1-3 fusion (TAPISTRY, cohort B) (DE,BE,CH,DK,FR,IT,PL,ES,UK,IL)
pI/II **Repotrectinib** (NCT03093116) solid ALK/ROS1/NTRK1-3 fusion (TRIDENT-1) (NL,BE,DK,UK,FR,IT,ES,PL) ≥12y



Priority	Target type	Alteration type	Action of drug	Current evidence for clinical activity
High[a]	Confirmed driver	Genetic	Direct	positive



Presentation for internal use within the INFORM Target Decision Board only.
Do not forward to patients.

Registry patient I014_059 – Top scored drugs (1/3)

QC: ●

Drug Hit	Drug Class	Target/s	Approval status	Quantile rank %	% inhibition at Cmax	$IC50_{abs}$ [nM]
Selitrectinib	Kinase inhibitor	TrkA, TrkB, TrkC	Phase I/II (discontinued)	99.3	n.a.	0.02
Entrectinib	Kinase inhibitor	TrkA, TrkB, TrkC, ROS1 and ALK	Approved	99.4	91.7	0.4
Larotrectinib	Kinase inhibitor	TrkA, TrkB, TrkC	Approved	99.4	91.4	11
Trametinib	Kinase inhibitor	MEK-1/2	Approved	99.4	91.7	0.4
Selumetinib	Kinase inhibitor	MEK-1/2	Approved	99.4	91.5	14
Cobimetinib	Kinase inhibitor	MEK-1/2	Approved	98.8	93.9	3.3

library compounds (n=79, full screen, 3 plates)

A-1155463	Chloroquine	Erlotinib	Mercaptopurine	Ribociclib	Thiotepa
A-1210477	Cisplatin	Etoposide	Merestinib	Ruxolitinib	Topotecan
A-1331852	Cobimetinib	Everolimus	Methotrexate	Selinexor	Trametinib
Afatinib	Crizotinib	Foretinib	Mitoxantrone	Selitrectinib	Valproic acid
Alectinib	Cytarabine	Gemcitabine	Navitoclax	Selumetinib	Vandetanib
Alpelisib	Dabrafenib	I-BET151	Nilotinib	SN-38	Vemurafenib
AMG-232	Dactinomycin	Idasanutlin	Olaparib	Sorafenib	Venetoclax
APR-246	Dasatinib	Imatinib	Paclitaxel	Sunitinib	Vinblastine
Axitinib	Daunorubicin	Irinotecan	Palbociclib	Talazoparib	Vincristine
Bortezomib	Decitabine	Lapatinib	Panobinostat	Tazemetostat	Vinorelbine
Busulfan	Doxorubicin	Larotrectinib	Pazopanib	Temozolomide	Vismodegib
Cabozantinib	Entinostat	Lorlatinib	Ponatinib	Temsirolimus	Volasertib
Ceritinib	Entrectinib	Melphalan	Rapamycin (Sirolimus)	Thioguanine	Vorinostat

Staurosporine_drug (technical control)

Comments: Screen was performed after prolonged pre-culture time (45 days)
In-class effects towards:

- NTRKi
- MEKi
- METi
- ROS/ALKi
- MDM2i
- BCL-xLi (confirmed by outlier response towards A-1155463 and A-1331852)
- PARPi (Olaparib and Talazoparib show above-average effects, but do not qualify as hits due to low effect at cmax)
- Topoisomerase I/II inhibitors

DSS_asym = Drug sensitivity score (cut-off for sensitivity: DSS_asym≥ 10)
DSS_asym (ElHarouni et al., 2022. Pharmacol Res. 2022 Jan;175:105996. doi: 10.1016/j.phrs.2021.105996)
$IC50_{abs}$ = concentration resulting in 50% inhibition of metabolic activity (ex vivo)
c_{max} = maximal achievable plasma concentration (in vivo)
Quantile rank % : based on percentage rank within the INFORM DSP cohort

● QC failed
● QC intermediate
● QC high

Disclaimer: Please note that ex-vivo drug screening testing has not been clinically validated. It is in the sole responsibility of the treating physician if he/she wants to make use of the drug screening results for clinical decision making. In case of questions, please contact INFORM_TDSU@kitz-heidelberg.de

Registry patient I014_059 – Summary

relapse of I014_012

Target	Priority	Target type	Alteration type	Action of drug	Current evidence for clinical activity
SPECC1L:NTRK2	**High**[a]	Confirmed driver	Genetic	Direct	positive
CDKN2A/B	**Moderate**[b]	Confirmed pathway activation	Genetic	Pathway	unclear benefit / missing

Disclaimer: Further study options (e.g. biomarker-negative trials) should be discussed with the GPOH study group.

Registry patient I014_059 – TDB Decision

relapse of I014_012

- ☐ Analysis of the current tumor sample did not identify any target results with high clinical evidence for patient's benefit when treated with matching drugs according to van Tilburg et al. Cancer Discovery 2021.

- ☑ The identified **NTRK2 fusion** suggests that the patient may benefit from treatment with matching **NTRK inhibitors**, such as **Entrectinib** or **Repotrectinib**, according to van Tilburg et al. Cancer Discovery 2021, Doebele et al. Lancet Oncol. 2020 and Demetri et al. Clin Cancer Res. 2022.
  Open clinical trials in which the patient could potentially be enrolled in are pII Entrectinib (NCT04589845) and pI/II Repotrectinib (NCT03093116) if eligibility criteria are met.
  Inclusion in clinical trials, if available, should always be preferred over off-label therapy.

- ☐ Evaluation of sequencing results not possible due to a low tumor cell content (rate: 1-3% of all cases).

Disclaimer: Inclusion in clinical trials, if available, should always be preferred over off-label therapy.
Therapy decisions on the basis of INFORM results remain in the responsibility of the treating physician.

Beispiel INFORM-Tumorboard: 12j Junge
Target mit niedriger Priorität

Registry patient I044_035 – Borderline targets & below

KIT overexpression

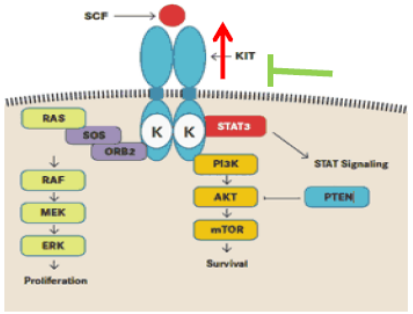
KIT is a receptor tyrosine kinase and plays a role in different cellular processes (e.g. proliferation and differentiation). KIT alterations are found in many tumor entities, especially in GIST (PMID: 15869870). KIT overexpression may lead to an activation of downstream oncogenic signaling pathways.
A recent phase II trial demonstrated clinical efficacy of Cabozantinib in patients with advanced EWS or OS (PMID: 32078813).

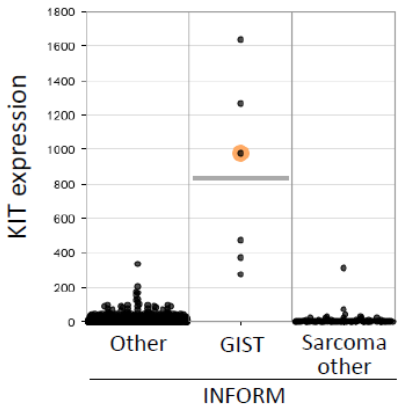
→ consider KITi

potential matching drugs: approved: Imatinib, Dasatinib, Sorafenib, Axitinib, Pazopanib, Sunitinib Cabozantinib,, Ponatinib, Regorafenib, Nilotinib, Midostaurin

open clinical trials: no suitable trials

Priority	Target type	Alteration type	Action of drug	Current evidence for clinical activity
Borderline[c]	Overexpressed driver	Expression	Direct	NA





Registry patient I044_035 – Summary

Target	Priority	Target type	Alteration type	Action of drug	Current evidence for clinical activity
KIT	**Borderline**[c]	Overexpressed driver	Expression	Direct	NA
DDR2	**Borderline**[c]	Overexpressed driver	Expression	Direct	NA
FGF3	**Low**[c]	Possible pathway activation	Expression	Pathway	NA

Disclaimer: Further study options (e.g. biomarker-negative trials) should be discussed with the GPOH study group.

Registry patient I044_035 – TDB decision

- [x] Analysis of the current tumor sample did not identify any target results with high clinical evidence for patient's benefit when treated with matching drugs according to van Tilburg et al. Cancer Discovery 2021.

- [ ] The identified xxx suggests that the patient may benefit from treatment with matching xxx inhibitors, such as xxx, as single drug or in combination with xxx inhibitors, according to van Tilburg et al. Cancer Discovery 2021 and xxx (cite other references if available). Open clinical trials in which the patient could potentially be enrolled in are xxx if eligibility criteria are met. Inclusion in clinical trials, if available, should always be preferred over off-label therapy.

- [ ] Evaluation of sequencing results not possible due to a low tumor cell content (rate: 1-3% of all cases).

Disclaimer: Inclusion in clinical trials, if available, should always be preferred over off-label therapy.
Therapy decisions on the basis of INFORM results remain in the responsibility of the treating physician.

Das molekulare INFORM Tumorboard:
Zusammensetzung & Bewertung der Informationen

KiTZ Hopp Children's Cancer Center Heidelberg

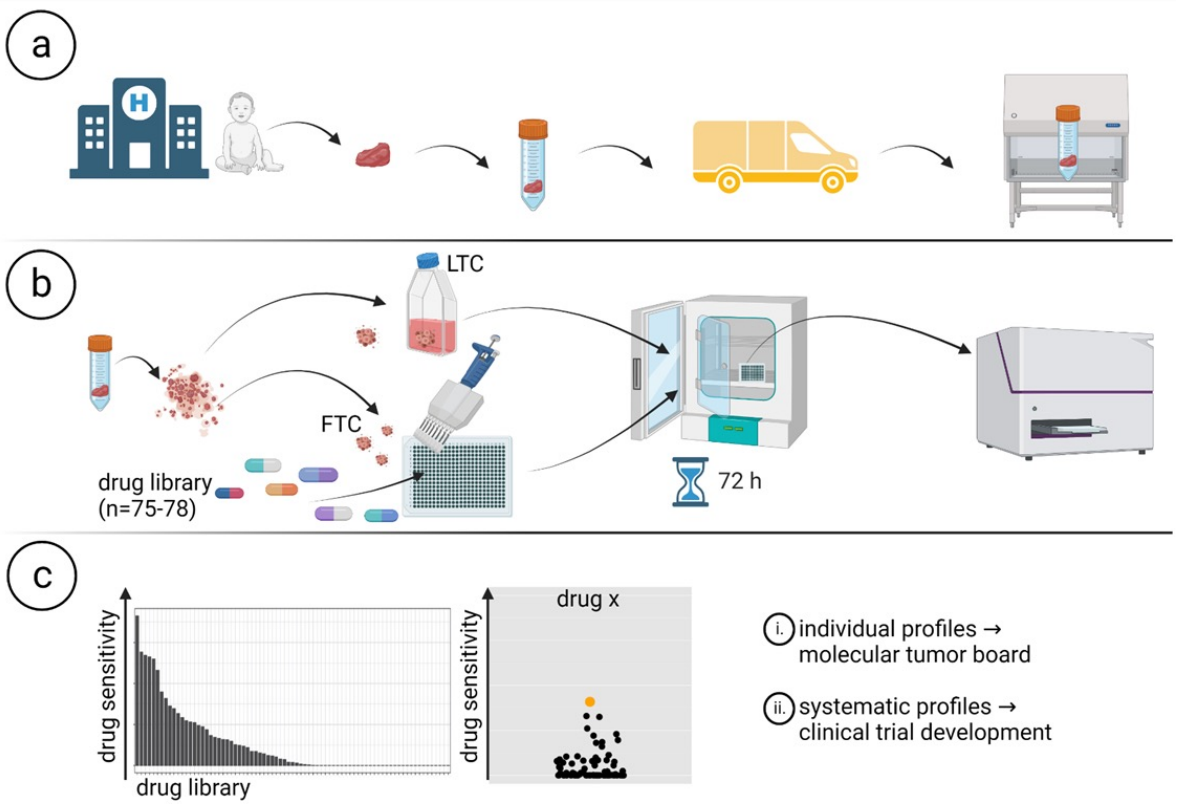
- **Targets mit hohem Evidenzgrad** für einen klinischen Benefit für den Patienten in ca. 10%
- Die **Mehrzahl** von gefundenen molekularen Alterationen sind Stand heute klinisch **nicht relevant**
- Bei Vorliegen eines Targets mit hohem Evidenzgrad
  => zugelassenes **Medikament**?
  => offene klinische **Studie**?
  => Off-label Therapieoptionen?
- **Keimbahnbefunde:** erbliches Tumordisposition in der Familie
  => Facharzt:In für Humangenetik vorgestellt
- **Diagnoseänderung** insbesondere bei Hirntumoren
  => Facharzt für (Neuro)Pathologie

Ausblick INFORM-Programm

- **„Upgrade“ der bioinformatischen Algorithmen**
  => Immunologische Eigenschaften des Tumors/TME
  => Immuntherapien
  (Mutationslast, T-Zell Infiltration)
- **Erweiterung der molekularen Diagnostik**
  => Proteom und Phosphoproteom
  => Aktivitätszustände von Signalpfaden
- **Liquid Biopsies**
  => Früherkennung, Heterogenität

Ausblick INFORM-Programm

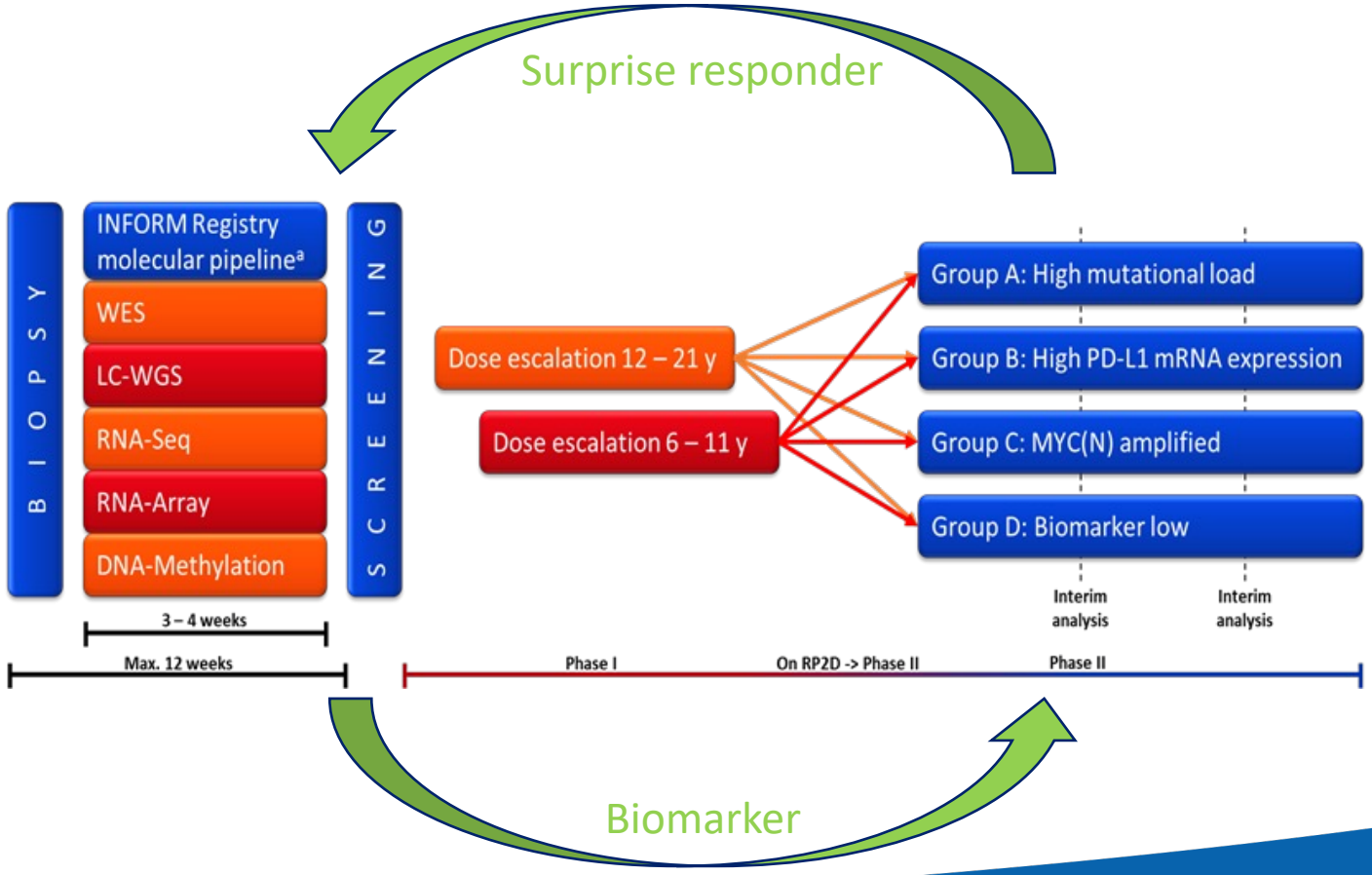
- **Medikamenten-Sensitivitäts-Testungen**
  => Testung an lebendigen 3D Minitumoren
  => Sensitivitäten und Resistenzen gegen viele Medikamente gleichzeitig



Peterziel et al., *npj* precision oncology 2023

Ausblick INFORM-Programm

- Entwicklung von klinischen Studien „**INFORM2-Studienserie**“
- Kontinuierlicher **zyklischer Wissenszuwachs**



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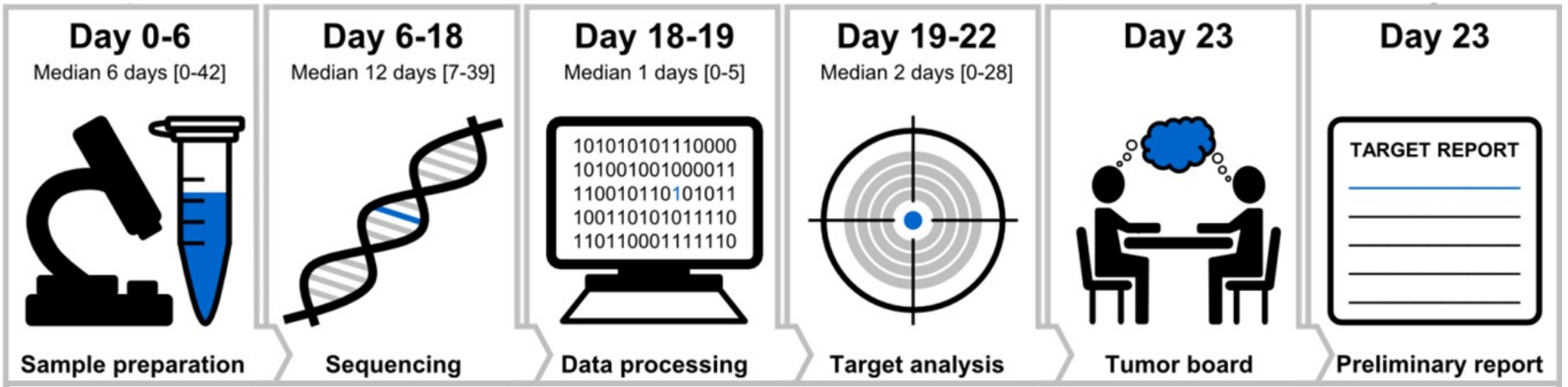
INFORM molekulare Analyse: State-of-the-Art



		Technical success rate	Validation rate
Low-cov. WGS	Copy number alterations	100 %	100 %
Exome Seq	SNVs/Indels Somatic and germline	100 %	98 %
RNA Seq	Fusionsgenes Expression of variants & genes	~ 85 %	100 %
850k methylation	Diagnosis Brain and sarcoma tumor classifier	99 %	

adapted from Worst BC et al. *EJC* 2016