Regulation of Biomarkers Used in Personalised Medicine

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Disclaimer

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What is Personalized Medicine?

Encompasses many actions to improve patient outcomes

Broadest sense

- Optimal adaptation of healthcare decisions (HC maintenance, monitoring, preventative and therapeutic steps) based on a persons individual characteristics, HC status and situation.
- Includes use of diagnostics, choice of therapy, choice of dose, timing and frequency of dose

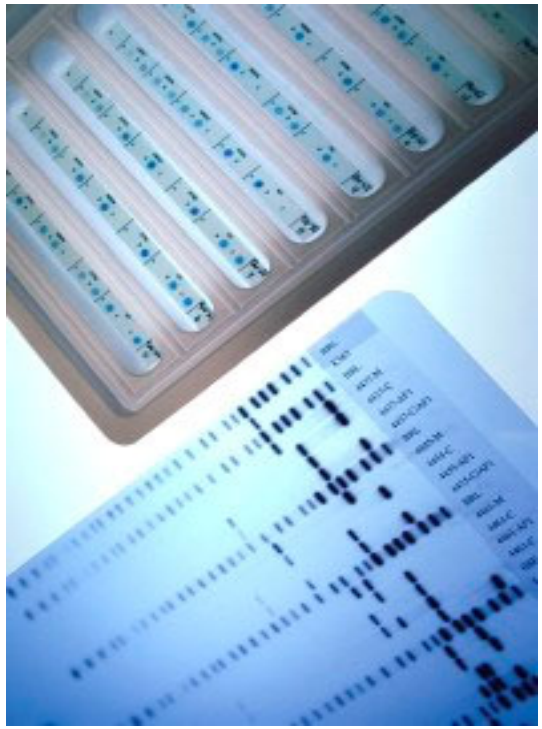
For companies in the pharma/biotech industry workspace

- Pharma and Biotech, in their capacity as industry members which discover, develop and market innovative medicines are strongly positioned to impact a critical part of Personalized Medicine
- To ensure that we develop our medicines in such a way that we understand which groups of patients derive the most net benefit (efficacy and safety) from the novel medicines that we develop

Biomarkers lie at the core of Personalised Healthcare

Essential to enabling translational medicine and drug development

- **Understanding pathways and mechanisms**
  (e.g. targets, molecular mechanisms and pathophysiology)
- **Improved decision making in R&D**
  (e.g. tools for profiling targets, compounds, PD and safety Markers)
- **Drivers for pharmacodiagnostic development**
  (enhancing response rates, improving benefit/risk ratio, companion diagnostics)



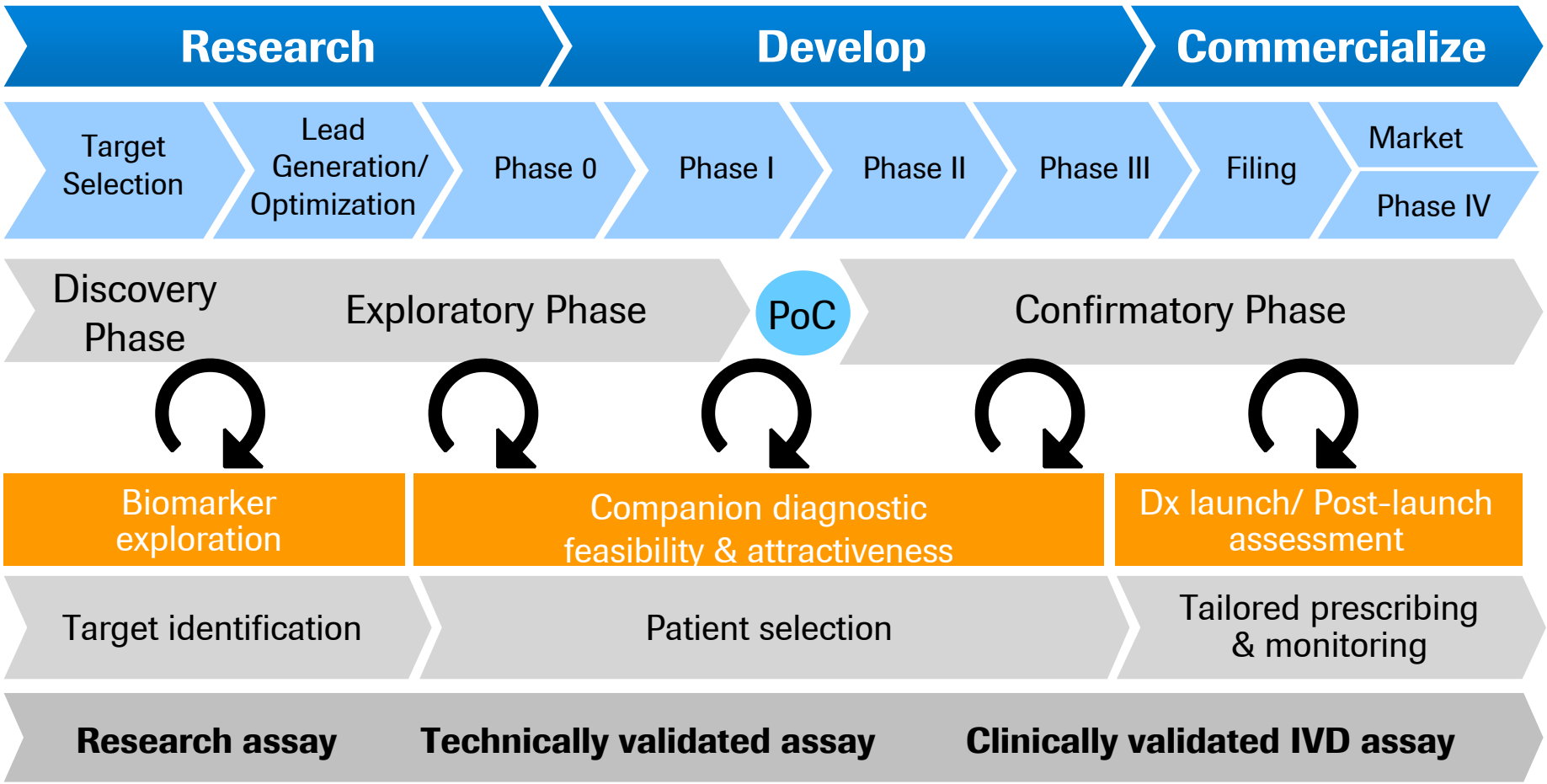
Companion diagnostic tests used to select patients, particularly for potentially life-saving therapies, need to be analytically robust and should reliably improve the benefit/safety ratio for both the selected and non-selected patient populations

Components of Personalized Healthcare

Key steps to bringing new value to the practice of medicine

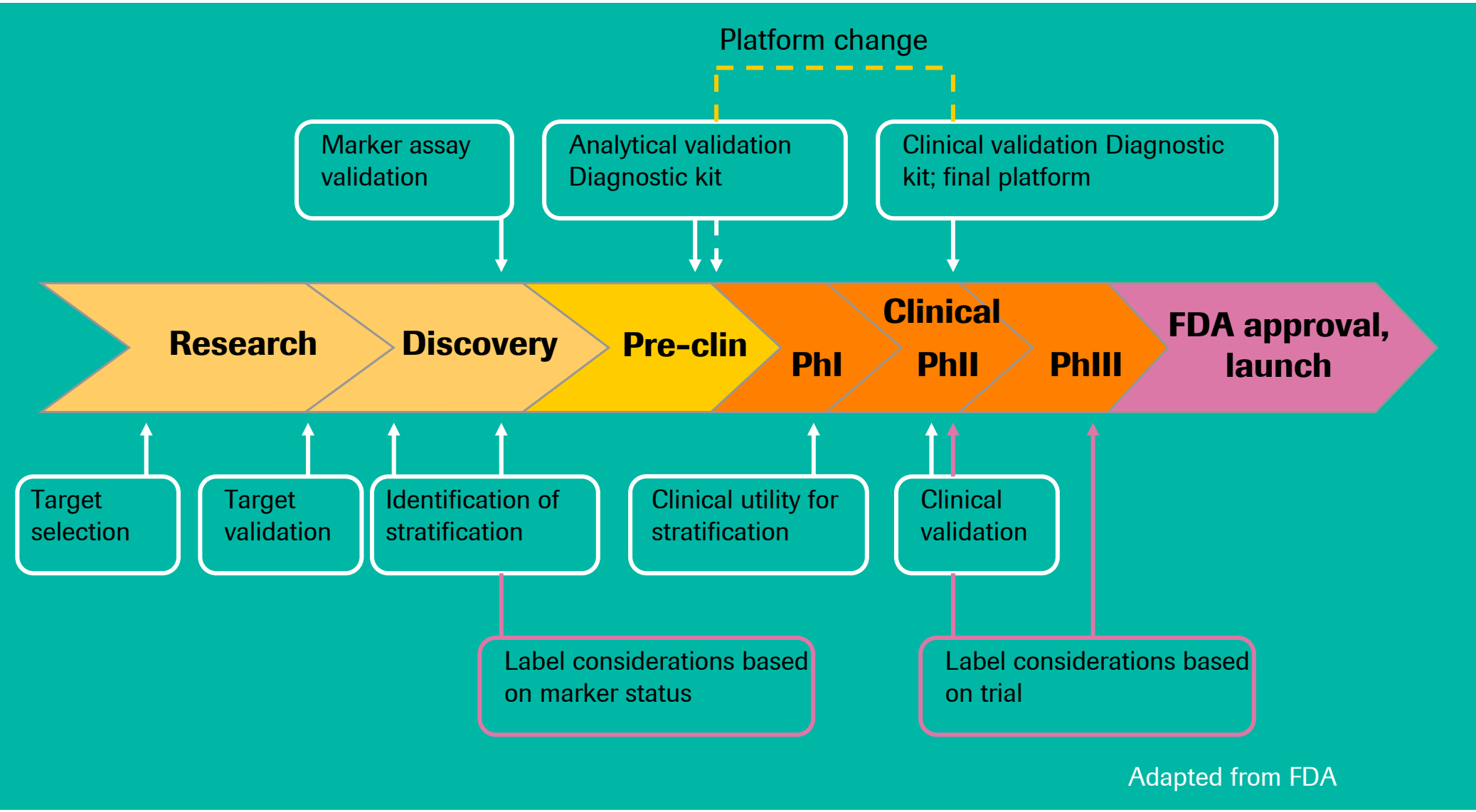
1. Understand heterogeneity of diseases and inter-patient differences
2. Discover and develop relevant biomarkers (analytical validation, clinical qualification)
3. Stratify patients with diagnostic test /biomarkers
4. Build evidence for improved benefit-risk ratio

Ideally, development of biomarkers and novel medicines are perfectly aligned….



Drug – Diagnostic Test co-development

Regulatory perspective



Adapted from FDA

But drug development and companion diagnostic development are often not aligned

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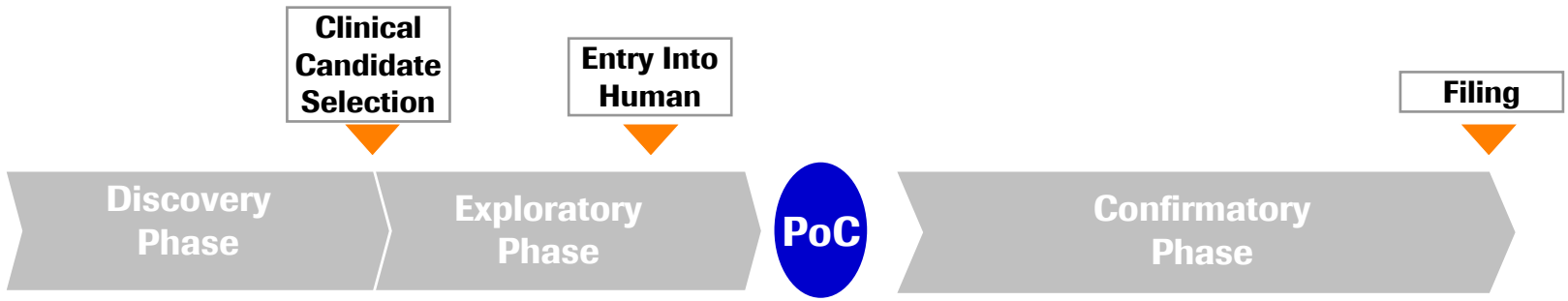
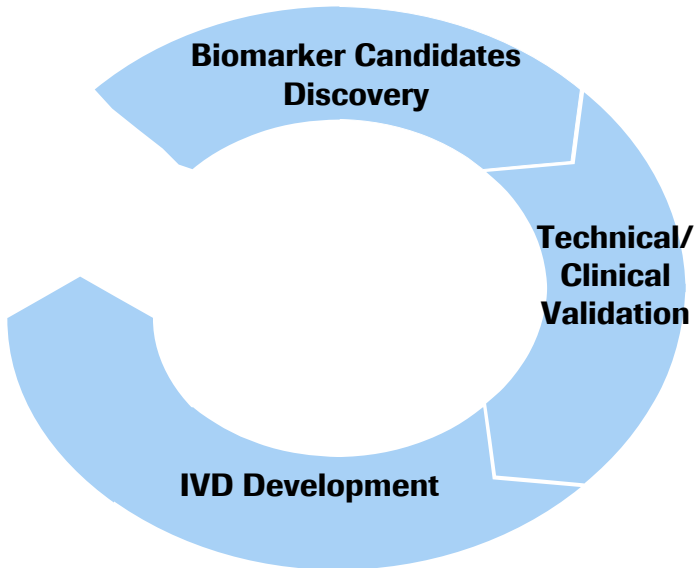
Pharma R&D process & decision points



Biomarker Discovery & Development



Biomarker Candidates Discovery: Novel hypothesis- Generating strategy

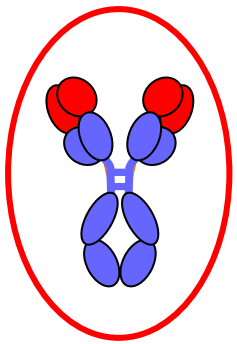
Technical/ Clinical Validation: Hypothesis is being validated / entering clinical validation

IVD Development: Biomarker assay in clinical validation

EGFR – a target for intervention

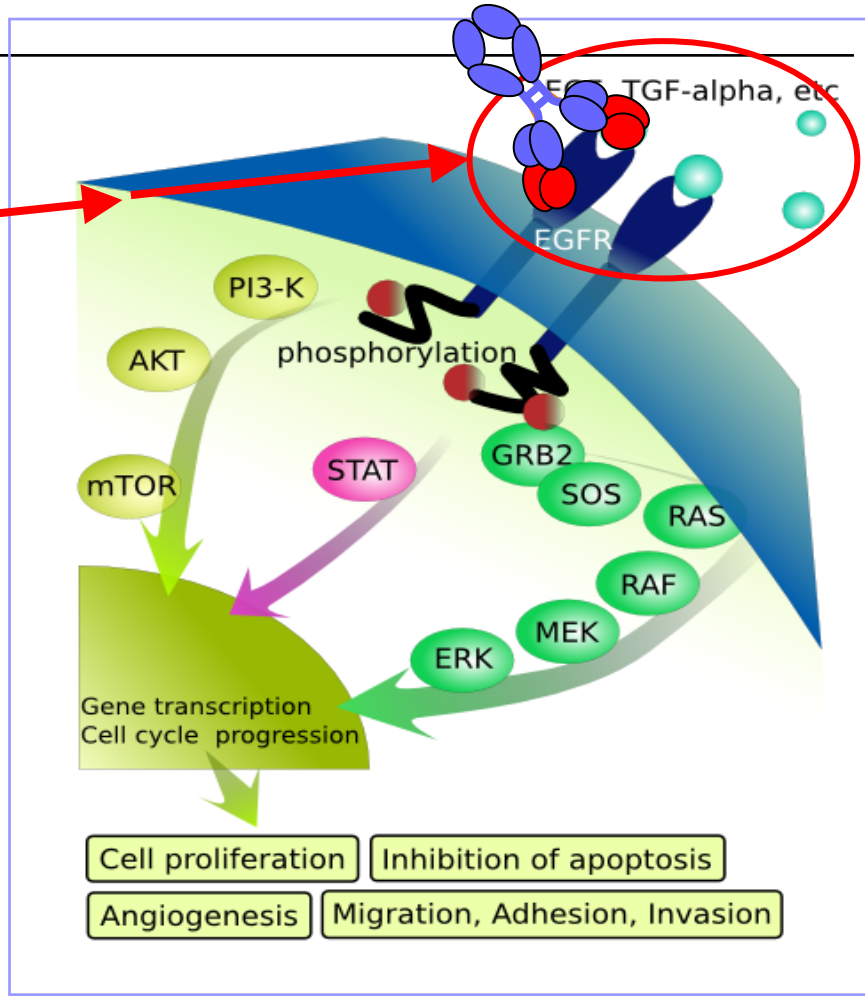
Clinical background and scientific rationale…

Antibodies that target EGFR



Cetuximab (Erbitux®)
Panitumumab (Vectibix®)

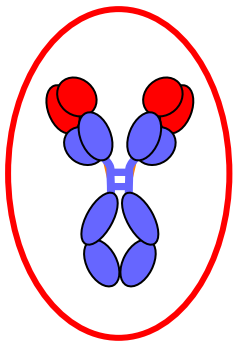
- High affinity binding to EGFR/Her1 extracellular domain



EGFR – a target for intervention

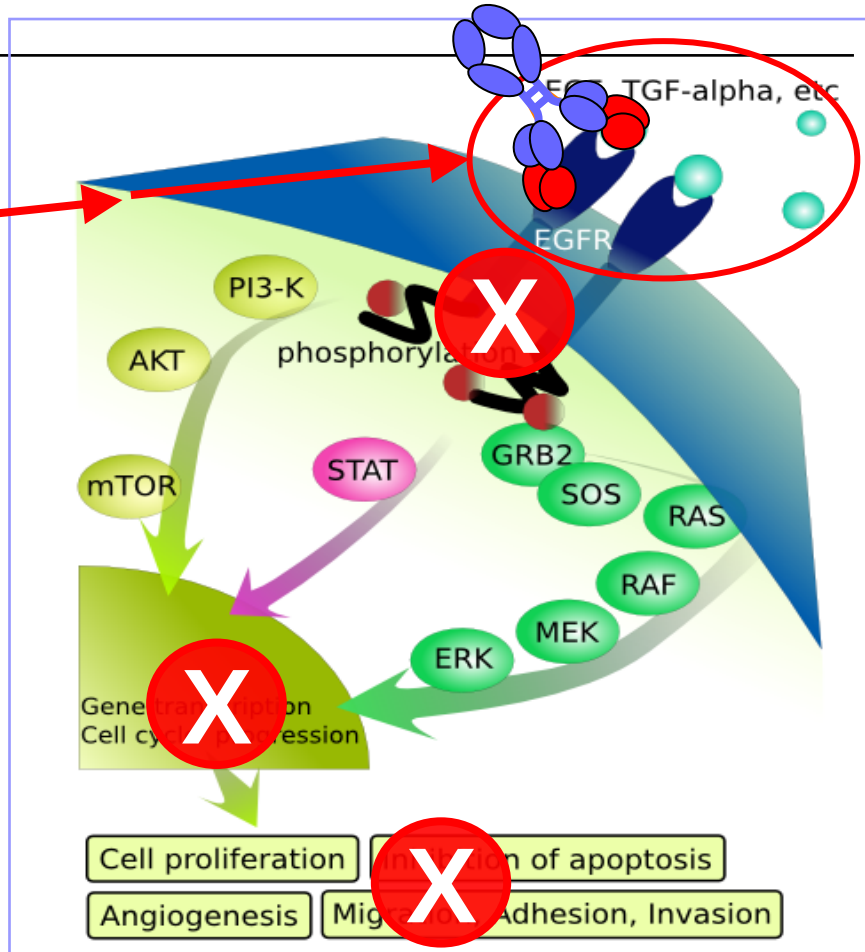
Clinical background and scientific rationale…

Antibodies that target EGFR



Cetuximab (Erbitux®)
Panitumumab (Vectibix®)

- High affinity binding to EGFR/Her1 extracellular domain
- Blockade of EGFR/Her2 hetero-dimerization
- Significant inhibition of EGFR downstream signaling
- Significant inhibition of cell proliferation

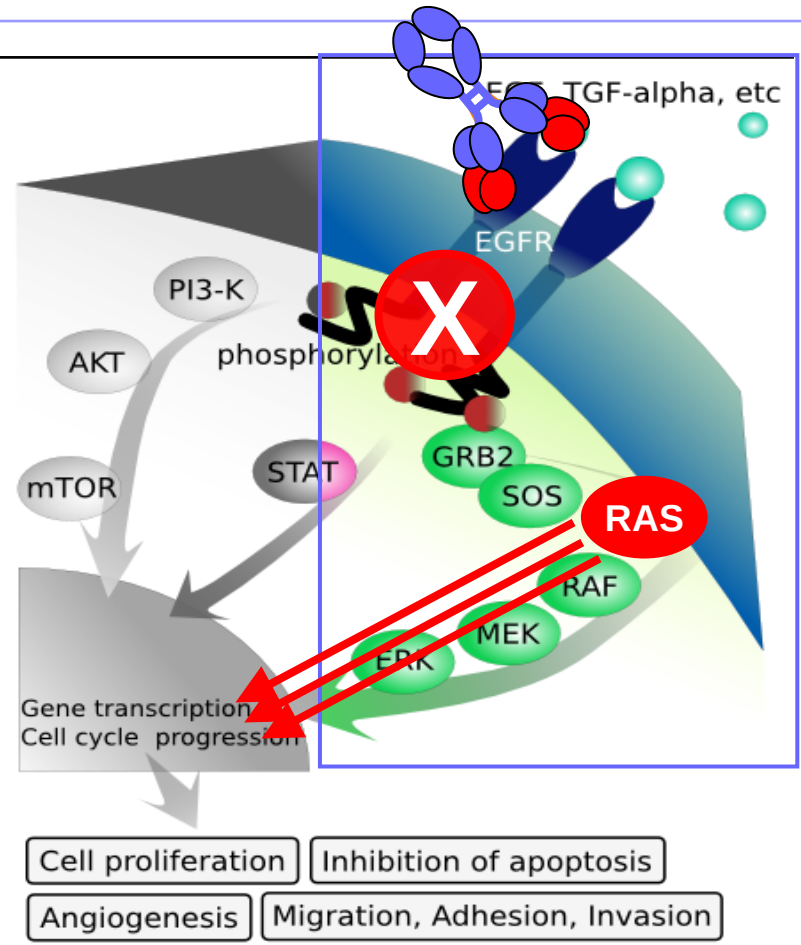


EGFR – a target for intervention

The issue of kRAS…

…when mutated…

- EGFR signalling becomes constitutively activated
- Sensitivity to EGFR pathway inhibition significantly reduced or lost
- Similarly, clinical efficacy of Cetuximab or Panitumumab significantly reduced or lost



EGFR – a target for intervention

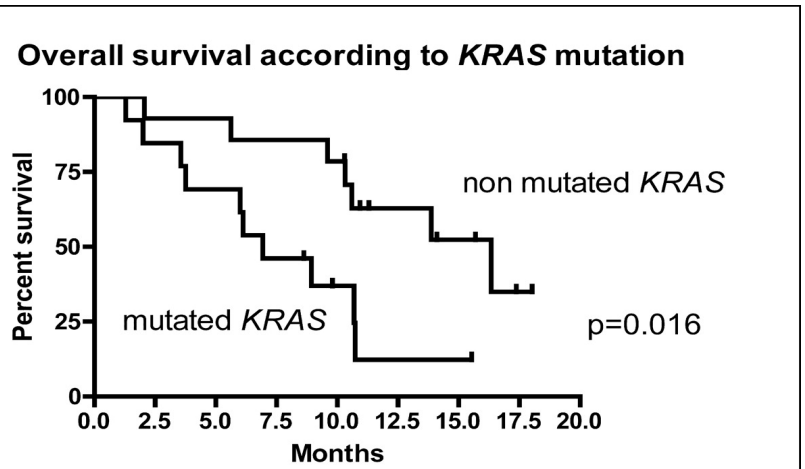
The issue of kRAS…

Cetuximab

Priority Report

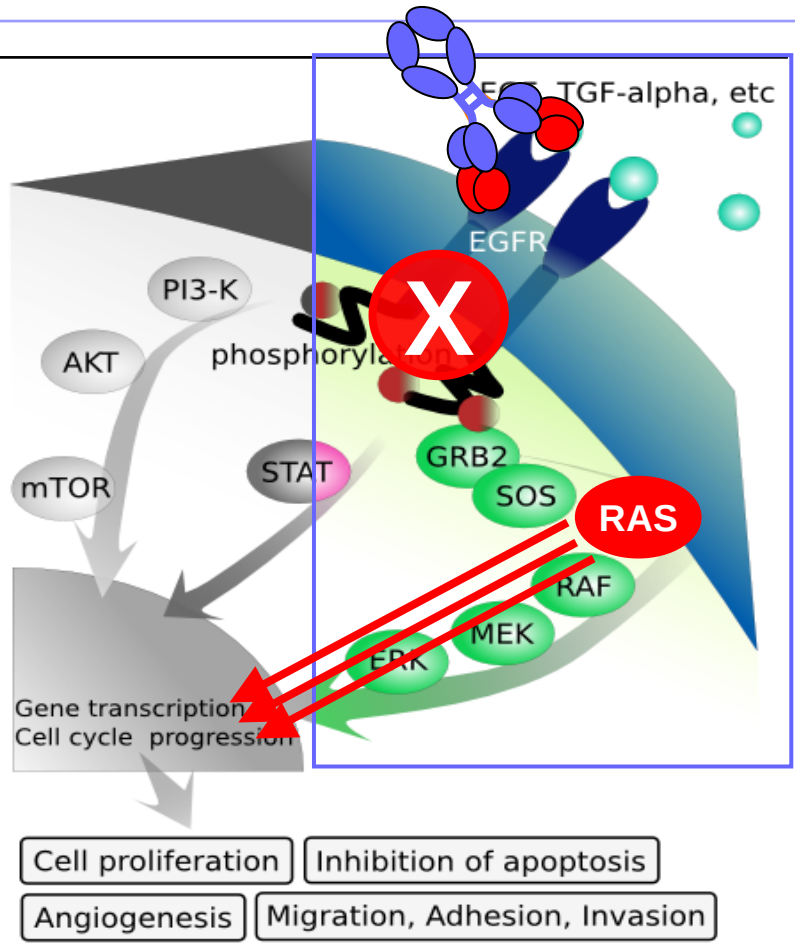
***KRAS* Mutation Status Is Predictive of Response to Cetuximab Therapy in Colorectal Cancer**

Astrid Lièvre,[1,3] Jean-Baptiste Bachet,[3] Delphine Le Corre,[1] Valérie Boige,[4] Bruno Landi,[2] Jean-François Emile,[3] Jean-François Côté,[1,2] Gorana Tomasic,[4] Christophe Penna,[3] Michel Ducreux,[4] Philippe Rougier,[3] Frédérique Penault-Llorca,[5] and Pierre Laurent-Puig[1,2]



Cancer Res 2006; 66: (8). April 15, 2006

Lievre, A. et al. Cancer Res 2006;66:3992-3995



EGFR – a target for intervention

The issue of kRAS…

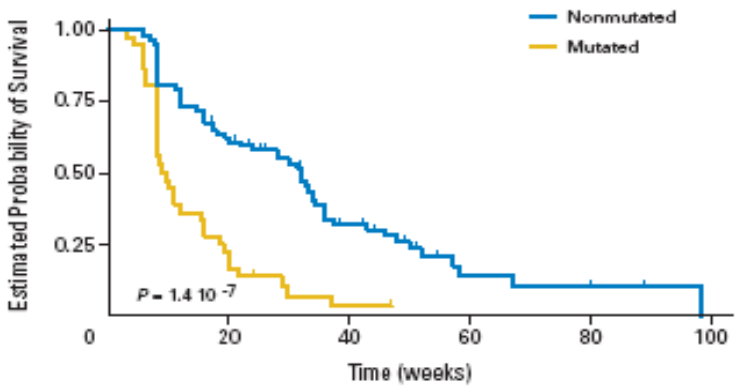
Cetuximab

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

KRAS Mutations As an Independent Prognostic Factor in Patients With Advanced Colorectal Cancer Treated With Cetuximab

Astrid Lièvre, Jean-Baptiste Bachet, Valérie Boige, Anne Cayre, Delphine Le Corre, Emmanuel Buc, Marc Ychou, Olivier Bouché, Bruno Landi, Christophe Louvet, Thierry André, Fréderic Bibeau, Marie-Danièle Diebold, Philippe Rougier, Michel Ducreux, Gonana Tomasic, Jean-François Emile, Frédérique Penault-Llorca, and Pierre Laurent-Puig

A **Progression Free Survival**

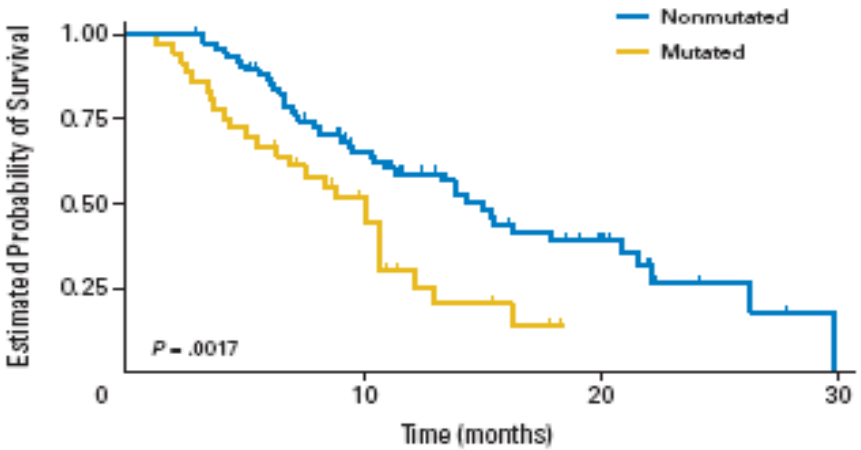


No. at risk	Weeks 0	20	40	60	80
KRAS nonmutated	77	46	19	5	3
KRAS mutated	36	8	2	0	0

Lievre, A. et al. J Clin Oncol 2008;26:374-379

Overall Survival

B



No. at risk	Months 0	6	12	18	24
KRAS nonmutated	77	65	32	17	4
KRAS mutated	36	25	7	1	0

EGFR – a target for intervention

The issue of kRAS…

Table 1 *KRAS* status and response to EGFR antibodies in colorectal cancer

Publication	Treatment (panitumumab or cetuximab)	Number of subjects (wild type; mutant)	Objective response, *n* (%)	
			Mutant	Wild type
Lancet Oncol. **6**, 279–286 (2005)	Panitumumab or cetuximab or cetuximab + chemotherapy	31 (21; 10)	2 (20)	8 (38)
Cancer Res. **67**, 2643–2648 (2007)	Panitumumab or cetuximab or cetuximab + chemotherapy	48 (32; 16)	1 (6)	10 (31)
J. Clin. Oncol. **25**, 4132 (2007)	Cetuximab ± chemotherapy	37 (20; 17)	0 (0)	17 (46)
J. Clin. Oncol. **2**, 4021 (2007)	Cetuximab ± chemotherapy	81 (49; 32)	2 (6.3)	13 (26.5)
J. Clin. Oncol. **25**, 3230–3237 (2007)	Cetuximab	80 (50; 30)	0 (0)	5 (10)
AACR Meeting Abstracts **2007**, 5671 (2007)	Cetuximab ± chemotherapy	78 (49; 27)	0 (0)	24 (49)

Nature Biotech 2009; 27:110-12

Erbitux (cetuximab): Regulatory Approval History

February 2001	Erbitux (cetuximab) received fast track status from FDA for treatment of refractory colorectal cancer
July 2001	ImClone initiated filing of a rolling BLA w/FDA for Erbitux in combination w/irinotecan to treat irinotecan-refractory colorectal cancer
December 2001	FDA advised ImClone that its BLA for Erbitux (cetuximab) was not acceptable for filing
February 2002	ImClone met w/FDA to discuss resubmission of the BLA w/additional European clinical data
August 2003	ImClone resubmitted a BLA for (cetuximab) in combination w/irinotecan for EGFR-expressing colorectal cancer
October 2003	FDA granted the Erbitux (cetuximab) BLA priority review
February 12, 2004	FDA approved Erbitux for use in combo w/irinotecan to treat EGFR-expressing, colorectal cancer patients refractory to irinotecan-based chemotherapy, & as a single agent in the treatment of patients w/EGFR-expressing mCRC who are intolerant to irinotecan-based chemotherapy
July 17, 2009	Changes were made to the product labels of Erbitux and Vectibix. Retrospective subset analyses of trials in patients with colorectal cancers having KRAS mutations noted a lack of benefit associated with these monoclonal antibodies. The percentage of study populations for which KRAS status was assessed ranged from 23% to 92%.
March 2004	CHMP recommended approval of cetuximab in combination w/irinotecan
June 2004	EMEA granted approval of cetuximab in the EU. Indication at this time did not include KRAS.
July 2008	EMEA granted conditional approval for use in patients whose mCRC tumors are EGFr expressing and wild-type KRAS (indication change was driven by data analyses requests by CHMP subsequent to Vectibix indication change in December 2007).

Background for Oncologic Drugs Advisory Committee meeting of 16.12.2008

- Emerging data from exploratory biomarker analysis of single-arm studies, including Vectibix (panitumumab) phase 2 studies, lead to the hypothesis that KRAS mutations correlate with lack of response to anti-EGFR mAB's in mCRC (the KRAS hypothesis)
- At the time these initial KRAS data became available, the pivotal phase 3 study of panitumumab monotherapy in refractory mCRC had been completed and led to the accelerated approval of panitumumab in the US in 2006
- During this study, Amgen collected tumor samples with the intent of performing subsequent biomarker analysis
- Both Erbitux (cetuximab) and Vectibix, currently indicated for treatment of colorectal cancer, have submitted retrospective genomic analyses of previous ongoing clinical trials to demonstrate the predictive capacity of the KRAS mutation genomic biomarker as an exclusionary component of clinical trials
- AdComm convened to seek guidance on whether retrospective studies could be used to support predictive biomarkers

FDA Basis for ODAC meeting of 16.12.2008

- Guidance on how to incorporate new scientific information from a retrospective biomarker analysis without compromising the legal mandate to ensure that marketed drugs show substantial evidence of efficacy and are reasonably safe
  - Optimal: prospective, adequate, well-controlled trials based on a validated assay
  - Pragmatic: retrospective analysis considered on specific conditions

Questions Posed to ODAC

- When would it be appropriate to limit use of a drug to a subgroup based on retrospective analysis of one or more studies that were not designed to examine this subgroup?
- When would a prospective study, designed for the purpose of examining treatment effects on a pre-specified subgroup, be needed to establish treatment effects in this group?
- Discuss the properties of clinical studies, originally designed for non-selected populations, that would make such studies unsuitable for demonstrating efficacy in a biomarker subgroup.
- When is it acceptable to limit future enrollment to a biomarker selected subset of an actively accruing clinical trial based on external information (e.g., results from another study)? What would be the primary analysis population? Would the answer depend on the proportion of unselected patients, i.e., those enrolled prior to the study modification?

Starting point to assess retrospective analysis of a clinical trial (FDA): practical considerations

- The trial must be adequate, well-conducted and well-controlled;
- The sample size must be sufficiently large to be likely to ensure random allocation to each of the study arms for factors (such as KRAS status) that were not used as stratification variables for randomization;
- Tumor tissue must be obtained in in a high proportion (95%?) of the registered and randomized study subjects and an evaluable result (presence of wild-type or mutant KRAS) must be available for 90% of the registered and randomized study subjects.
- Before analysis, the FDA must have reviewed the assay methodology and determined that it has acceptable analytical performance characteristics (for example, sensitivity, specificity, accuracy, precision) under the proposed conditions for clinical use; (type of k-ras assay used)
- Genetic analysis must be performed according to the qualified assay method by individuals who are masked to treatment assignment and clinical outcome results;
- Before analysis of clinical outcomes based on the genetic testing, agreement with the FDA must be reached on the analytical plan for hypothesis testing for proposed labeling and promotional claims.

Source: Adapted from FDA's Oncologic Drugs Advisory Committee meeting briefing document, 16 December 2008 (Nature Biotech 2009; 27:110-12

Chutes and Ladders on the Critical Path: Comparative Effectiveness, Product Value, and the Use of Biomarkers in Drug Development

- The imperative to produce high-value, innovative drugs will intensify, creating a higher performance hurdle for new therapeutics. Basic biomedical science will churn out candidate biomarkers with tantalizing potential to improve value, whereas methods to use them effectively in drug development will evolve more slowly. The balance between these forces may well determine the success or failure of the drug development enterprise over the next decade.

J. Woodcock, Clin. Pharm. and Ther. (2009); 86, 1, 12–14.

Current FDA Position on Multiplex Assays (MPx)

There is a shift towards higher regulatory burden

- The FDA is currently clarifying the pathways for pharmacogenomics (MPx) products from concept to market with regard to data collection and submission, including drug/diagnostic co-developments
- Currently, a MPx test sold as an in vitro diagnostic (IVD) *product* is regulated as a medical device, being under the scrutinity of the FDA. A MPx test provided as a laboratory *service* is considered a laboratory-developed test (LDT), based on analyte specific reagents (ASRs), and is under CLIA oversight
- However, recent FDA guidance documents on ASRs and IVDMIAs revisit FDA's regulation of diagnostic testing conducted by clinical laboratories, including LDTs
- LDTs – even for high complexity tests such as Genomic Health's Oncotype Dx test for breast cancer recurrence are not currently subject to FDA regulation. Roche believes that LDTs should be regulated in the same way that IVDs are.

Abbreviations: CLIA - Clinical Laboratory Improvement Amendments (1998)

Issues and challenges

- It is highly likely that relevant biomarker data for many new medicines will be produced after initial licensing of a drug
  - Modification of the drug label
  - Qualification/approval of novel biomarkers/IVDs
- Lack of clarity regarding the process for biomarker qualification, particularly with respect to biomarkers used for patient stratification, in both US and Europe
  - However, FDA and EMEA working closely together to address this
- FDA and EMEA have, apparently, differing views on the value of retrospective data and the need for prospective randomized trials for the qualification of novel stratification biomarkers
- IVDs in US are regulated by the FDA (OIVD of CDRH). In Europe, the EMEA has no oversight over IVDs and there is the potential for differences in the way that notified bodies regulate IVDs used for patient stratification in Europe.

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