Challenges and Opportunities in Development of Personalized Medicine

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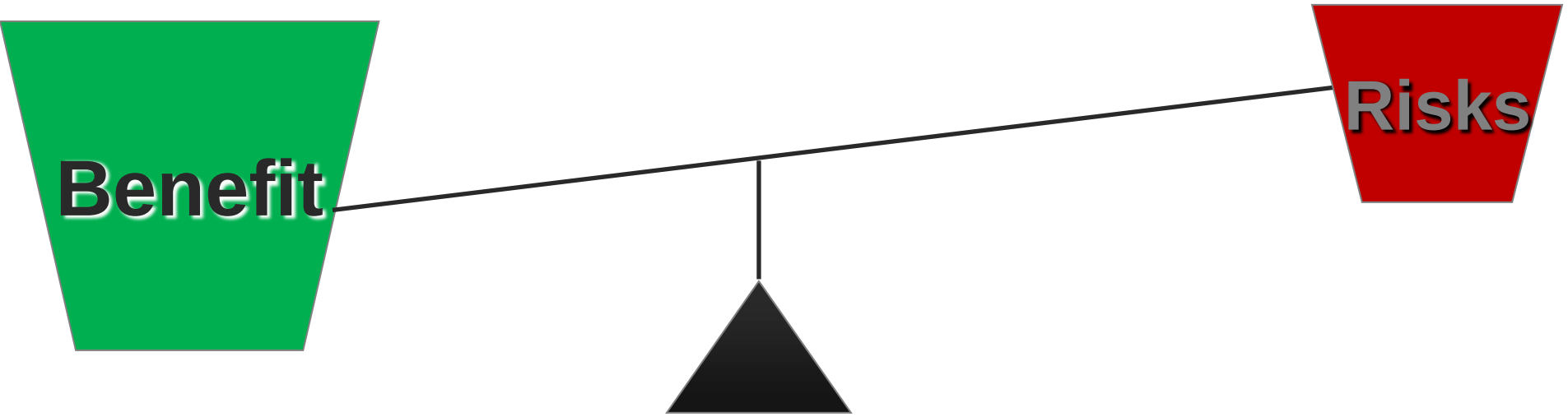
What's our job?

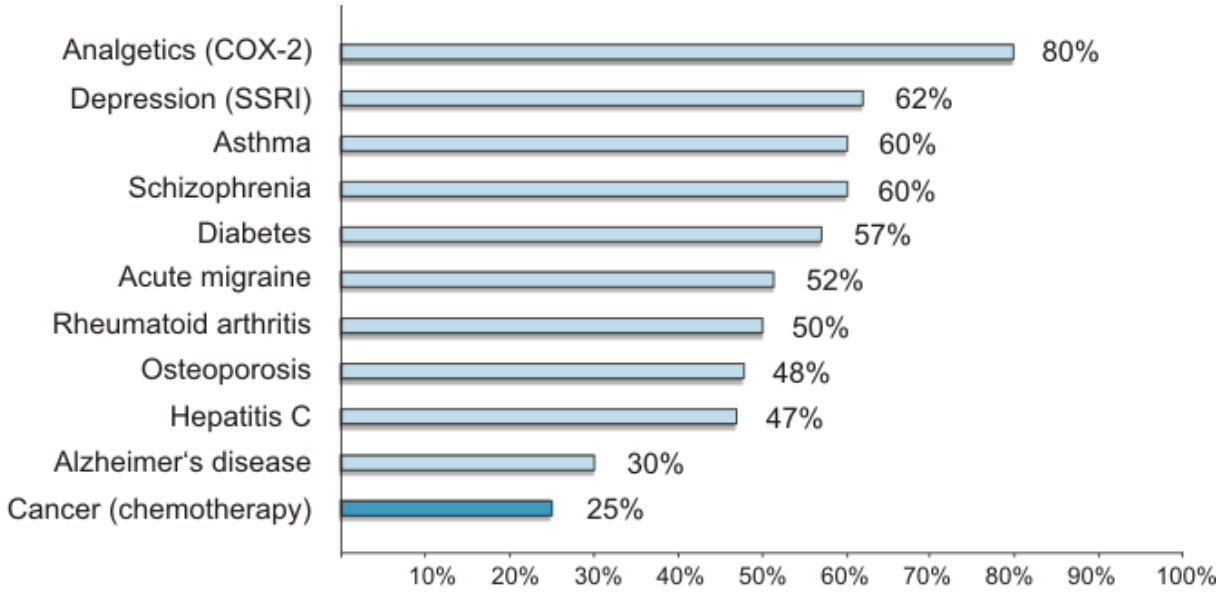


Transform research and discovery to

patient benefit in the real world health care setting

….as soon and safe as possible

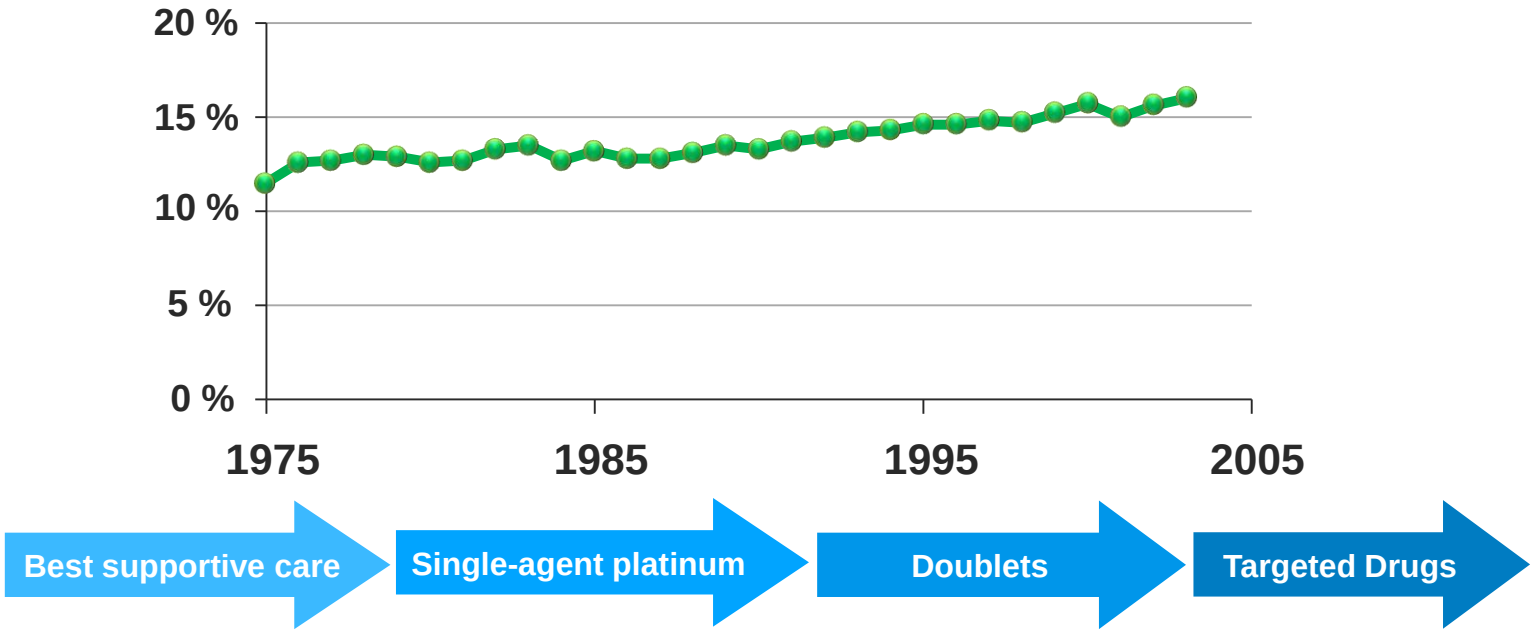
Efficacy of Medicines in Different Therapeutic Areas



modified from Spear et al., Trends in Molecular Medicine, 2001, Vol 7: 201-204

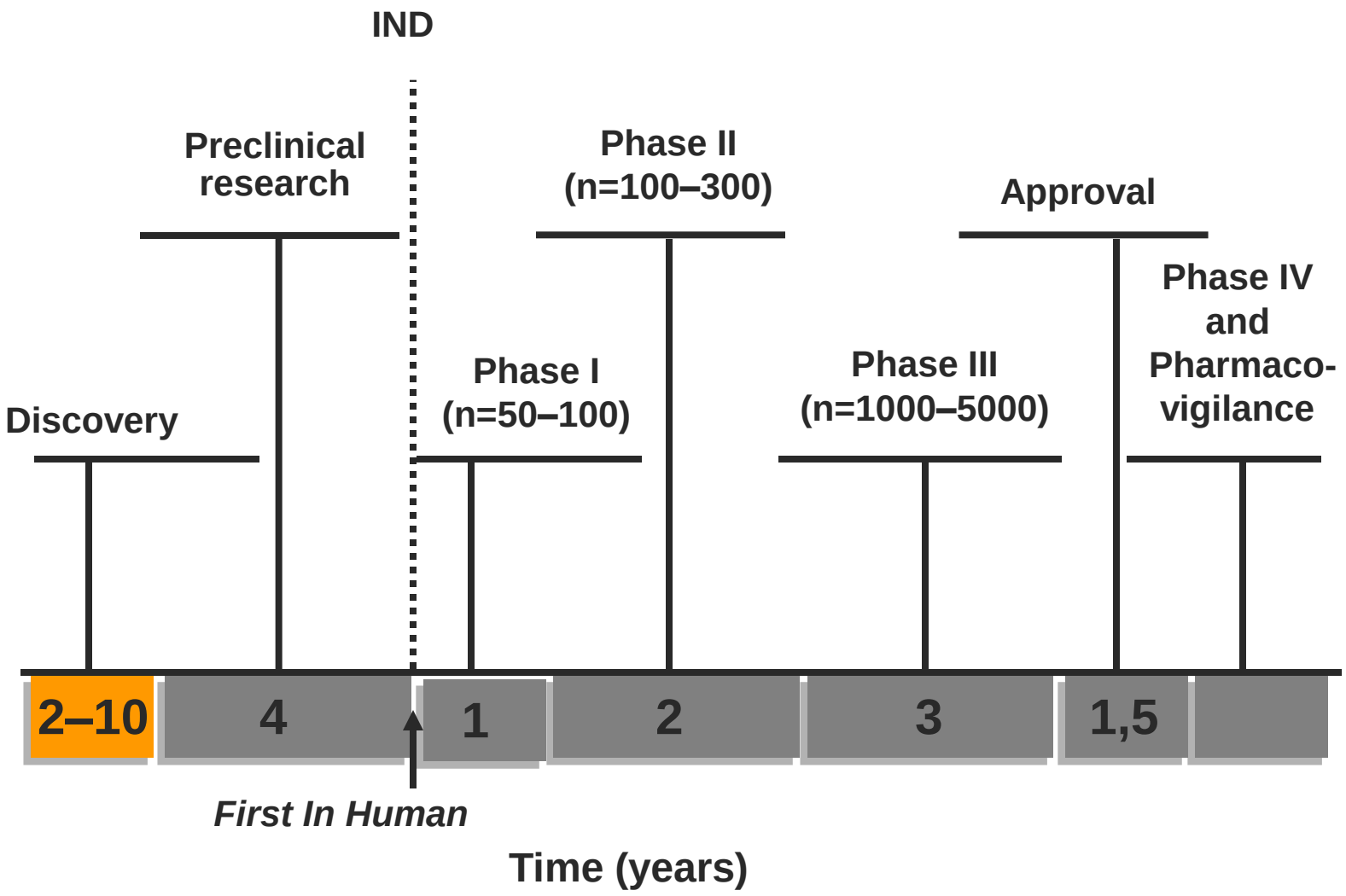
Traditional Strategies Failed to Significantly Improve the Outcomes of Lung Cancer Patients

- Lung cancer is the most common cause of cancer death
- Over the last decade, ~27,000 NSCLC patients have been enrolled in negative phase 3 trials[1]
- Minimal gain in 5-year OS over the past 3 decades in lung cancer



1. Soria J. Presented at Clinical Science Symposium at ASCO 2011

Traditional drug development



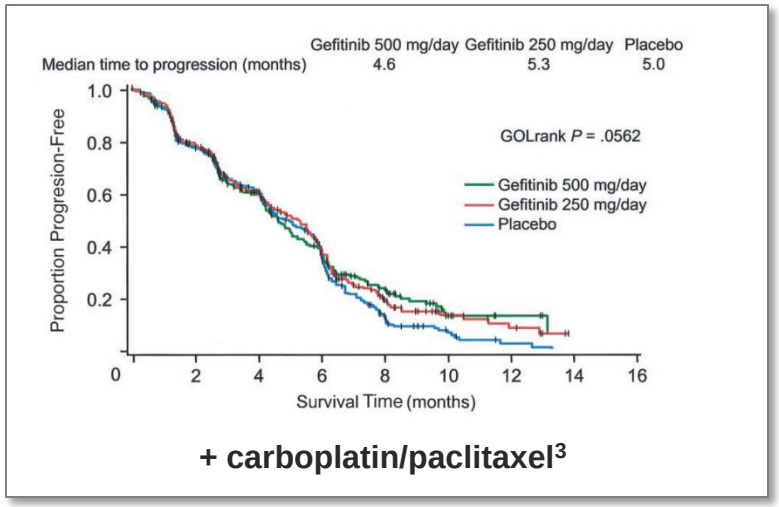
Källa: PhRMA. Tufts Center for the Study of Drug Development.

Targeted Drugs Applied Without a Biomarker

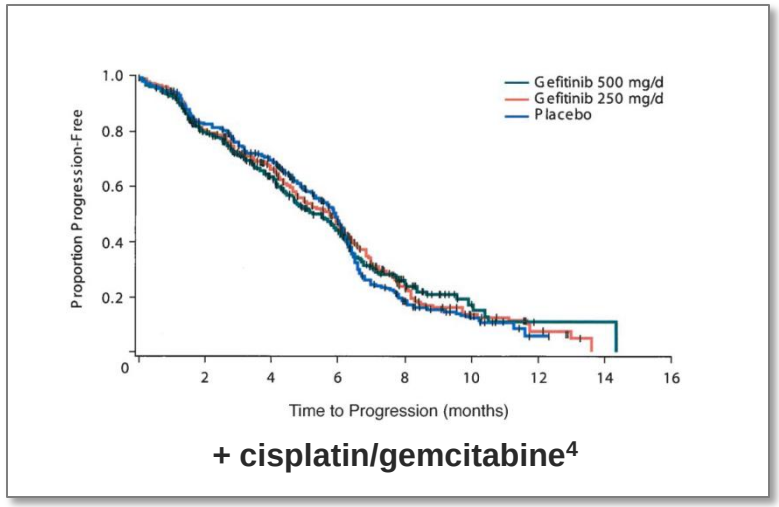
- Gefitinib single agent

Sites	Japan [1]	Europe [1]	United States [2]
Patients entered	106	102	216
Response rate	28%	10%	10%

- Gefitinib combination with Chemotherapy



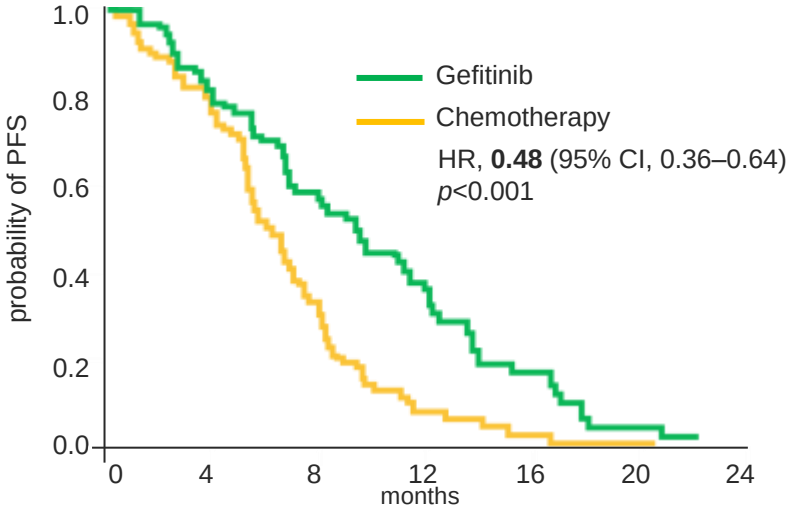
+ carboplatin/paclitaxel[3]



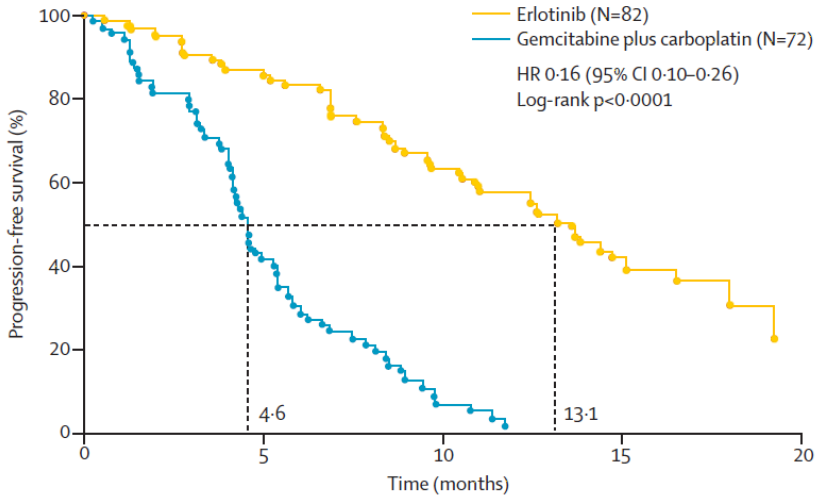
+ cisplatin/gemcitabine[4]

1) Fukuoka et al JCO 2003 2) Kris et al JAMA 2003
3) Herbst JCO 2004 4) Giaccone JCO 2004

A First Breakthrough with Biomarkers in Lung Cancer: Activating Mutations in the EGFR Gene



IPASS / gefitinib[1]



OPTIMAL / erlotinib[2]

Activating mutations in the EGFR drive the disease

This oncogeneic driver can be identified with a diagnostic test

Targeted therapy to silence the activated EGFR

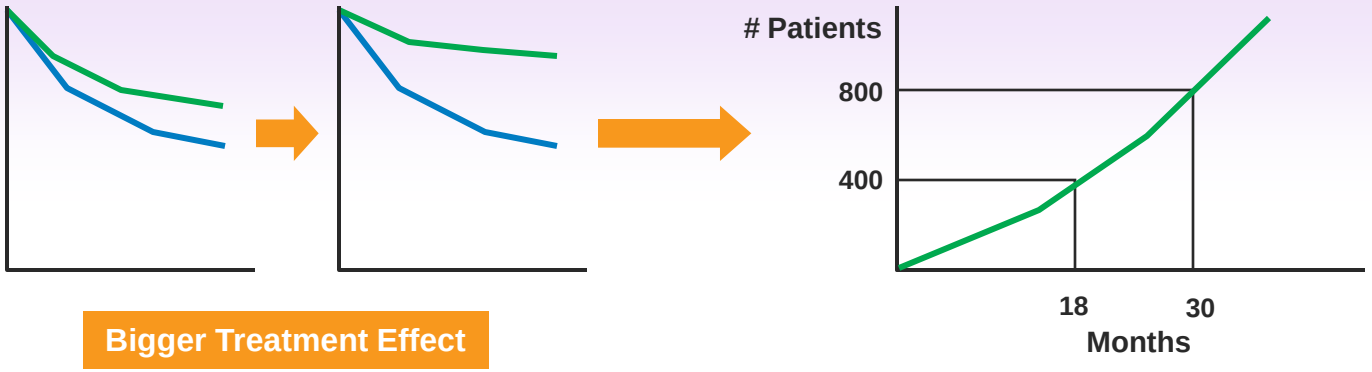
1. Mok et al., NEJM 2009; 361: 947-957
2. Zhou et al., *Lancet Oncol* 2011; 12:735-742

A more Personalized Medicine R&D Approach

- Critical focus on **human biology and pathogenic mechanisms**
- Effective interpretation and application of **genomic information**
- Application of this knowledge to **every stage of drug discovery and development**

Benefits of Drug Development Linked to a Biomarker

Benefit to Clinical Development

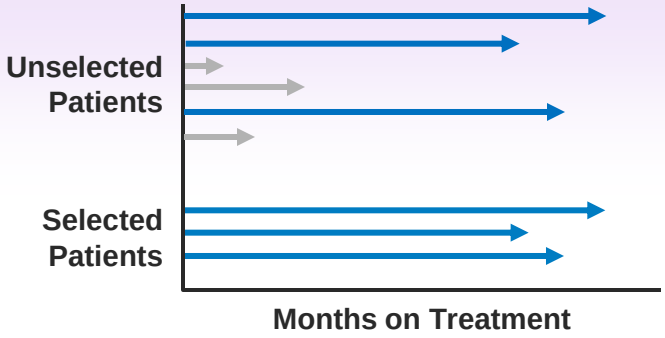


Bigger Treatment Effect

Smaller Clinical Trials
Faster Trial Completion

Benefit to Patients

Patients Treated More Likely to Benefit



Longer Time on Treatment

Earlier Regulatory Submission
+ patient access

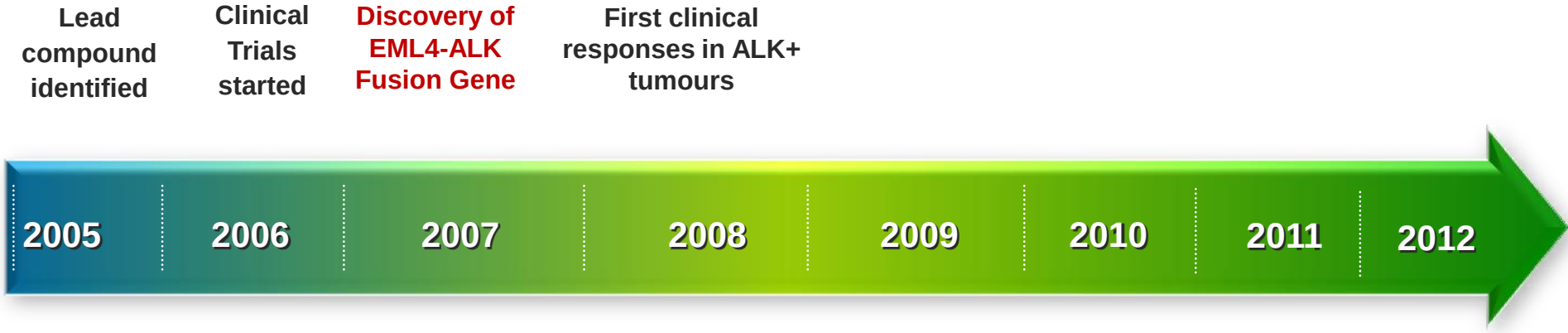
More Dramatic Effect in Treated Patients

Minimized exposure to drugs if not likely to benefit and

Unnecessary costs to patients and payers

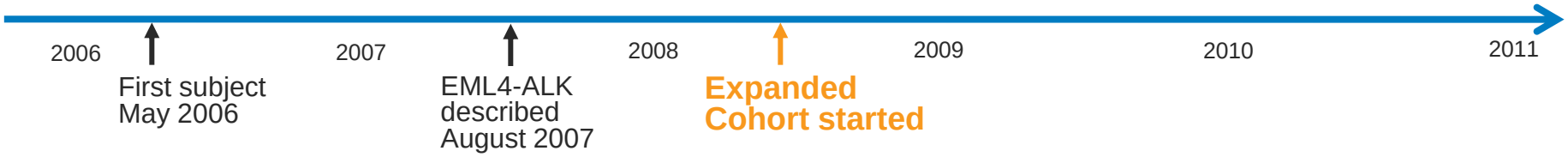
Molecular selection may enable faster drug development

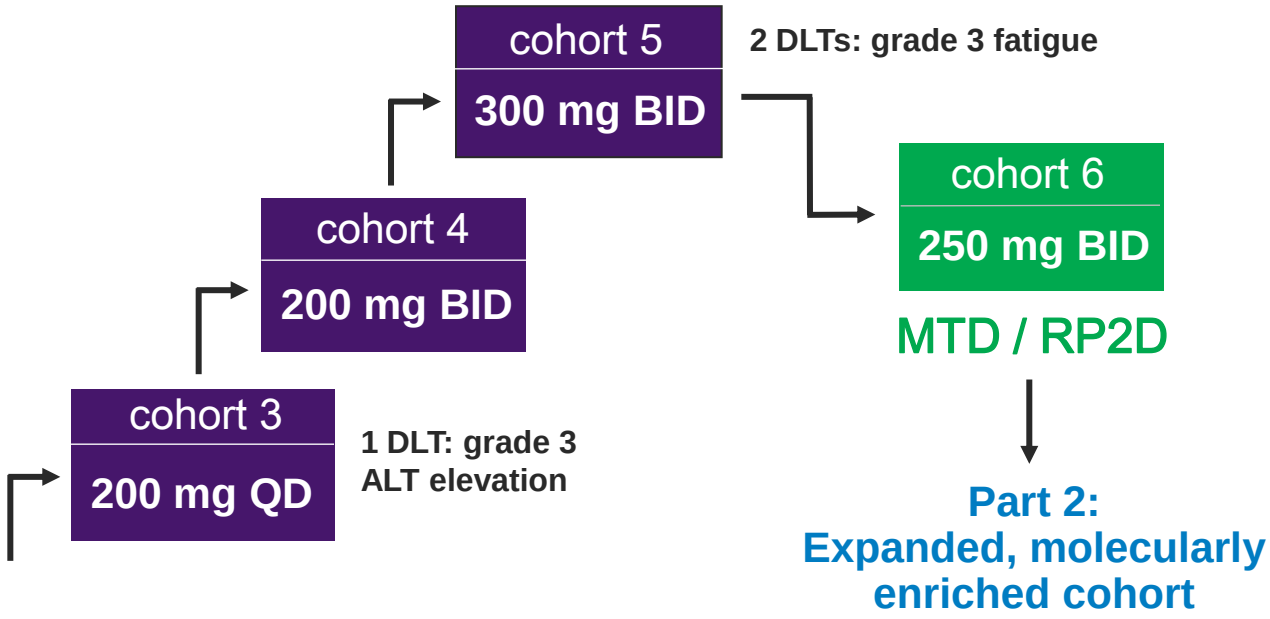
Development of crizotinib



1. Kwak et al. *New Engl J Med*. 2010;363:1693−03

Start of a Biomarker Driven Drug Development





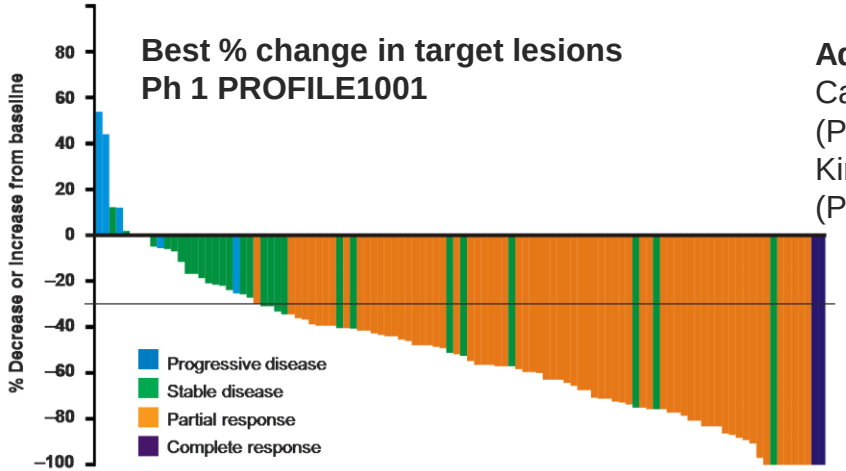
Enrolling patients with *ALK*-positive NSCLC after preliminary observation clear activity in a few patients

Molecular selection and collaboration enable faster drug development

Development of crizotinib

2005	2006	2007	2008	2009	2010	2011	2012
Lead compound identified	Clinical Trials started	**Discovery of EML4-ALK Fusion Gene**	First clinical responses in ALK+ tumours	Phase 3-studies initiated ALK+NSCLC incl. Karolinska	NEJM publication of ALK+ cohort[1]	**FDA Accelerated approval**	**CHMP positive opinion Europe**

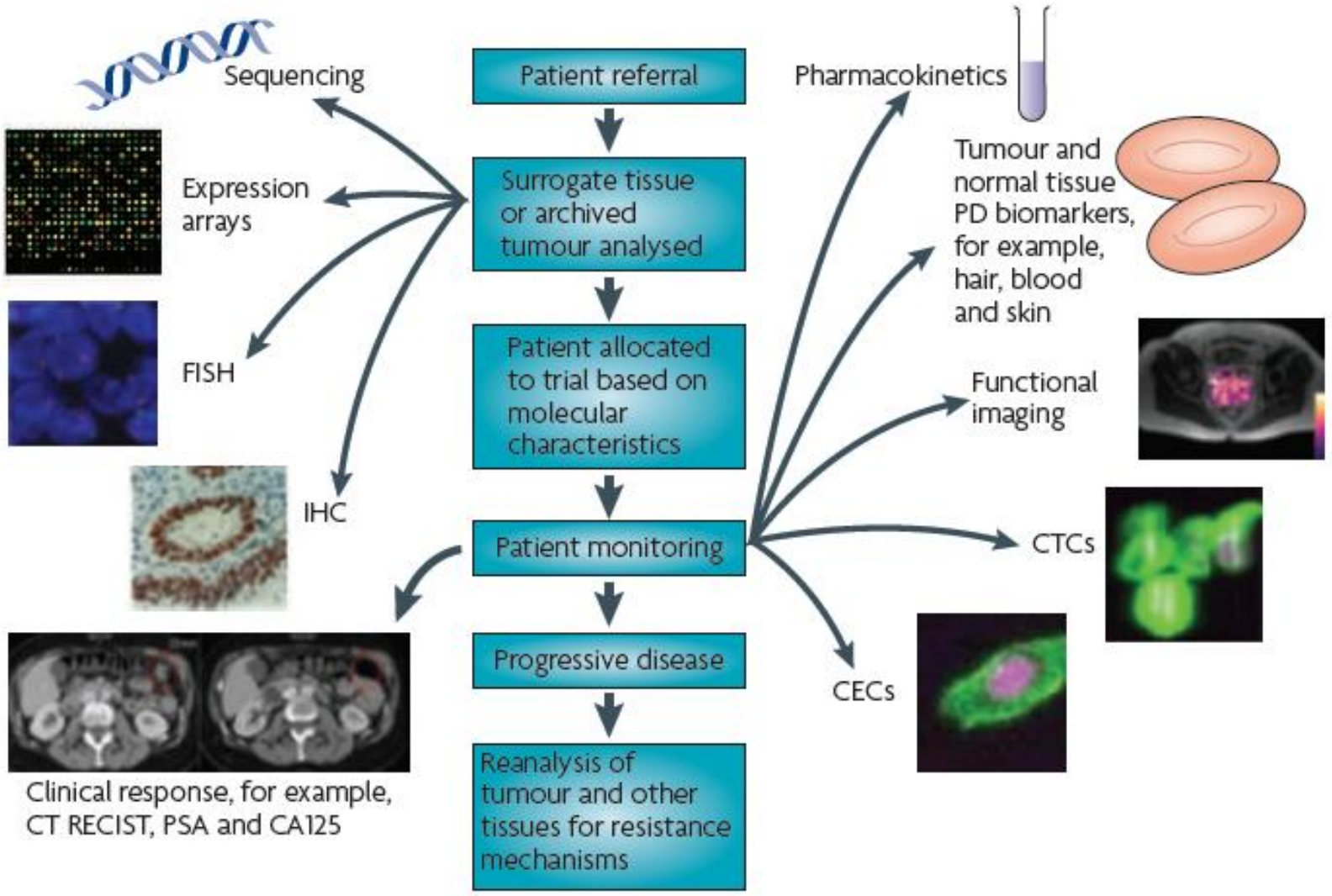
Abbott Laboratories develop diagnostic test 2009 ->



Additional references:
Camidge R, et al. Lancet 2012 (PROFILE1001)
Kim, et al, ASCO 2012 #7533 (PROFILE1005)

1. Kwak et al. *New Engl J Med*. 2010;363:1693−03

A new vision for future trials



Yap TA et al. *Nat Rev Cancer.* 2010. Epub ahead of print.

Experience to date

- **Identification of targets and biomarkers**
  - Not always a sequential process
  - Often easier said than done
- **Considerable areas of unmet need with no identified biomarkers**
- **Cost , speed of discovery and development**
  - Still an emerging picture, but so far not always clear advantages in cost and speed
- **The Regulatory Environment important for**
  - the development process and
  - the review process of the Marketing Authorization Application

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 July 2010
EMA/CHMP/EWP/433478/2010
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need to revise the guideline on the evaluation of anticancer medicinal products in man

Companion Diagnostics

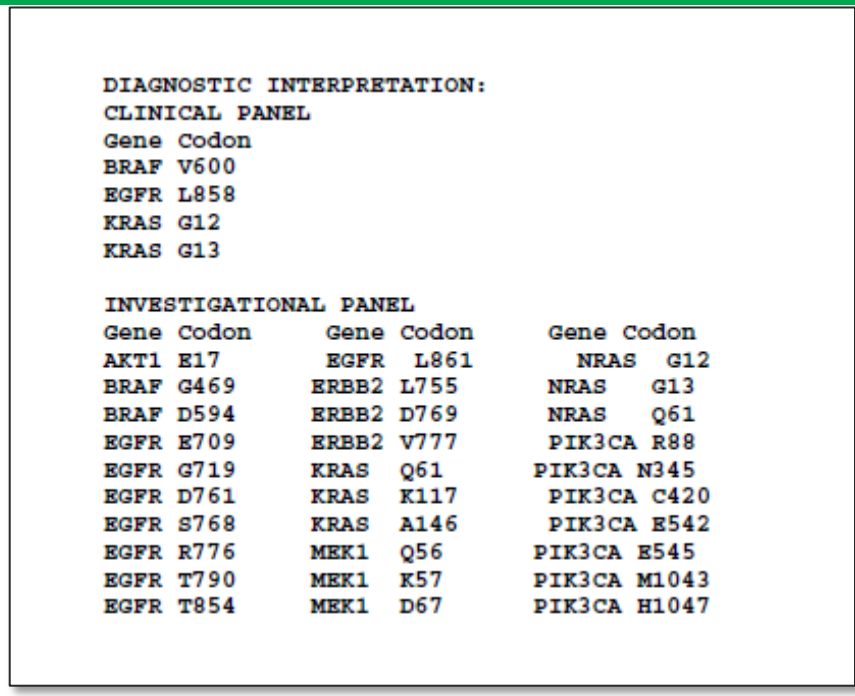
- A validated specific target is necessary for development of Companion Diagnostics (CDx)

- CDx are currently regulated through the In Vitro Diagnostic Directive (IVDD) in the framework of Medical Devices (MD) legislation

- Role of EMA / national board of health
  - Guidance and review
  - Flexible approach needed regarding developing CDx in parallel to drug development
    - A CE marked CDx may not be available at the time of the Marketing Authorization Application – or the best one is yet to come…

From research to everyday health care
Practical management and collaboration

- Amount of tissue needed
- Accuracy and availability of the test
- What is the best method?
- Reporting time vs need to start treatment
- Interpretation of pathology reports
- Change of clinical practice and logistics
- Who should be tested?



DIAGNOSTIC INTERPRETATION:
CLINICAL PANEL

Gene	Codon
BRAF	V600
EGFR	L858
KRAS	G12
KRAS	G13

INVESTIGATIONAL PANEL

Gene	Codon	Gene	Codon	Gene	Codon
AKT1	E17	EGFR	L861	NRAS	G12
BRAF	G469	ERBB2	L755	NRAS	G13
BRAF	D594	ERBB2	D769	NRAS	Q61
EGFR	E709	ERBB2	V777	PIK3CA	R88
EGFR	G719	KRAS	Q61	PIK3CA	N345
EGFR	D761	KRAS	K117	PIK3CA	C420
EGFR	S768	KRAS	A146	PIK3CA	E542
EGFR	R776	MEK1	Q56	PIK3CA	E545
EGFR	T790	MEK1	K57	PIK3CA	M1043
EGFR	T854	MEK1	D67	PIK3CA	H1047

Molecular Diagnostic Pathology
Report from the MSKCC, NY

Who are the discussion partners during planning
and introduction of a new drug / biomarker / CDx?
Who makes decisions?
Communication and knowledge?
Quality?

From research to everyday health care
What about cost?

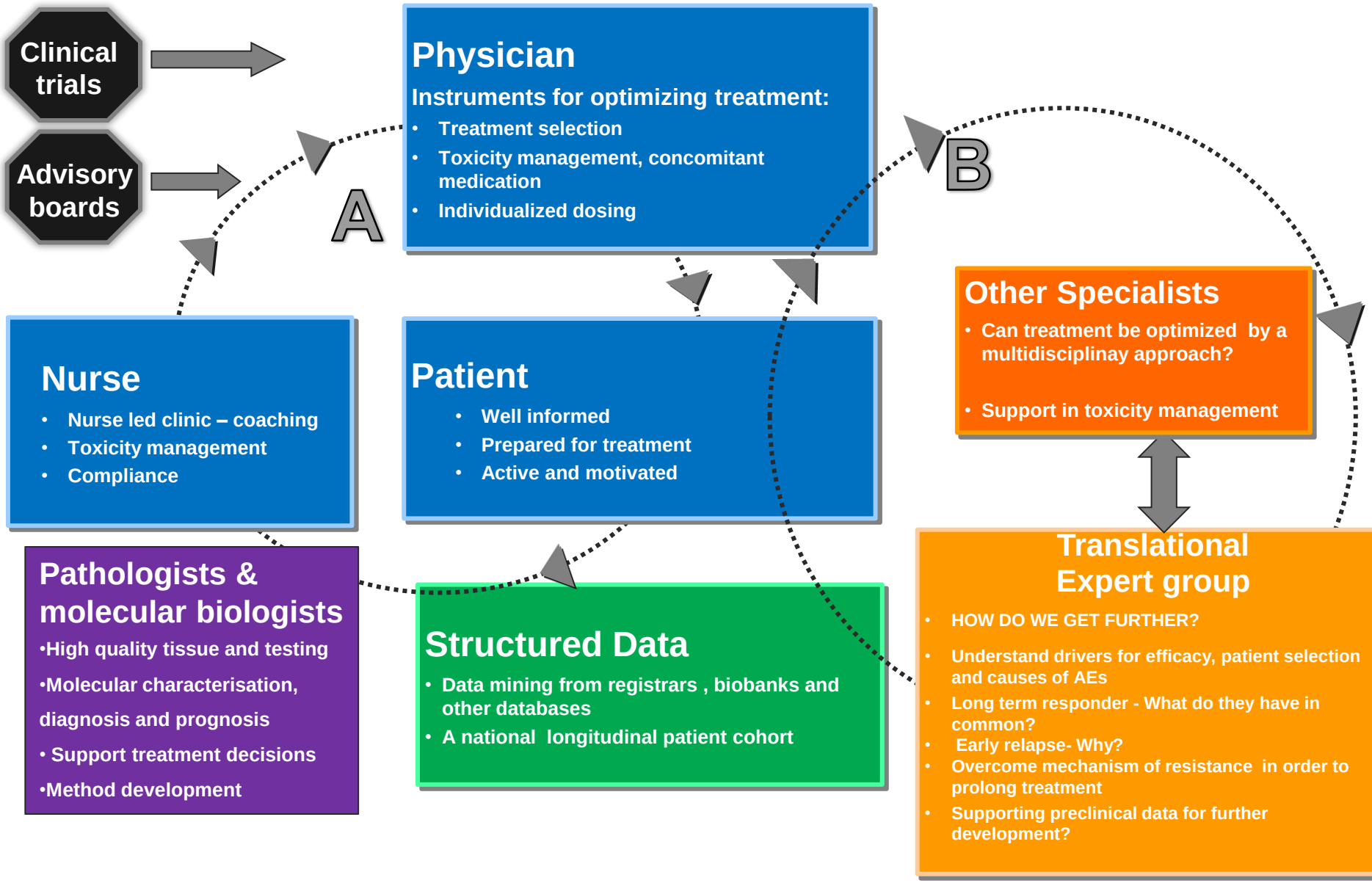
Diagnostic Access

- Lack of transparent system for reimbursement of diagnostic costs
- ➢ Risk of suboptimal diagnosis and treatment, inequality

Value and the cost/benefit of drugs

- Society perspective: We want innovation but new therapies are considered expensive
  - Not every patient responds – initial or acquired resistance / patients eventually progress
  - Reimbursement and Guideline recommendations - when is a yes a yes?
- Pharma perspective: Proven efficacy and safety basis for approval, responsibility for providing safety and efficacy data remains the same regardless of population size
  - Data evolve over time
- Personalized medicines have a targeted, self-limiting patient population and predictable budget impact

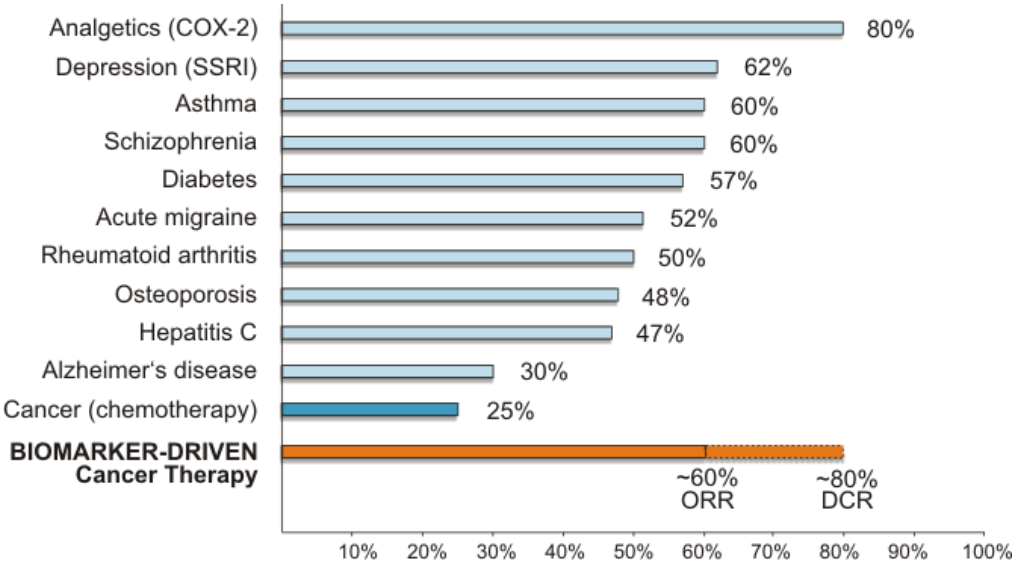
Learn more from every patient in every day health care



Potential Benefits From Biomarker-driven Treatment Approaches

- Reduced toxicities
- Higher response rates and greater treatment benefits
- Smaller and more ethical clinical trials
- Faster drug development
- Reduced costs for companies and payers

- Multidisciplinary collaboration is key for sucessful implementation
- Learn more from every patient – also in everyday health care



Thank you for your attention!