TAT 2011

International Symposium on
*Targeted Anticancer Therapies*

**MDICT Task Force Meeting 2011**

**Date**

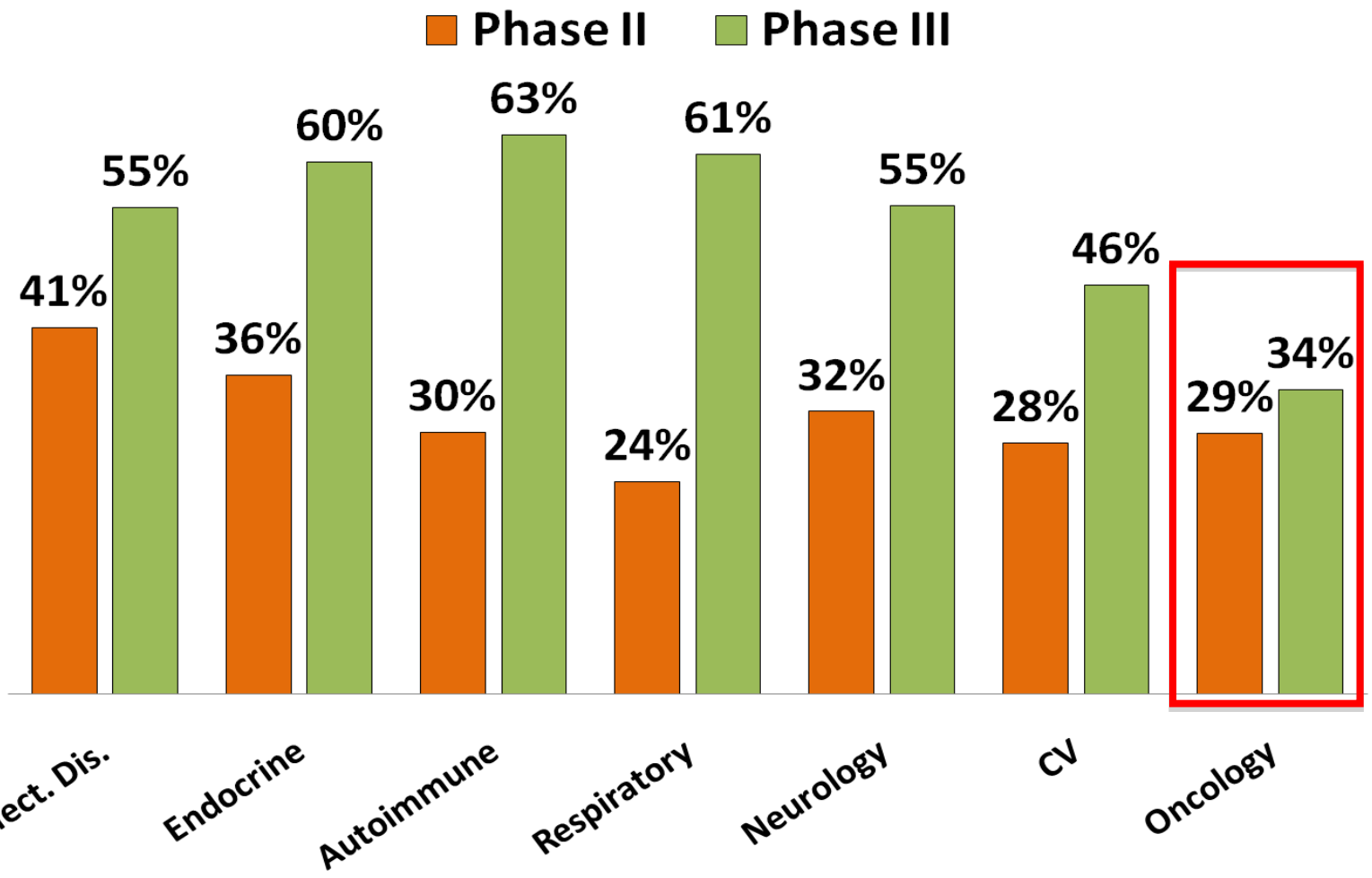
Sunday, March 6, 2011

**Agenda**

***Identification of patients in phase II likely to benefit from a targeted agent***

- Introduction of topic: Stuart Lutzker, Genentech, San Francisco, CA, USA
- Plenary discussion
- Conclusions
- Planning plenary presentation in TAT 2011 program
- Planning paper for publication

# Success Rate Phase II and Phase III
# Oct 2003 – Dec 2010






Source: BIO CEO and Investor Conference, Feb 15, 2011

# Predictive Diagnostic Biomakers may be as Important in Drug Development as the Drug

- Cancer is a heterogeneous disease defined by dysregulation of various diverse cellular pathways
- Targeted agents interact with these pathways

- Patients in whom a given pathway is active and important will derive disproportionate efficacy from a targeted agent
- Patients in whom a given pathway is not active or isn't important will derive disproportionate toxicity from a targeted agent

- Targeted agents *require* predictive diagnostic biomarkers (*aka* Diagnostic or Dx) to maximize both efficacy and safety

# Phase II Trial Design Issues

- Mandatory tissue (adequate amounts and QC'd)
- Single arm studies appropriate only for signal seeking
- Randomized studies necessary to determine the prognostic vs predictive nature of the Dx
- Either prospective or retrospective Dx analysis
- Prospective: Stratification or selection based on the strength of the Dx hypothesis
- Retrospective: Need adequate distribution of Dx+ patients between study arms
- Need adequate number of events in Dx+ patients to make Phase III Go/No Go decisions

# What is a robust Dx hypothesis and Dx test ?

Dx Hypothesis:

- Reflects the MOA of the drug and is mechanistically plausible
- Substantiated by preclinical experiments (in vitro and in vivo) and supportive clinical data

Dx Test:

- Is readily measurable in cancer patients
- Stable and reproducible
- Dynamic range suitable for determining cut-off values

# Questions for the MDICT

- Under what circumstances if any should a targeted agent move into Phase II without a diagnostic hypothesis ?
- How important is it that the diagnostic reflect pathway biology ?
- When should multi-agent, multi-arm, multi-diagnostic trials be considered (ex. BATTLE) and what are their strengths and weaknesses ?
- What is the MDICT's view on the role of the Dx in replicating Phase II success in Phase III ?

# Questions for the MDICT

- Q
  - Under what circumstances if any should a targeted agent move into Phase II without a diagnostic hypothesis ?
- A
  - If there is a compelling rationale for the agent's mechanism but it has not been possible to identify a suitable biomarker candidate (bevacizumab)
  - If it has not been possible to identify a suitable biomarker but significant clinical activity has been seen in Phase I

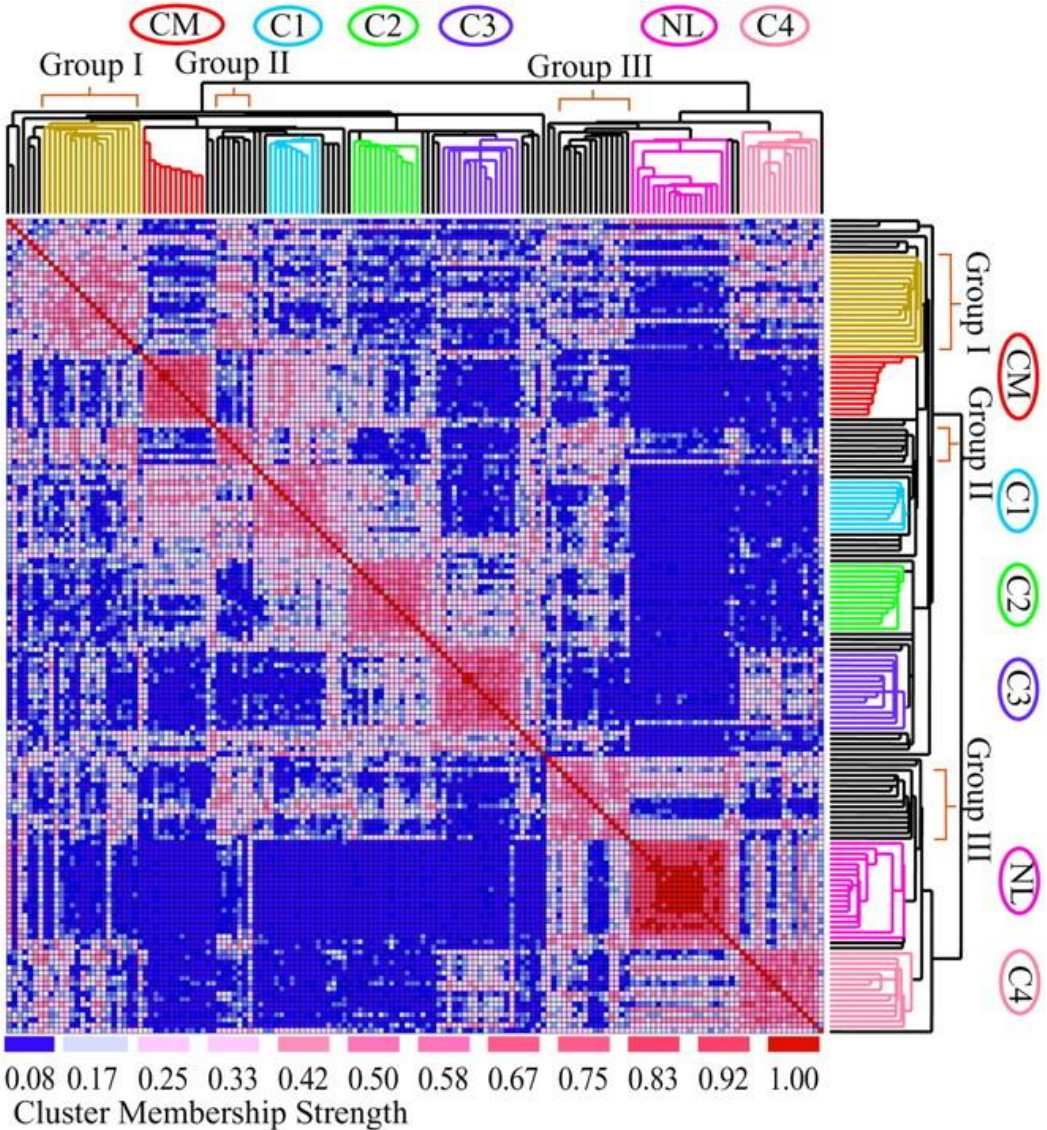
# Questions for the MDICT

- Q
  - Under what circumstances if any should a targeted agent move into Phase II without a diagnostic hypothesis ?
- Comments
  - depends on class of agent – microenvironment and antiangiogenic agents are difficult
  - Not enough subset analysis of mutation subtypes
  - More than one diagnostic hypothesis may exist – for example alk expression versus translocation
  - EGFR both predictive and prognostic
  - The more convinced we are that we know everything the more likely we are to be wrong
  - RAS is a resistance biomarker – leads to denial of therapy to the patients.
  - Clinical responses justify progression to Phase II
  - Biomarkers for combinations even more difficult

# Questions for the MDICT

- Q
  - How important is it that the diagnostic reflect pathway biology ?
- A - Very
  - Expression arrays can produce interesting classifications and hypotheses. For example they can identify HER2 amplified breast cancer as a distinct type.
  - However they may not identify pathways crucial to the pathway biology
  - A similar reservation applies to genome sequencing (Andrew Futreal's Keynote)

# Gene Expression Reveals Multiple Clusters within NSCLC Adeno CA




- Clusters by themselves do not provide evidence as to which pathways are driving the malignancy
- They *may* provide an enrichment for certain activated pathways

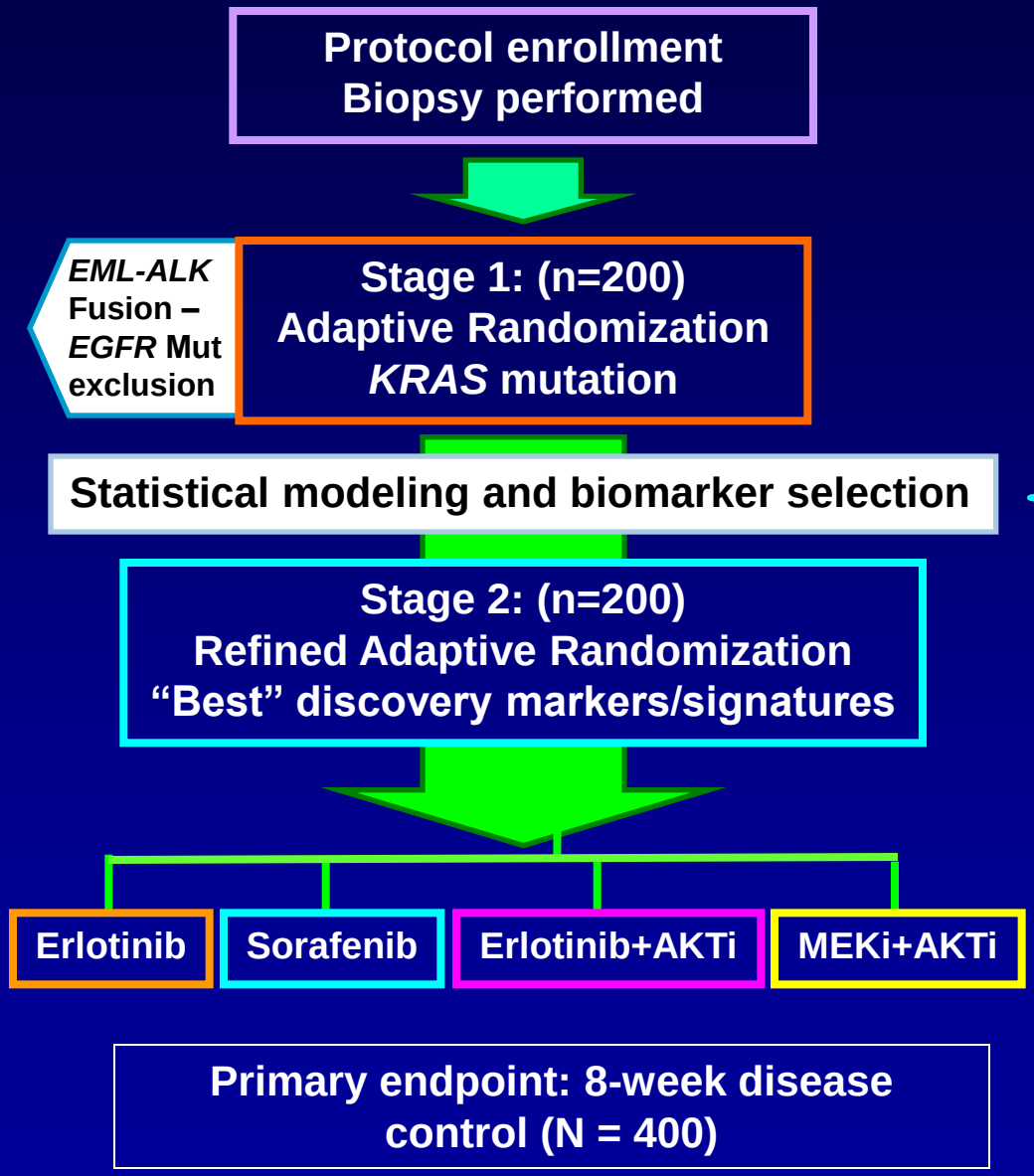


Bhattacharjee et al. PNAS 2001

# Questions for the MDICT

- Q
  - When should multi-agent, multi-arm, multi-diagnostic trials be considered (ex. BATTLE) and what are their strengths and weaknesses ?
- Background
  - These types of trials are designed an answer the criticism that diagnostic markers characterized in animal situations may not be relevant in humans

# BATTLE-2 Study Schema - 2nd line NSCLC




## Discovery Markers:

- **Protein expression (IHC):** FOXO3A, nuclear EGFR, p-AKT (Ser473), PTEN, HIF-1α, LKB1
- **Mutation analysis (Sequenom):** *PI3KCA*, *BRAF*, *AKT1*, *HRAS*, *NRAS*, *MAP2K1* (*MEK1*), *MET*, *CTNNB1, STK11* (*LKB1*)
- **mRNA pathways activation signatures: Affymetrix®**
  - BATTLE-1: WT-*EGFR*-Erlotinib, EMT, and Sorafenib
  - BATTLE-2: new "discovery" signatures
- **Protein profiling – RPPA (n=174)**
- **miRNA profiling**

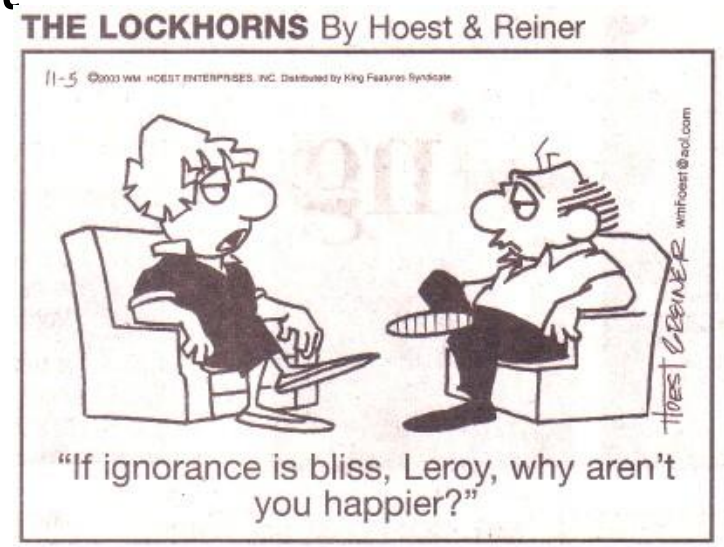
Courtesy of Edward Kim, MD

# Questions for the MDICT

- Q
  - When should multi-agent, multi-arm, multi-diagnostic trials be considered (ex. BATTLE) and what are their strengths and weaknesses ?
- A
  - They may identify candidate biomarkers where none are already known
  - Such biomarkers would require independent validation
  - There may be logistic / consent problems with such studies (biopsy without direct benefit to the patient or a clear hypothesis)

# Questions for the MDICT

- Q
  - What is the MDICT's view on the role of the Dx in replicating Phase II success in Phase III ?
- A
  - Patient enrichment and personalized medicine are perceived as essential aims in progressing research and improving cancer treatment
  - Ignorance is not bliss!



# MDICT Summary

- Thanks to Marinus Lobbezoo, Stuart Lutzker and all NDDO Staff for making the meeting possible
- I hope I have covered the everyone's views. Please say if you don't agree for adoption into the manuscript
- Experimenting with drugs is fun!