



**Individualized THERapies voor kinderen met kanker:  
Precision medicine programma iTHER  
GGG Congres 2023**

# Disclosure

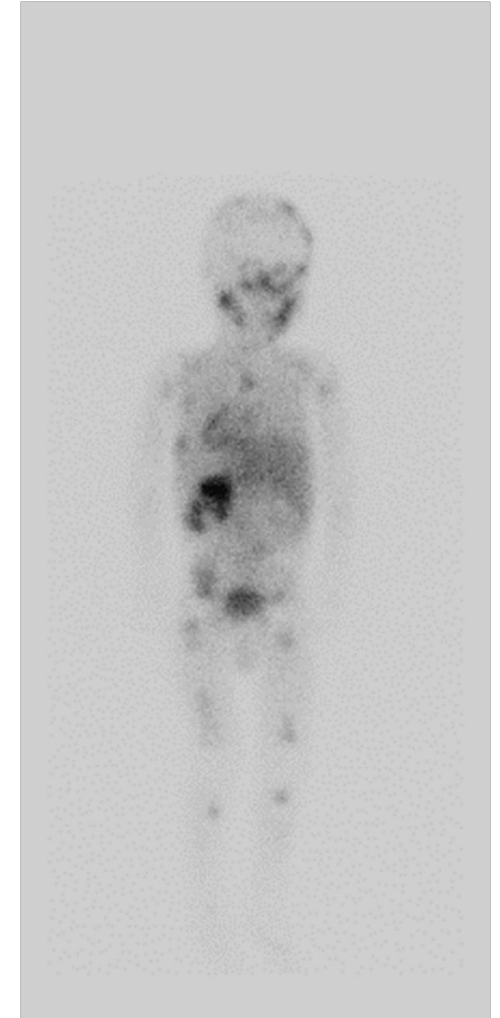
- Geen

# iTHER patiënt 072

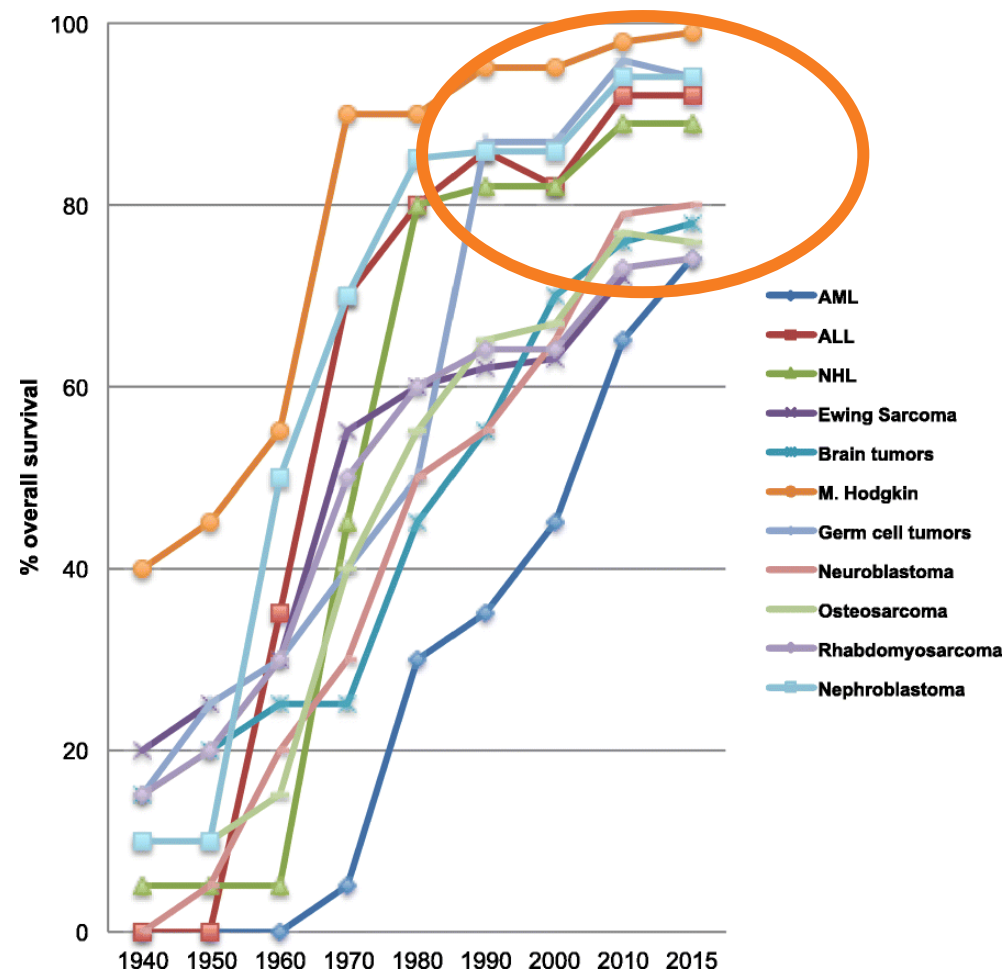
- Meisje van 4 jaar
- Neuroblastoom stadium 4, rechter bijnier. MYCN-A.

## Treatment:

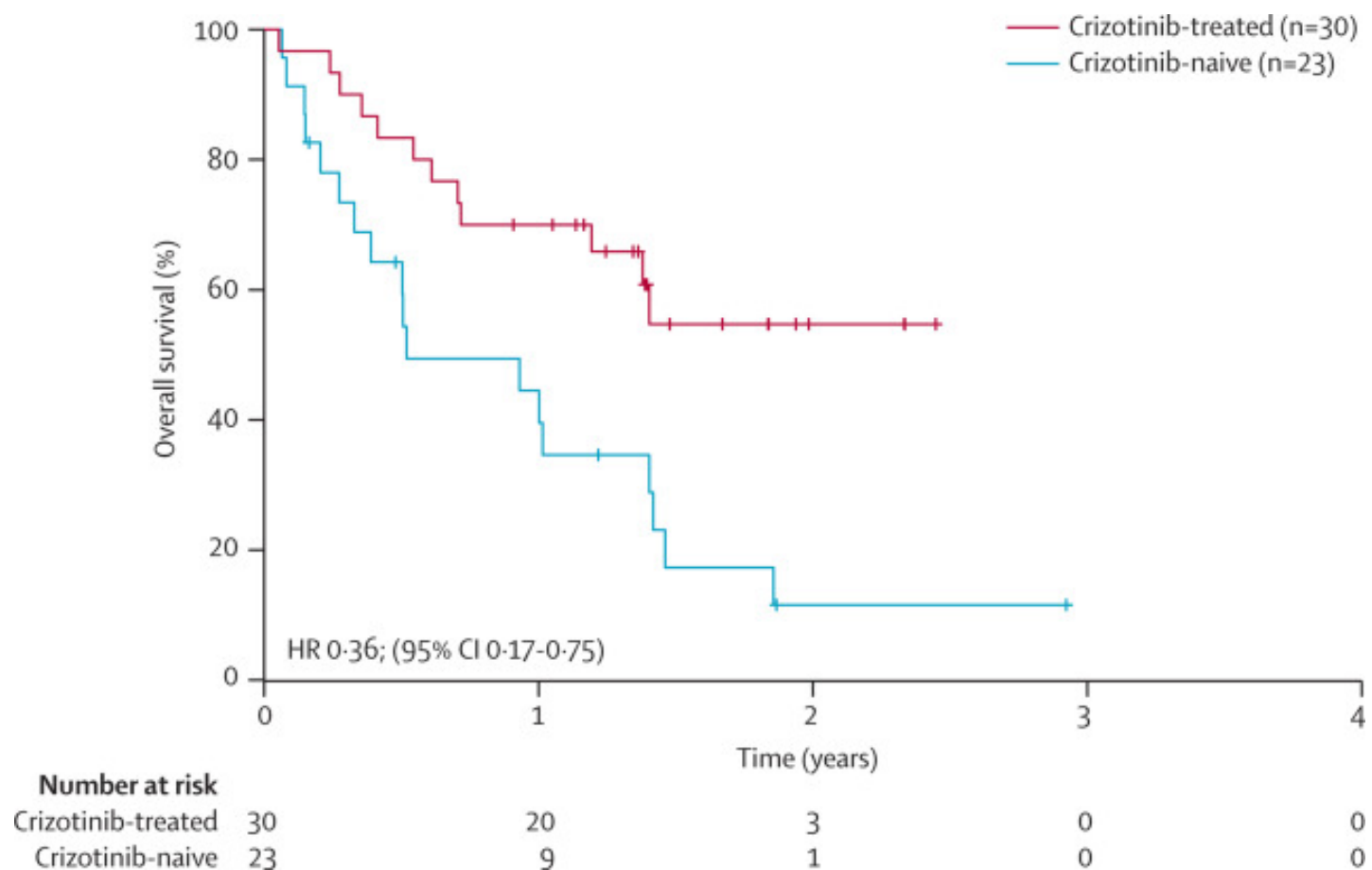
- NBL2009 HR protocol
  - 3xN5/2xN6 → complete remissie
  - HD CEM + ASCT
  - Resectie van de primaire tumor
  - Radiotherapie
  - Immunotherapie
- Onder IT nieuwe lesie in de rechternier
- **Behandelopties?**



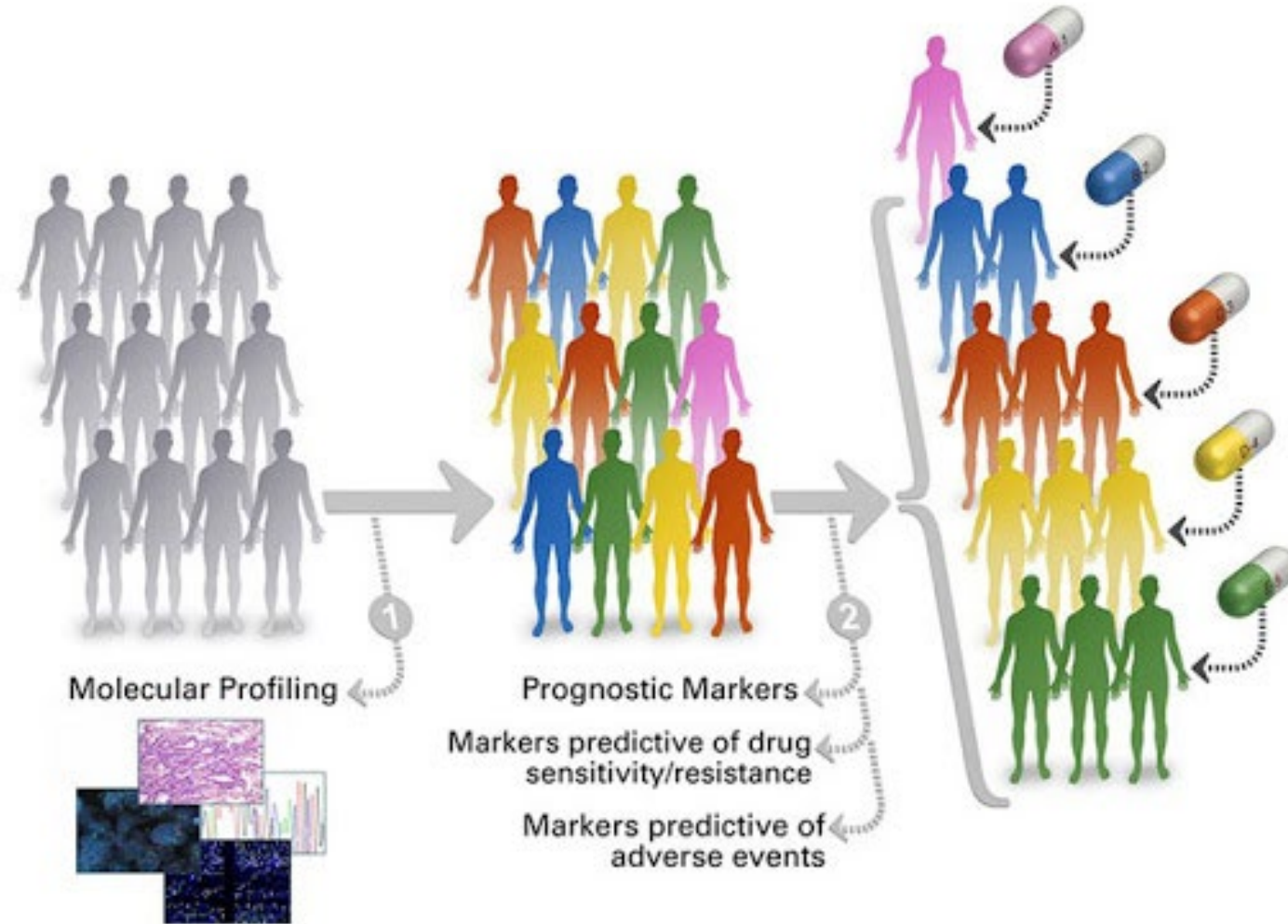
# Achtergrond: overleving kinderen met kanker



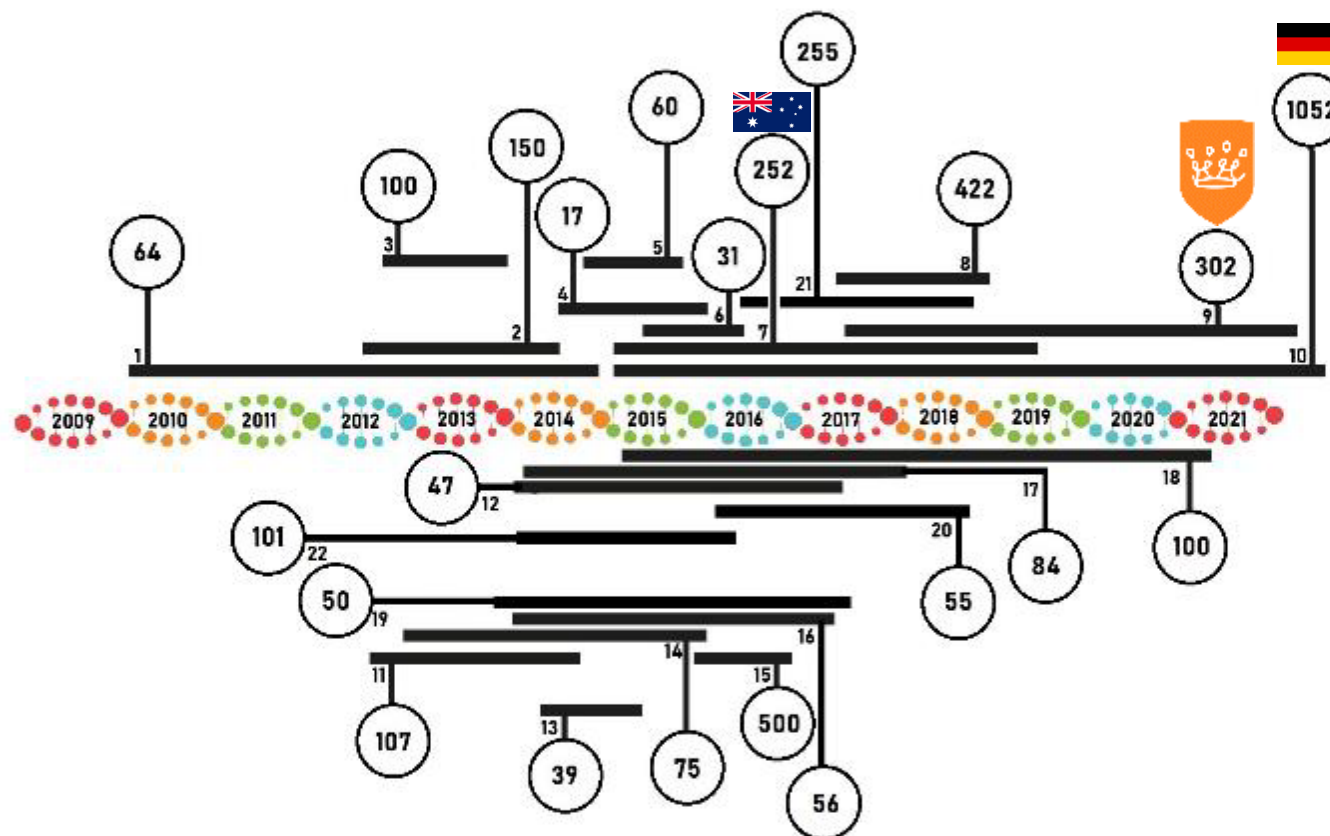
# Targeted therapy: crizotinib in ALK-rearranged NSCLC



# De hypothese



# Landschap van precision medicine voor kinderen met kanker

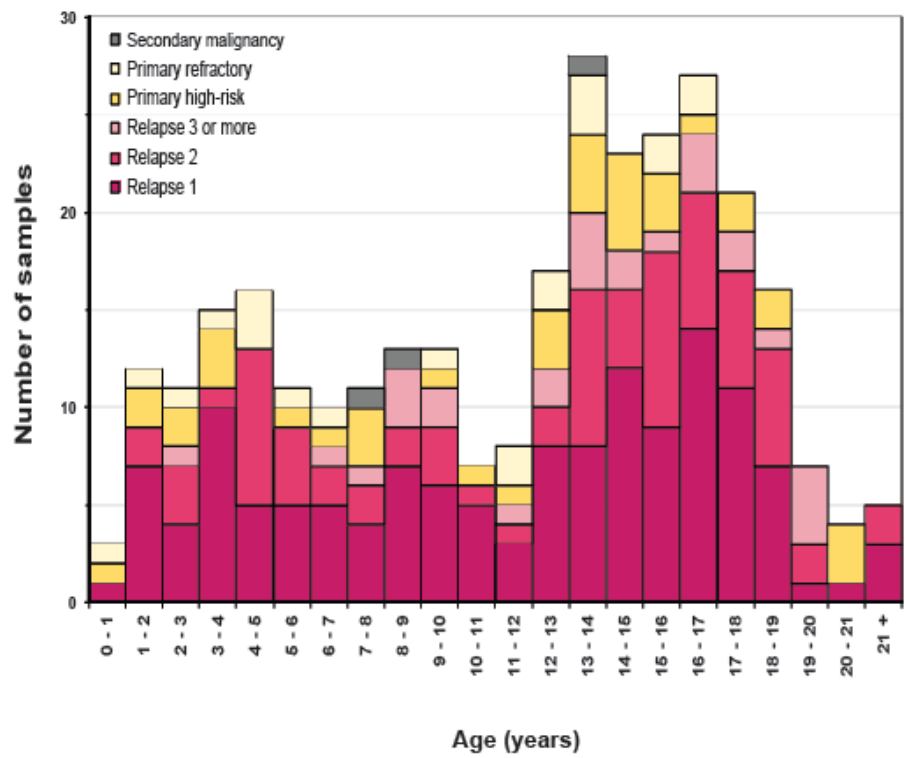
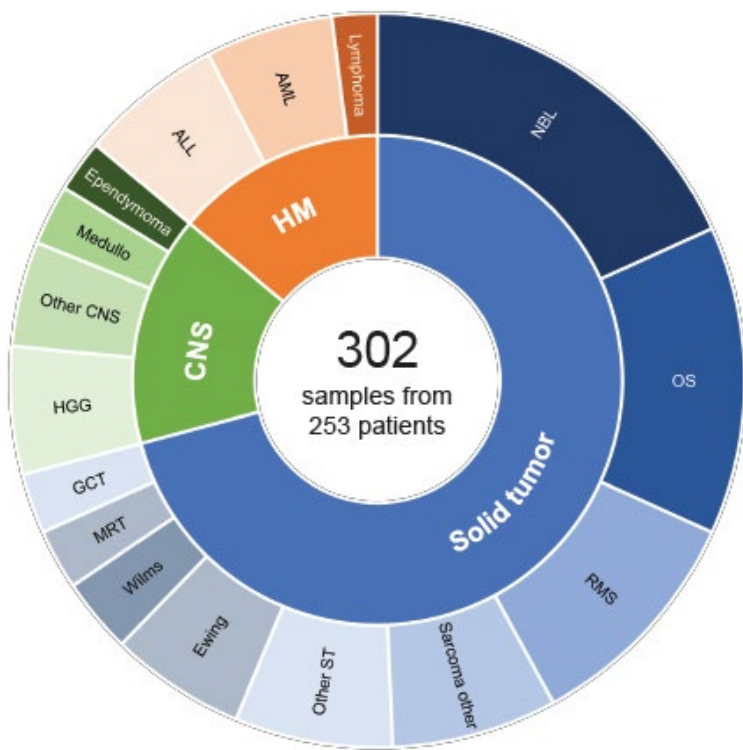
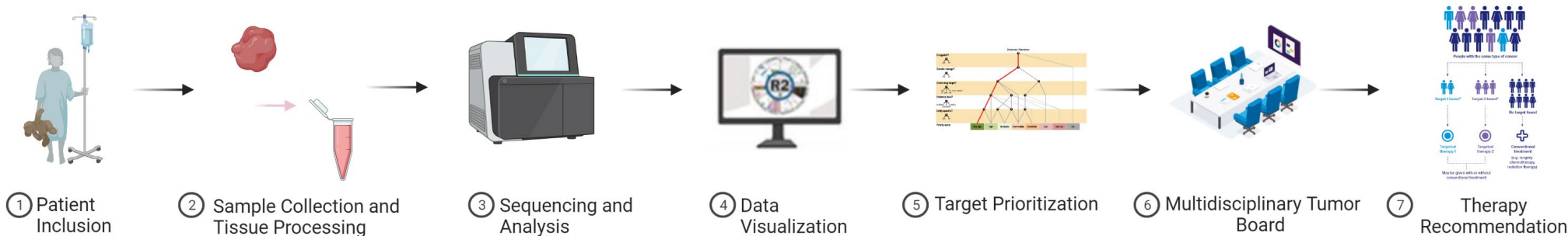


- |             |                   |                   |             |
|-------------|-------------------|-------------------|-------------|
| 1 ClinOmics | 6 UCSF            | 11 Peds-MiOncoSeq | 17 TRICEPS  |
| 2 BASIC3    | 7 Zero Childhood  | 12 TARGET         | 18 PROFYLE  |
| 3 ICAT      | 8 Pediatric MATCH | 13 PMTB           | 19 ProfiLER |
| 4 Pacific   | 9 iTHER           | 14 MOSCATO-01     | 20 SMC      |
| 5 MMB       | 10 INFORM         | 15 MAPPYACTS      | 21 SMPAEDS  |
|             |                   | 16 PIPseq         | 22 KiCS     |

# iTHER 2.0 – gefinancierd door ZonMW

| Year                                                                            | 1 | 2 | 3 |
|---------------------------------------------------------------------------------|---|---|---|
| Clinical implementation of precision medicine within the Princess Máxima Center |   |   |   |
| Evaluation of clinical benefit                                                  |   |   |   |
| Implement personalized models                                                   |   |   |   |

# iTHER workflow en cohort



# iTHER visualizatie van resultaten: R2

DNA analyse  
WES

Puntmutaties

InDels

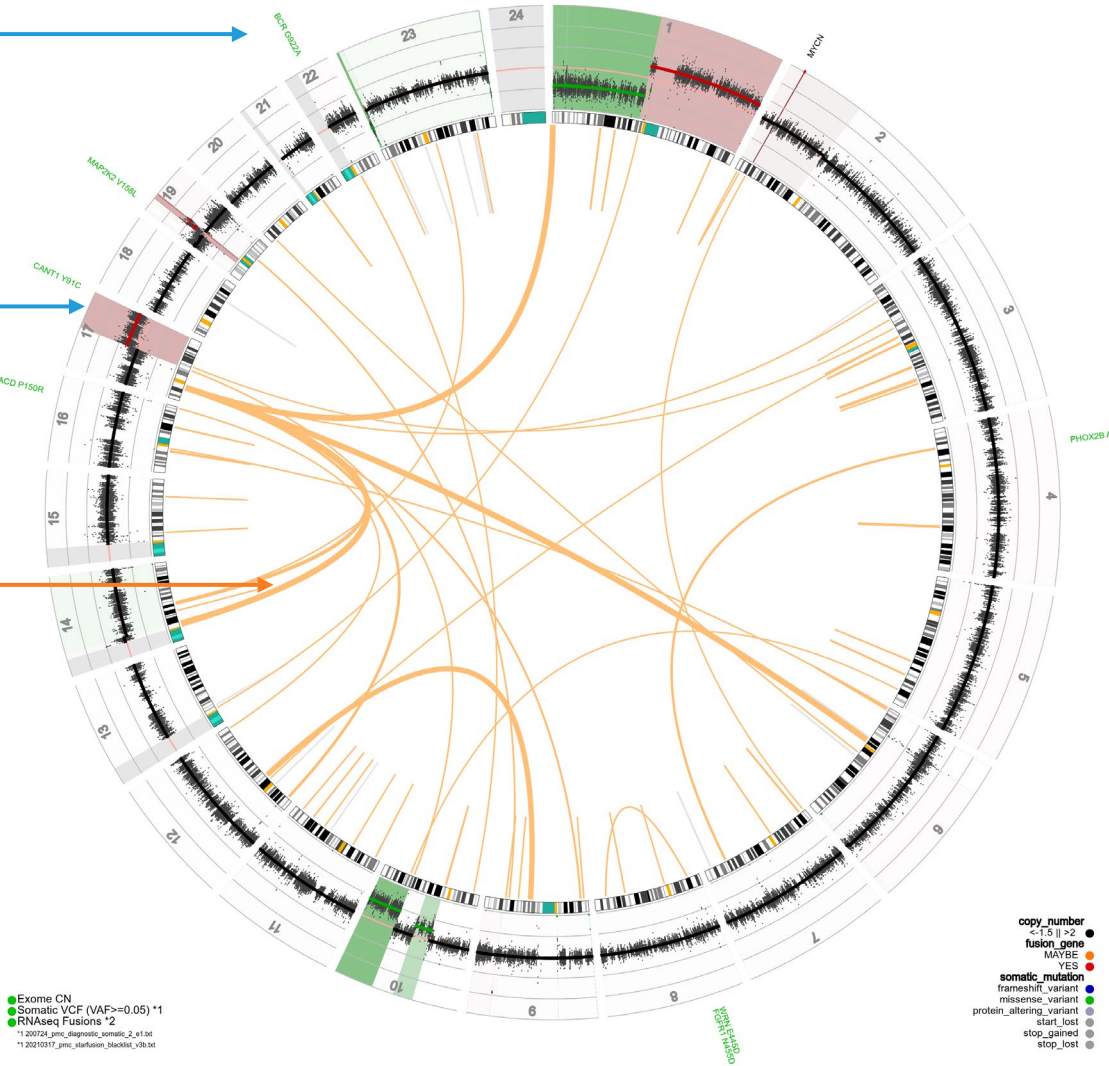
Copy Number Variation

RNA analyse  
RNAseq

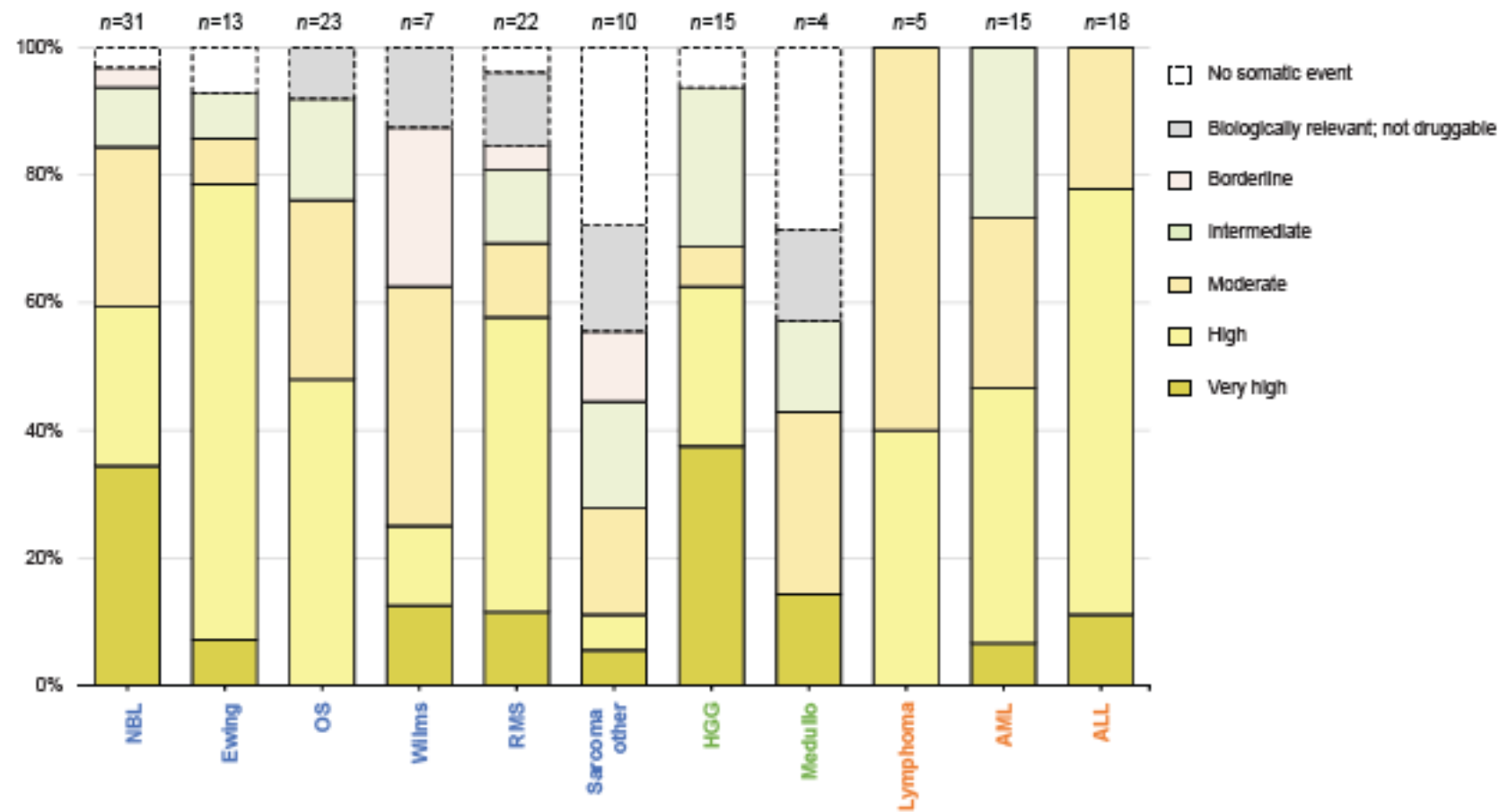
Diff expressie

Genfusies

Methylatie array



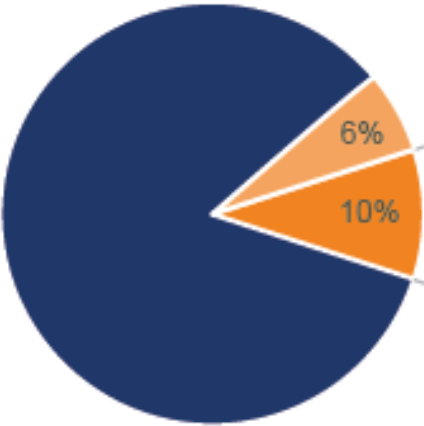
# iTHER targets



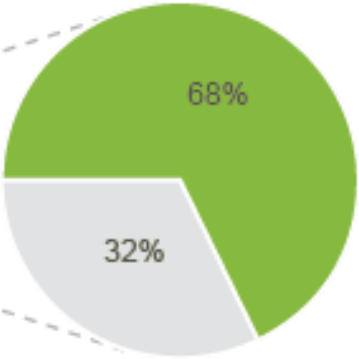
# iTHER – Kiembaan mutaties

Patients with a germline pathogenic variant (16%)

Causality



total cohort n = 219



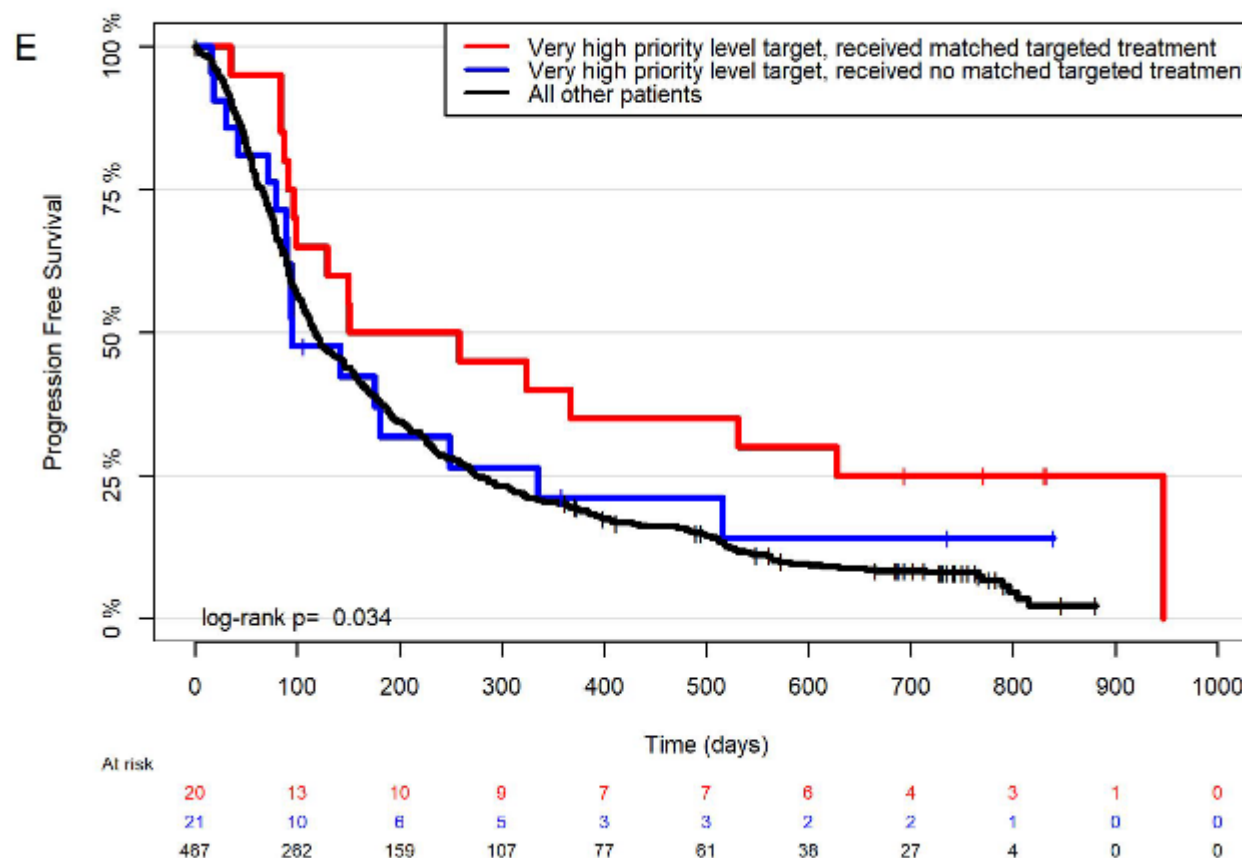
- monoallelic variant in genes purely causing autosomal recessive inherited conditions<sup>1</sup>
- reportable germline pathogenic variants
- causative
- uncertain causality

# Terug naar de patiënt

| Target & Alteration           | Priority     | Therapeutic options           |                                                                                                               | Trial                                            | Identifier                                        |
|-------------------------------|--------------|-------------------------------|---------------------------------------------------------------------------------------------------------------|--------------------------------------------------|---------------------------------------------------|
| <b>FGFR1</b><br>mutation      | very high    | FGFRi                         | <b>ponatinib</b><br><br>lenvatinib<br><br>other: dovitinib, erdafitinib, pazopanib<br>In development: AZD4547 | Ph I/II – open at PMC<br><br>Ph I/II<br><br>NA   | NCT03934372<br><br>NCT02432274                    |
|                               | high         | MEKi                          | cobimetinib, trametinib, selumetinib, binimetinib                                                             | NA                                               |                                                   |
| <b>MYCN</b><br>amplification  | moderate     | HDAC/BETi/CDKi/<br>CHKi/AURKi | entinostat, panobinostat, vorinostat, belinostat, valproic acid                                               | NA (INFORM2 >6y)                                 |                                                   |
| <b>BCL2</b><br>overexpression | intermediate | BCL2i                         | <b>venetoclax</b>                                                                                             | Ph I – open at PMC                               | NCT03236857                                       |
|                               |              |                               | navitoclax                                                                                                    | venetoclax - idasanutlin<br><br>NA               | NCT04029688                                       |
| <b>RET</b><br>overexpression  | intermediate | RETi                          | <b>ponatinib</b><br><br>lenvatinib<br><br>regorafenib                                                         | Ph I/II – open at PMC<br><br>Ph I/II<br><br>Ph I | NCT03934372<br><br>NCT02432274<br><br>NCT02085148 |
|                               |              |                               | other: alectinib, cabozantinib, sorafenib, selpercatinib, sunitinib, vandetanib.                              | NA                                               |                                                   |

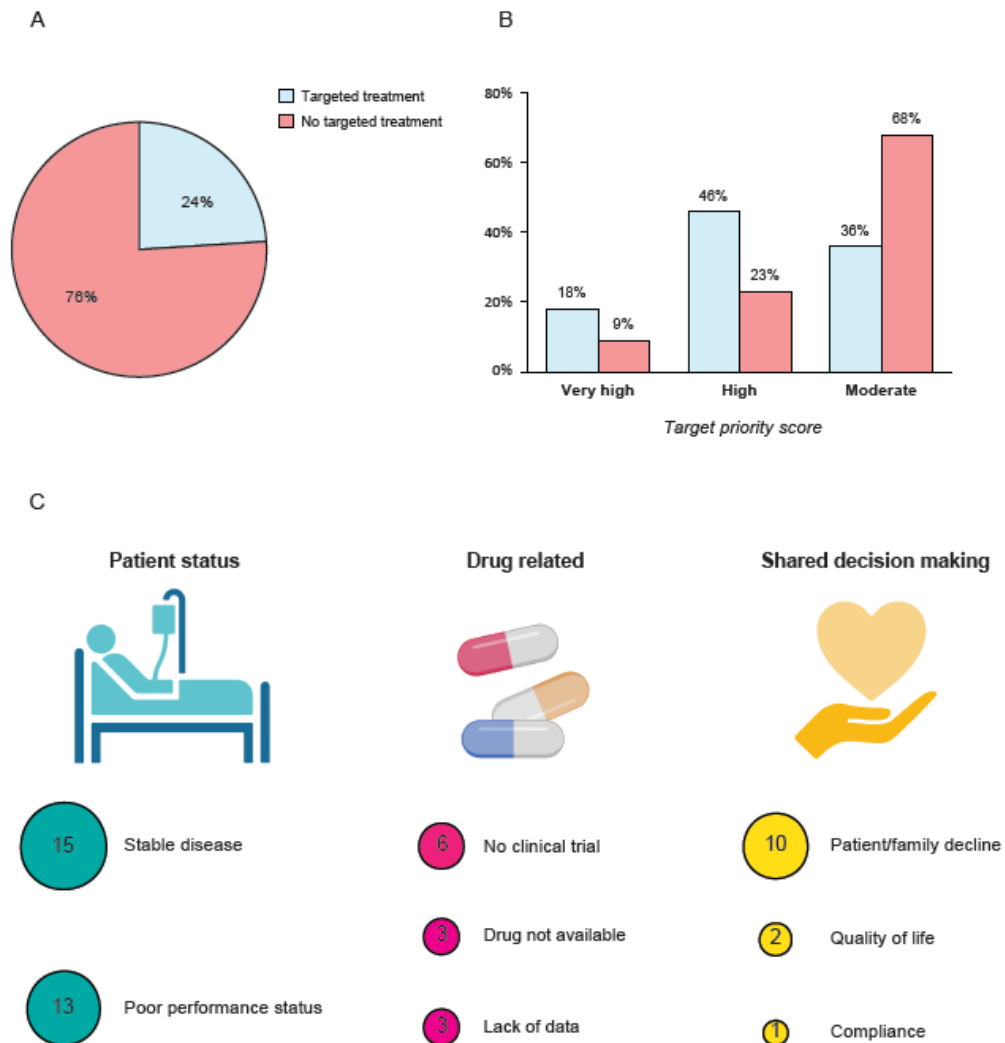
# iTHER – Clinical benefit voor patiënten met een very-high priority target

- Analyse samen met INFORM
- Mediane PFS: 204.5 dagen  
(vs 114 days)
- Time-to-progression ratio 1.0  
(vs 0.7)

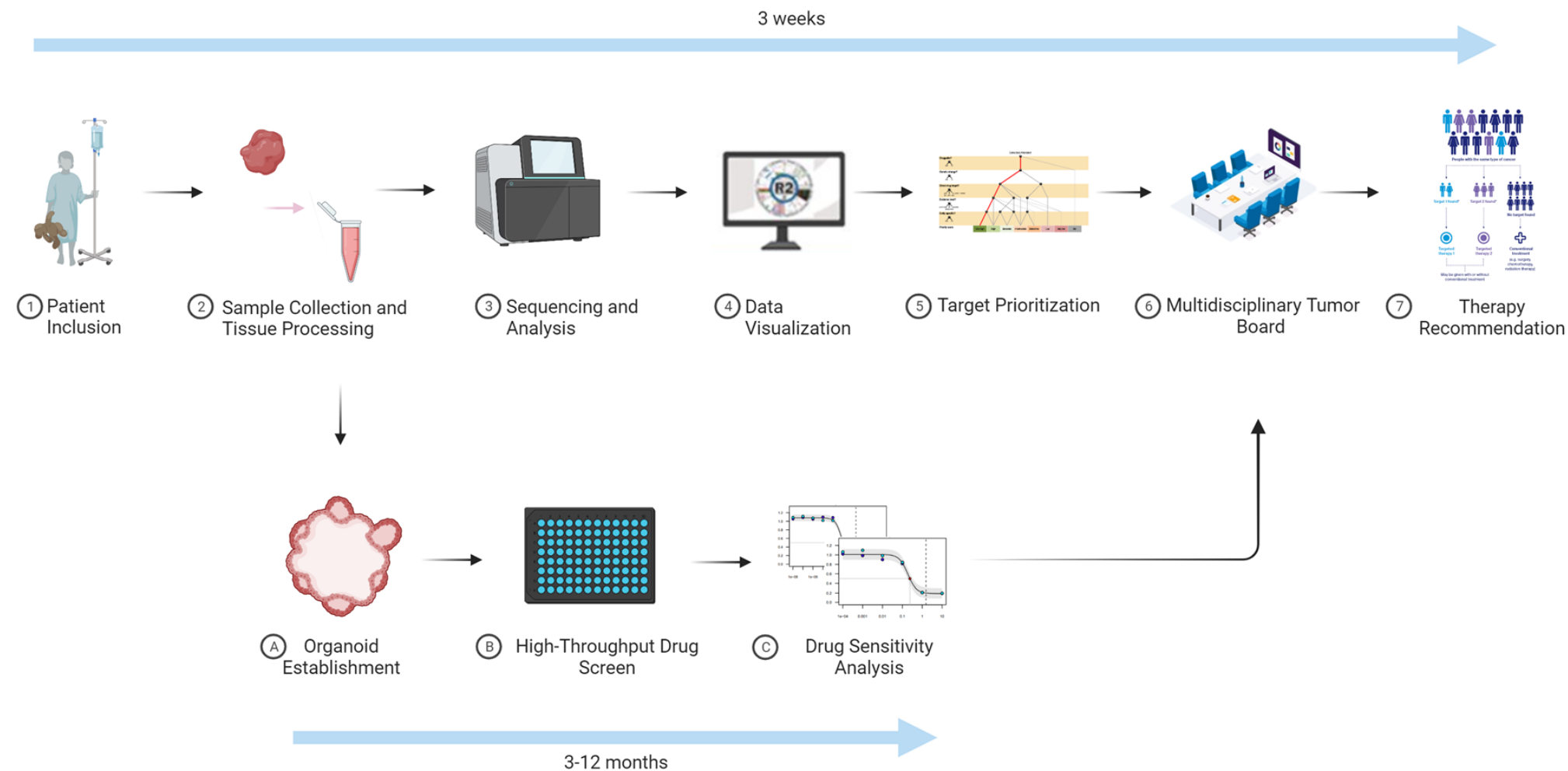


- WES en RNAseq als standard-of-care
  - Concentratie kinderoncologische zorg
  - Best practices
- Uitdagingen
  - Binnen Nederland
  - Europees
  - Enrolment in klinische trials

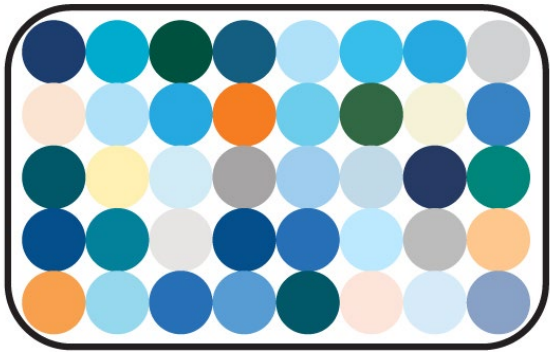
# iTHER – Exploratie van klinische implementatie



# iTHER: drug screening

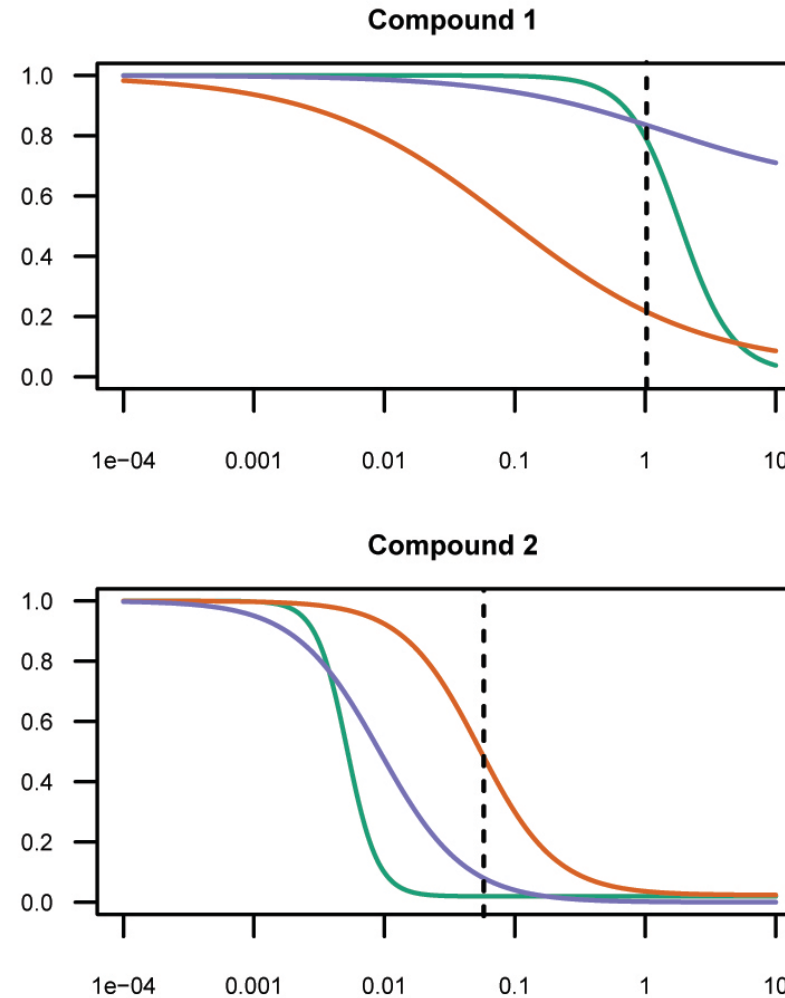


# PMC Drug library



~200 geneesmiddelen  
6-10 concentraties

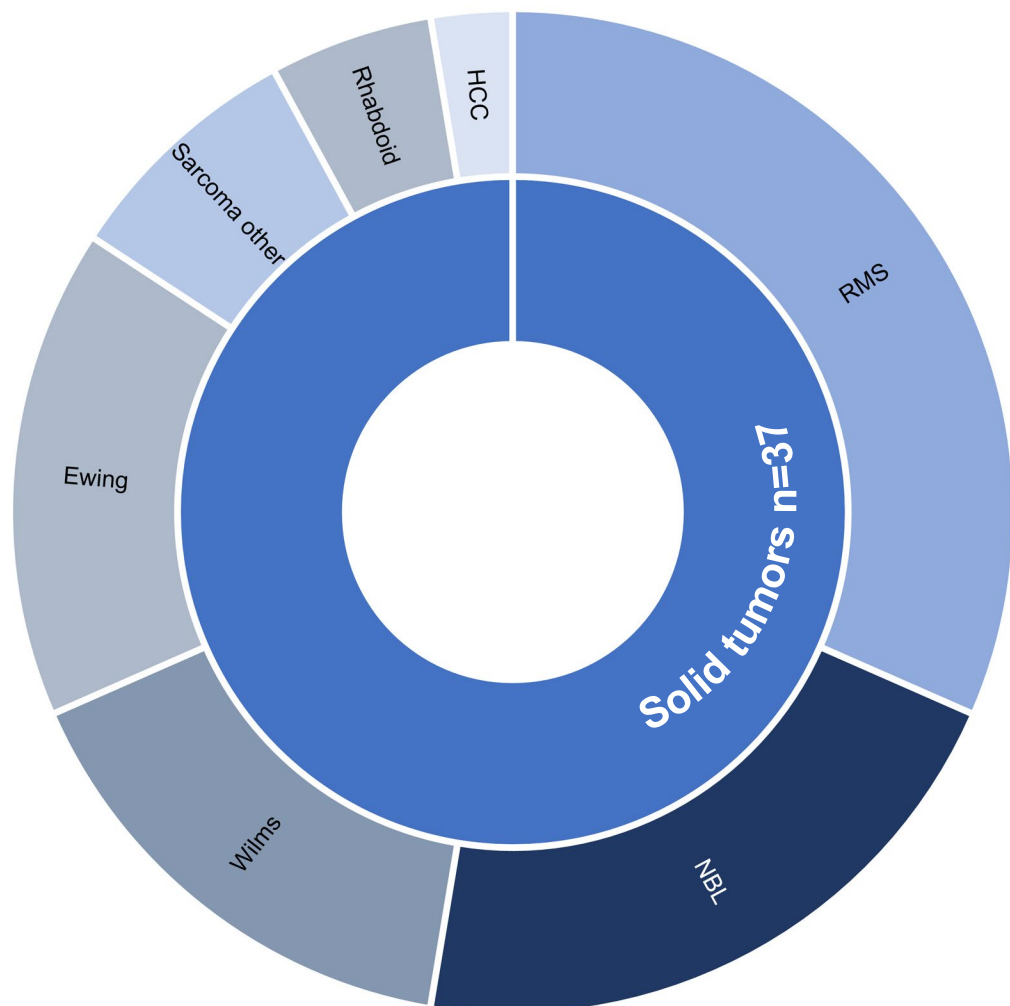
20% chemotherapie  
80% targeted geneesmiddelen



AUC

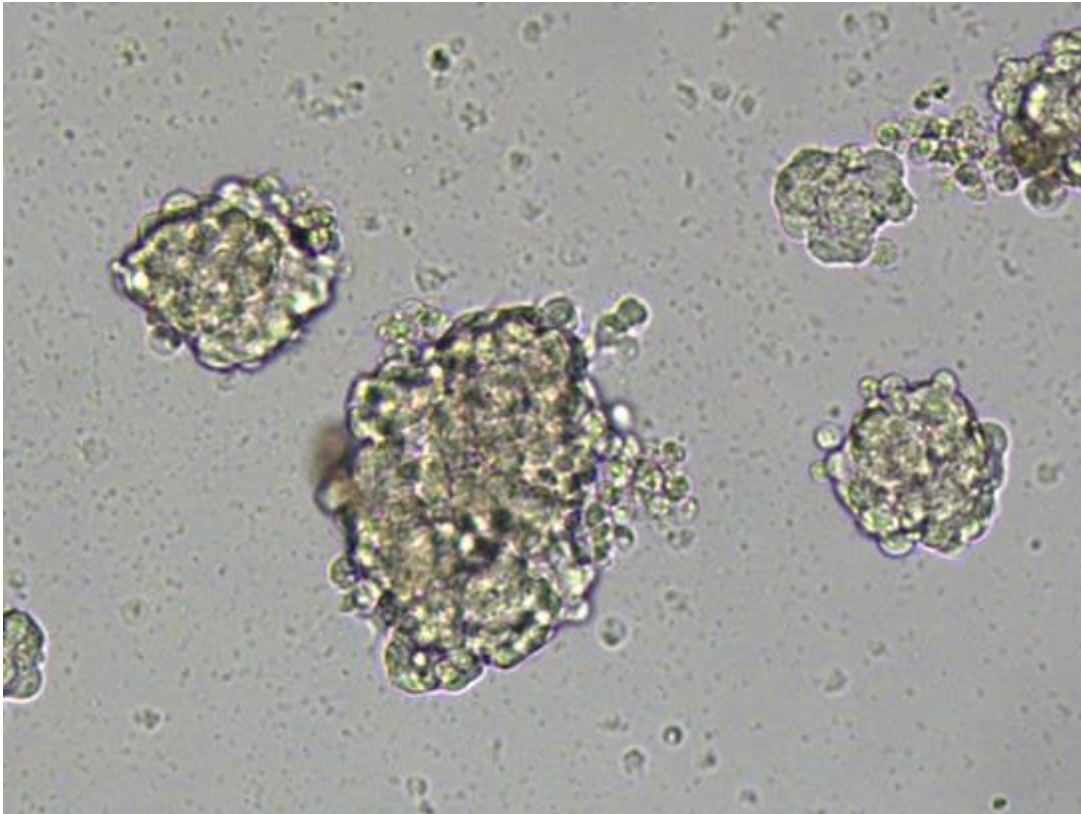


Z-score

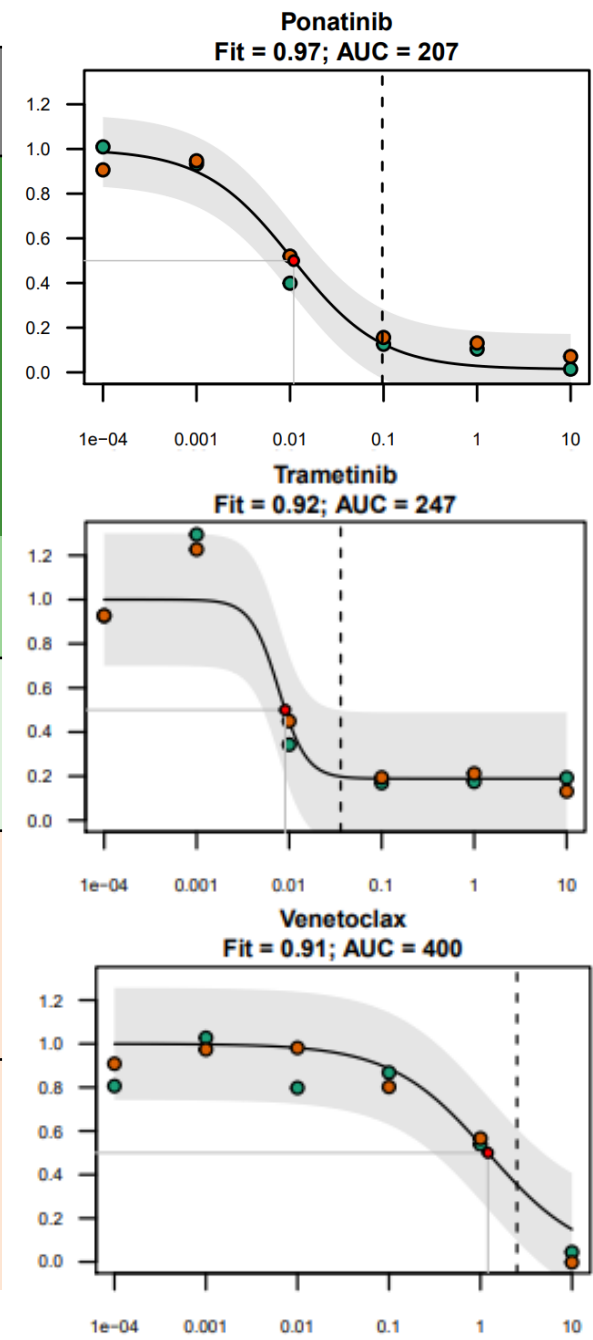


**Pilot studie in solide tumoren**  
37 samples succesvol

# Terug naar de patiënt: organoids en drug screening

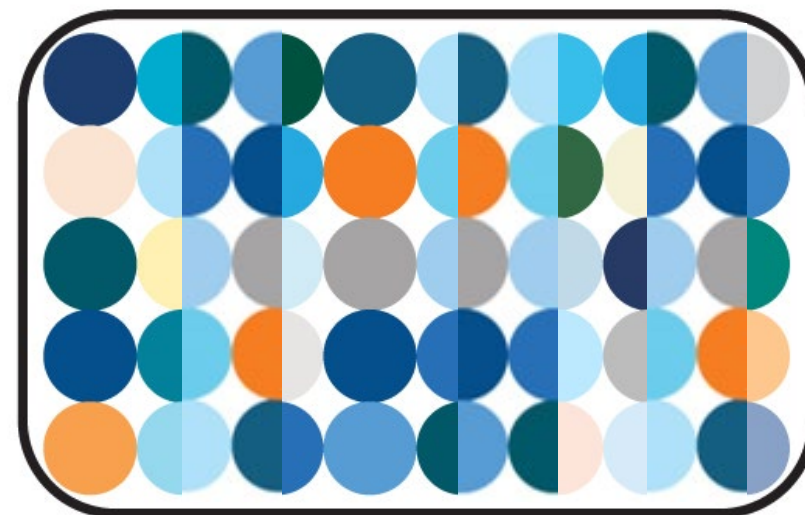
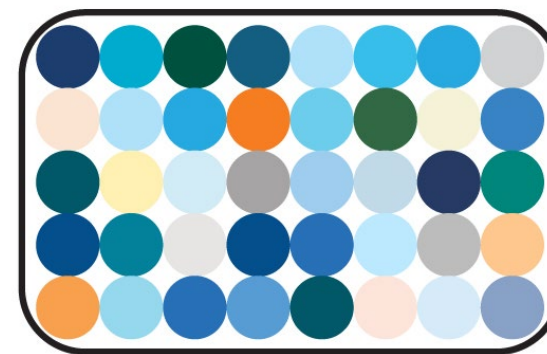


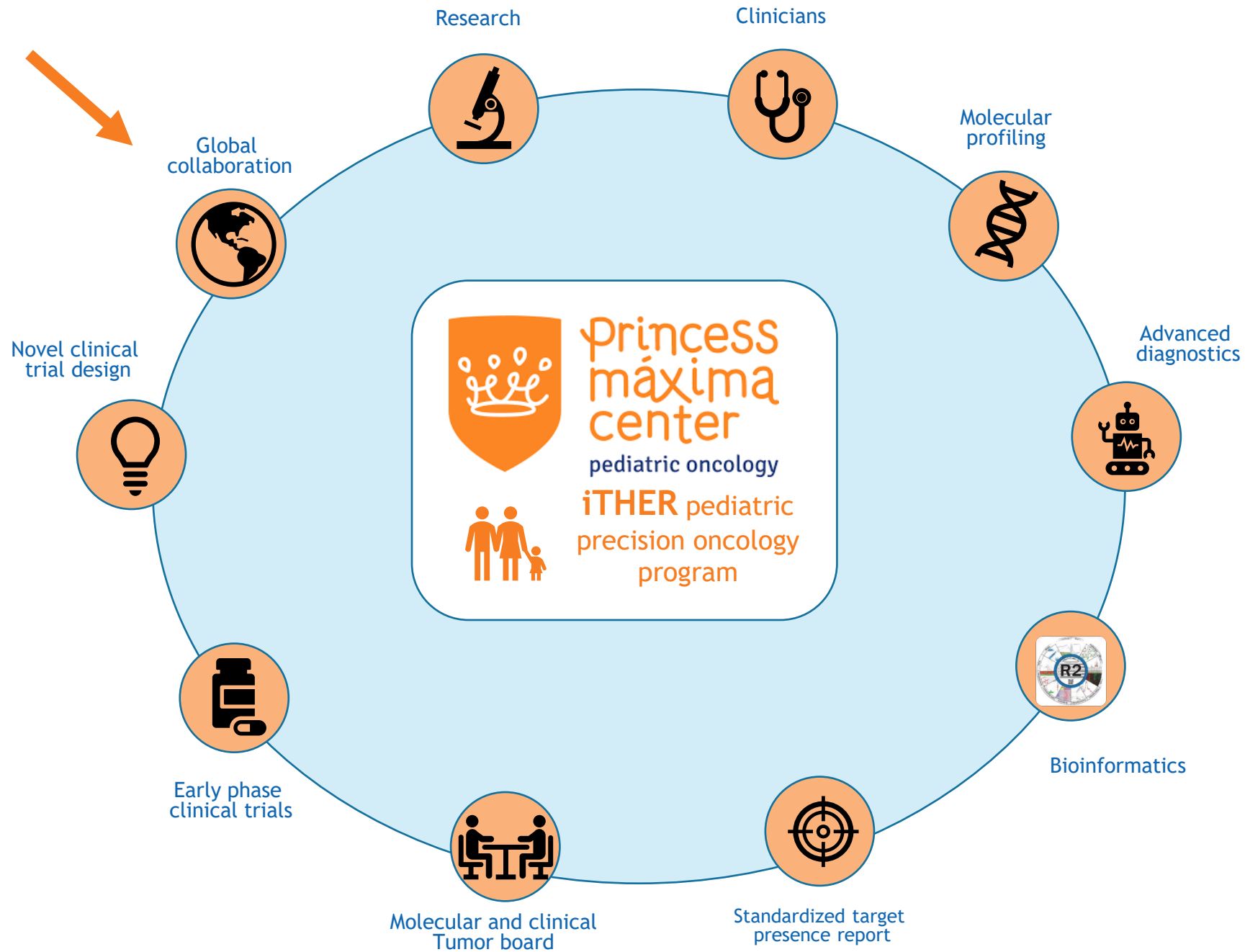
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|----------------------------|--------------|---------------------------|---------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| <b>FGFR1</b> mutation      | very high    | FGFRi                     | <b>ponatinib</b><br><br>lenvatinib<br><br>other: dovitinib, erdafitinib, pazopanib<br>In development: AZD4547 | <b>Ph I/II – open at PMC</b><br><br>Ph I/II<br><br>NA |
|                            | high         | MEKi                      | cobimetinib, trametinib, selumetinib, binimetinib                                                             | NA                                                    |
| <b>MYCN</b> amplification  | moderate     | HDAC/BETi/CDKi/CHKi/AURKi | entinostat, panobinostat, vorinostat, belinostat, valproic acid                                               | NA (INFORM2 >6y)                                      |
| <b>BCL2</b> overexpression | intermediate | BCL2i                     | <b>venetoclax</b>                                                                                             | <b>Ph I – open at PMC</b>                             |
|                            |              |                           | navitoclax                                                                                                    | NA                                                    |
| <b>RET</b> overexpression  | intermediate | RETi                      | <b>ponatinib</b>                                                                                              | <b>Ph I/II – open at PMC</b>                          |



# Toekomst

- Prospectieve studie: voorspellende waarde
  - Klinische trials
- Model systemen
  - Immunotherapie
- **Combinatie** screens





# Acknowledgements



Patients & parents



## Princess Máxima Center

|                          |                           |
|--------------------------|---------------------------|
| Jan Molenaar             | Frank Holstege            |
| Michel Zwaan             | Hans Clevers              |
| Bianca Goemans           | Jarno Drost               |
| Max van Noesel           | Marc vd Wetering          |
| Sebastiaan Tops          | Claudia Janda             |
| Patrick Kemmeren         | Marcel Kool               |
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| Marc Wijnen              | Marijn Scheijde-Vermeulen |
| Lennart Kester           | Marc van Tuil             |
| Michael Meister          | Pathology assistants      |
| Esther Hulleman          | Miriam Stumpf             |
| Judith Boer              | Jenny Smink               |
| Uri Ilan                 | Margot Geerdink           |
| Simone Punt              | Ria Koolma                |
| Monique den Boer         | Saskia Rasser             |
| Jasper vd Lugt           | Martha Lopez              |
| Lieve Tytgat             | Yvonne Rucht              |
| Josef Vormoor            | All nurses & physicians   |
| Eelco Hoving             |                           |

## Team Molenaar

|                         |                             |                             |
|-------------------------|-----------------------------|-----------------------------|
| <b>Kim Ober</b>         | <b>Marlinde vd Boogaard</b> | <b>Kaylee Keller</b>        |
| <b>Sander van Hooff</b> | <b>Judith Wienke</b>        | <b>Michael v Gerven</b>     |
| <b>Selma Eising</b>     | <b>Bianca Koopmans</b>      | <b>Nil Schubert</b>         |
| <b>Linda Schild</b>     | <b>Vicky Amo-Addae</b>      | <b>Femke van den Ham</b>    |
| <b>Marli Serbanescu</b> | <b>Jessica van der Hoek</b> | <b>Jennemieke van Arkel</b> |
| <b>Celina Szanto</b>    | <b>Lindy Vernooij</b>       | <b>Josephine Strijker</b>   |
|                         | <b>Stijn Couwenbergh</b>    | <b>Michelle Tas</b>         |



## R2, Amsterdam UMC

Jan Koster  
Richard Volckmann  
*et al.*

## Geert Frederix, UMCU (HTA)

## DKFZ / INFORM

## MAPPYACTS

## SM-PAEDS

## ITCC

## CCI, Sydney

Emmy Dolman

# Prioritiseren van targets

