UMC Utrecht

One arm, many views: the future of evidence generation

The role of single-arm trials in regulatory and clinical context, RSSN workshop 2025

Nov 18th 2025, Utrecht

Prof. dr. Miriam Koopman

Medical Oncologist UMC Utrecht

DISCLOSURES

- **Personal financial interests:** -

- **Institutional financial interests (grants/presentations/advisory role -> all payments to institution):** Amgen, Bayer, BMS, GSK, IqVIA, Merck-Serono, Nordic Farma, PdGx, Pierre Fabre, Roche, Servier, Sirtex, Sanofi-Aventis

- **Non-financial interests**: PI PLCRC (national observational cohort study), chair ESMO RWD & digital health working group, involved in several clinical trials as PI or co-investigator in CRC

- **Other,** -

> Being able to give a personalized treatment advise for each (CRC) oncology patient, irrespective of hospital, region or country

Prof. Dr.
Miriam Koopman

Trial participation versus real-world

Efficacy-effectiveness gap

Trials

- Homogeneous population
- Strictly monitored RCTs
- More often academic health care providers
- Stringent in- and exclusion criteria

Efficacy vs effectiveness

Real-world

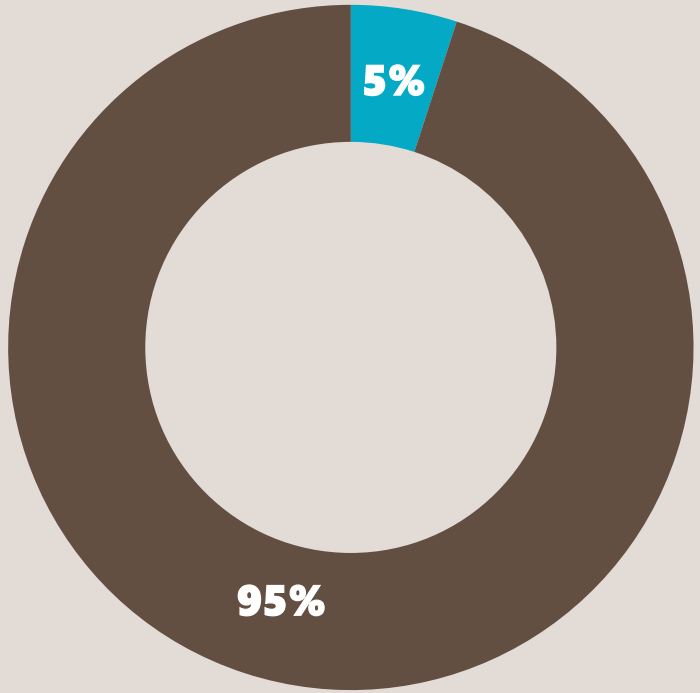
- Heterogeneous population
- Daily clinical care
- General health care providers

Characteristics and circumstances are different

Guidelines are based on results of clinical trials in which only 5% of our patients participate

Trials

- Homogeneous population
- Strictly monitored RCTs
- Often academic health care providers
- Stringent in- and exclusion criteria



Trial participation versus real-world

Efficacy-effectiveness gap

Trials

- Results of clinical trials in which only 5% of our patients participare are being incorporated in clinical guidelines

Efficacy vs effectiveness

Real-world

- 95% of our patients are being treated outside clinical trials with a treatment advice according to these guidelines

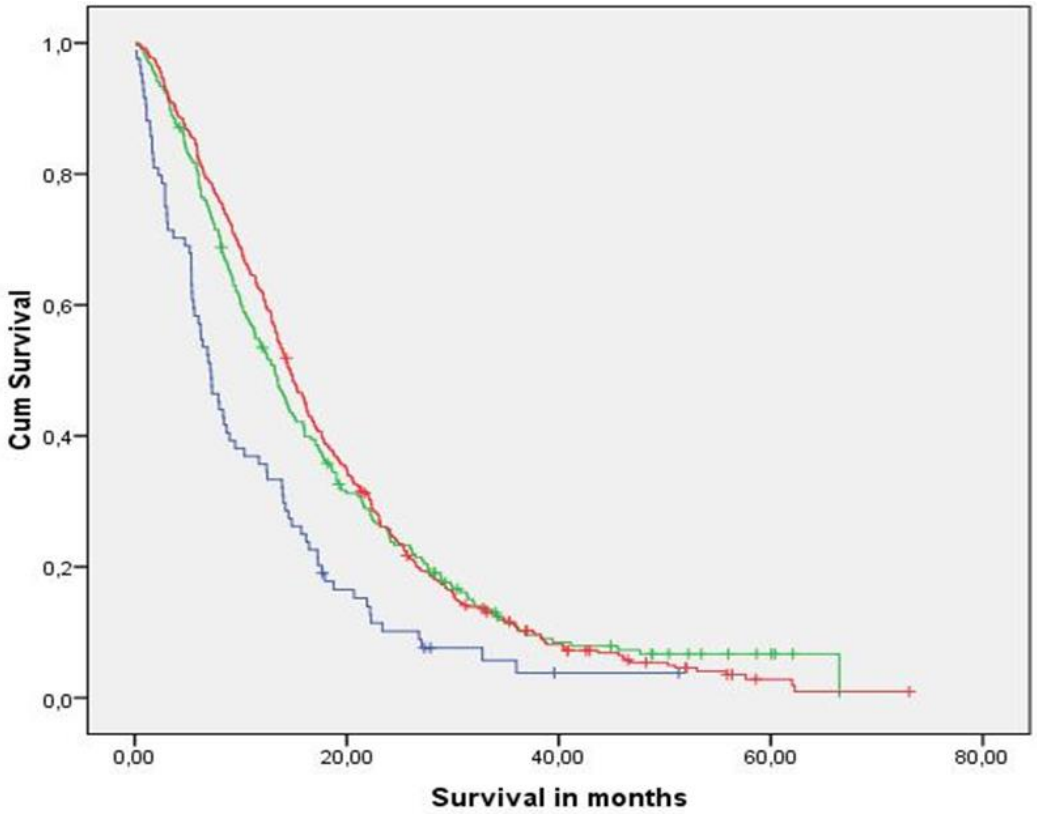
Characteristics and circumstances are different, what about outcome?

Comparison of RWD with a RCT including 2 standard of care treatment arms

Median overall survival

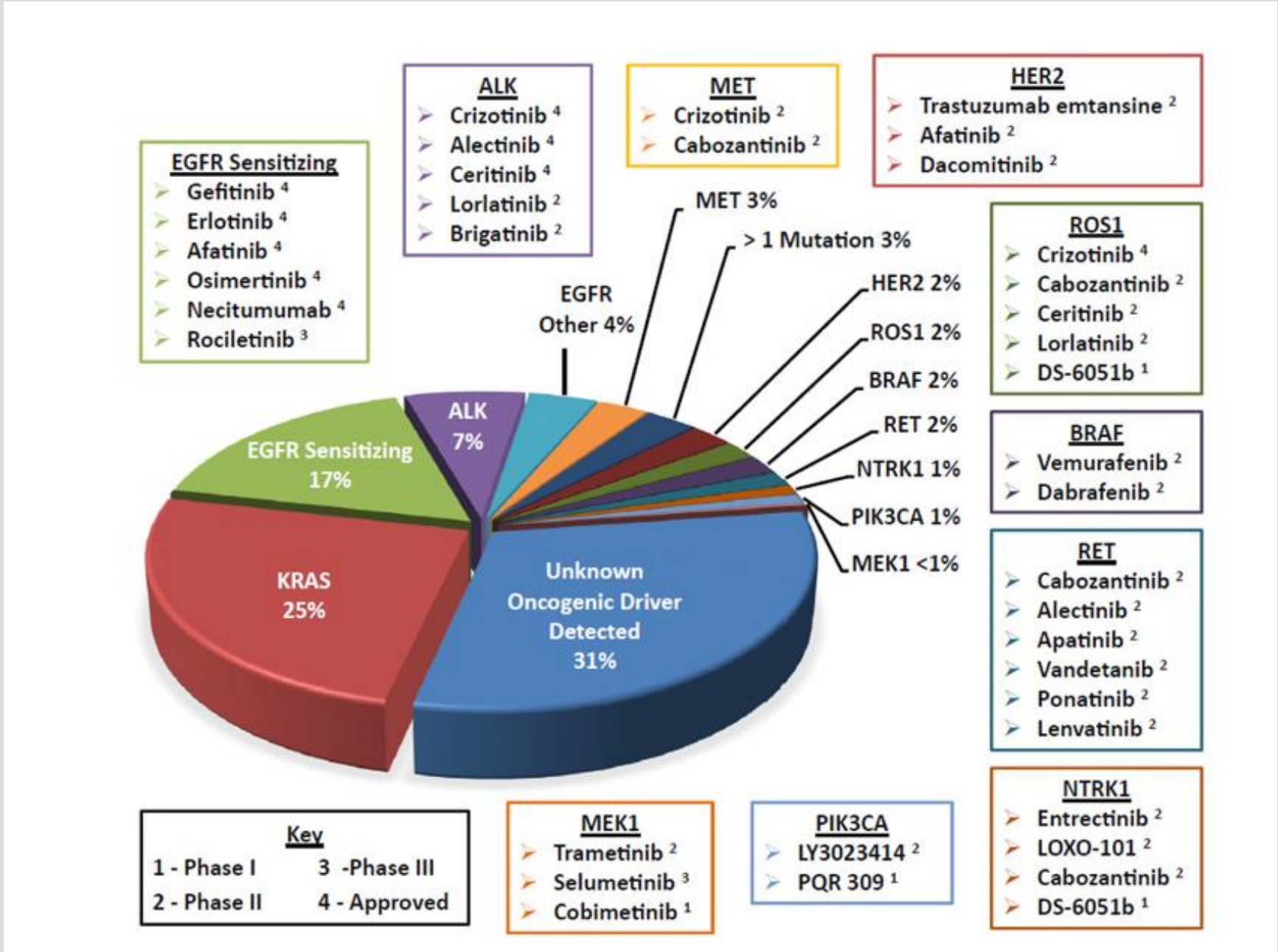
(CAIRO: chemo sequential or combination)

Trial patients	17.0 m
Eligible non-trial patients	15.7 m
Non-eligible non-trial patients	9.3 m p<0.001



Trial results are not (always) applicable to daily clinical practice

Heterogeneity with increasing number of small subgroups



THUS:

- data of RCT are not (always) applicable to daily clinical practice
- we are facing an increasing number of smaller subgroups
- therefore, a different approach is warranted
- we need to learn from every patient, in other words use the full potential of Real-World Data
- Real-World Data will enable pragmatic clinical trials including single arm trials using Real World Data as external comparator

2025 ESMO SARCOMA AND RARE CANCERS
Annual Congress

PERCEPTIONS OF HEALTHCARE PROFESSIONALS AND REGULATORS ON THE USE OF REAL-WORLD DATA (RWD) AS EXTERNAL COMPARATORS IN LATE-STAGE ONCOLOGY SINGLE-ARM TRIALS

Diogo Martins-Branco[+], D. Postmus[+], T.C. El-Galaly[+], A. Valachis, D. Trapani, M. Di Maio, P. Mol, K. Porkka, K. Robertson, U.-P. Rohr, R. Doeswijk, M. Kaiser, M. Koopman, N. Cherny, R. Cordoba[‡],G. Pentheroudakis[‡], F. Pignatti[‡]

[+,‡] *Contributed equally*

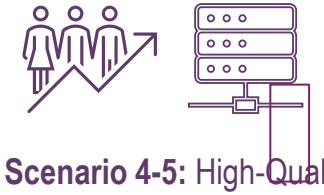
20.03.2025, Lugano

METHODS

Cross-sectional survey of healthcare professionals (HCP) and regulators (May-Sept'24)

Scenario 1: Single-arm trial

Scenario 2-3: Low-Quality RWD



OS gain: 1.5mos

OS gain: 3mos

Scenario 4-5: High-Quality RWD

OS gain: 1.5mos

OS gain: 3mos

Scenario 6-7: Randomised controlled trial

OS gain: 1.5mos

OS gain: 3mos

Clinical setting: late-stage disease, no effective treatment, mOS 3 mos (1 to 5).

Four RWD external comparator scenarios:

- *Quality of RWD*: Low-Quality vs High-Quality
- *OS gain*: 1.5 vs 3 months

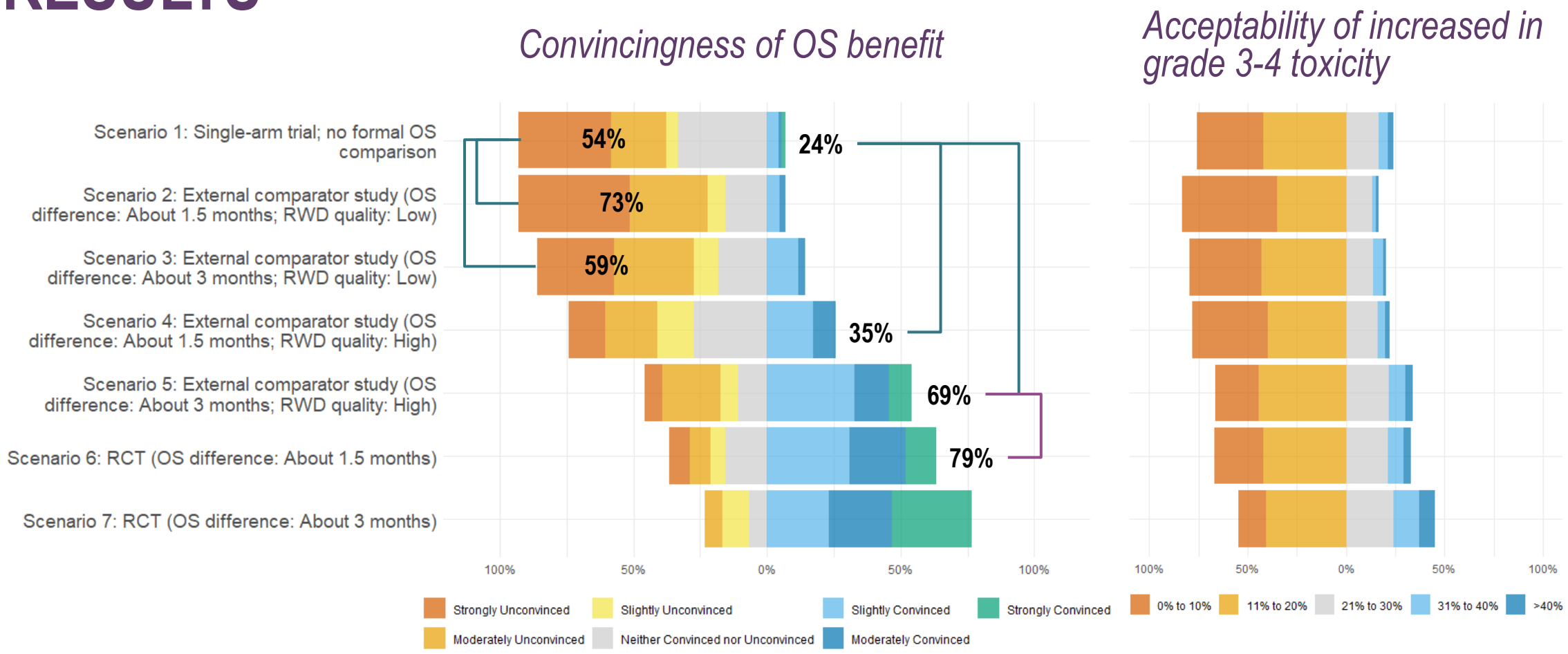
Three control scenarios: SAT and RCT with OS gain 1.5 or 3 months

Participants

- *Healthcare professionals* (faculty and working group members of ESMO/EHA)
- *EU and non-EU regulators* (active assessors in of oncology drug application)

Diogo Martins-Branco, MD MSc

RESULTS



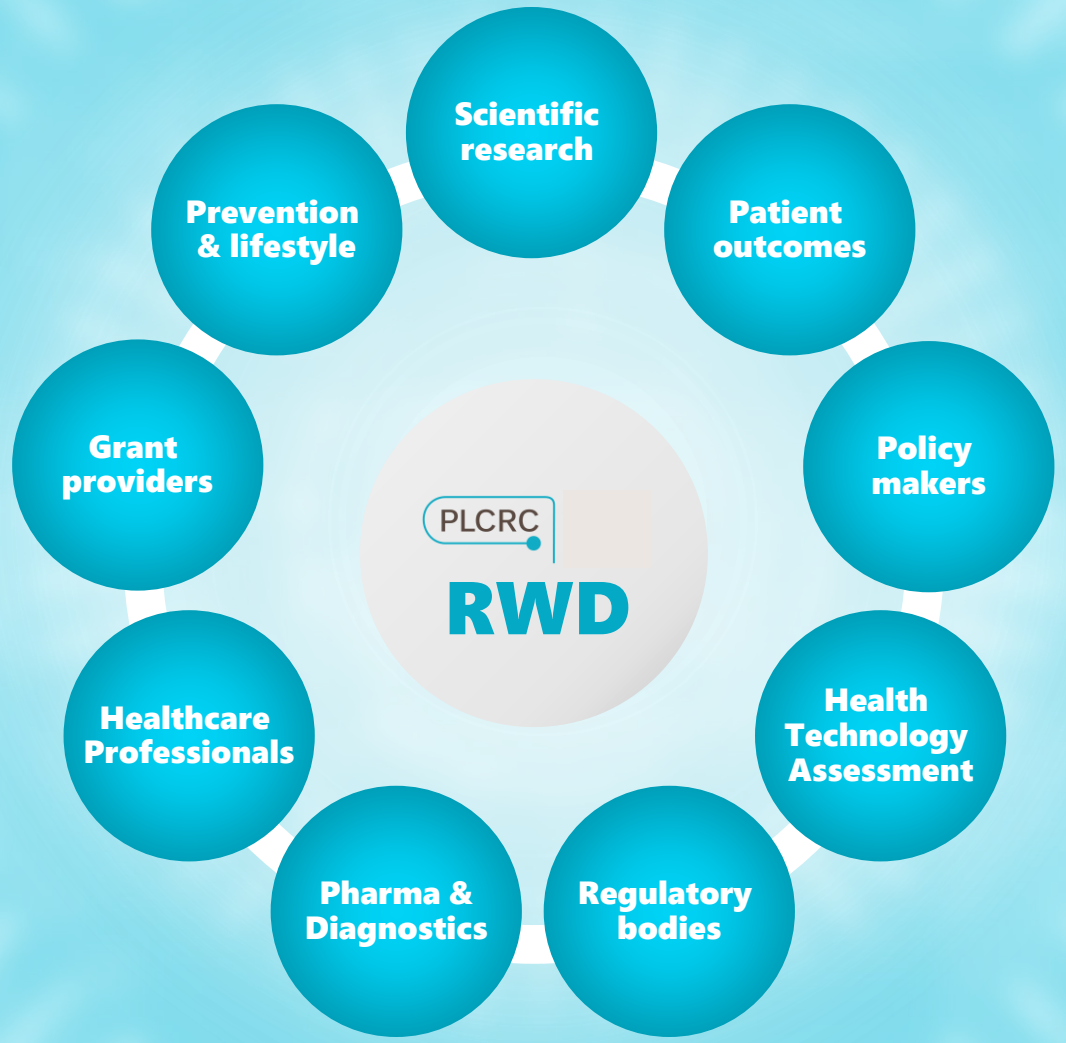
Outcomes for the new treatment (common to all scenarios): ORR = 30%; mDoR = 6 months; mOS = 6 months
mOS "standard care" estimated from the literature: 3 months (1-5 months)

Diogo Martins-Branco, MD MSc

CONCLUSIONS

- *Differences* between HCP and regulators on **familiarity with RWD studies** and beliefs related to **advantages/disadvantages of RWD studies** call for activities that increase alignment.
- HCP and regulators *share* a **positive perception of the use of high-quality RWD** as an external comparator to SAT of advanced cancer of high unmet medical need.
- Higher **trust in OS benefit** was associated with **higher acceptability of severe toxicity** increase.
- **Quality attributes in RWD studies** must be clearly defined for the streamlined use of this methodology.

Diogo Martins-Branco, MD MSc



PROSPECTIEF LANDELIJK CRC COHORT

Unique Design

DCCG

Prospective Dutch Colorectal Cancer Cohort Study (PLCRC)

All patients diagnosed with colorectal, small bowel, anal cancer (Stage I – IV) at any time, all stages:

Observational studies:

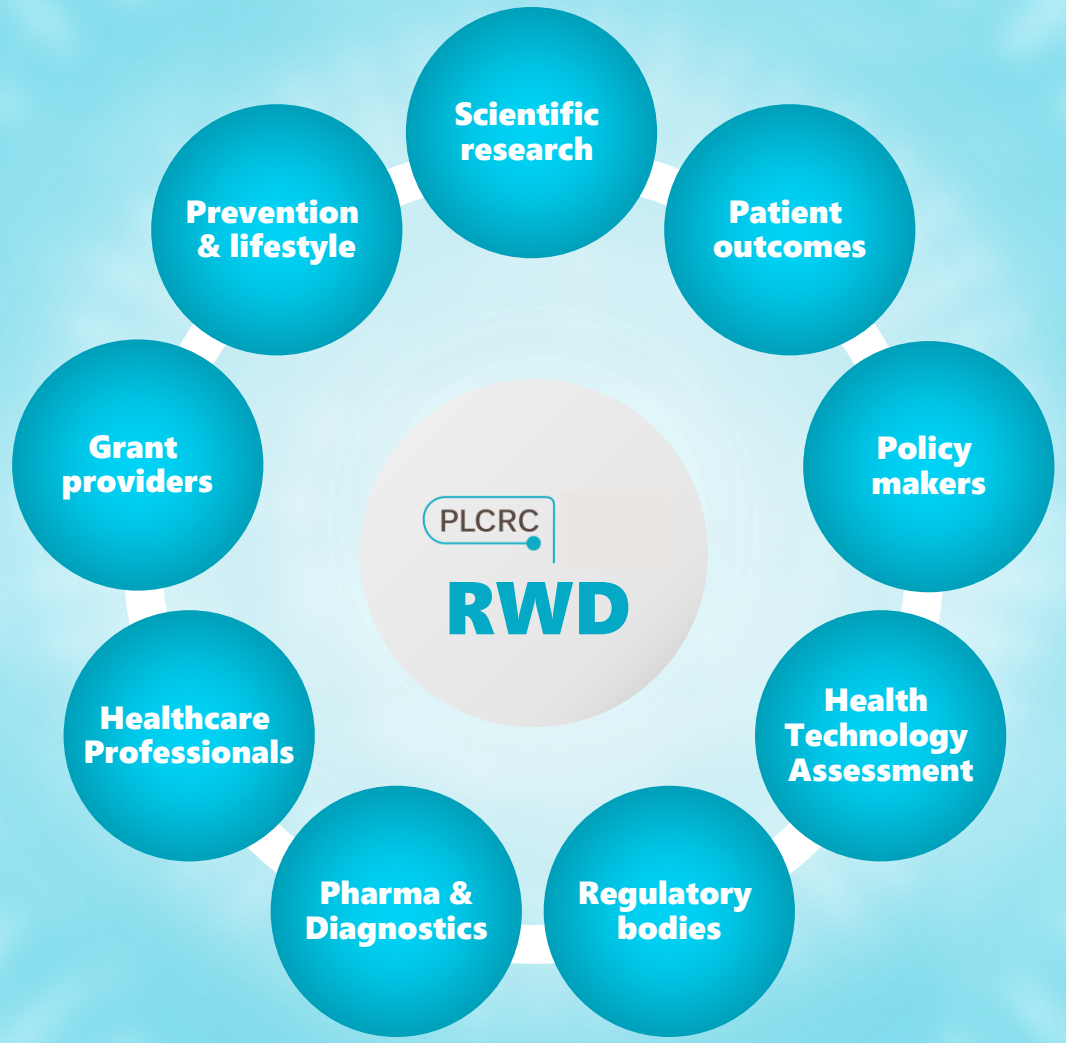
- ☑ Clinical data
- ☑ Tissue
- ☑ Blood
- ☑ PROM's

Interventional studies:

- ☑ Trials within cohorts (TwiCs)

>90%

☑ **Informed Consent Patient**



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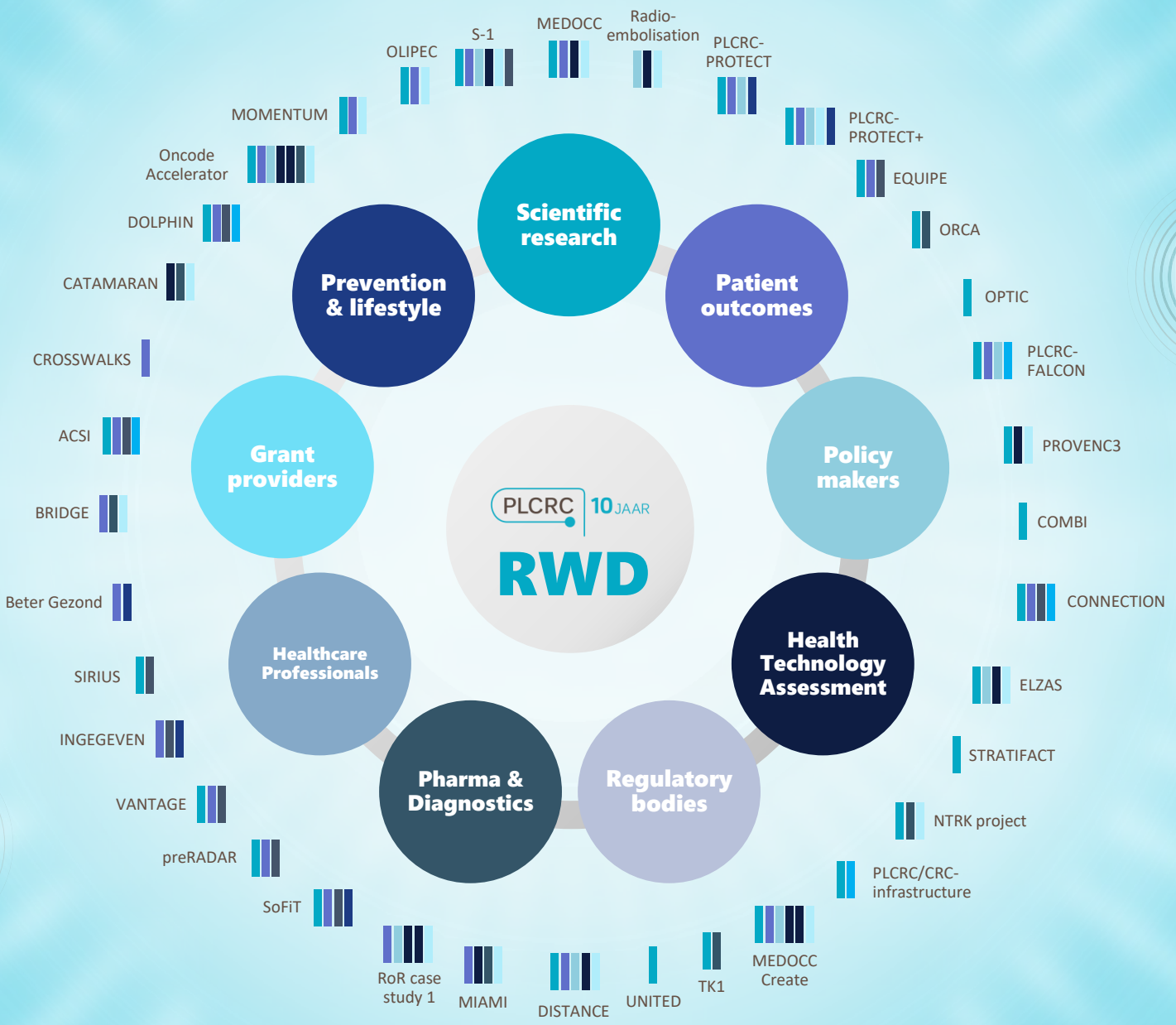
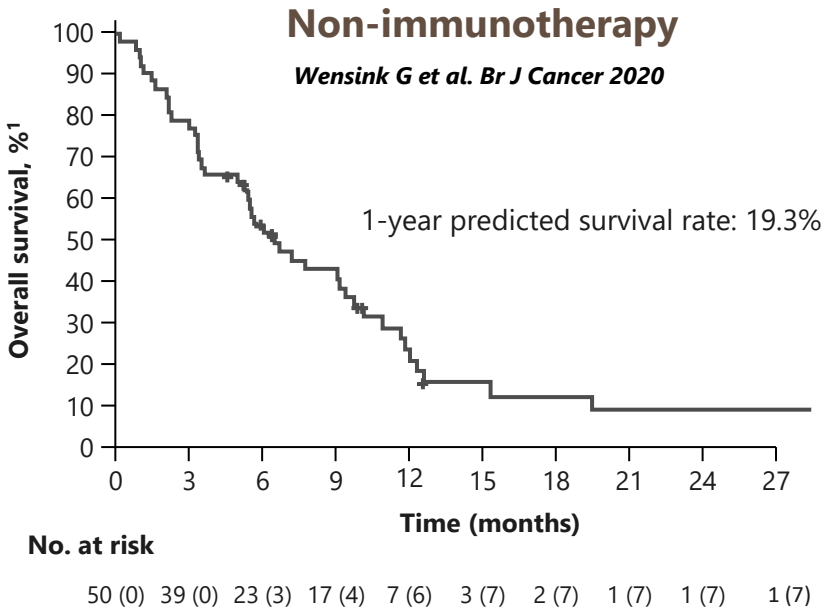
- ❖ > 25,000 patients
- ❖ 69 hospitals in NL participate (99% national coverage)
- ❖ > 90 ongoing projects (40 projects using data, 50 using infrastructure)

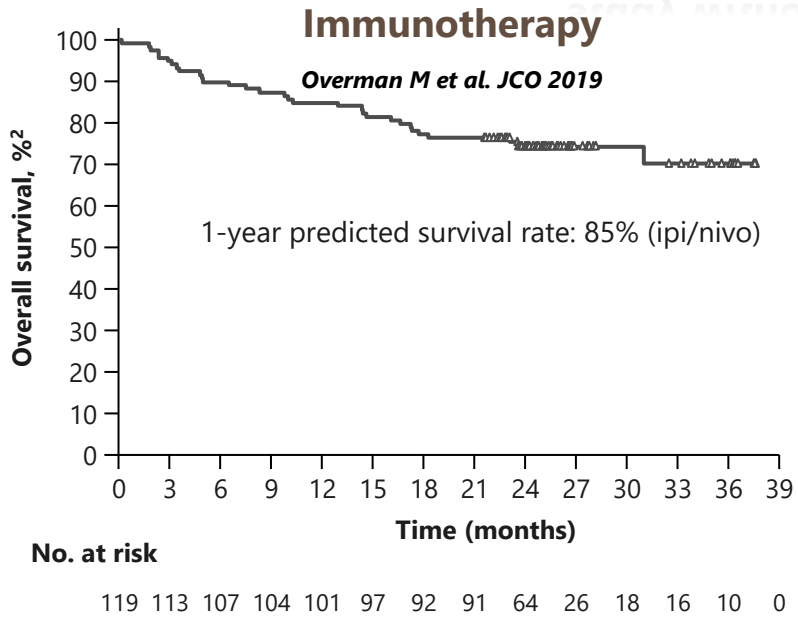
☑ **Informed Consent Patient**


PLCRC 10 JAAR
RWD
Scientific research
Patient outcomes
Policy makers
Health Technology Assessment
Regulatory bodies
Pharma & Diagnostics
Healthcare Professionals
Grant providers
Prevention & lifestyle
OLIPEC
S-1
MEDOCC
Radio-embolisation
PLCRC-PROTECT
PLCRC-PROTECT+
EQUIPE
ORCA
OPTIC
PLCRC-FALCON
PROVENC3
COMBI
CONNECTION
ELZAS
STRATIFACT
NTRK project
PLCRC/CRC-infrastructure
MEDOCC Create
TK1
UNITED
DISTANCE
MIAMI
RoR case study 1
SoFiT
preRADAR
VANTAGE
INGEGEVEN
SIRIUS
Beter Gezond
BRIDGE
ACSI
CROSSWALKS
CATAMARAN
DOLPHIN
Oncode Accelerator
MOMENTUM

Pretreated metastatic dMMR patients +/- immunotherapy

Provide data for single arm study without control arm





ipi=ipilimumab; nivo=nivolumab; no=number; OS=overall survival.

Non-immunotherapy data were expanded with PLCRC data including responses and were used for EMA application of nivolumab + ipilumumab -> **EMA approval!!**

Success factors

- Centralize the data
- Collaboration with all stakeholders
- Patient's informed consent

  (including IC for sharing data with pharma & regulators!)

Unique Design

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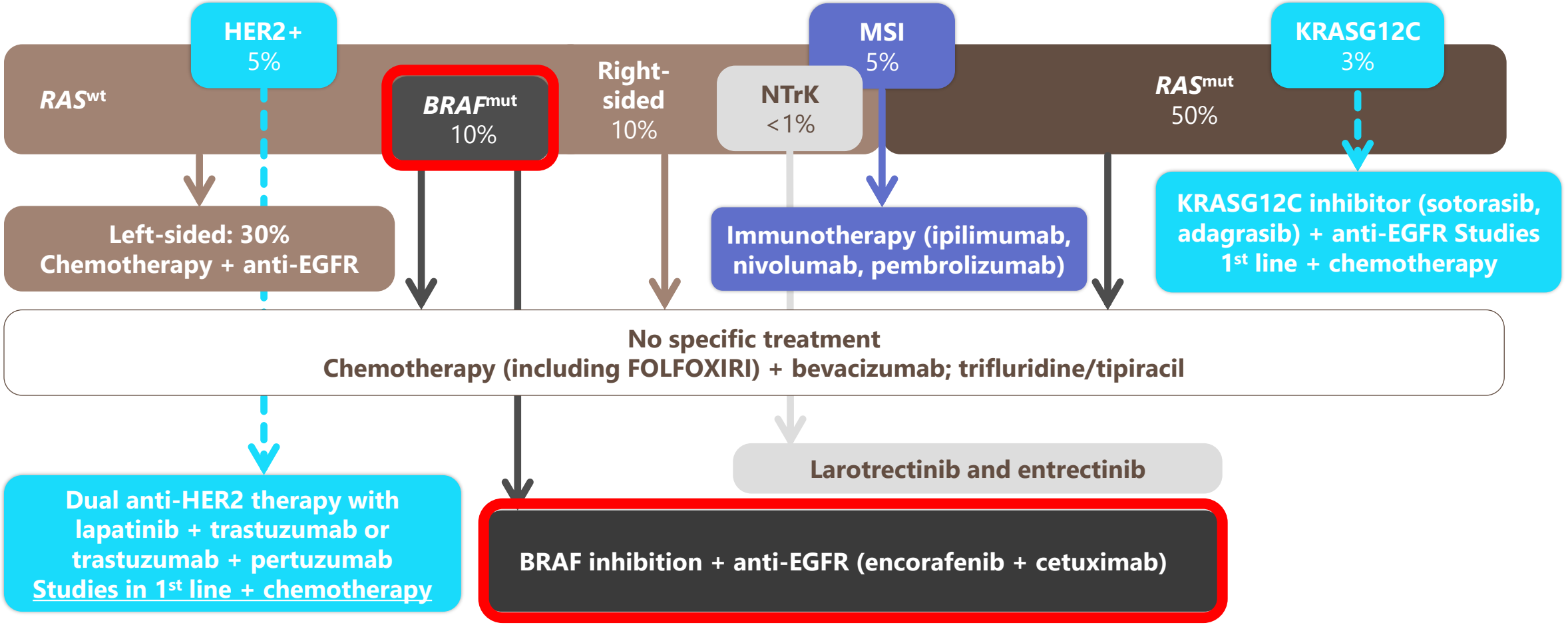
☑ **Informed Consent Patient**

PROSPECTIEF LANDELIJK CRC COHORT

Metastatic colorectal cancer: a heterogeneous disease

Different subtypes with increasing number of treatment options



Adapted from Punt CJA, Koopman M, and Vermeulen L. *Nat Rev Clin Oncol*. 2017;14(4):235-246.

Survival benefit for encorafenib + cetuximab in patients with BRAFV600E mutated metastatic colorectal cancer

PROSPECTIEF LANDELIJK CRC COHORT

- Efficacy demonstrated in randomized phase 3 trial
- Drugs approved by FDA/EMA and CieBOM for reimbursement
- Trial population is younger and fitter compared to patients outside clinical trials

Question
is there comparable effectiveness in daily practice?

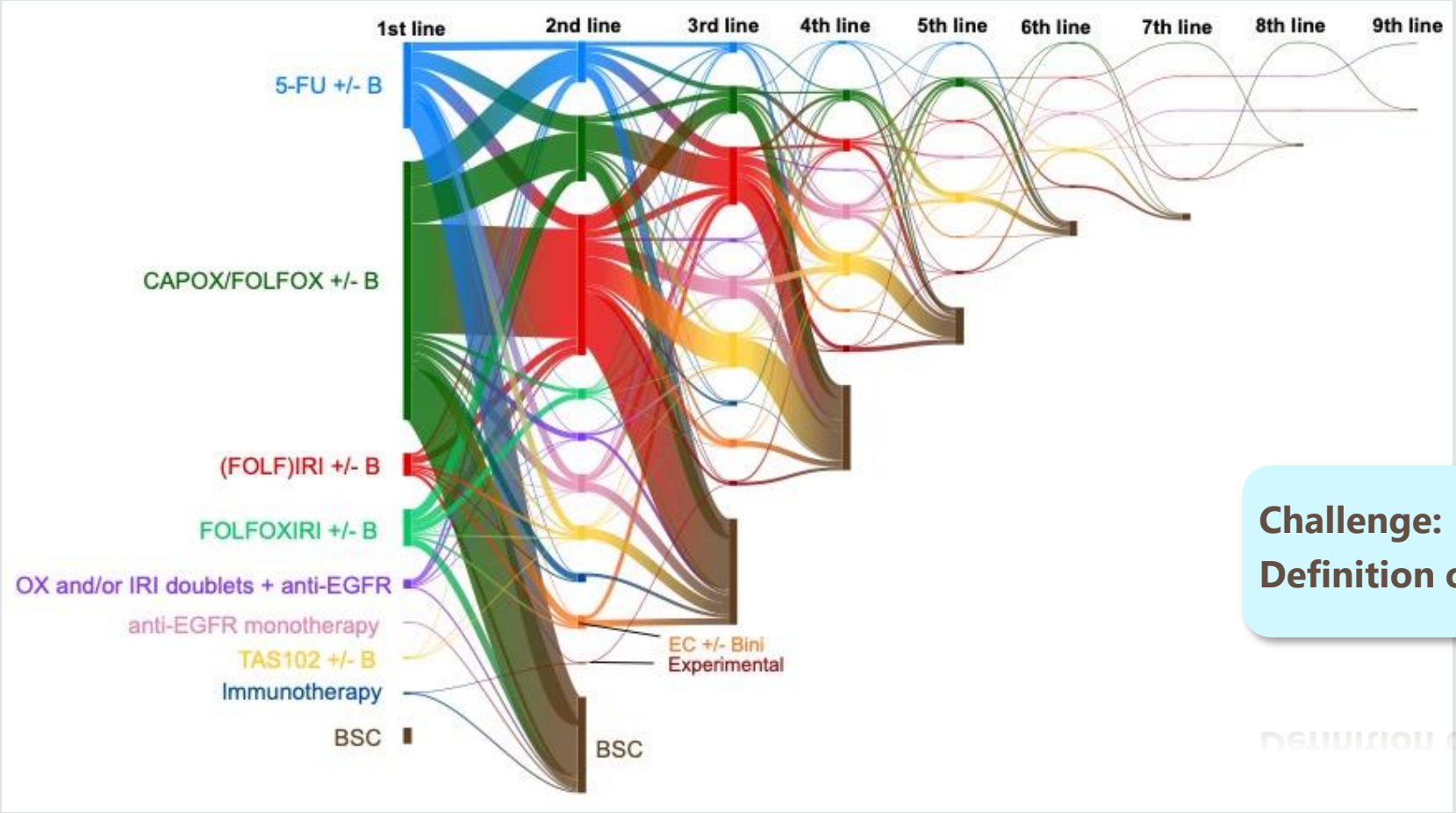
Solution
PLCRC: outcome and characteristics of control group who did not receive new drugs and comparable group who did receive new drug.

-> first use-case in “Regie op Registers” project of the Dutch regulatory health institute (ZiN)

-> BRIDGE project with clinical data of 218 BRAFmt – 436 BRAF wt mCRC patients

Real world treatment patterns: heterogeneity

~60% oxaliplatin doublet, ~20% fluoropyrimidine monotherapy

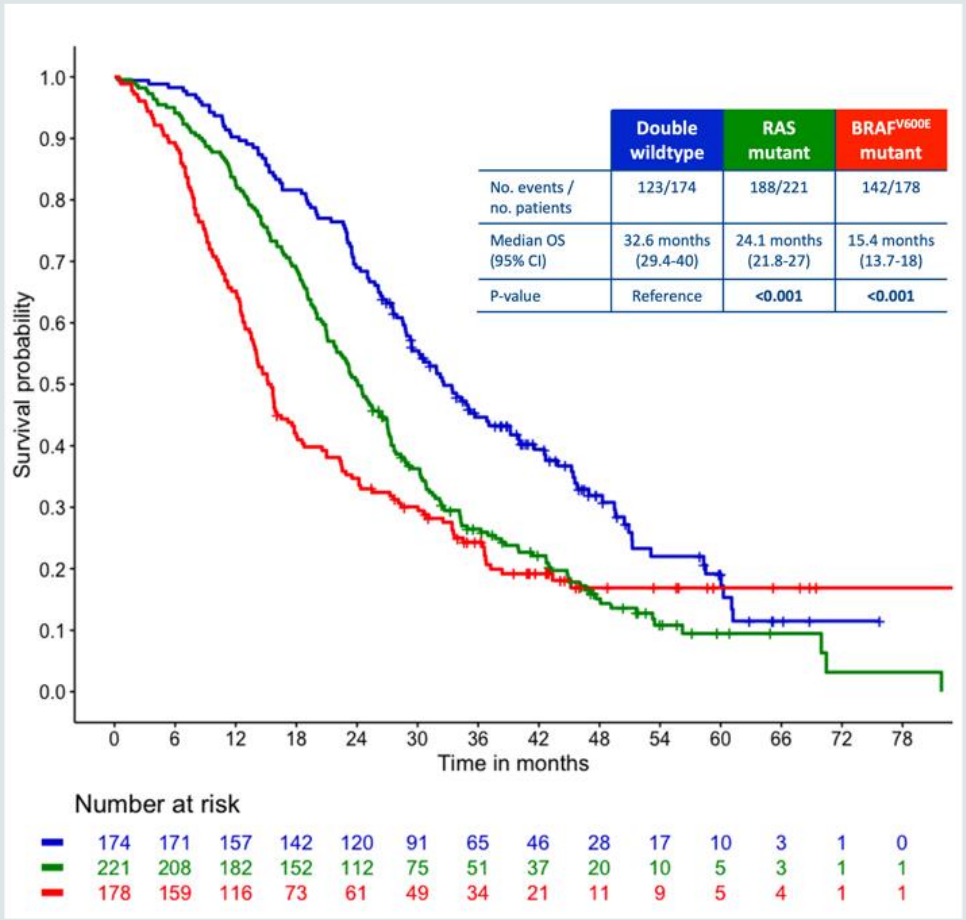


Challenge:
Definition of lines of treatment

Nassau et al. Int J Cancer 2025

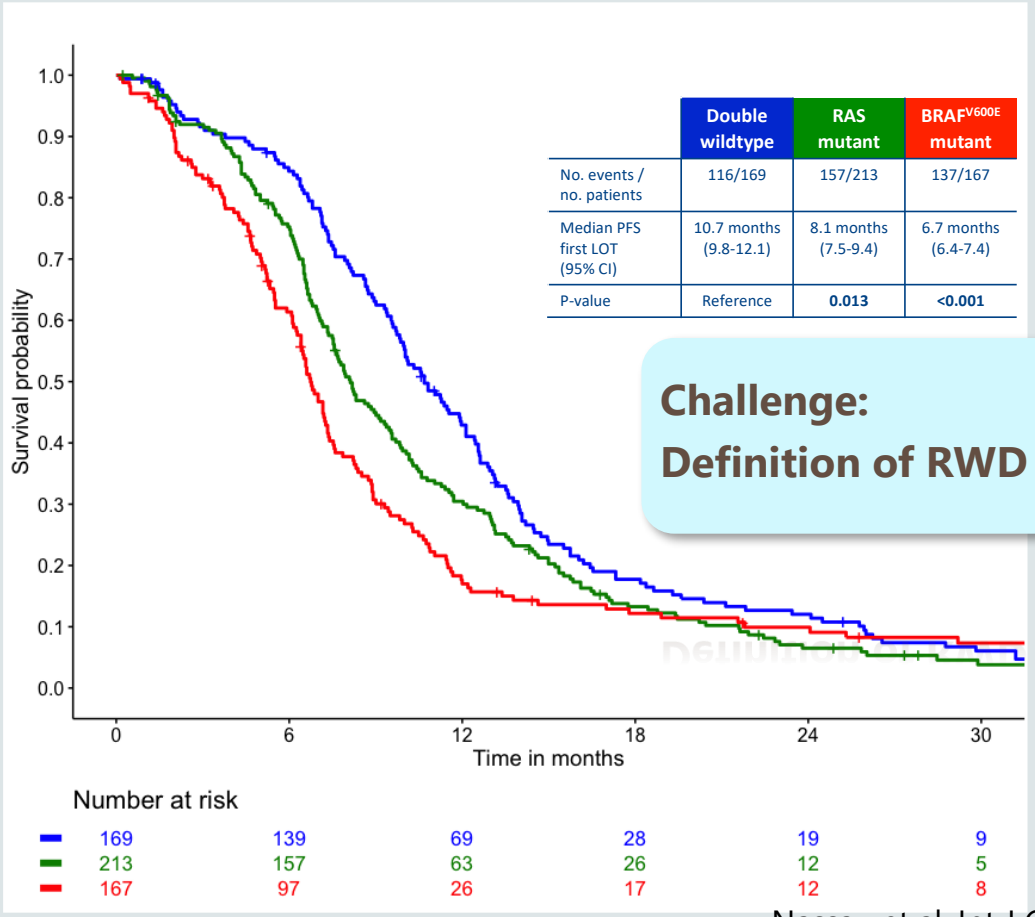
OS & PFS per molecular subgroup

A. Kaplan Meier curve - median OS from mCRC diagnosis



	Double wildtype	RAS mutant	BRAF^{V600E} mutant
No. events / no. patients	123/174	188/221	142/178
Median OS (95% CI)	32.6 months (29.4-40)	24.1 months (21.8-27)	15.4 months (13.7-18)
P-value	Reference	**<0.001**	**<0.001**

B. Kaplan Meier curve - median PFS 1st line systemic



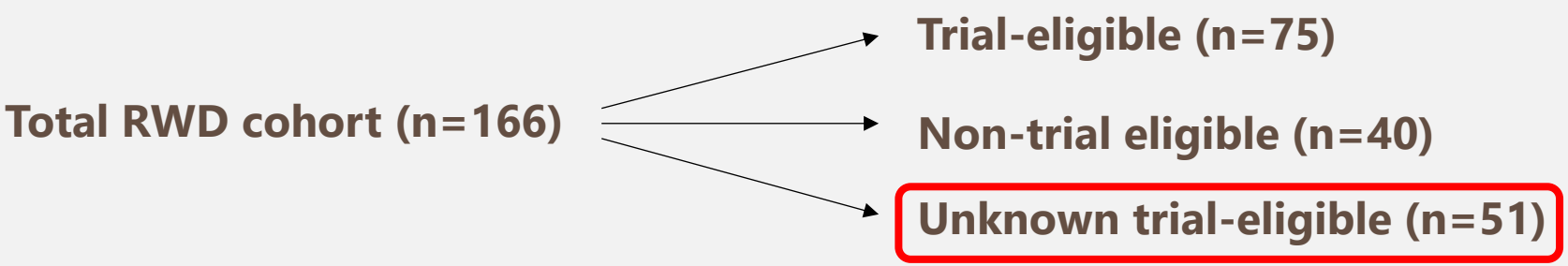
	Double wildtype	RAS mutant	BRAF^{V600E} mutant
No. events / no. patients	116/169	157/213	137/167
Median PFS first LOT (95% CI)	10.7 months (9.8-12.1)	8.1 months (7.5-9.4)	6.7 months (6.4-7.4)
P-value	Reference	**0.013**	**<0.001**

Challenge:
Definition of RWD endpoints

Nassau et al. Int J Cancer 2025

Cetuximab + encorafenib in real-world

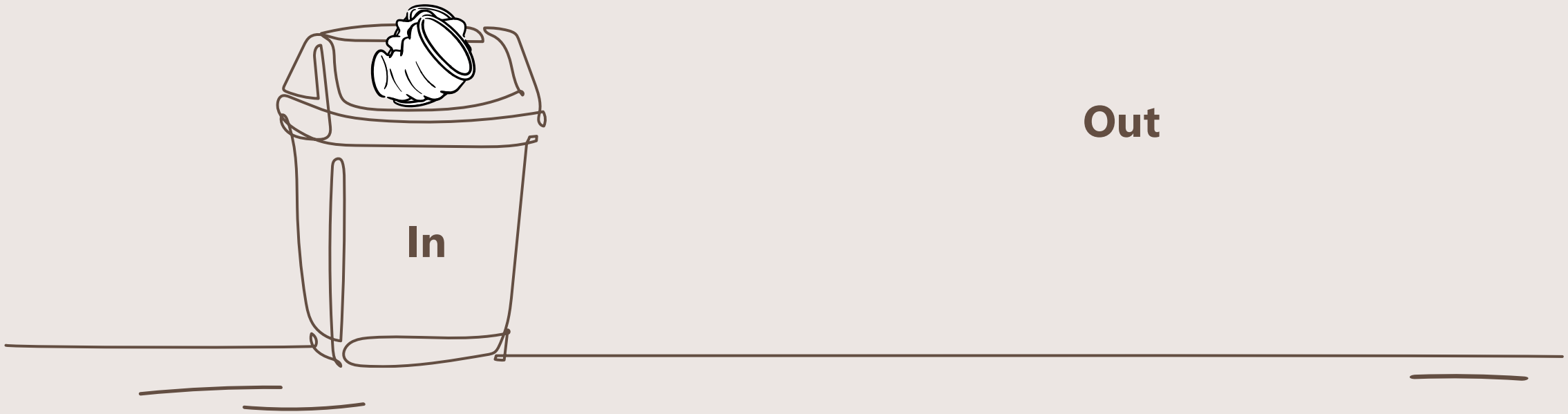
The phase III BEACON trial had 39 in- and exclusion criteria!

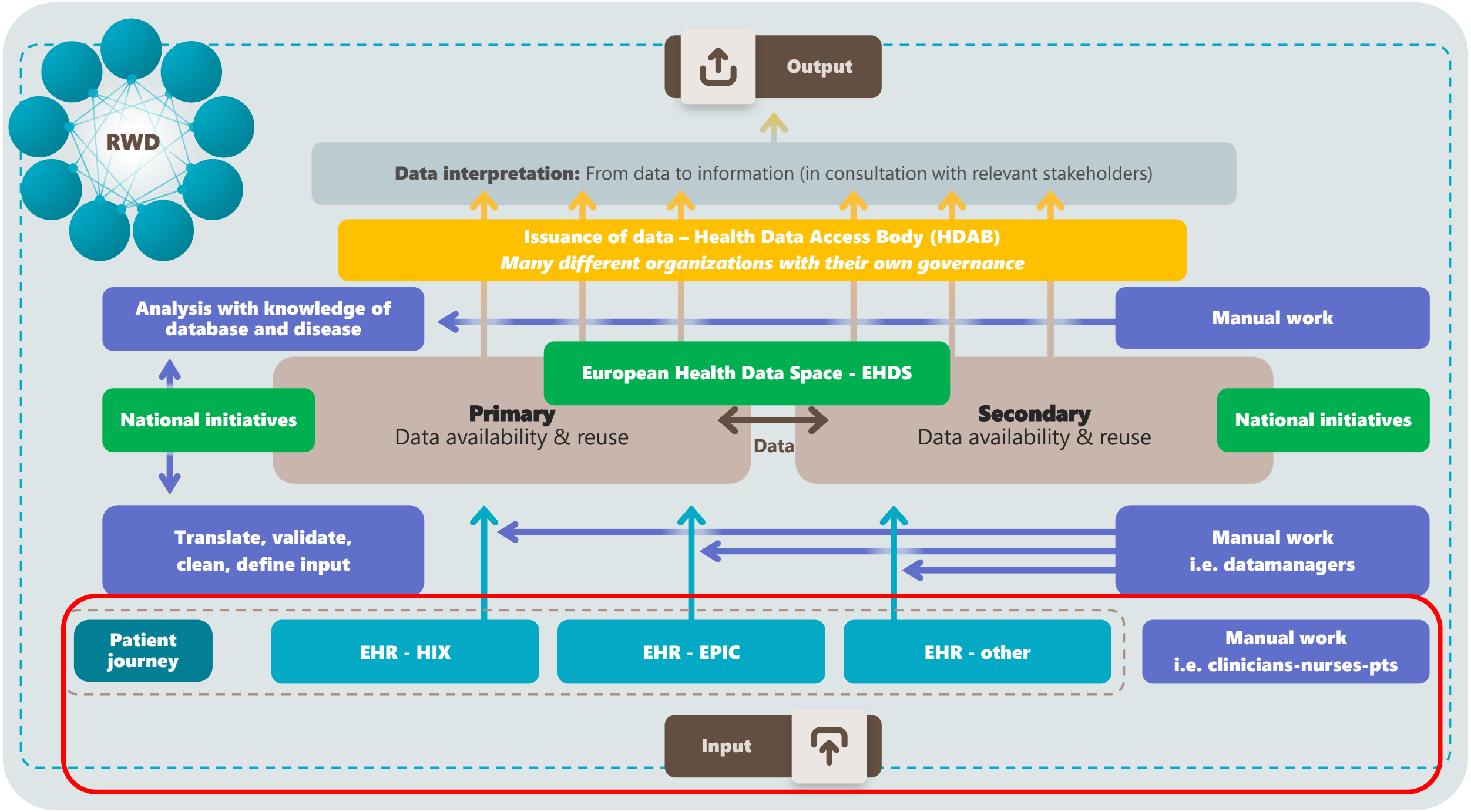


Challenge: Missing data

Key eligibility criteria	Non-trial eligible
$BRAF^{V600E}$	n = 3
Less than three prior regimens.	n = 10
Absence of brain metastases	n = 7
No other malignancy 5 years before start encorafenib-cetuximab	n = 9
No prior RAS/RAF/MEK	n = 2
Neutrophiles ≥1.5	n = 3
WHO-score <2	n = 16 (unknown, n=63)

The quality of (real world) data depends on the quality of the input



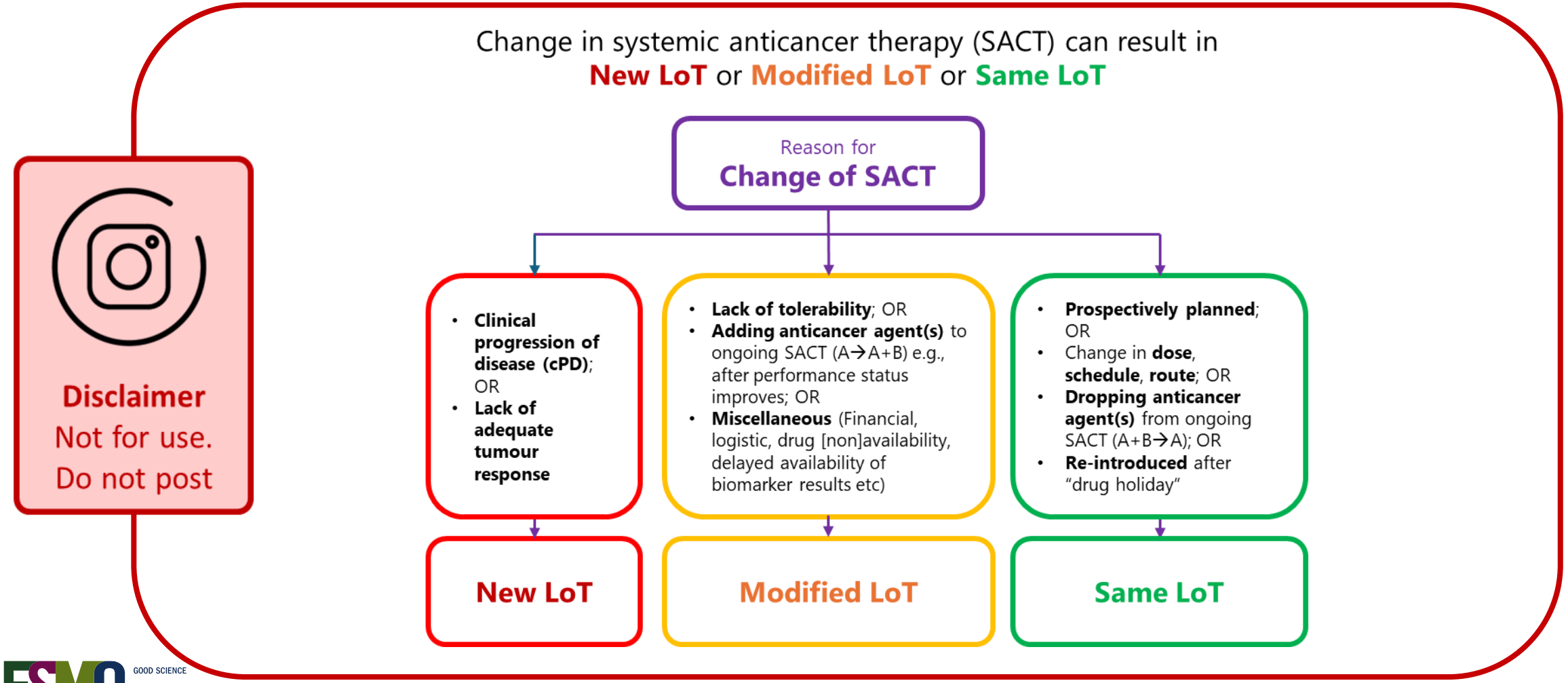

RWD
Output
Data interpretation: From data to information (in consultation with relevant stakeholders)
Issuance of data – Health Data Access Body (HDAB)
Many different organizations with their own governance
Analysis with knowledge of database and disease
Manual work
European Health Data Space - EHDS
National initiatives
Primary
Data availability & reuse
Data
Secondary
Data availability & reuse
National initiatives
Translate, validate, clean, define input
Manual work i.e. datamanagers
Patient journey
EHR - HIX
EHR - EPIC
EHR - other
Manual work i.e. clinicians-nurses-pts
Input

IN CONCLUSION:

- The potential value of Real-World Data is impressively high
- To fully unlock this potential, we must continue to improve the availability and quality of Realtime Real-World Data
- EHDS will help us move in this direction, however, international agreements on guidelines, standards and definitions related to oncology are essential to make this possible
- And at the same time, we need innovations – including AI within collaborative networks – to facilitate and accelerate the journey from Real-World Data to Real-World evidence

ENLIST

"ESMO ADAPTATION OF LINES OF SYSTEMIC THERAPY: A CONSENSUS FRAMEWORK FOR STANDARDISING THE DESIGNATION OF LINES OF THERAPY IN SOLID TUMOURS"



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Manuscript SUBMITTED TO Annals of Oncology October 2025

Learning health care system

Guideline development 5

RWE / Clinical studies 4

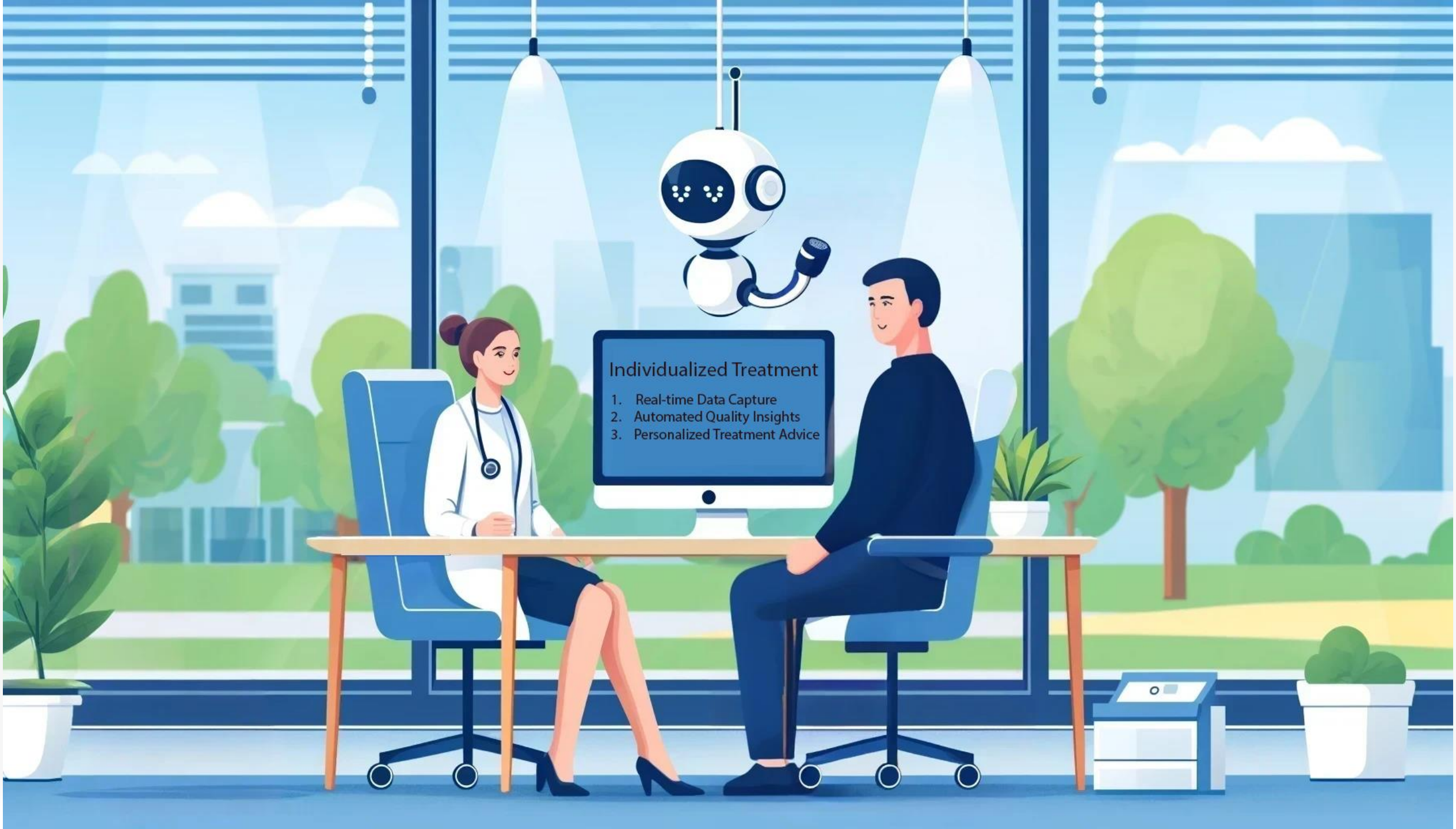
Participation in a cohort with patient's IC

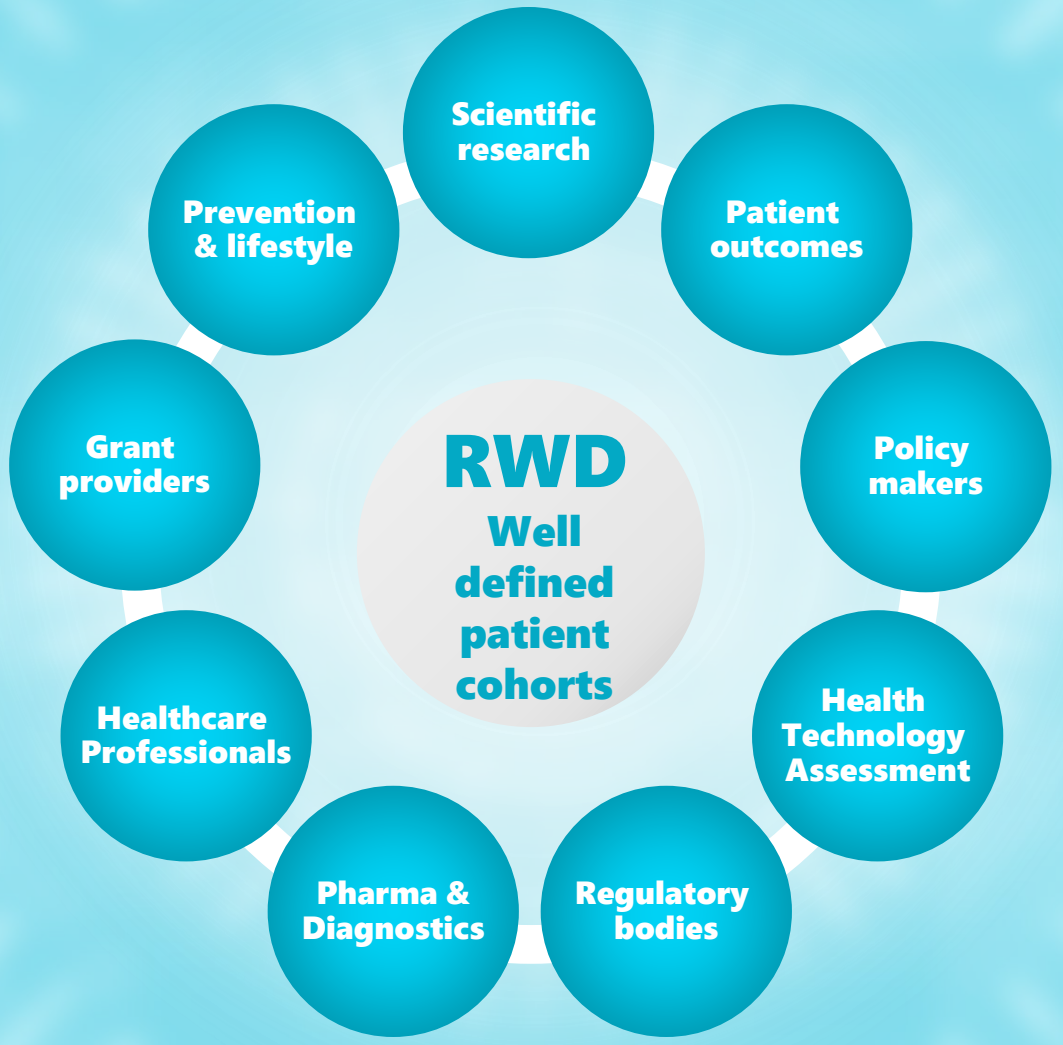
Items are defined and available for primary and secondary use 3

1 **Patient is treated in daily clinical care**

Shared decision making (patient & physician) supported by a 'patient like me' dashboard and/or selection aid

2 **Data are registered in a hospital system**


Individualized Treatment
1. Real-time Data Capture
2. Automated Quality Insights
3. Personalized Treatment Advice



Integration of care and research by learning from every patient

using Real-World Data to treat today's patient ....

and tomorrow's patient