

Biomarker Applications in Oncology Drug Development

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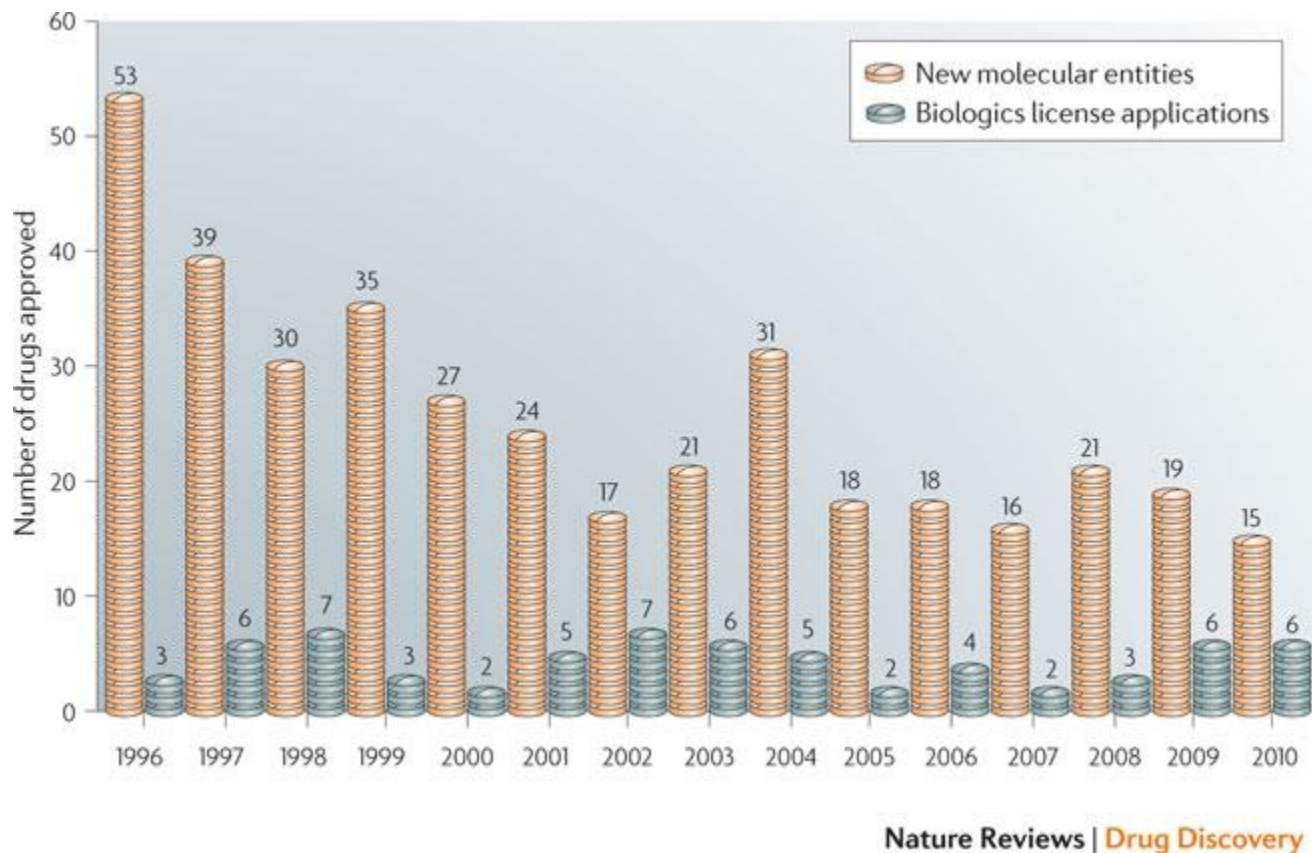
Ortho Biotech R&D
Johnson & Johnson

Biomarker Development: Lost in Translation?
CQDM/Montreal in vivo Symposium
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Empirical Drug Development Strategies are Unsustainable

- Overall attrition rates are too high during development:
 - Poor *in vivo* and *in vitro* disease models lead to failure early in development
 - Too many compound fail for lack of efficacy late in development
- Disease heterogeneity means too few patients respond to any one therapeutic approach:
 - Need better markers to monitor status of the drug target and cognate pathway
- Development costs for novel drugs with low response rates are too high:
 - Large Phase III trials required to demonstrate clinical benefit
 - High risk of registrational failure
 - Length of time required to show overall survival benefit

New Drug Approvals in US: 1996-2010



Mullard, A. (2011) 2010 FDA drug approvals, Nature Reviews Drug Discovery 10:82-85

Biomarkers in Drug Development

| Marker | Function | Test |
|------------|---|--|
| PD/MOA | <ul style="list-style-type: none">• Determine whether a drug hits the target and has impact on the biological pathway• Evaluate mechanism of action (MOA)• PK/PD correlations and determine dose and schedule• Determine biologically effective dose | <ul style="list-style-type: none">• Research test used during drug development• Not developed as companion diagnostic |
| Predictive | <ul style="list-style-type: none">• Identify patients most likely to respond, or are least likely to suffer an adverse event when treated with a drug. | <ul style="list-style-type: none">• Companion diagnostic test (e.g. herceptin, EGFR) |
| Resistance | <ul style="list-style-type: none">• Identify mechanisms driving acquired drug resistance | <ul style="list-style-type: none">• Mutation analyses (e.g. Bcr-Abl mutation in imatinib treated CML) |
| Prognostic | <ul style="list-style-type: none">• Predicts course of disease independent of any specific treatment modality | <ul style="list-style-type: none">• Approved tests (e.g. CellSearch, MammaPrint) |
| Surrogate | <ul style="list-style-type: none">• Approved registrational endpoints | <ul style="list-style-type: none">• Commercial diagnostic tests (e.g. LDL, HbA1c, viral load, blood pressure) |

The Biomarker Hypothesis

- Biomarkers will:
 - Reduce development time for active compounds
 - Accelerate failure of unsafe or inactive compounds
 - Reduce average development costs for approved compounds
 - Lead to better outcomes for cancer patients
- The costs for biomarker research will be more than compensated by increased efficiency of the drug development process:
 - Early at-risk investment in biomarkers leads to more approved compounds with better patient outcomes and stronger cases for reimbursement

The Biomarker Paradox

There are 11,166 biomarkers listed in GOBIOM database
(01/31/2011)

- **BUT** -

only 32 valid genomic biomarkers in FDA approved drug
labels

- **AND** -

0 are multiplex IVD's based on proteomic or genomic profiles

Approved Companion Diagnostics: 2011

| Markers | Direct Markers | Secondary Markers | Molecular Profiles* |
|-----------------|--|--------------------|-----------------------|
| Readout | Drug target status | Downstream pathway | Consolidated profiles |
| Examples | HER2+ ER+ CD20+ Ph+ chromosome KIT+ EGFR+ | KRAS wt | |

*: mRNA, protein or metabolite profiles, epigenetics, genotypes/genome scans *etc.*

- All approved companion diagnostics directly query the status of the drug target:
 - Diagnostic markers identified before FIH and validated in Phase II/III
- Downstream pathway markers (e.g. KRAS) will become increasingly important:
 - KRAS being validated in Phase III (panitumumab) and after launch (cetuximab, erlotinib)
- There are no approved molecular profiles (IVDMIA) for predictive markers

No IVD/MIA Tests Approved as Companion Diagnostics

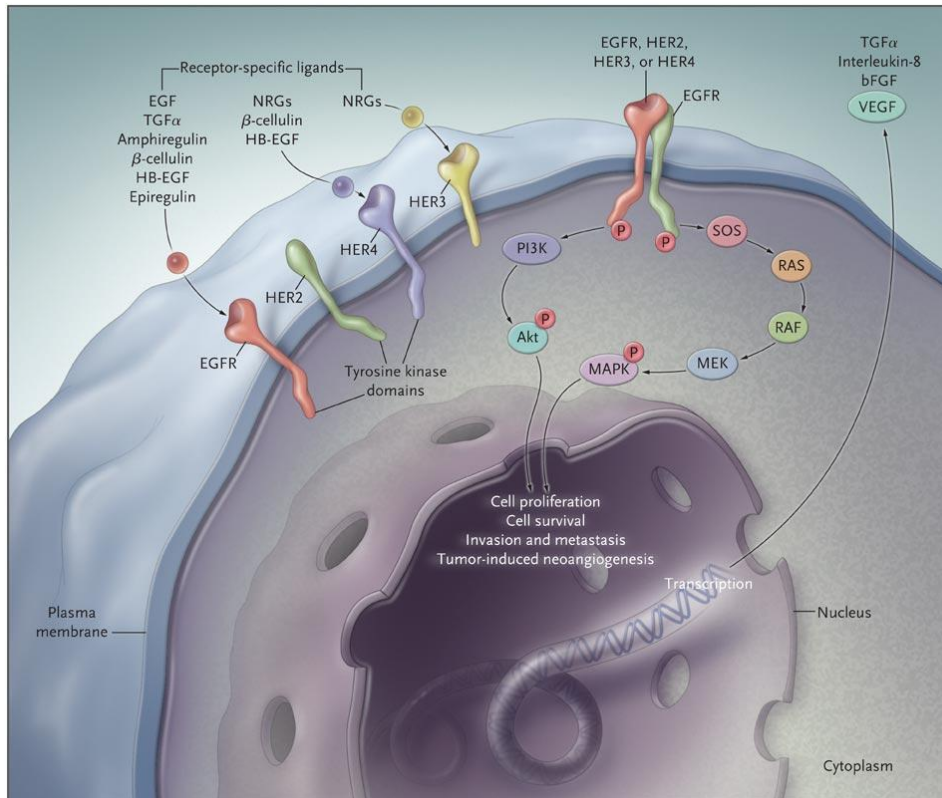
| Test | Company | Companion Diagnostic | Prognostic Test |
|-------------------------|----------------------|----------------------|-----------------|
| Mammaprint | Agendia | No | Yes |
| Tumor of Unknown Origin | Pathwork Diagnostics | No | Yes |
| Allomap | XDx | No | Yes |

Protein Kinase Inhibitors: A Model for Biomarker Development in Oncology

- 216* protein kinase drugs in Phase II or III for cancer indications (23%):
 - Most common cancer drugs in oncology development (23%*)
 - 2nd most common drug class after G-protein coupled receptors (GPCR) in all indications
- 12 drugs approved by FDA for cancer indications that target receptor tyrosine kinases (RTK):
 - 7 have predictive markers in the drug label
 - No other cancer drug classes have predictive markers in their labels when launched
- Biomarkers are required for RTK drug development to:
 - Predict dependency on specific signaling pathways
 - Screen for acquired drug resistance
 - Monitor pathological changes during disease progression

*The Beacon Group, 2010

Targeted Therapy with Tyrosine Kinase Inhibitors



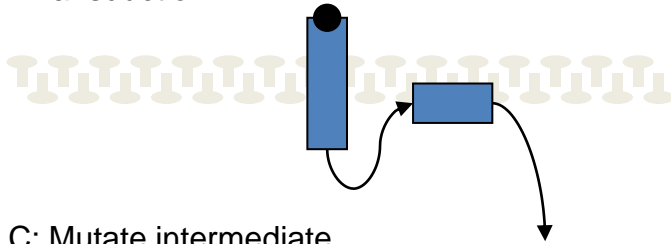
Ciardiello & Tortora, New Engl. J. Med. 358:1160, 2008

Multiple druggable approaches to inhibiting protein kinase signaling:

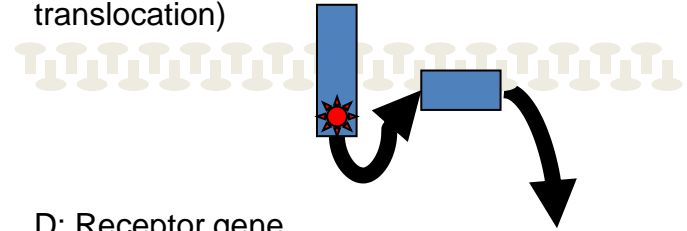
- Reduce ligand – bevacizumab (Avastin) binds VEGF and reduces ligand-dependant receptor activation
- Block receptor – cetuximab (Erbix) blocks EGFR and prevents ligand-induced receptor activation
- Inhibit intracellular kinase – erlotinib (Tarceva) inhibits the intracellular phosphorylation of EGFR kinase

Signal Transduction Pathways are Initiated by Multiple Pathological Events

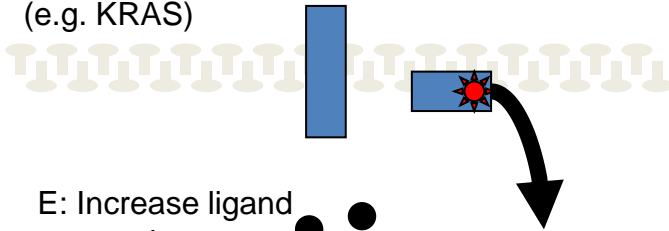
A: Normal signal Transduction



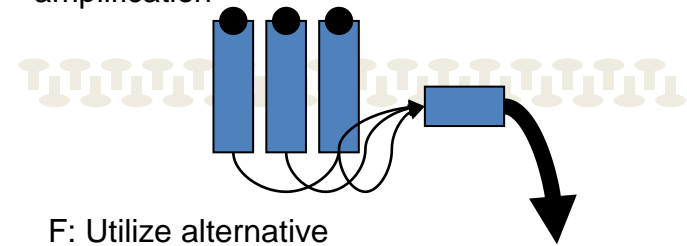
B: Activate intracellular Kinase (mutation or translocation)



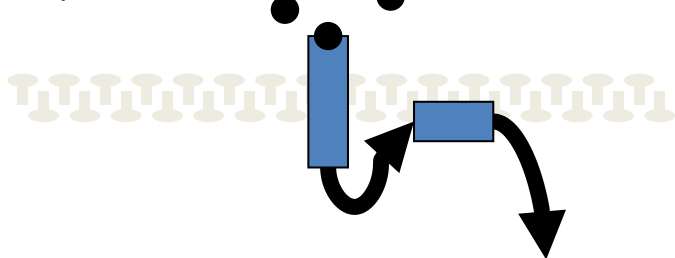
C: Mutate intermediate pathway member (e.g. KRAS)



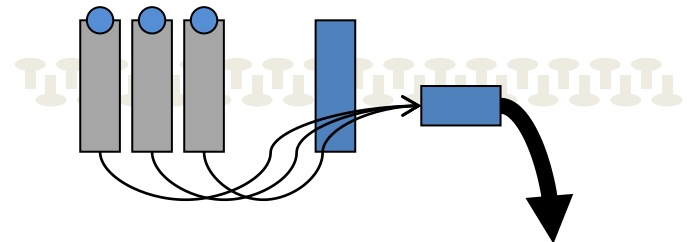
D: Receptor gene amplification



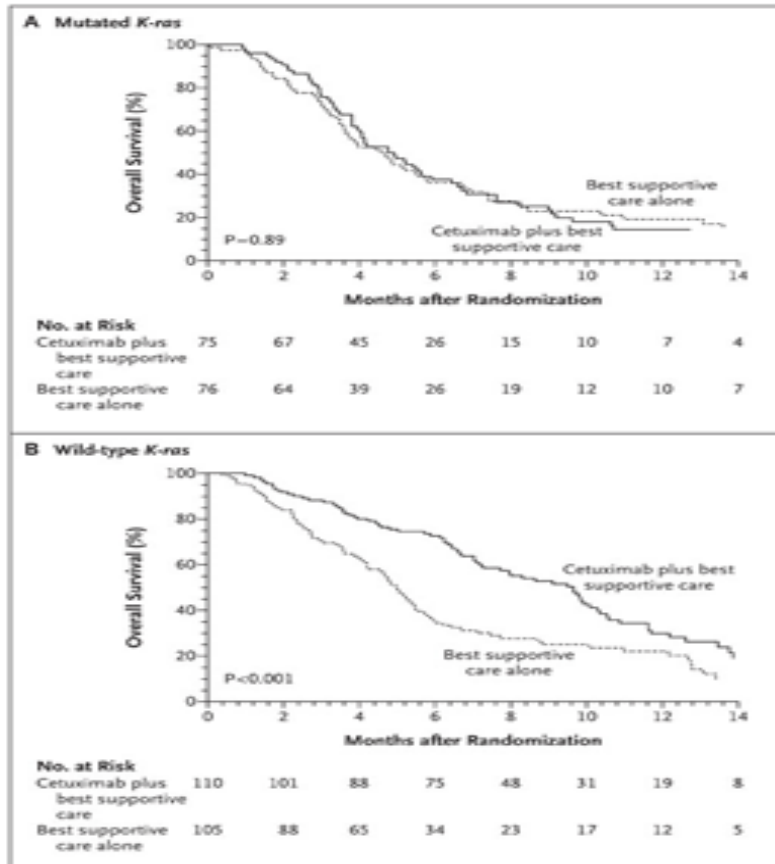
E: Increase ligand expression



F: Utilize alternative Receptor (e.g. MET)

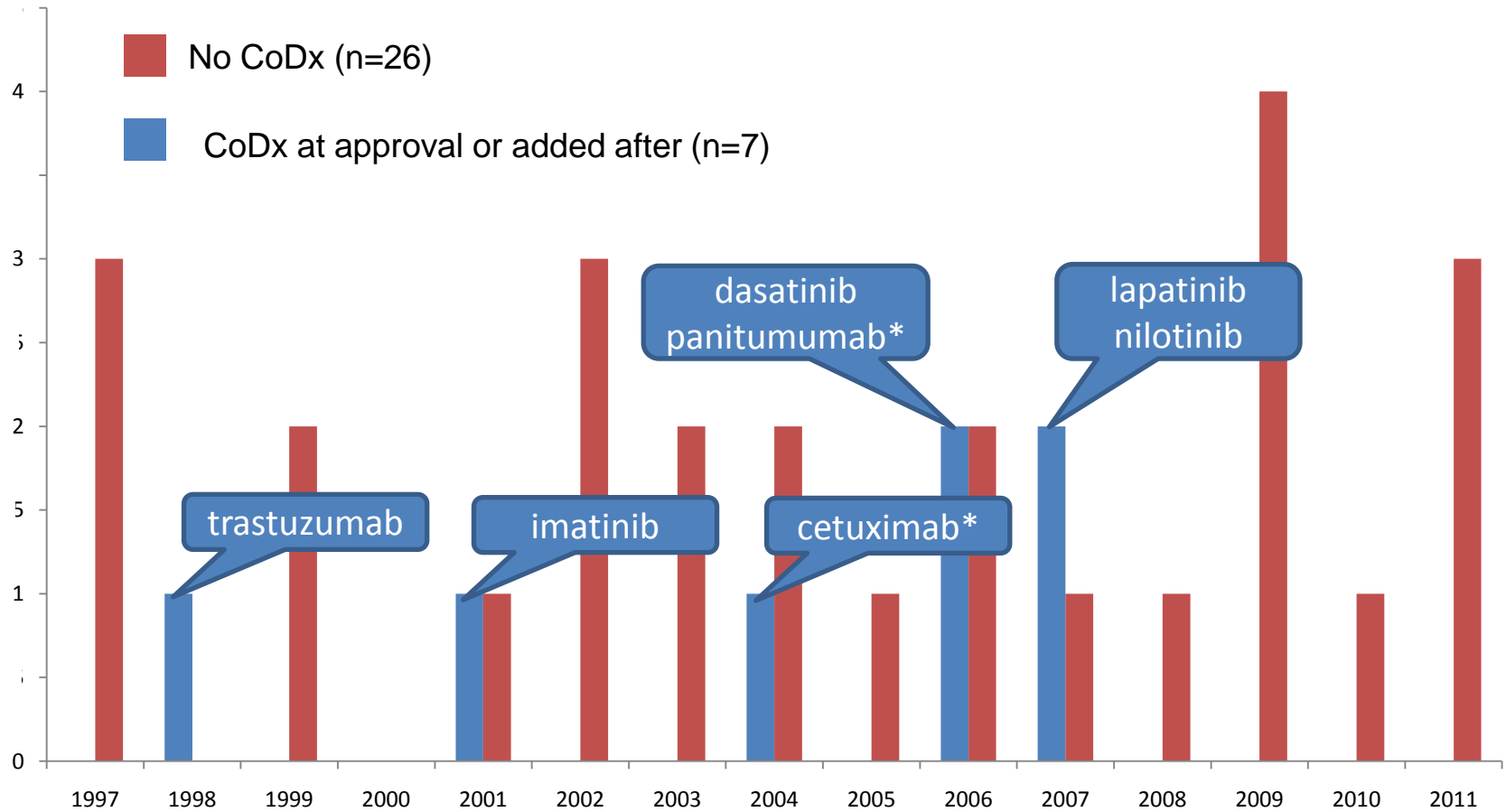


Companion diagnostics: KRAS in colorectal cancer



- Predictive values of KRAS mutations in colorectal cancer:
 - 35% PPV, 97% NPV (Raponi *et al.*, 2008)
- Would KRAS mutation screening data have impacted clinical utilization of anti-EGFR agents without:
 - Consistent data from several clinical trials with four drugs with different MOAs?
 - Evidence that PFS and OS is higher in KRAS wt patients?
 - Evidence that KRAS is predictive of response to therapy and not just a prognostic marker?
 - A plausible biological hypothesis for the role of KRAS mutations in determining response to therapy?
- How much of these type of data can be expected to be collected and prospectively validated before launch of a new compound?

Oncology Targeted Therapeutic Drug Approvals: 1997-2011



Biomarkers for Oncology Targeted Therapies

PD/MOA Biomarkers

CD3, CD4, CD5, CD8, CD19, CD20, CD41, IgA, IgM, IgG, Estradiol, Estrone, Estrone sulfate, soluble HER2, PET tratsuzumab, Testosterone, Androstenedione, SHBG, plasma HDL, Albumin, Treg, CD8, CBC, CD4+, Caspase 3-9, Bcl2, PDGFR, cKIT, ER, PR, Ki67, pS2, IgA, IgG, IgM, IgG, IgA, IgM, 20S proteasome, EGFR, pEGFR, Ki67, p27, pMAPK, AKT, pAKT, keratin 1, STAT3, VEGF, FDG-PET, CT, DCE-MRI, plasma PLG, CECs, EGFR, pEGFR, Ki67, p27, TGFalpha, amphiregulin, epiregulin, EGFRvIII, MEK, ERK1, pERK1, ERK2, pERK2, actin, Acetylated H3, H4, HDAC2-6, Topolla, HP1, KRAS, SRC, pSRC, pBCR/ABL, pCRKL, IGF1R, pS6, TGF-alpha, p95, 4EBP1, p4EBP1, eIF-4G, S6, pS6, IDO, TNFalpha,

.....

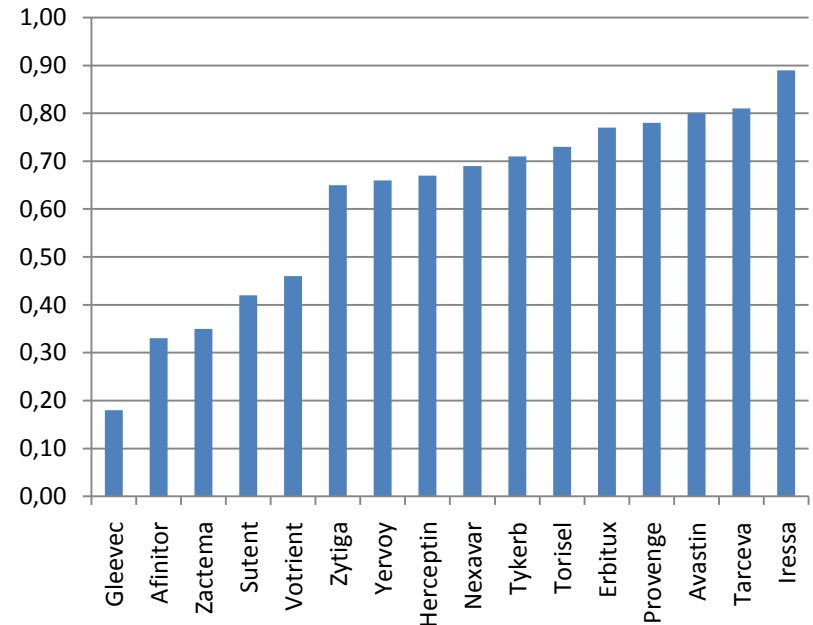
Predictive Biomarkers

Ph+, KRAS, EGFR, KIT, HER2

Hazard Ratios of Approved Oncology Drugs Show Need for Better Patient Selection

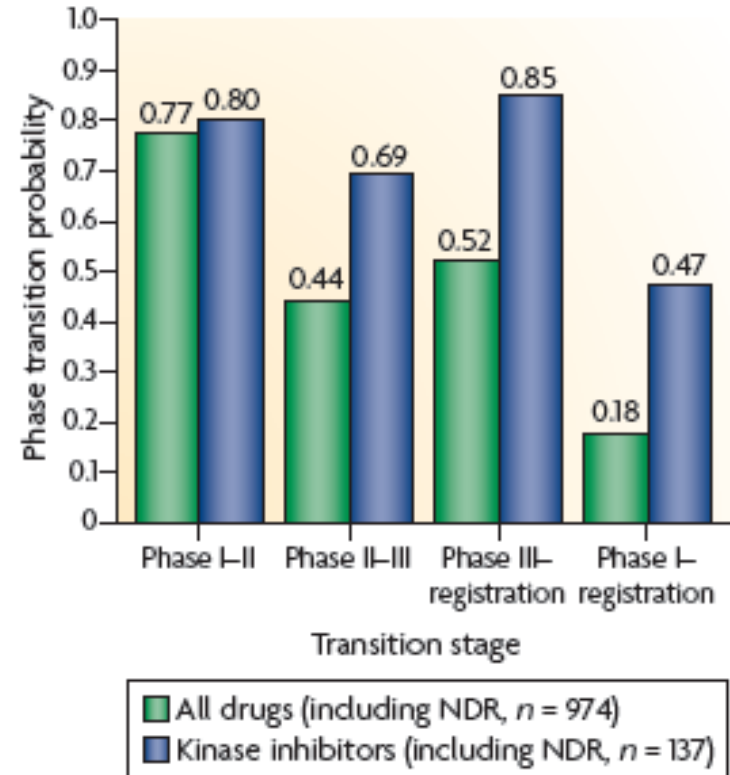
- Most recently approved Oncology drugs have only modest improvements in hazard ratios (HR)
- Effective targeting of tumors with predictive markers could significantly improve HR in defined subsets:
 - BRAF mutation in melanoma
 - ALK mutation in NSCLC

HR in randomized, controlled trial supporting 1st approved indication



Attrition in Drug Development: 2009

- Overall clinical success (Phase I entry to approval) has risen:
 - 2004 estimate: 11%
 - 2009 estimate: 18%
- Companion diagnostics have impacted approval of some kinase inhibitors:
 - cKIT for imatinib (GIST)
 - KRAS for panitumumab (colorectal cancer)
 - HER2 for lapatinib (breast cancer)
- Clinical success for kinase inhibitors is ~2.5-fold higher than the overall average:
 - How much of this is due to undifferentiated fast follow on compounds?
 - Has the transition from cytotoxic to targeted therapies reduced overall attrition?
 - How much is this due to precedented chemistry and biology for kinase inhibitors?



Walker & Newell, 2009

Biomarkers Can be the Difference in Eventual Approval of New Drugs

Probability of Success

| | MOA poorly understood | MOA well understood |
|------------------------------|-----------------------|---------------------|
| Available clinical biomarker | 15% | 75% |
| No clinical biomarker | 5% | 35% |

Adapted from E. Zerhouni – with permission

What have we learned ?

- Biomarker strategy:
 - Biomarker strategy often not considered when targets are selected
 - Retrofitting biomarkers to clinical programs has rarely been successful
 - Discovery of predictive markers in Phase II and validation in Phase III has not been successful
- Collect more samples:
 - “Voluntary” sample collection rates in clinical trials have often been insufficient to enable biomarker driven decisions
 - Too much dependence on serial invasive procedures to obtain matrices for biomarker analyses
- Validate assays before starting clinical trials:
 - “Fit-for-purpose” assays were not ready for use on clinical samples when required

What have we learned?

- Biological pathways:
 - Insufficient credible markers to evaluate target or pathway status
 - Lack of pre-specified biomarker targets:
 - What level of enzyme inhibition, receptor occupancy, or downstream pathway modulation is required for the desired therapeutic effect?
- Insufficient power to support biomarker decisions:
 - Non-innovative trial designs
 - Too few biomarker focused clinical studies (not just add on to standard clinical plans)
- Find better biomarkers (easier said than done):
 - Need more biomarkers like KRAS with very high predictive values to drive clinical decisions

Conclusion

- Clinical innovation always takes longer than expected:
 - Biomarkers are no exception!
 - Diseases are complex and individual biomarker effect sizes are often too small
- Biomarker science is the major cause of the delay:
 - When important markers emerge (*e.g.* KRAS), regulatory authorities have adapted quickly and adjusted previous requirements to include them in the drug labels
 - We have been much more successful with PD/MOA than predictive biomarkers
 - To date, we have largely failed to develop complex molecular profiles as useful predictive markers
- Companion diagnostics will remain rare until we can develop more biomarkers with:
 - Strong predictive values
 - Evidence they are predictive not prognostic
 - Available “fit-for-purpose” assays
 - Actionable data
- To be successful, we must change the way we implement biomarker research in pharmaceutical development:
 - Implement biomarker work much earlier in the development plan
 - Modify clinical trial design to enable biomarker discovery validation
 - Demonstrate that biomarker data improves the drug development process