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Implementation of stratification throughout drug development – examples from oncology

Michael Zühlsdorf / AGAH Annual Meeting, Leipzig
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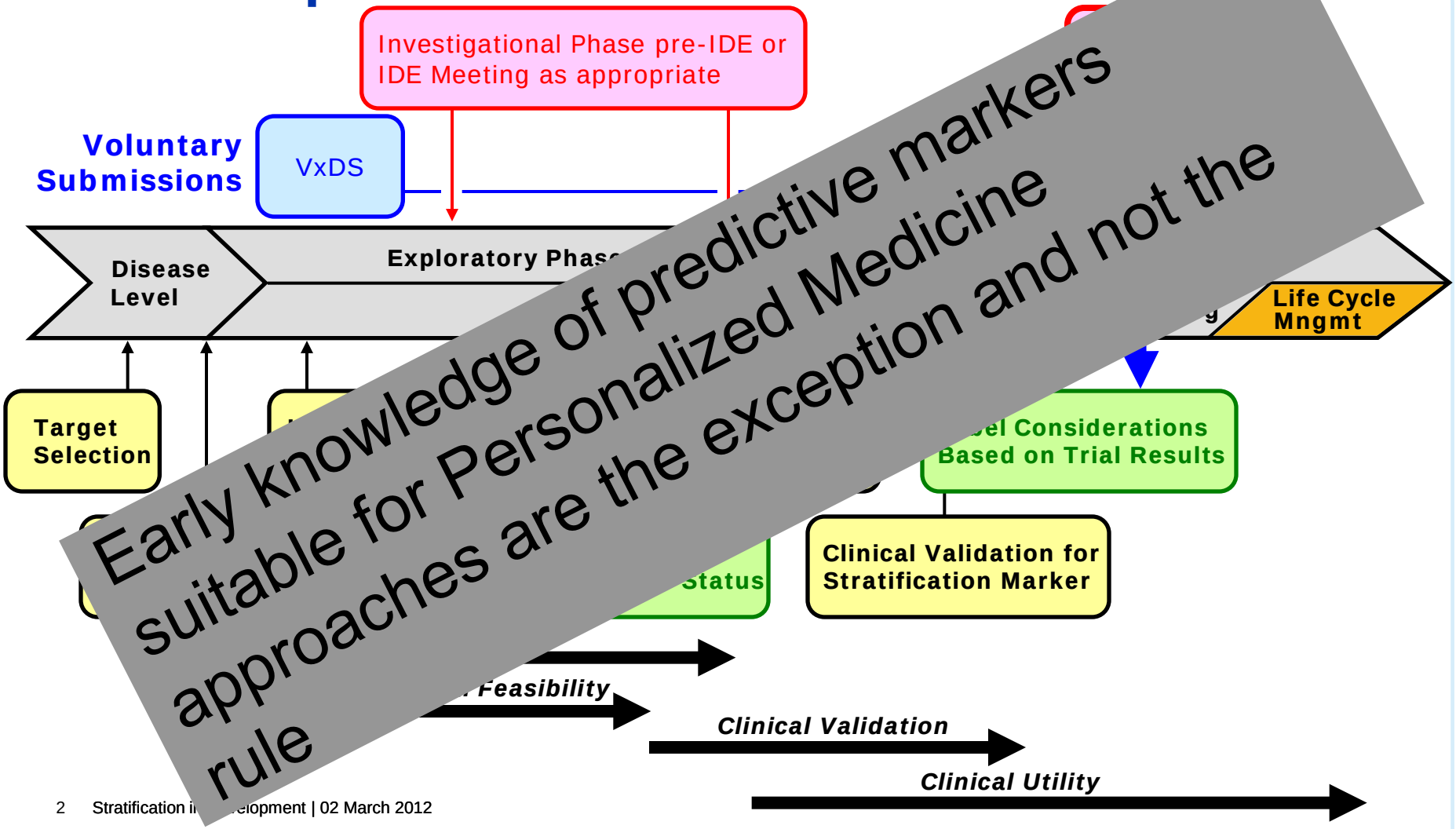
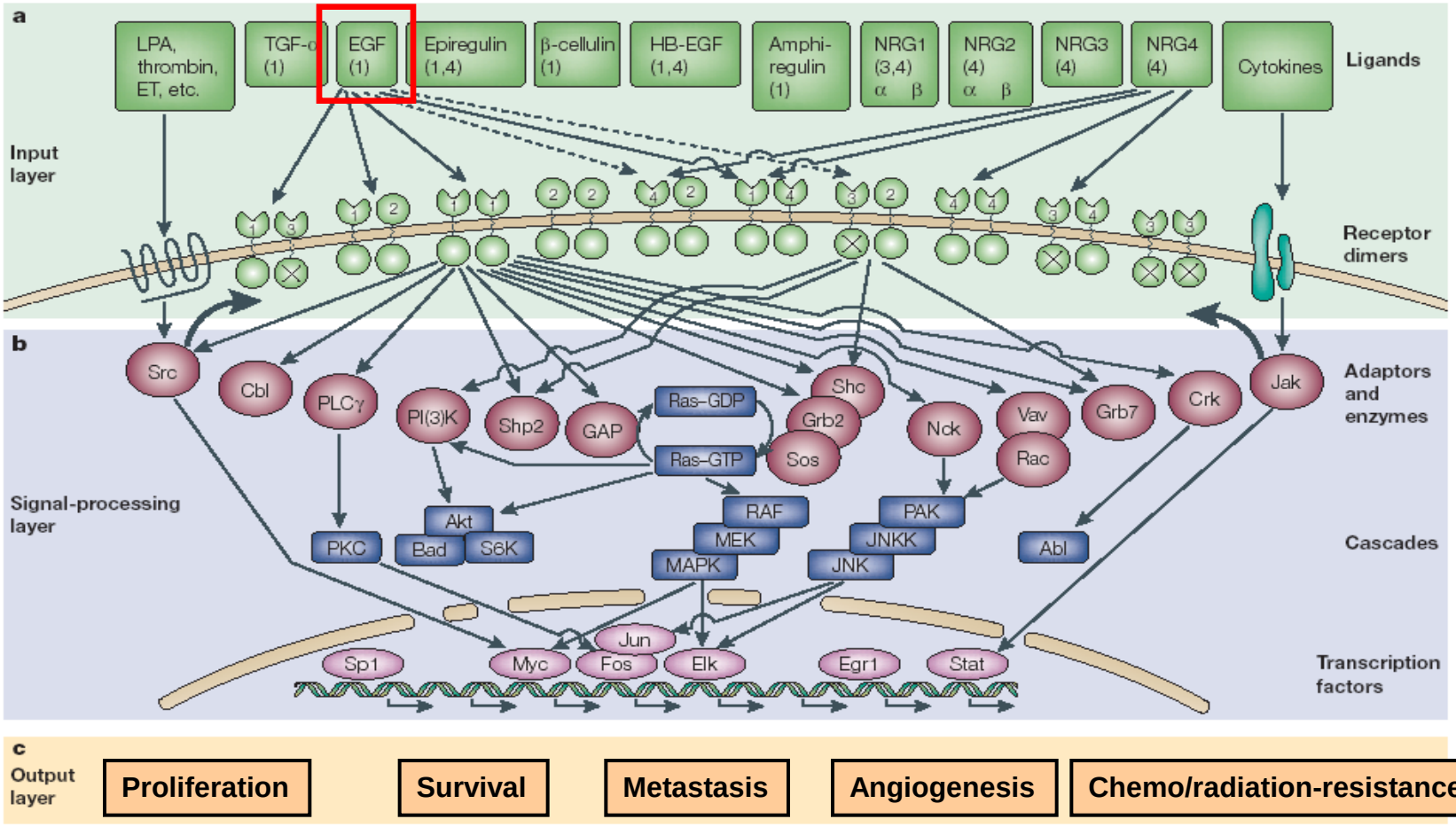
Application of the PM Strategy throughout the R&D process



Early knowledge of predictive markers suitable for Personalized Medicine approaches are the exception and not the rule

Biomarkers for anti-EGFR therapy - low hanging fruits or challenge?



Scenario 1: Erlotinib and Gefitinib in NSCLC Predictive Marker available after approval

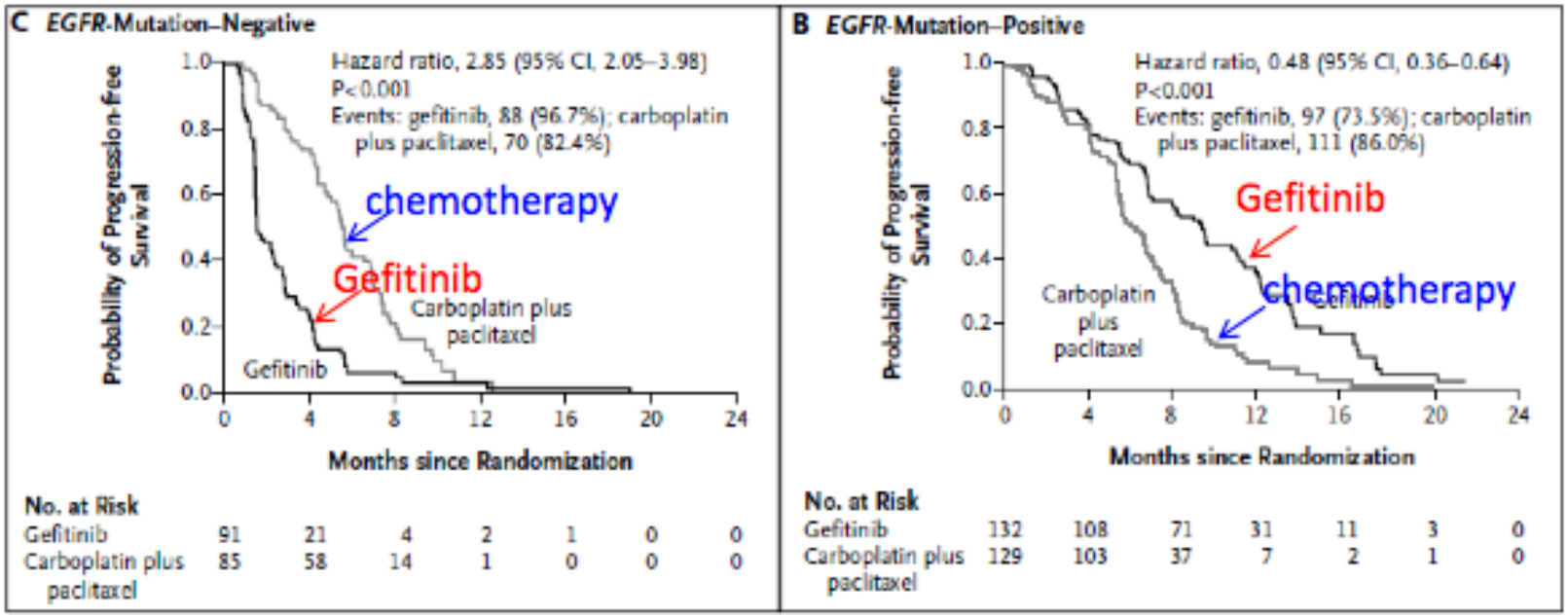
- 1st "EGFR-inhibitors (TKIs)
- Response rate: 10% in North America patents with Nonsmall cell lung cancer (NSCLC)
- Predictive markers unknown
- May 2003, FDA granted accelerated approval of Iressa (based on ~10% RR) as 3rd line therapy
- Full approval requires positive results from the Phase III trial (based on survival endpoint)

Phase III trials of Erlotinib and Gefitinib in advanced lung cancers (n=6716)

Trial	N	Treatment	Outcome (OS)
ISEL	1692	Gefitinib vs Placebo	Negative
INTACT1	1093	Gefitinib + CTx vs. CTx	Negative
INTACT2	1037	Gefitinib + CTx vs. CTx	Negative
TALENT	1127	Erlotinib + CTx vs. CTx	Negative
TRIBUTE	1079	Erlotinib + CTx vs. CTx	Negative
BR21	638	Erlotinib vs Placebo	**Positive** (6.7 vs 4.7 m)

- Iressa did not meet the criteria for full approval by FDA
- Tarceva approved in Nov 2004, based on modest OS improvement

EGFR mutation predicts the Gefitinib response in NSCLC



- Without patient selection - no difference between chemotherapy vs. Gefitinib
- In patients without EGFR mutation: Gefitinib was worse than chemotherapy
- In patients with EGFR mutation: significant benefit with Gefitinib (PFS @ 12 months: 24.9% vs. 6.7%, RR with EGFR Mutation: 53-94% vs 1%); Incidence 10% in Caucasians but 30–50% in East Asians)

US labels of Erlotinib and Gefitinib

Tarceva (Erlotinib)

In Germany: 1st line NSCLC patients with activating EGFR mutations

- PFS & OS HR: EGFR pos 0.69 and 0.77 vs, 0.77 and 0.91 in EGFR IHC-negative tumors

Iressa (gefitinib)

September 30, 2011 – Withdrawal of Accelerated Approval New Drug Application (NDA) for IRESSA

- In light of positive survival data with other agents including another oral EGFR

In Germany: locally advanced or metastatic NSCLC with activating EGFR mutations

Scenario 2: Erbitux® (Cetuximab) in mCRC Predictive BM becomes available at Phase 3

First approval in 2004 (combination with Irinotecan) in EGFR expressing Colorectal tumors

- Early clinical development assumed EGFR expression would be predictive of benefit
- Precedent for other targeted mAbs (e.g. trastuzumab, rituxumab)

Ongoing academic and industry studies could not demonstrate relevant differences between EGFR expressors or no expressors

Label claim in US: EGFR expressing CRC tumors

First data supporting KRAS mutation status predicting clinical response April 2008

History of Companion Drug-Diagnostic Considerations for Cetuximab (2002 - 2007)

Early clinical development assumed EGFR expression would be predictive of benefit

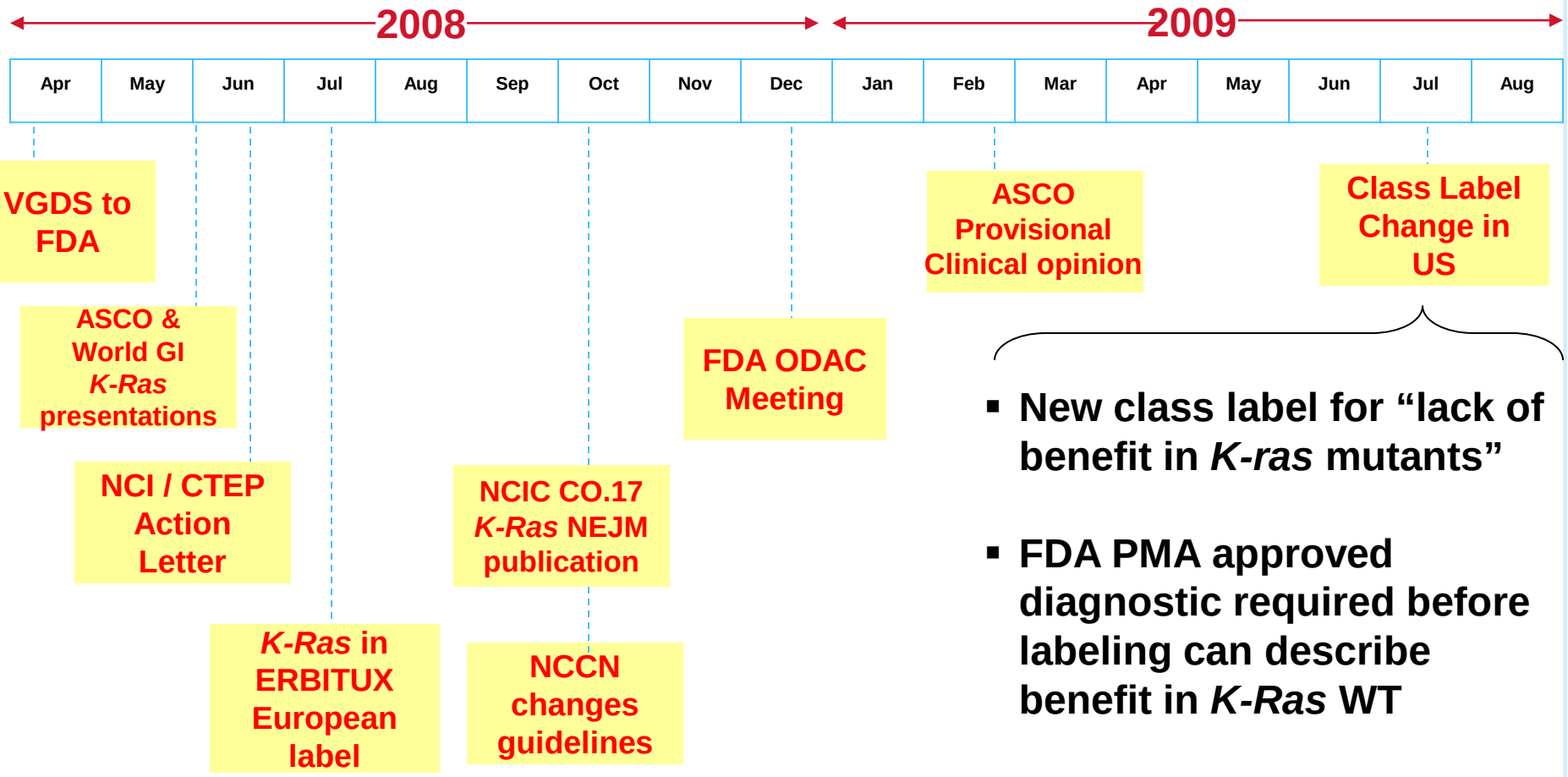
- Specificity of cetuximab for its target
- Precedent for other targeted mAbs (e.g. trastuzumab, rituxumab)

Continuous and dedicated effort by academic and industry scientists to validate EGFR expression as a predictive marker and to further improve patient selection criteria for improved therapeutic index

- Preclinical models and biomarker discovery
- Exploratory prospective pharmacogenomic trial

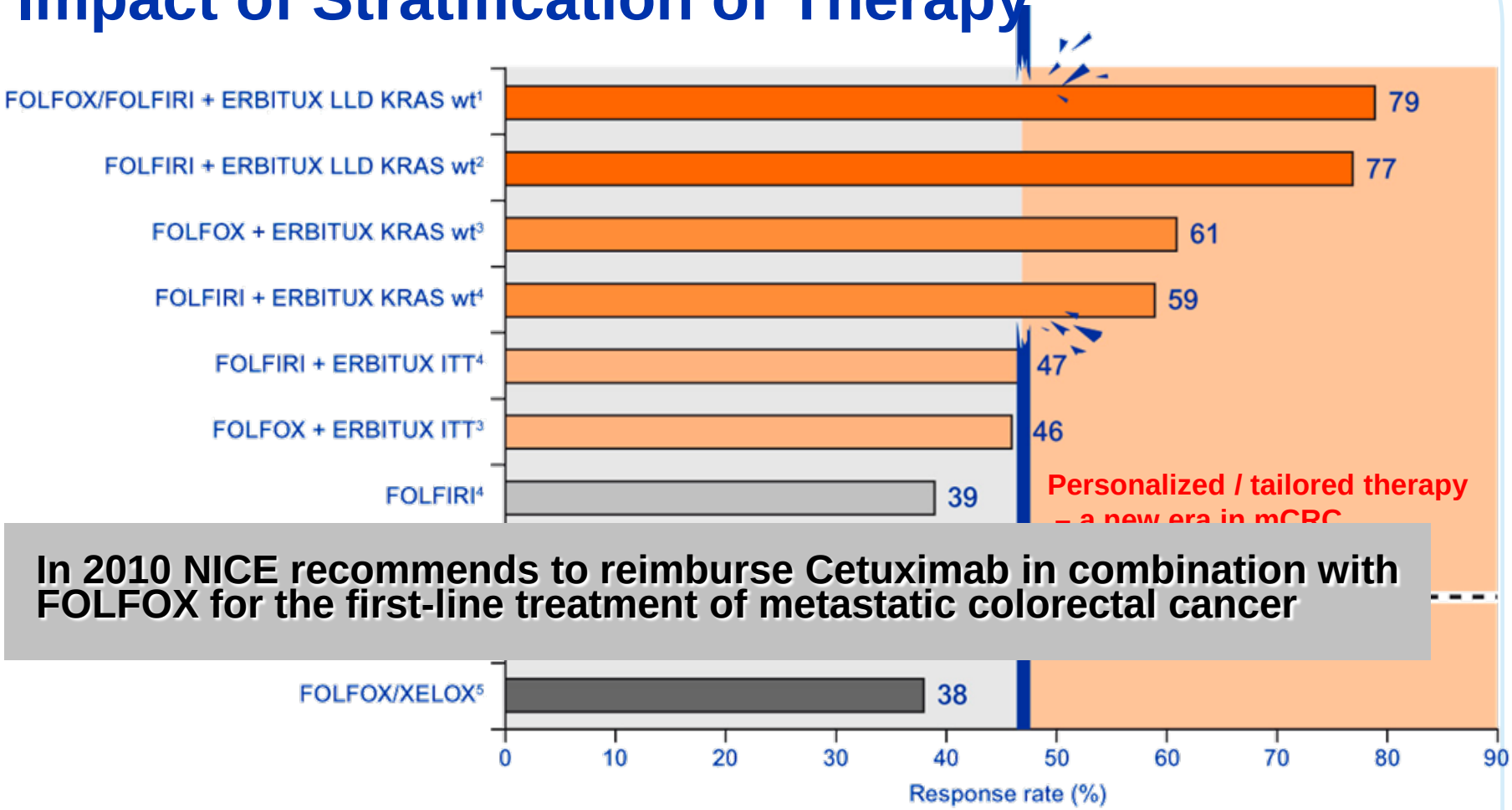
Insufficient scientific foundation for prospectively incorporating other predictive markers (e.g. KRAS) at the time that 4 large randomized clinical trials were initiated in 1st, 2nd, & 3rd line treatment for CRC

Key *K-Ras* Events: April 2008 – July 2009



- New class label for "lack of benefit in *K-ras* mutants"
- FDA PMA approved diagnostic required before labeling can describe benefit in *K-Ras* WT

Improving Tumor Responses in mCRC: Impact of Stratification of Therapy



In 2010 NICE recommends to reimburse Cetuximab in combination with FOLFOX for the first-line treatment of metastatic colorectal cancer

ITT, intent-to-treat population; wt, wild-type; LLD, liver-limited disease

1. Folprecht *et al*. ESMO 2008; 2. Van Cutsem *et al*. ESMO 2008; 3. Bokemeyer *et al*. ASCO 2008; 4. Van Cutsem *et al*. ASCO 2008; 5. Saltz *et al*. WCGIC 2007

KRAS Testing and Regulation

EU

Vectibix and Erbitux are indicated for KRAS WT CRC

- Approval supported by retrospective data
- EMEA required a CE marked test
  - Not considered a high risk device by EU directive

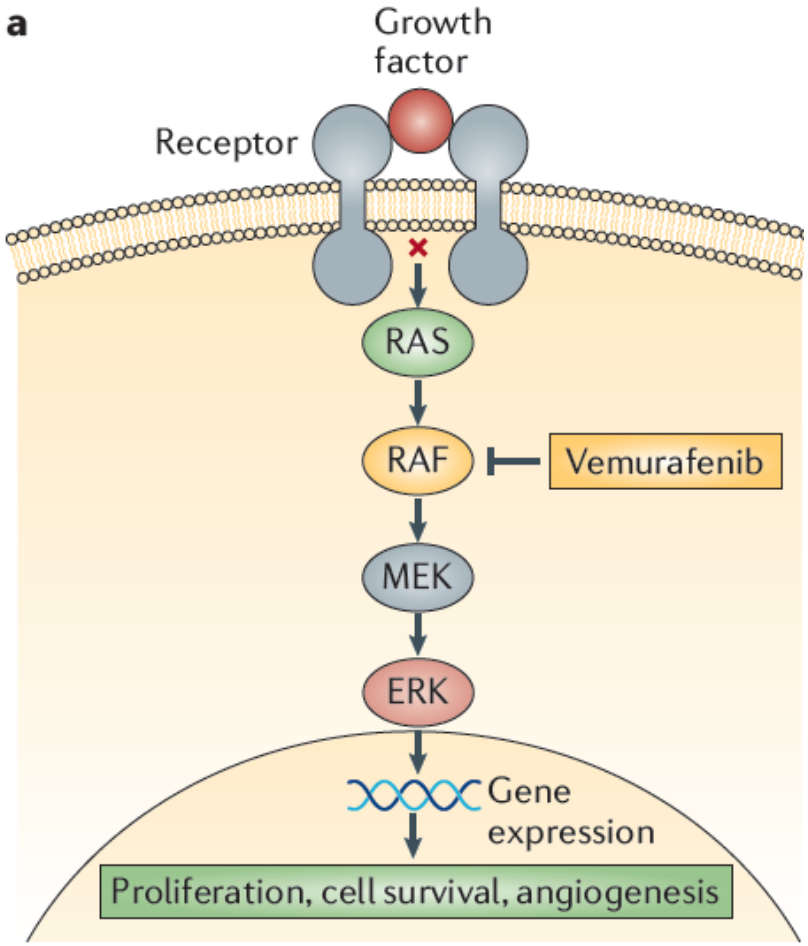
USA

Vectibix and Erbitux label update in 2009 based on safety information – no treatment benefit for patients with KRAS mutations. Treatment not recommended for patients with KRAS mutations

Since treatment decisions will be based on test results, a PMA approved kit is required before a efficacy claim on benefit for KRAS WT

- Considered Class III high risk device
- FDA approved KRAS test

Scenario 3: Vemurafenib for advanced melanoma Predictive Marker available before Phase 1



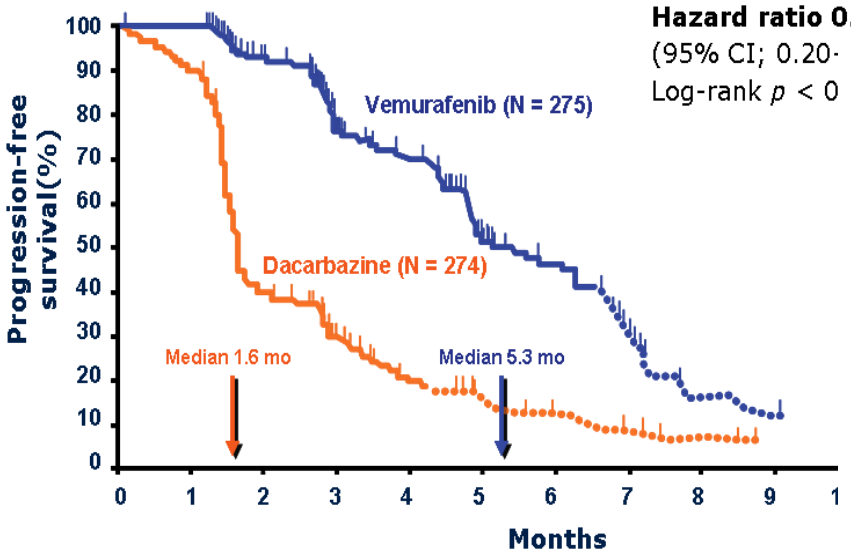
- Nature publication on BRAF mutation in 2002
- BRAF gene mutations in about 40%–60% of patients with melanoma
- Vemurafenib targets a common mutation in melanoma in the *BRAF* gene (BRAFV600E)
  - Vemurafenib inhibits also other kinases such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5 and FGR

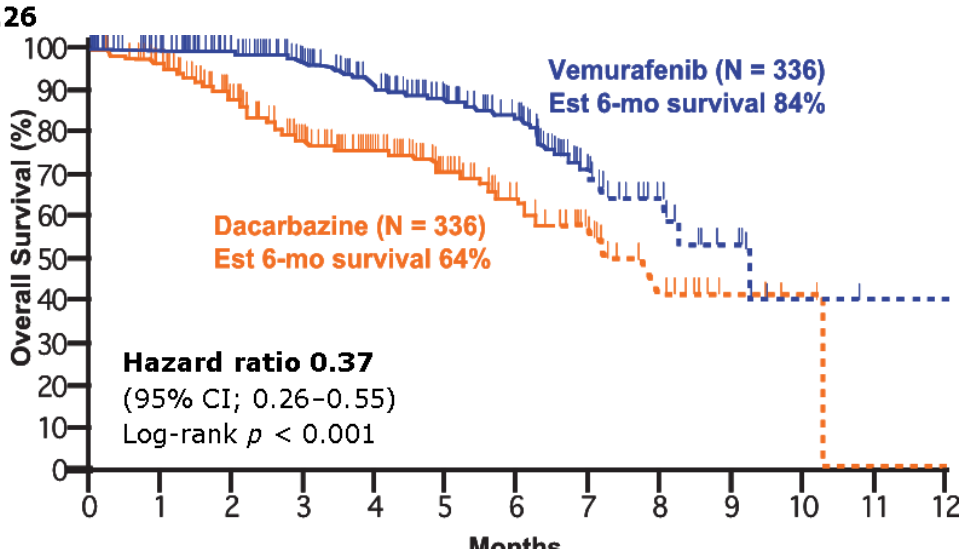
Scenario 3
Stratification Biomarker available before Phase 1

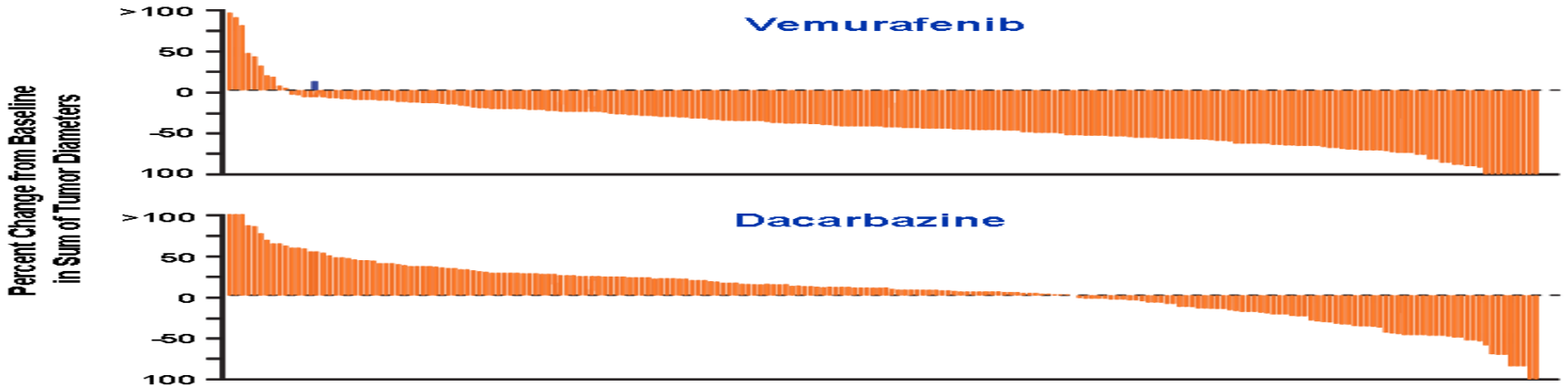
2002	Nature publication on BRAF mutation
2005	BRAF discovery program (Plexicon) & companion Dx (Roche) development started
2006	Phase 1 trial initiation
2009	ASCO Phase 1 data with 80% response rate
	Phase 2 trial initiation (BRIM2)
	Phase 3 trial initiation (BRIM3)
2010	SMR Phase 2 data with 52% response rate
2011	Phase 3 trial co-primary endpoints met--OS and PFS
	Announced marketing applications submitted to FDA and EMA, with companion diagnostic

August 2011 Fast track approval of Vemurafenib by FDA in BRAF V600E mutation-positive melanoma

Vemurafenib for advanced melanoma Interim Analysis (December 30, 2010 Cutoff)







Predictive Biomarkers: Lessons Learned

- Subgroup analyses –prospective or retrospective - have become routine
  - Often exploratory but may influence labeling/approval
  - Even when not required/recommended/mentioned in drug label may rapidly influenced medical practice
- Erlotinib/Gefitinib
  - Long development history, still unclear target subpopulation
- Cetuximab
  - Retrospective analysis is risky and timely, may lead to different labels in different regions
- Vemurafenib
  - Within only 2 years from EoPhI meeting to accelerated approval (excellent efficacy in target suppopulation, HR 0.26; OS)
  - Only in interim analysis, only tested in BRAF V600E patients, caucasians only, 38% required dose reduction, only 64% were evaluated for tumor response

Overall conclusions

Currently 500 personalized-medicine based therapeutic programs ongoing, focusing on 140 drug targets in various stages of development (Foundation Medicine)

Key hurdles of stratified development

- Understanding of diseases (KRAS cetuximab in CRC not in NSCLC)
- Identification and validation of appropriate predictive marker(s)
- Timing and collaboration with Dx partners (from BM identification to approval)
- Healtheconomics (price vs value and patient ratios)

- **Start early with screening and fit for purpose validation of Biomarkers**
- **Integrate potential (predictive) BM as early as possible in development**
- **Start early with development of a companion diagnostic, it may take as long as drug development**