Post-approval confirmatory / supplementary data: registries and observational trials

A potential role for ‘comprehensive’ cancer registries

15th of December 2017 | Vincent Ho, Netherlands Cancer Registry (NCR)
Netherlands Comprehensive Cancer Organisation (IKNL)

Disclosure

(potential) conflicts of interests	None
Sources of conflicts of interest may include (but are not limited to):	
• Research funding • Fees for presentations / publications • Sponsoring	

Postapproval data

- General motivation
  - providing stakeholders information on the continued safety and effectiveness of drugs, medical devices etc.
  - extension beyond experimental context (controlled conditions, selected patient populations, limited time horizons)

- Particularly
  - expedited / conditional approval allowing manufacturers to address unresolved issues (optimal dosing, long-term side effects, use in specific subgroups)

The Fate of FDA Postapproval Studies

Steven Woloshin, M.D., Lisa M. Schwartz, M.D., Brian White, B.A., and Thomas J. Moore, A.B.

NEJM, September 2017

Table 1. Status of Postapproval Studies Established in 2009 and 2010.*

Study Status	2009	2010	Total
	number (percent)		
Total	296	318	614
Never started	78 (26)	47 (15)	125 (20)
Pending	17 (6)	13 (4)	30 (5)
Terminated	2 (1)	0	2 (<1)
Released	59 (20)	34 (11)	93 (15)
Still ongoing	68 (23)	88 (28)	156 (25)
Delayed	27 (9)	30 (9)	57 (9)
On schedule	41 (14)	58 (18)	99 (16)
Completed	150 (51)	183 (58)	333 (54)
Submitted	11 (4)	27 (8)	38 (6)
Fulfilled	139 (47)	156 (49)	295 (48)

Accelerated Approval of Oncology Products: The Food and Drug Administration Experience

John R. Johnson, Yang-Min Ning, Ann Farrell, Robert Justice, Patricia Keegan, Richard Pazdur

JNCI, 2011

- accelerated approval to 35 products for 47 new indications
- clinical benefit confirmed for 26/47 (conversion to regular approval)
- median time 3.9 years (range 0.8–12.6 years) for conversion
- confirmatory trials not completed for 14 indications

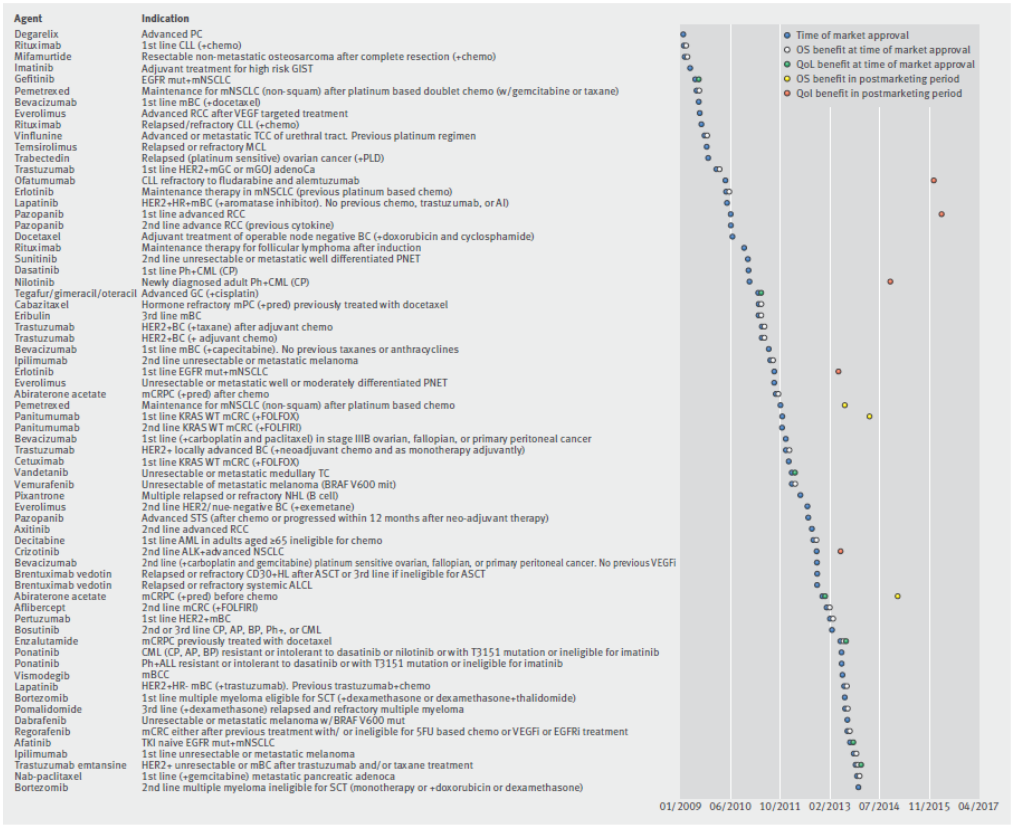
"*The slow, irregular pace of postapproval studies contrasts starkly with the short, rigid deadlines and other shortcuts used to speed marketing approval*"

"The "catch 22" is that we only know the true performance of a product after approval, but the product must be safe and effective in order to be approved" (Muni, 2005)

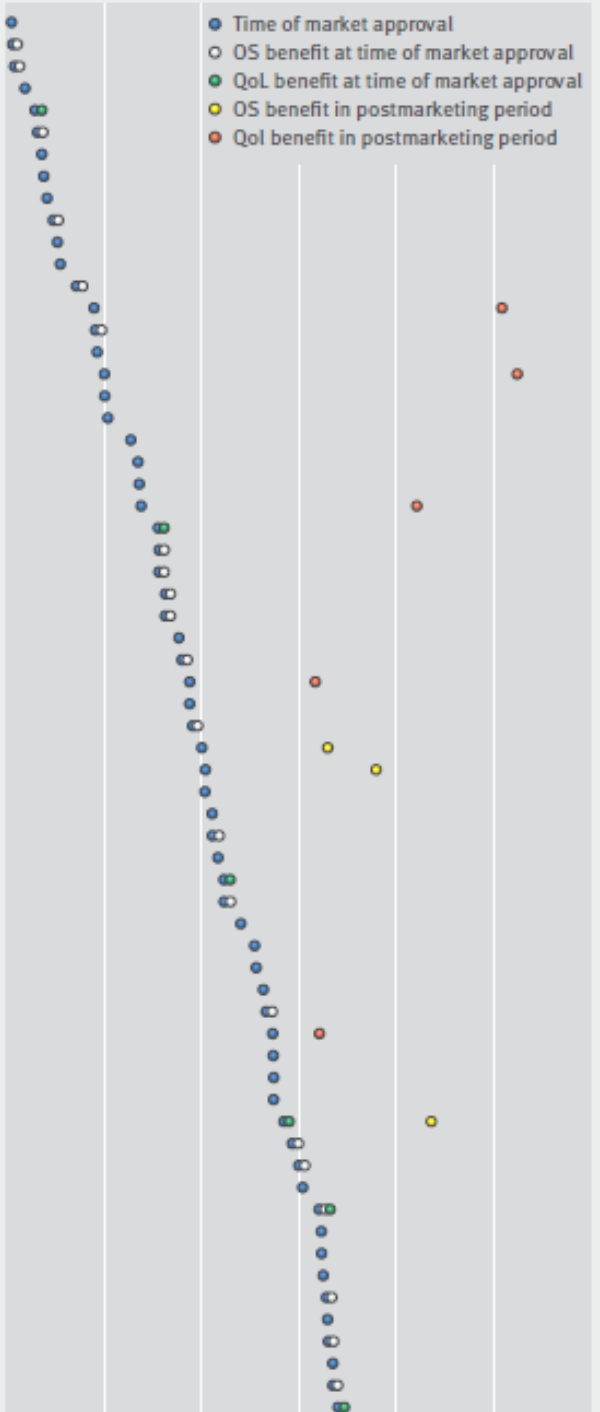
Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13

Courtney Davis,[1] Huseyin Naci,[2] Evrim Gurpinar,[2] Elita Poplavska,[3] Ashlyn Pinto,[2] Ajay Aggarwal[4,5]

BMJ, September 2017



Agent	Indication
Degarelix	Advanced PC
Rituximab	1st line CLL (+chemo)
Mifamurtide	Resectable non-metastatic osteosarcoma after complete resection (+chemo)
Imatinib	Adjuvant treatment for high risk GIST
Gefitinib	EGFR mut+mNSCLC
Pemetrexed	Maintenance for mNSCLC (non-squam) after platinum based doublet chemo (w/gemcitabine or taxane)
Bevacizumab	1st line mBC (+docetaxel)
Everolimus	Advanced RCC after VEGF targeted treatment
Rituximab	Relapsed/refractory CLL (+chemo)
Vinflunine	Advanced or metastatic TCC of urethral tract. Previous platinum regimen
Temsirolimus	Relapsed or refractory MCL
Trabectedin	Relapsed (platinum sensitive) ovarian cancer (+PLD)
Trastuzumab	1st line HER2+mGC or mGOJ adenoCa
Ofatumumab	CLL refractory to fludarabine and alemtuzumab
Erlotinib	Maintenance therapy in mNSCLC (previous platinum based chemo)
Lapatinib	HER2+HR+mBC (+aromatase inhibitor). No previous chemo, trastuzumab, or AI)
Pazopanib	1st line advanced RCC
Pazopanib	2nd line advance RCC (previous cytokine)
Docetaxel	Adjuvant treatment of operable node negative BC (+doxorubicin and cyclosphamide)
Rituximab	Maintenance therapy for follicular lymphoma after induction
Sunitinib	2nd line unresectable or metastatic well differentiated PNET
Dasatinib	1st line Ph+CML (CP)
Nilotinib	Newly diagnosed adult Ph+CML (CP)
Tegafur/gimeracil/oteracil	Advanced GC (+cisplatin)
Cabazitaxel	Hormone refractory mPC (+pred) previously treated with docetaxel
Eribulin	3rd line mBC
Trastuzumab	HER2+BC (+taxane) after adjuvant chemo
Trastuzumab	HER2+BC (+ adjuvant chemo)
Bevacizumab	1st line mBC (+capecitabine). No previous taxanes or anthracyclines
Ipilimumab	2nd line unresectable or metastatic melanoma
Erlotinib	1st line EGFR mut+mNSCLC
Everolimus	Unresectable or metastatic well or moderately differentiated PNET
Abiraterone acetate	mCRPC (+pred) after chemo
Pemetrexed	Maintenance for mNSCLC (non-squam) after platinum based chemo
Panitumumab	1st line KRAS WT mCRC (+FOLFOX)
Panitumumab	2nd line KRAS WT mCRC (+FOLFIRI)
Bevacizumab	1st line (+carboplatin and paclitaxel) in stage IIIB ovarian, fallopian, or primary peritoneal cancer
Trastuzumab	HER2+ locally advanced BC (+neoadjuvant chemo and as monotherapy adjuvantly)
Cetuximab	1st line KRAS WT mCRC (+FOLFOX)
Vandetanib	Unresectable or metastatic medullary TC
Vemurafenib	Unresectable of metastatic melanoma (BRAF V600 mit)
Pixantrone	Multiple relapsed or refractory NHL (B cell)
Everolimus	2nd line HER2/nue-negative BC (+exemetane)
Pazopanib	Advanced STS (after chemo or progressed within 12 months after neo-adjuvant therapy)
Axitinib	2nd line advanced RCC
Decitabine	1st line AML in adults aged ≥65 ineligible for chemo
Crizotinib	2nd line ALK+advanced NSCLC
Bevacizumab	2nd line (+carboplatin and gemcitabine) platinum sensitive ovarian, fallopian, or primary peritoneal cancer. No previous VEGFi
Brentuximab vedotin	Relapsed or refractory CD30+HL after ASCT or 3rd line if ineligible for ASCT
Brentuximab vedotin	Relapsed or refractory systemic ALCL
Abiraterone acetate	mCRPC (+pred) before chemo
Aflibercept	2nd line mCRC (+FOLFIRI)
Pertuzumab	1st line HER2+mBC
Bosutinib	2nd or 3rd line CP, AP, BP, Ph+, or CML
Enzalutamide	mCRPC previously treated with docetaxel
Ponatinib	CML (CP, AP, BP) resistant or intolerant to dasatinib or nilotinib or with T3151 mutation or ineligible for imatinib
Ponatinib	Ph+ALL resistant or intolerant to dasatinib or with T3151 mutation or ineligible for imatinib
Vismodegib	mBCC
Lapatinib	HER2+HR- mBC (+trastuzumab). Previous trastuzumab+chemo
Bortezomib	1st line multiple myeloma eligible for SCT (+dexamethasone or dexamethasone+thalidomide)
Pomalidomide	3rd line (+dexamethasone) relapsed and refractory multiple myeloma
Dabrafenib	Unresectable or metastatic melanoma w/BRAF V600 mut
Regorafenib	mCRC either after previous treatment with/ or ineligible for 5FU based chemo or VEGFi or EGFRi treatment
Afatinib	TKI naive EGFR mut+mNSCLC



Postapproval data

- Data collection methods?
  - randomized, double-blinded, controlled trial
  - randomized, unblinded clinical study
  - observational (conditions of approval) studies
  - non-randomized registry study with formal follow-up and data collection (single arm trial)
  - informal registry study (“open enrollment”) with less stringent follow-up and data collection
  - meta-analyses
  - model/laboratory studies

Postapproval data

Which methods are best for collecting and analyzing postapproval data?

- Potentially, a large array of methodologies may transfer information on a product's performance in the 'real world', provided that this information is understood in the proper context
- No single method can meet all of the needs of stakeholders
  - problem remains (and is perhaps even amplified):
    when do we consider evidence compelling enough?

Postapproval data

- practical considerations do foster preferences for some methods over others, particularly in case of rare instances:

Expected incidence adverse reaction	Numbers of patients to be observed to of detect 1, 2, or 3 events		
	1	2	3
1 in 100	300	480	650
1 in 200	600	960	1300
1 in 1000	3000	4800	6500
1 in 2000	6000	9600	13000
1 in 10000	30000	48000	65000

(Grahame-Smith and Aronson, 2004)

Observational trials?

- Well-known caveats in methodology

  (although sophisticated methods have emerged)

- Especially for rare conditions
  - low number of cases in clinical practices
  - representative samples (expertise across hospitals)?
  - need for adequate screening platforms to direct patients to the right doctor

(Clinical) registries

- Existing infrastructure with ‘real-world’ focus (population-based)
- Potential for flexible and adaptable data collection: retrospective and prospective data on a variety of different parameters
- Standardisation of longitudinal data collection with the capability to evolve (e.g. as more is learned about a given topic)
- Opportunities for linkage with other databases
- Rare conditions may be captured ‘along the way’

- Issues include:
  - (generally) voluntary on the part of doctors and patients
  - data quality and completeness

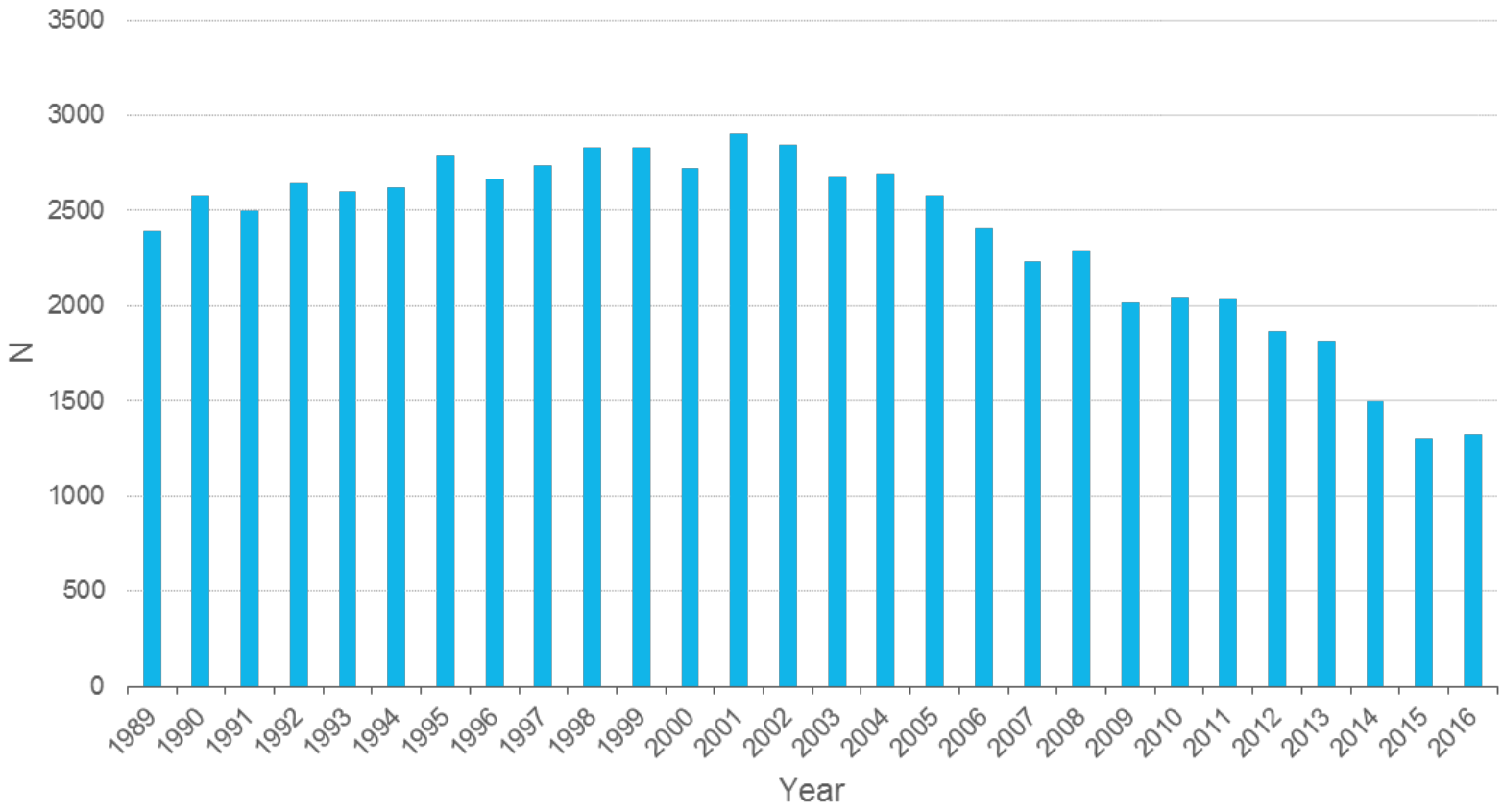
A role for cancer registries?

- Normally
  - person characteristics (date of birth, age at diagnose, date of death)
  - disease characteristics (topography, morphology)
- Sometimes
  - stage of disease
  - treatment (1st line)
  - cause of death
- Rarely
  - hormone receptors
  - comorbidity
  - recurrence, disease progression
- Hardly ever
  - genetic profile
  - 2nd and 3rd line treatment

(Kraywinkel, 2017)

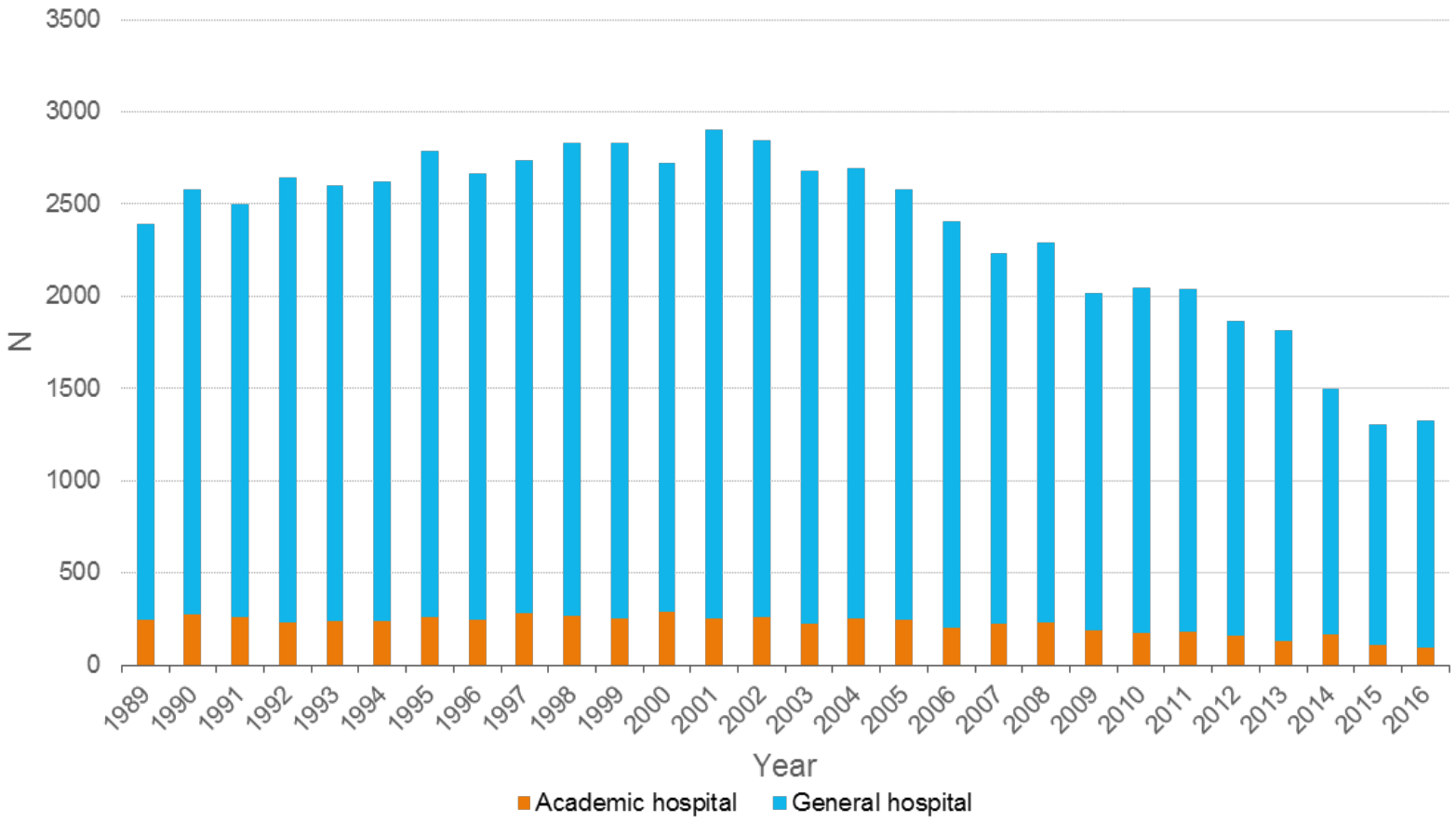
Examples from the NCR

Cancer of unknown primary (CUP): incidence



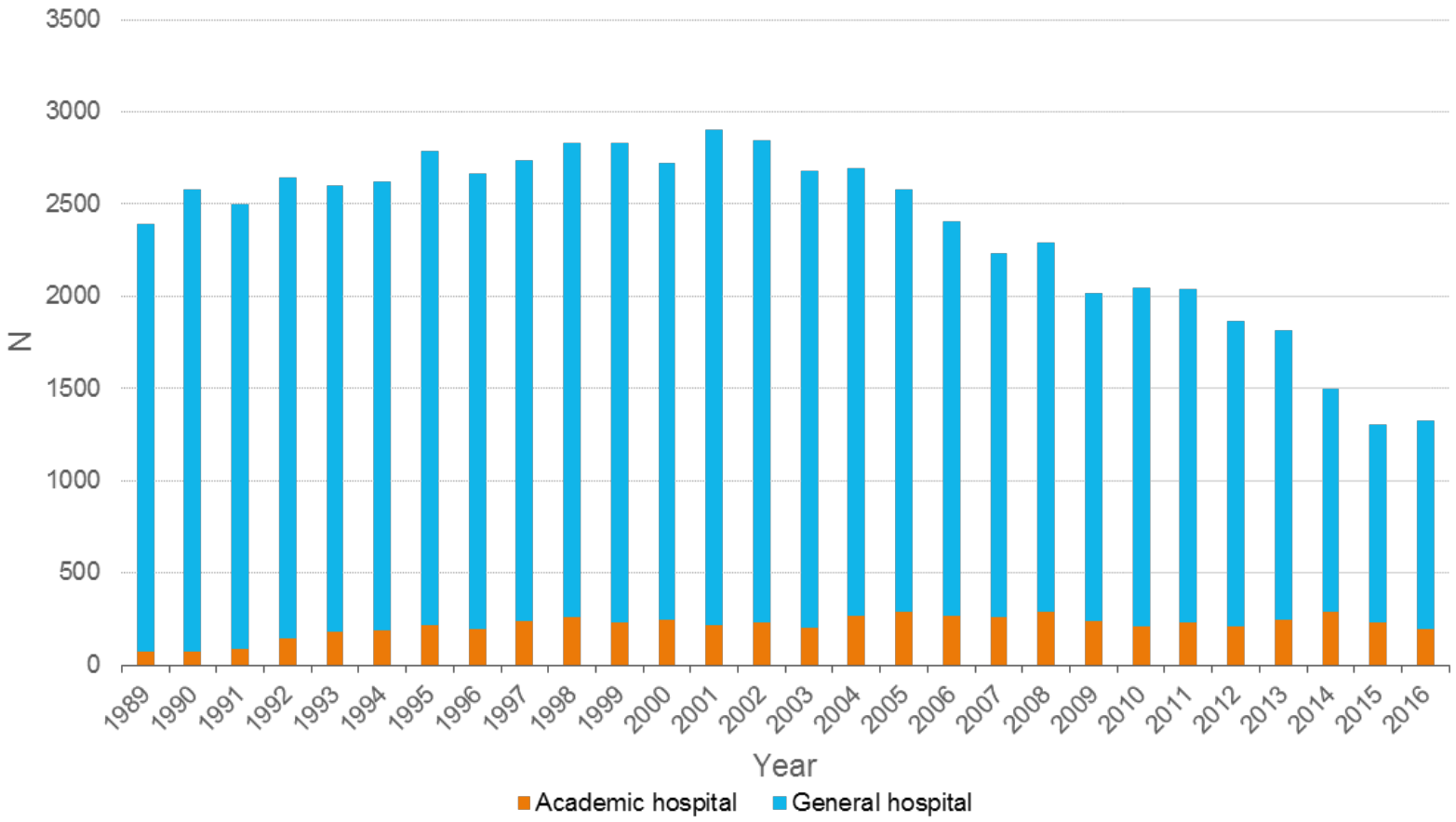
Examples from the NCR

Cancer of unknown primary (CUP): first visit



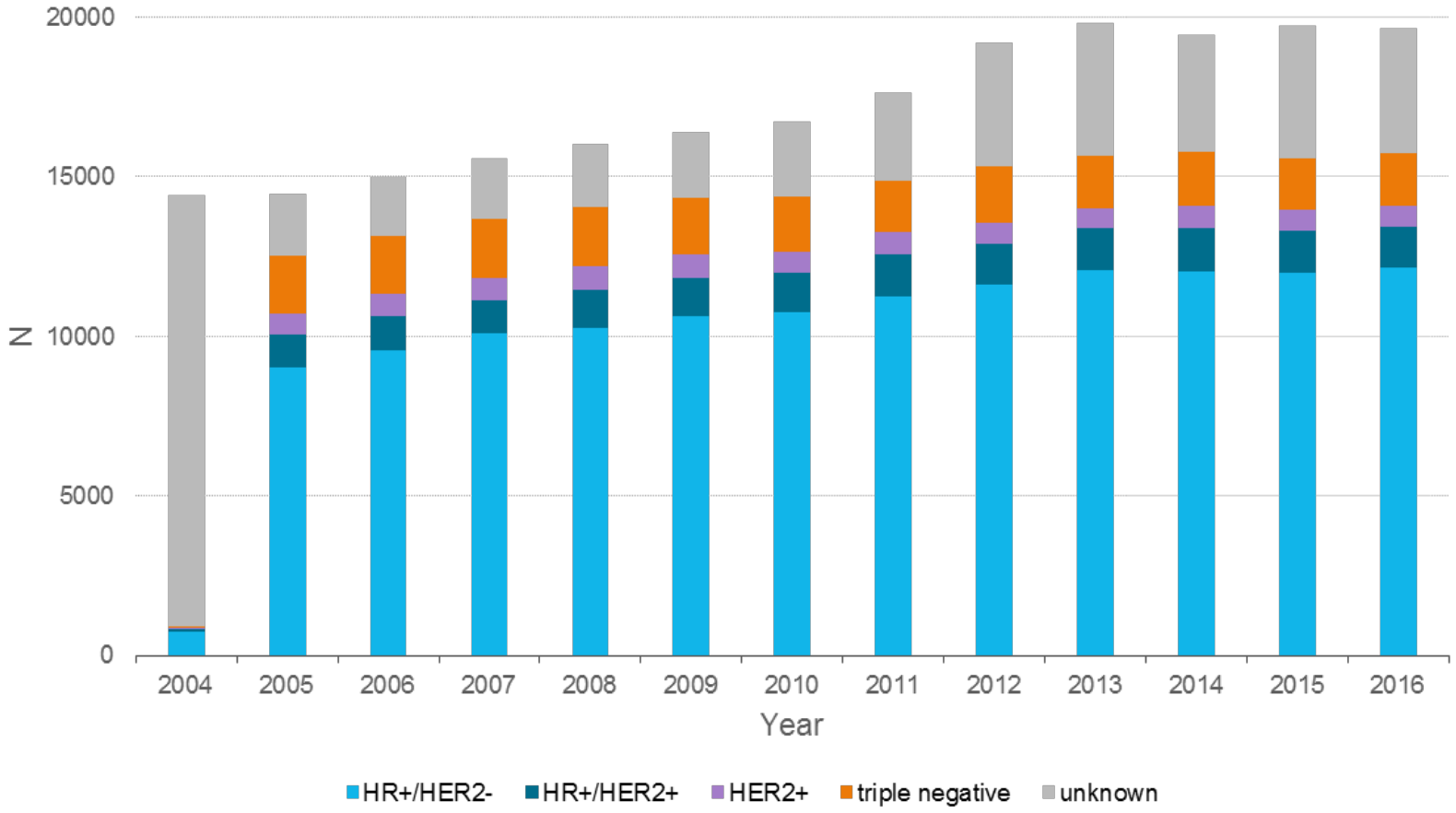
Examples from the NCR

Cancer of unknown primary (CUP): first treatment



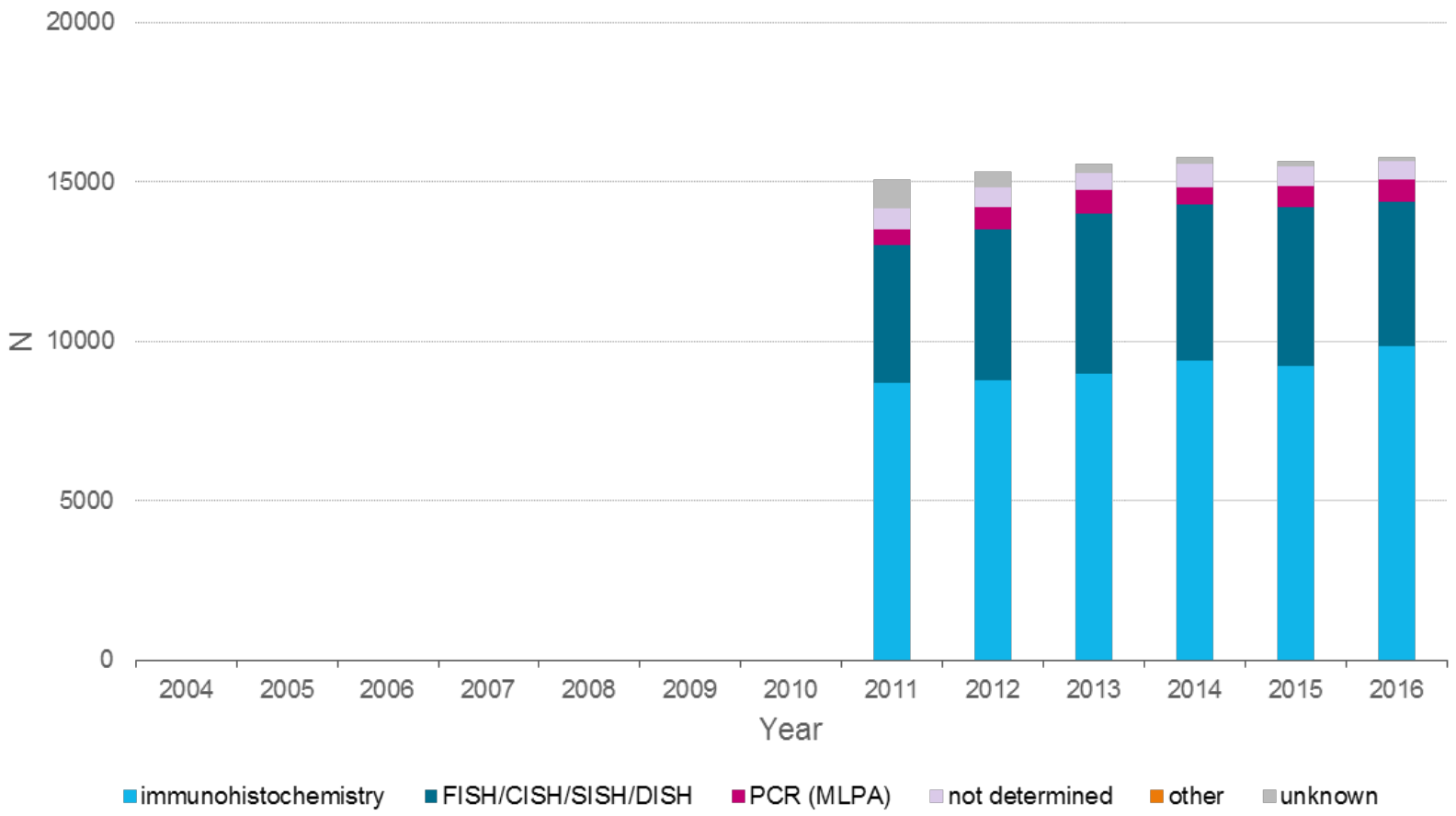
Examples from the NCR

Breast cancer receptors: ER, PR, HER2



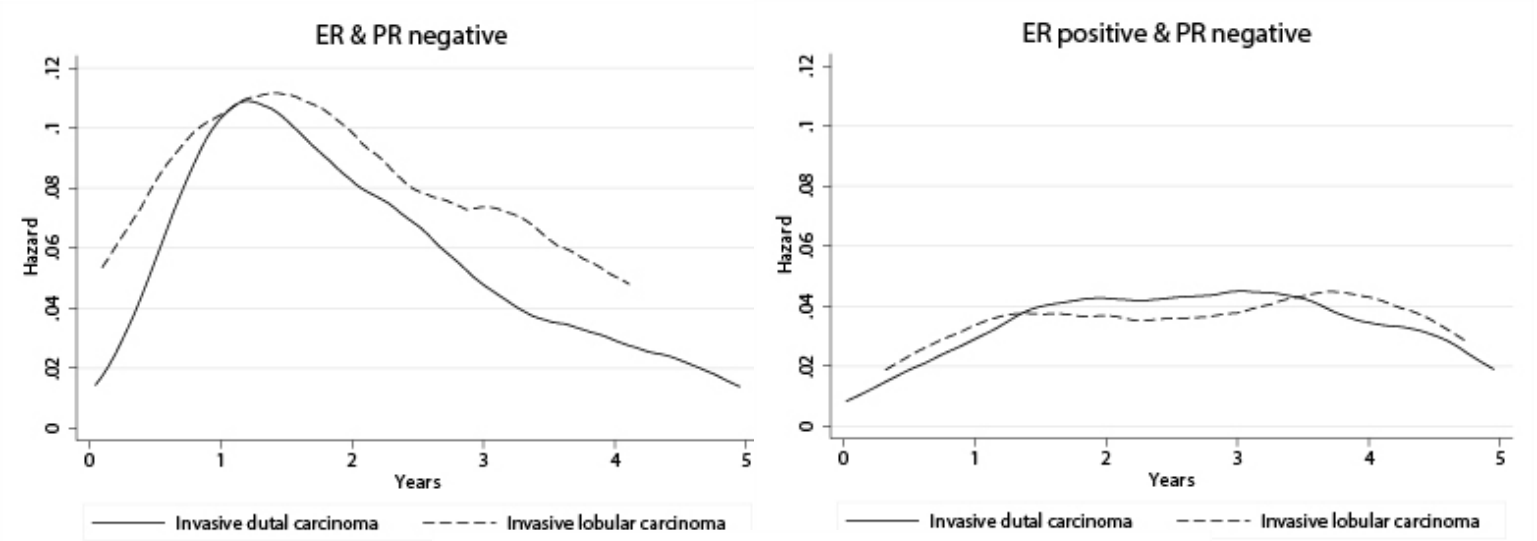
Examples from the NCR

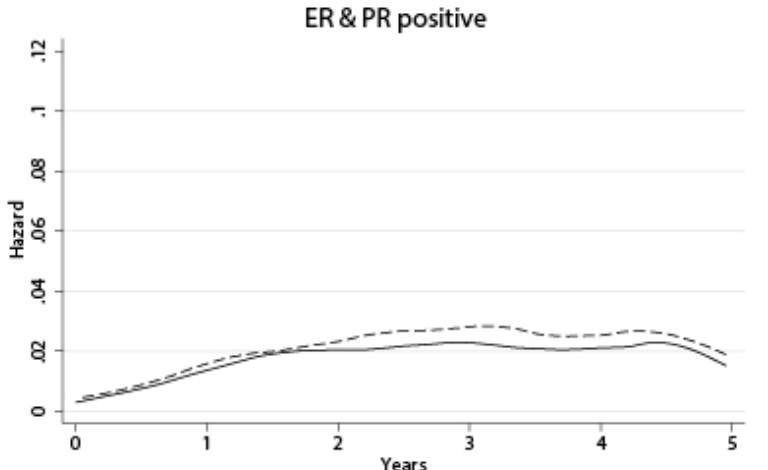
Breast cancer receptors: HER2 detection method



Examples from the NCR

Breast cancer receptors: relation with recurrence

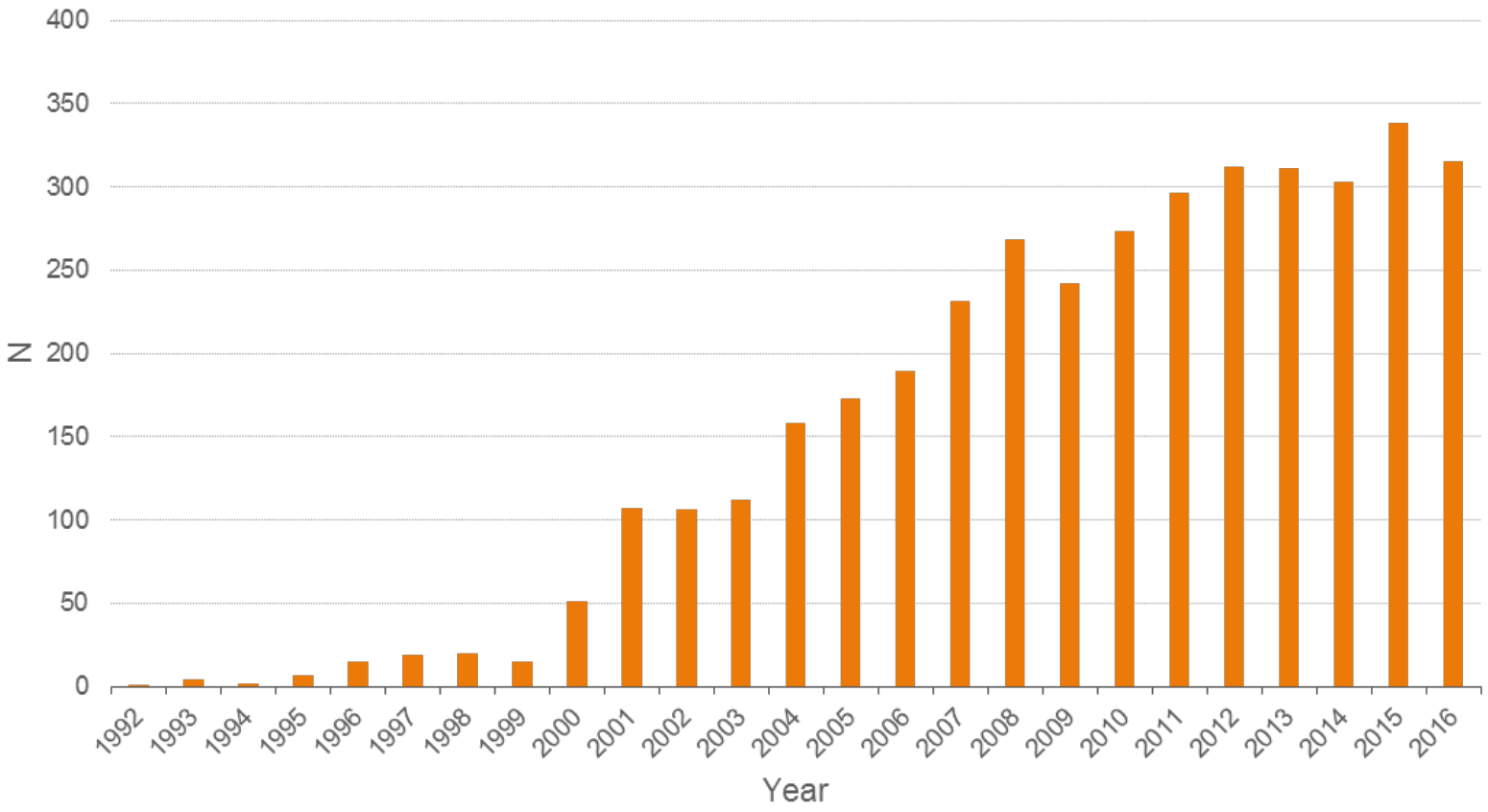




(Kwast et al, 2011)

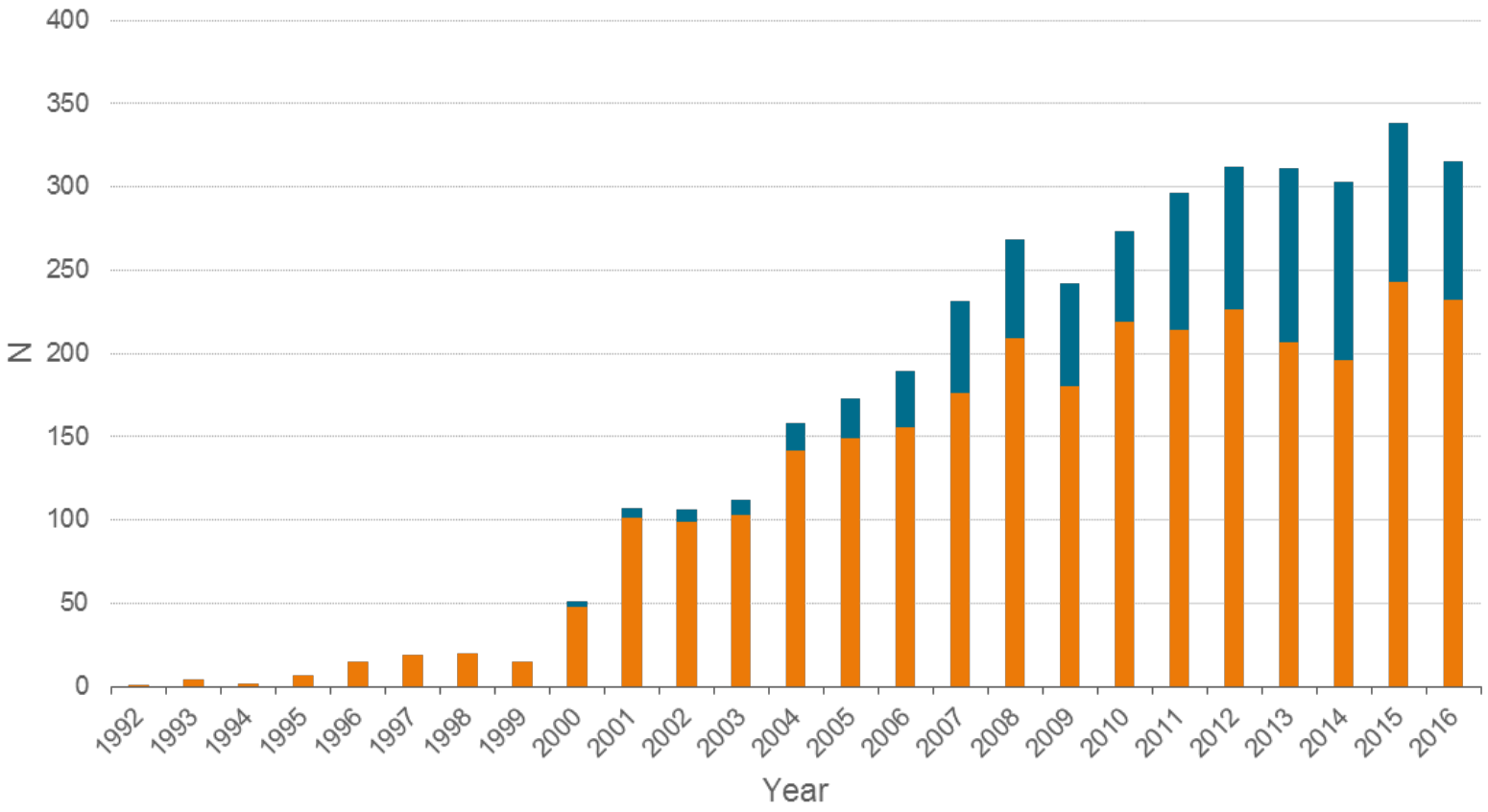
Examples from the NCR

- GIST: incidence



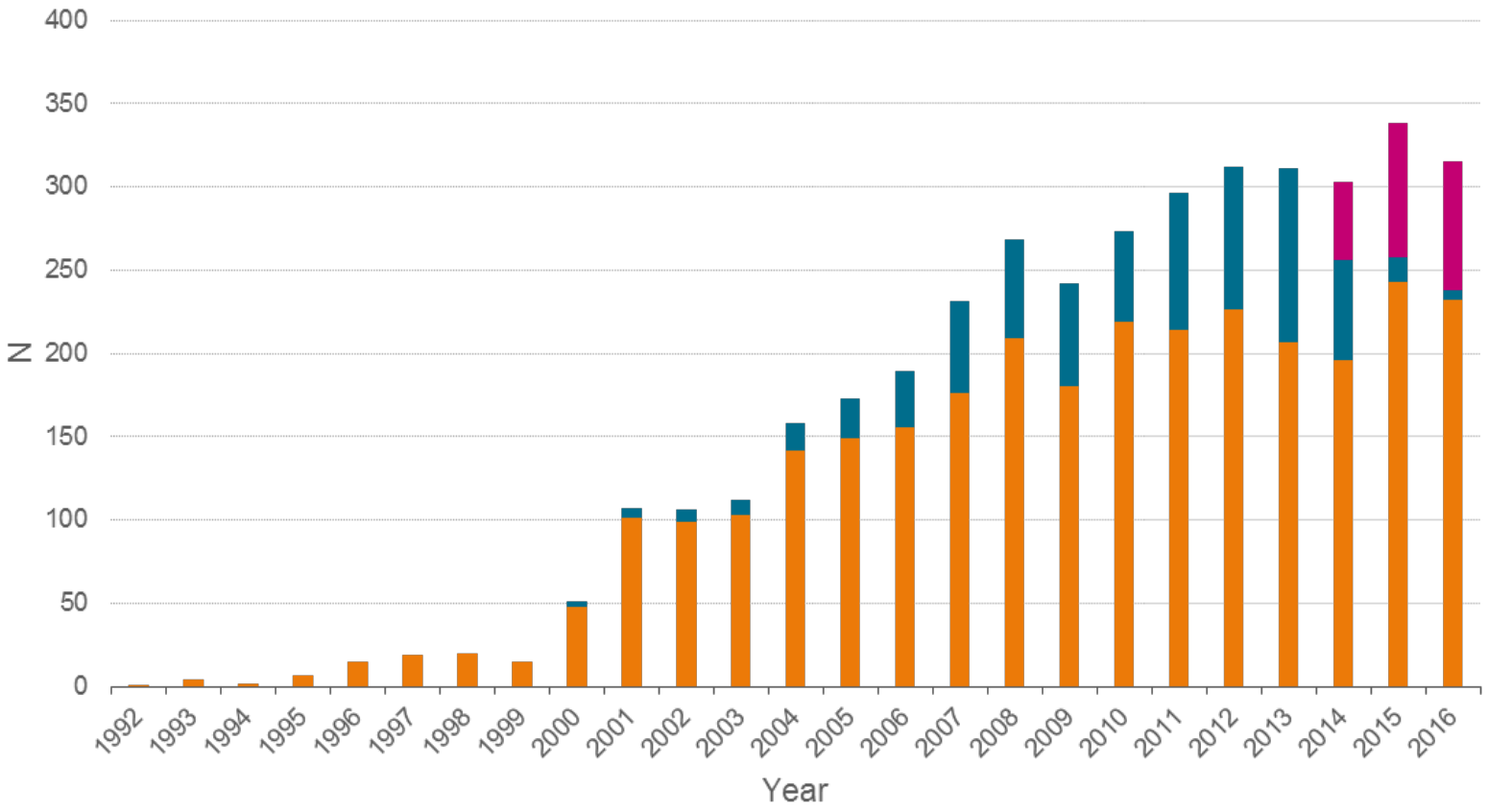
Examples from the NCR

- GIST: first line targeted therapy (blue)



Examples from the NCR

- GIST: first line imatinib (pink; in registry since 2014)



Examples from the NCR

- GIST: additional data collection as of 2016
  - immunohistochemistry

    CD117

    DOG1

    SDHB
  - mutations

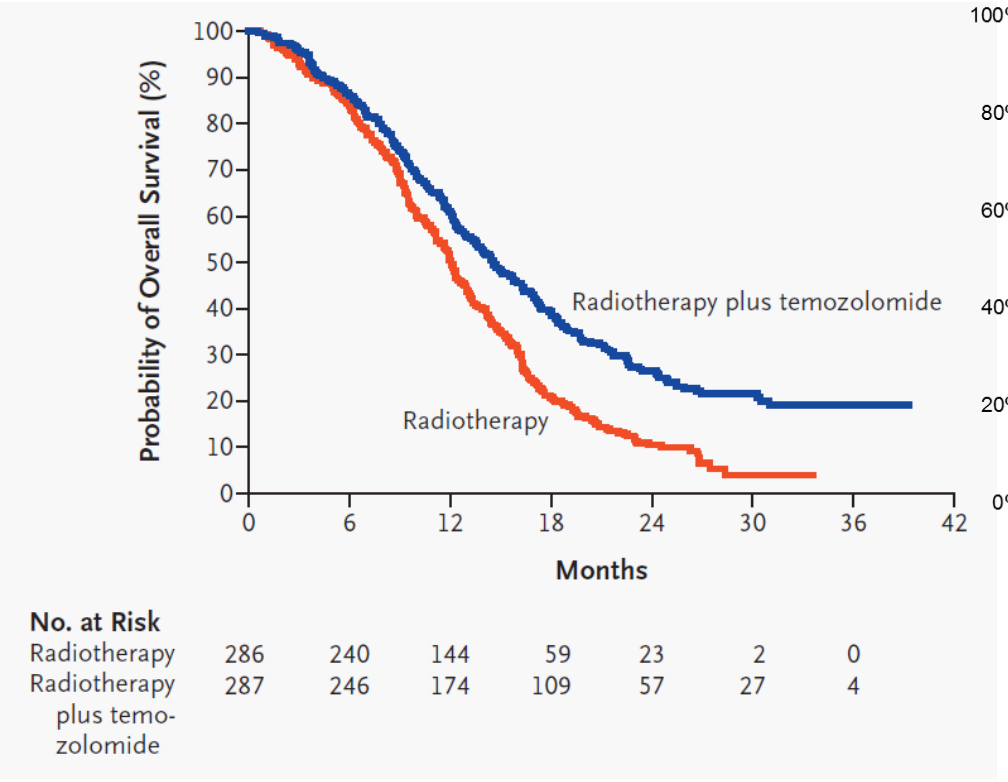
    BRAF

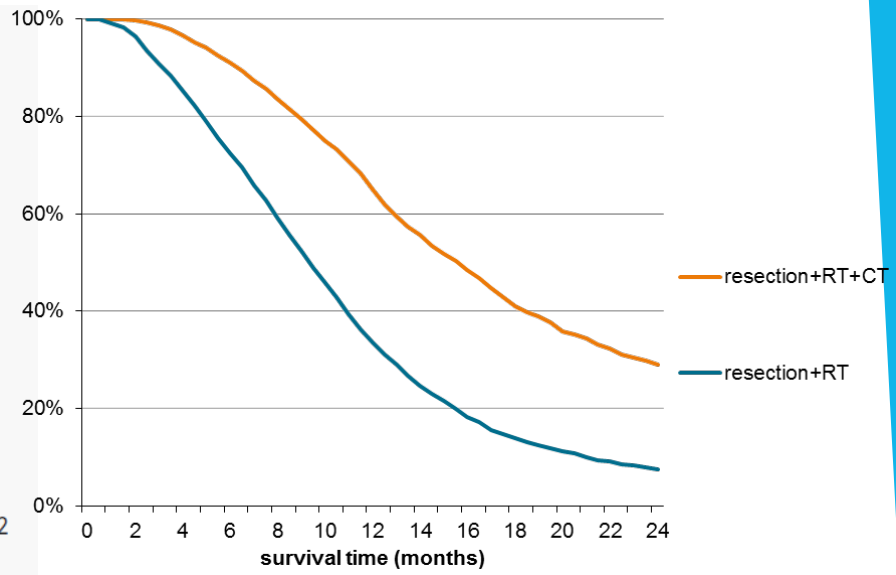
    PDGF

    SDH

Examples from the NCR

- Glioblastoma: ‘real world’ confirmation of Stupp-trial

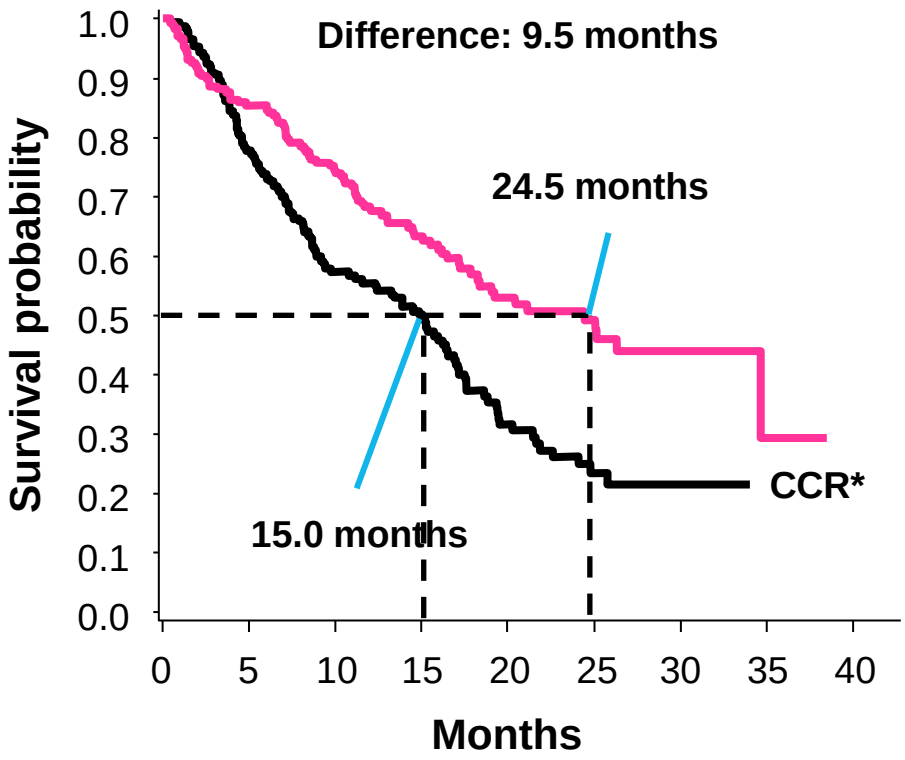




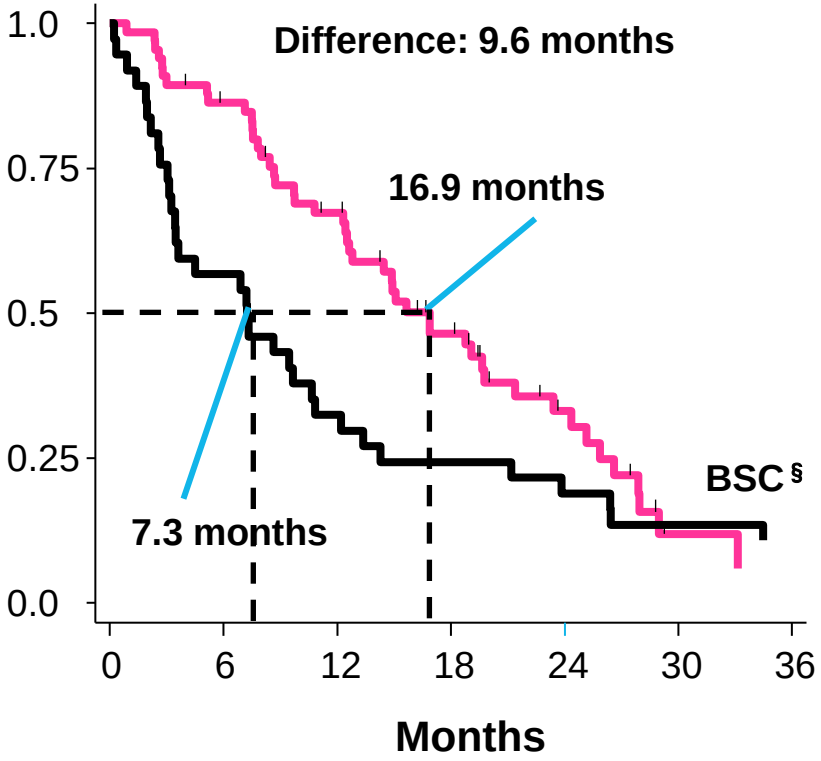
(Ho et al, 2014)

Examples from the NCR

The phase 3 AZA-001 trial[1]



Dutch daily practice (PHAROS MDS)[2]



[§]BSC, best supportive care

MDS, myelodysplastic syndromes; *CCR, conventional care regimens (includes best supportive care, low-dose cytarabine and intensive chemotherapy)

[2]Dinmohamed AG et al. *Leukemia*. 29:2449-51 (2015)

[1]Fenaux P et al. *Lancet Oncol*. 10: 223-32 (2009)

Examples from the NCR

Therapeutic effectiveness of novel, expensive agents in daily practice

Retrospective studies:

- Azacitidine: MDS patients (2008–2011)
- Ibrutinib: ibrutinib-treated CLL patients (2015–2016)
- Brenduximab vendotin: brentuximab vendotin-treated HL patients (2015–2016)
- Nivolumab: nivolumab-treated HL-patients (2016–2018)

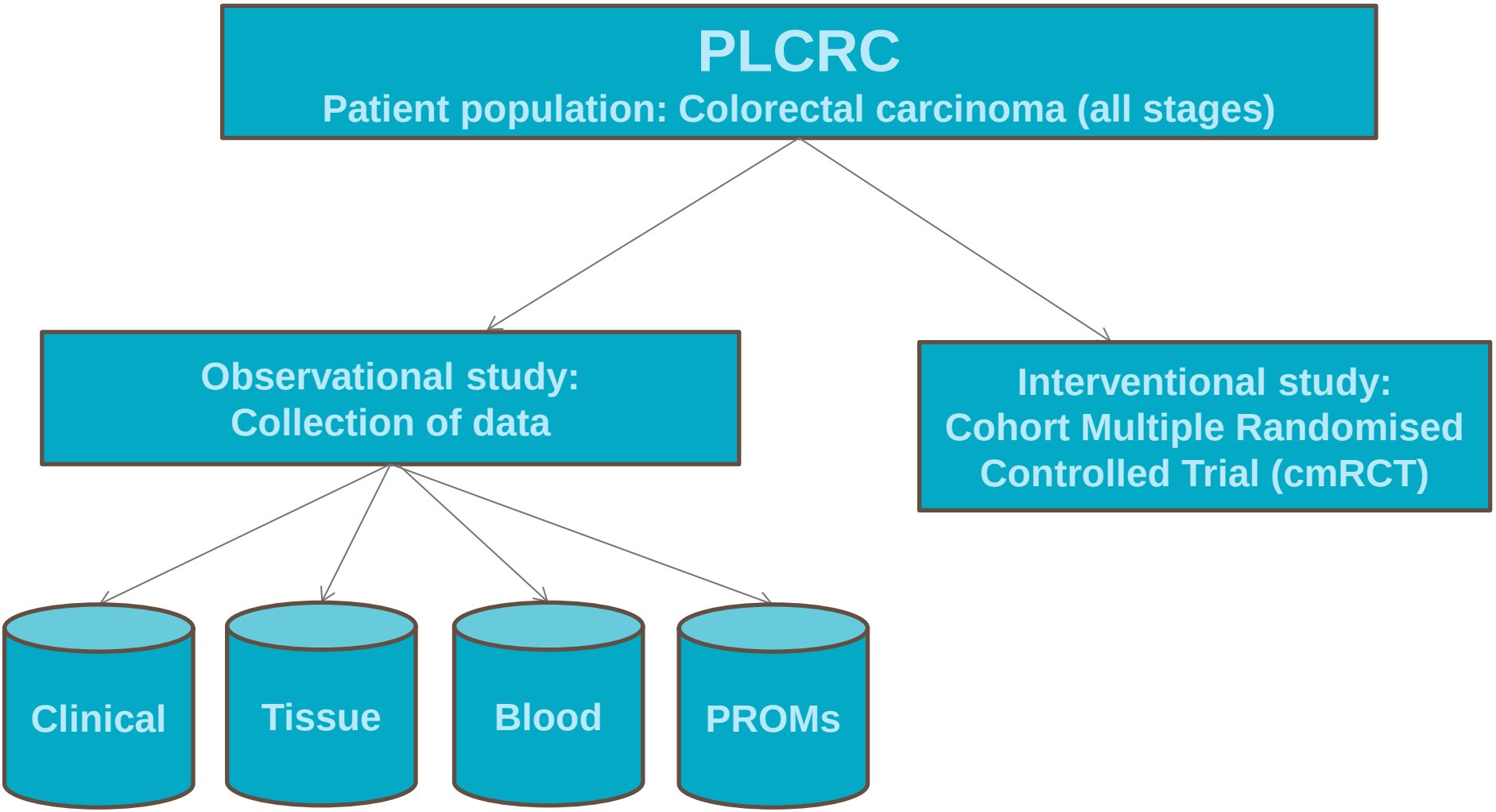
Prospective studies:

- Pomalidomide: MM patients (2015– ; pay-for-performance)
- Daratumumab: MM patients (2018– ; pay-for-performance)

‘Comprehensive’ cancer registry?

- National database since 1989
  - coverage estimated at 95%
  - > 2 million cases in database
  - > 100.000 cases per year

- Flexible registry…

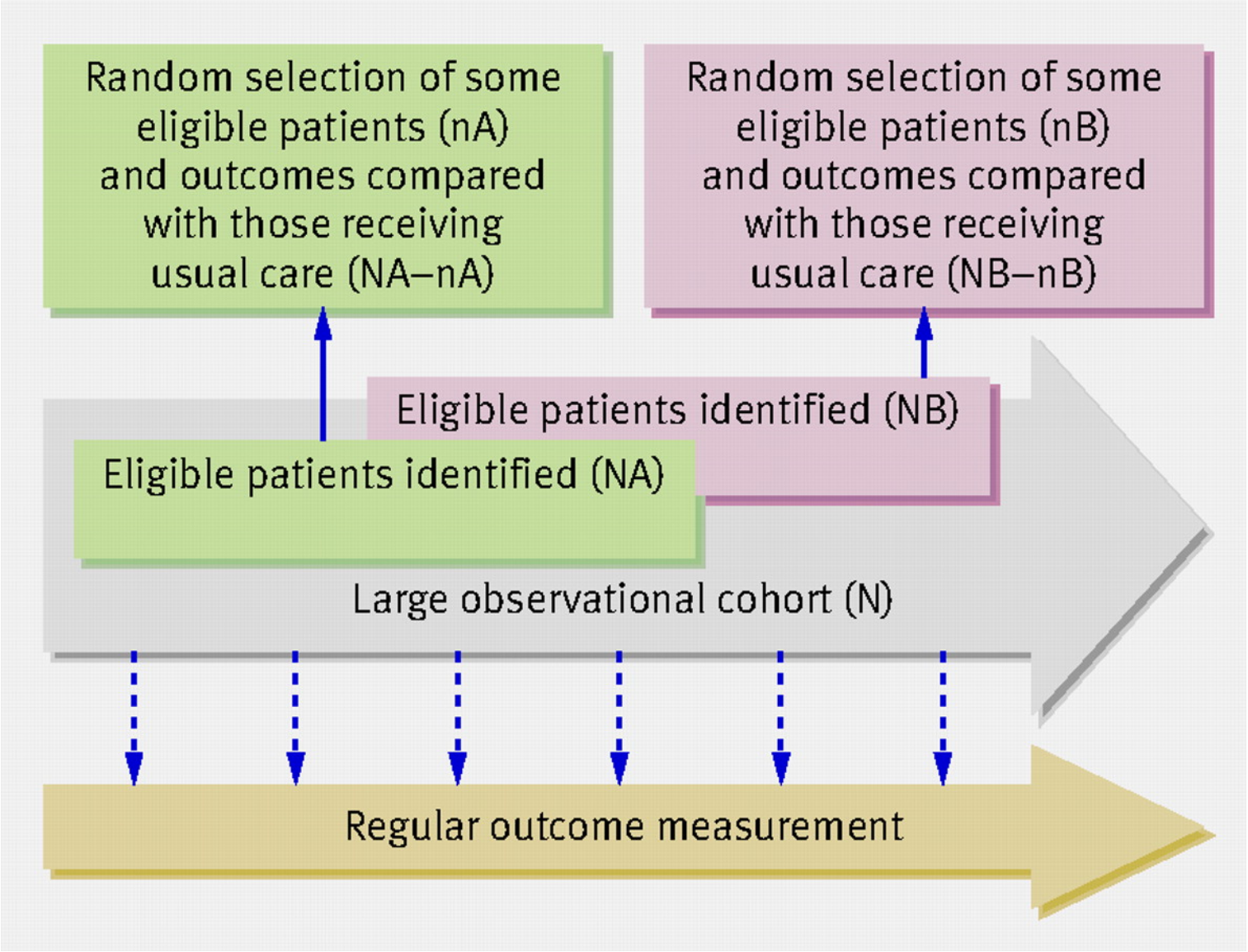


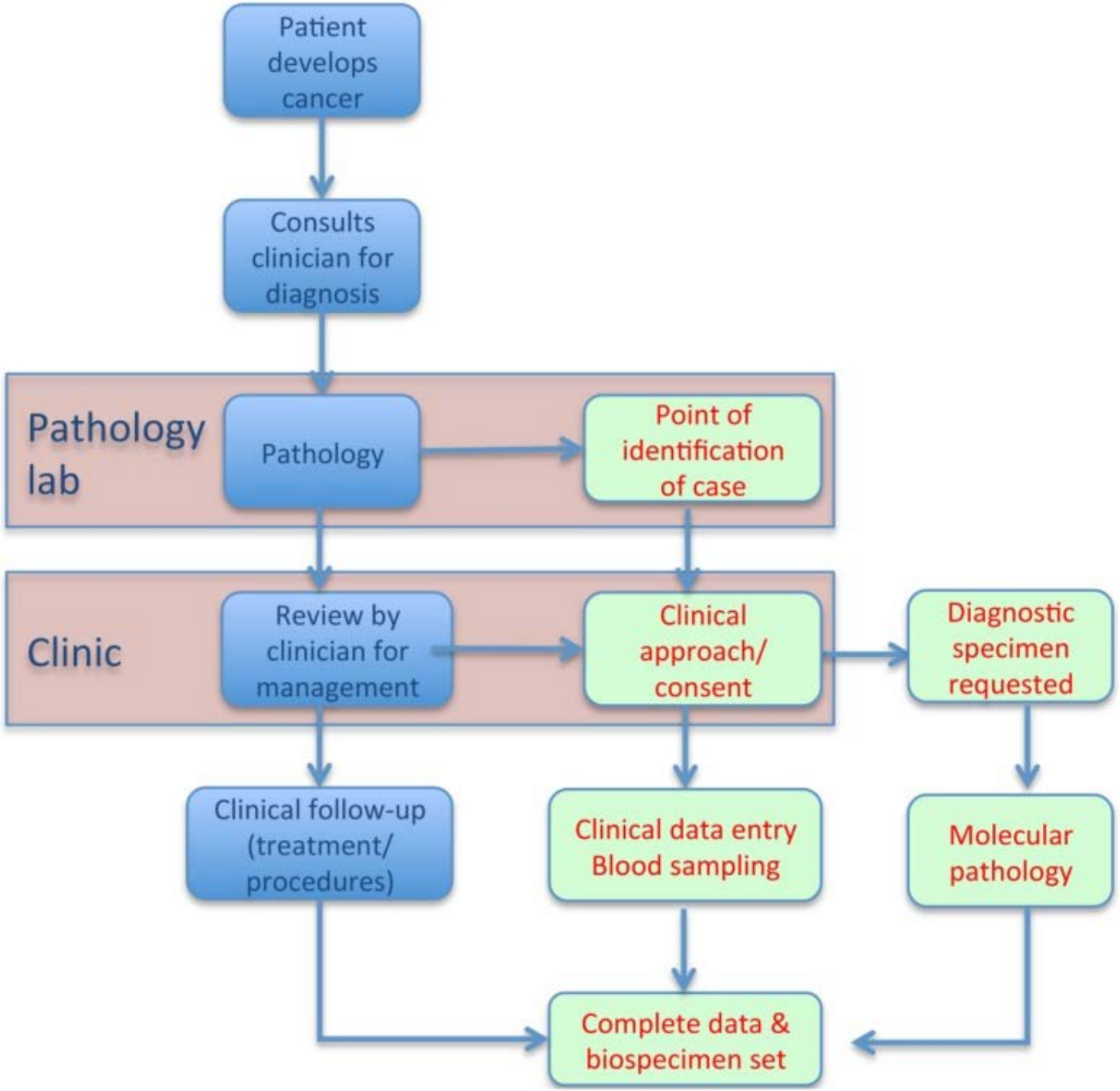
integraal
kankercentrum
Nederland

B B M R I • N L

profiles

(Relton et al, 2010)




Patient develops cancer
Consults clinician for diagnosis
Pathology lab
Pathology
Point of identification of case
Clinic
Review by clinician for management
Clinical approach/ consent
Diagnostic specimen requested
Clinical follow-up (treatment/ procedures)
Clinical data entry Blood sampling
Molecular pathology
Complete data & biospecimen set

Summary

- Data for postapproval evaluation of agents may be hard to come by.
- Most postapproval studies have yet to confirm preliminary results used to substantiate initial approval.
- Cancer registries may aid in collecting impactful data on well-defined outcomes of interest in postapproval evaluation and observatonial studies.

Netherlands comprehensive cancer organisation

www.iknl.nl

www.linkedin.com/company/iknl

twitter.com/iknl

Process

PALGA

LBZ

other **databases**

NCR

nederlandse kankerregistratie