Decade after BATTLE-1 Trial:
Opportunities and Challenges

Waun Ki Hong, M.D.
Vali Papadimitrakopoulou, M.D.

MD Anderson Cancer Center
Disclosures
Scientific Advisory Board

Molecular Health

Imaging Endpoints

PharmAbcine
Order of my Presentation

BATTLE-1

BATTLE-2

BATTLE Like Trials

BATTLE Adjuvant

Challenges and Opportunities
Results of Empirical Targeted Therapies in Lung Cancer

Positive Studies (OS)
- BR.21 (erlotinib)
- ECOG 4599 (bevacizumab)
- INTEREST (gefitinib)

Negative Studies
- INTACT-1 (gefitinib)
- INTACT-2 (gefitinib)
- ISEL (gefitinib)
- TALENT (erlotinib)
- TRIBUTE (erlotinib)
- BMS-099 (cetuximab)
- ESCAPE (Sorafenib)
- Farnesyltransferase inhibitors
- Bexarotene (SPIRIT I and II)
- Glutathione (NOV-002)
- ZEAL (vandetanib)
- ZEST (vandetanib)
- ZEPHYR (vandetanib)
- Affinitak (LY900003) antisense
- IGFR (Figitumumab)

Clearly we do not know how to choose the right therapy for patients with lung cancer

10,000+ patients
Empirical Targeted Therapy Strategy: “Shooting in the Dark”
“BATTLE” as a Novel Approach in 2004

Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination
BATTLE Strategy For Lung Cancer
BATTLE Concepts in 2004

Platform for integrated translational research

1. Personalized Targeted Therapy
2. Novel trial design
3. Biomarker discovery

Overall Hypotheses

1. Molecular analysis of fresh biopsies can accurately reflect aberrant signaling pathway

2. Matching targeted agents with altered signaling pathways will improve disease control in lung cancer patients
BATTLE-1 Trial Schema

- **Core Biopsy**
  - EGFR
  - KRAS/BRAF
  - VEGF
  - RXR/CyclinD1

- **Biopsy**
  - Equal $\rightarrow$ Adaptive

- **Therapies**
  - Erlotinib
  - Vandetanib
  - Erlotinib + Bexarotene
  - Sorafenib

- **Primary endpoint**: 8-week disease control
Skepticisms

Not feasible to do core biopsies for so many patients

Impossible to get biomarker data within 2 weeks

Impossible to get different drugs from four different companies

Highly controversial adaptive randomization as new concept

Will never complete trial
Study Accrual and Randomization

Patients Enrolled vs. Time (months)

- Est. reg
- Cum. reg
- Est. rand
- Cum. rand

- 341
- 255
BATTLE-1 Timeline

- Mid 2004: Concept Developed
- Mid 2005: Grant Submitted
- April 2006: Grant Approved
- Nov 2006: Trials Activated- 1st pt
- Oct 2009: Trials completed accrual!
Assessment of BATTLE-1 Trial

• Successful completion of a prospective, biopsy-driven, study in lung cancer
  • This is now an acceptable approach!

• Patients are guided toward more effective personalized treatments (Adaptive design)

• Traditional way to identify biomarkers
  • Retrospective analysis of patient archives sample

• The new way
  • Prospective biomarkers evaluation
  • Unprecedented biospecimen resources for discovery
BATTLE Manuscript: Lead Article in Inaugural Issue of Newest AACR Journal


*co-first authors
#co-senior authors
Champions for success of BATTLE-1 Trial

Ed Kim, MD  Roy Herbst, MD  George Blumenschein, MD  Ann Tsao, MD

J. Jack Lee, PhD  Scott Lippman, MD  Ignacio Wistuba, MD
Editorials

The Battle trial: A bold step toward improving the efficiency of biomarker-based drug development

Clinical Trials Game – Changer?

A New BATTLE in the Evolving War on Cancer

Time Has Come to Raise the Bar in Oncology Trials

Set a new standard for biopsy mandated personalized targeted therapy
Results from BATTLE-1 Trial
Led to develop BATTLE-2 Trial
BATTLE-2 Trial

Protocol enrollment
Biopsy performed

EML4-ALK Fusion or EGFR Mut exclusion

Stage 1: (n=200)
Adaptive Randomization by KRAS Mut status

Statistical modeling and biomarker selection

Stage 2: (n=200)
Refined Adaptive Randomization
“Best” discovery markers/signatures

Primary endpoint: 8-week disease control (N = 400)

Biomarkers:

- Protein expression (IHC): 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®

- Protein profiling – RPPA (n=174)

- NGS-Foundation Medicine

- RNA sequencing

Papadimitrakopoulou and Herbst
MUTATION FREQUENCY BY NGS (targeted 181 genes FMI)

Total = 1664 mutations of known significance

FMI - NGS Summary

Completed FMI NGS 117
No material available for processing 41

158

Papadimitrakopoulou
MOST FREQUENT GENOMIC EVENTS BY Targeted NGS (181 genes FMI)

Papadimitrakopoulou
## Primary Endpoint

**8-wk DC**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>not evaluable</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>90(48.1%)</td>
<td>97</td>
<td>13</td>
<td>187</td>
</tr>
</tbody>
</table>

**By arms**

<table>
<thead>
<tr>
<th>8 week disease control</th>
<th>Erotinib</th>
<th>E+AKT i</th>
<th>AKT + MEK i</th>
<th>Sorafenib</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8wk DC</strong></td>
<td>7(35.0%)</td>
<td>18(50.0%)</td>
<td>37(53%)</td>
<td>28(46%)</td>
<td>90(48.1%)</td>
</tr>
<tr>
<td><strong>No 8wk DC</strong></td>
<td>13(65.0%)</td>
<td>18(50.0%)</td>
<td>33(47.1%)</td>
<td>33(54.1%)</td>
<td>97(51.9%)</td>
</tr>
</tbody>
</table>

Papadimitrakopoulou
PFS by **KRAS Mutation**

Trend for benefit with MEKi+AKTi for **KRAS mut**+
AKTi+MEKi
%DC=53.1

KRASG12C, RUNX1 mut+, ALK mut, ARAF mut, ATRX, BTK, CDK4

CDKN2A, FBXW7 mut+, KDM5c mut+, MLL2, Tp53 mut+, ARID1A, BRIP1, CDK8, CREBBP, EP300

Papadimitrakopoulou
10/11/2011
Treatment: Arm 3 AKTi+MEKi
KRAS mut in codon 12 (GGT to TGT) Gly to Cys (G12C).

12/21/2011
KRASG12C, RUNX1 mut+, ALK mut, ARAF mut, ATRX, BTK, CDK4
Long Term Responder Profile

- **AKTi + MEKi**: PR, PFS 241 days
- **KRAS G12C**
- **ERB4** missense mutation activate PI3K/AKT
- **ARAF** missense mutation (Potential oncogene. Sensitivity to Sorafenib and the MEK inhibitor trametinib.)
- RUNX1 deletion (runt related transcription factor 1, associated with AML, deletion oncogenic)

Multiple alterations along the MEK, PI3K/AKT pathway may be predicting Sensitivity.
BATTLE-Like Trials at MDACC

**IMPACT-1**: Non-Randomized Targeted Therapy Trial

**IMPACT-2**: Randomized Trial based on Molecular Profiling

**ATTACC**: Assessment of Targeted Therapy Against Colon Cancer

**MeLTT**: Melanoma Targeted Therapy Trial

**BEAT-IT**: Breast Cancer evaluation and targeted investigational therapy
Randomized Trial Evaluating Targeted Agent based on Molecular Profiling (IMPACT-2)

- Tumor biopsy for molecular profiling, 100% (n≈1,362)
  - Targetable molecular aberrations (≥1 aberration)
    - Yes, 50% (n≈613)
    - No, 50% (n≈613)
  - FDA-approved drugs within labeled indication
    - Yes, 30% (n≈184)
    - No, 70% (n≈429)
  - Excluded from randomization
  - Is there commercially available targeted agent or clinical trial?
    - Yes, 70% (n≈300)
    - Randomize
    - Targeted Therapy*
    - Treatment not selected based on profiling

Tsimberidou
<table>
<thead>
<tr>
<th>Enrichment</th>
<th>Therapeutic Mechanism</th>
<th>Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN Loss or PIK3CA mut</td>
<td>Akt inhibitor</td>
<td>MK-2206</td>
</tr>
<tr>
<td>CpG Island Methylation</td>
<td>Demethylator</td>
<td>Azacitadine + XELOX</td>
</tr>
<tr>
<td></td>
<td>Mitotic inhib</td>
<td>Nab-paclitaxel</td>
</tr>
<tr>
<td>HER2 overexpression</td>
<td>HER2 inhibition</td>
<td>Trastuzumab +/- EGFR</td>
</tr>
<tr>
<td>KRAS or NRAS mutant</td>
<td>CDK4+MEK</td>
<td>Novartis</td>
</tr>
<tr>
<td></td>
<td>ERK inhibition</td>
<td>Biomed Valley</td>
</tr>
<tr>
<td>BRAF Mutation</td>
<td>BRAF+EGFR+irino</td>
<td>Vemurafenib + cetux + irino</td>
</tr>
<tr>
<td>PTEN Loss/Any KRAS</td>
<td>PI3K-beta inhibitor</td>
<td>SAR26031</td>
</tr>
<tr>
<td>cMET overexpression</td>
<td>MET inhibition</td>
<td>INC280</td>
</tr>
<tr>
<td>EGFR ectodomain mutation</td>
<td>Alternate EGFR</td>
<td>Panitumumab</td>
</tr>
<tr>
<td>KRAS and PIK3CA mutation</td>
<td>Dual MEK, PI3K</td>
<td>BYL719 and MEK162</td>
</tr>
<tr>
<td>MSI High</td>
<td>CTLA4 and PD1</td>
<td>Nivolumumab, Ipilimumub</td>
</tr>
<tr>
<td>Triple KRAS/BRAF/NRAS WT</td>
<td>EGFR+HER2</td>
<td>Cetuximab + trastuzumab</td>
</tr>
</tbody>
</table>
Ongoing BATTLE-Like Biomarker Integrated Trials

Umbrella

Test impact of different drugs on different mutations in a **single type of cancer**
- BATTLE
- I-SPY2
- SWOG Squamous Lung Master

Basket

Test the effect of a drug(s) on a single mutation(s) in a variety of cancer types
- Imatinib Basket
- BRAF+
- NCI MATCH
S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy

Biomarker Profiling (NGS/CLIA)

Multiple Phase II-III Arms with "rolling" Opening & Closure

CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

CT*  

Biomarker Non-Match

PD-L1i

CT*

Endpoints
PFS/OS

FGFRi  CT*

PI3Ki

CCND1, CCND2, CCND3, cdk4 ampl

CDK 4/6i  CT*

FGFR ampl, Mut, Fusion

C-MET Expr

PiK3CA Mut

PI3Ki

CCND1, CCND2, CCND3, cdk4 ampl

CDK 4/6i

FGFR ampl, Mut, Fusion

C-MET Expr

PiK3CA Mut

EndoPFS/OS

EndoPFS/OS

EndoPFS/OS

EndoPFS/OS

Pl: V. Papadimitrakopoulou (MDACC, SWOG)
Steering Committee Chair: R. Herbst (YALE, SWOG)
Lung Committee Chair: D. Gandara
Translational Chair: F. Hirsch
Statistical Chair: M. Redman
NCI-MATCH SCHEMA

1. Genetic sequencing
   - Actionable mutation detected
     - Study agent
       - Stable Disease, Complete or partial response (CR+PR)
         - Continue on study agent until progression
           - PD
     - Progressive disease (PD)
       - Check for additional actionable mutations
         - Yes
           - No additional actionable mutations, or withdraw consent
             - Off study
         - No

1 CR, PR, SD, and PD as defined by RECIST
2 Stable disease is assessed relative to tumor status at re-initiation of study agent
3 Rebiopsy; if additional mutations, offer new targeted therapy
BATTLE Strategy in Lung Cancer

- Identify molecular driver
- Match with right agent
EGFR Mutation in Normal Bronchial Epithelium: Localized Field Effect

EGFR Mapping Strategy

Lung Tumor

Microdissection

FISH

Sequencing

Immunohistochemistry

Mutant Tumors: 9/21 (43%)
Wild-Type Tumors: 0/16 (0%)

2/32 (6%) Distant
13/63 (21%) Adjacent
13/46 (28%) Inside

Tang and Wistuba et al
Lung Adenocarcinoma in Smokers

59 year-old Caucasian male – Current Smoker

Adenocarcinoma
A Strategy to Detect Molecular Drivers: Molecular Profiling of Bronchial Brushes and Biopsies

Samples: Brushes/Tissues (6 sites)
- Contralateral
- Non-adjacent
- Adjacent
- Left Upper Lobe
- Left Lower Lobe
- Right Upper Lobe
- Right Middle Lobe
- Right Lower Lobe
- Resected Tumor

Global Gene Expression Analysis

SITE-dependent Analysis
- Adjacent
- Non-adjacent
- Contralateral

TIME-dependent Analysis
- Baseline
- 12 months
- 24 months
- 36 months

Clinical Endpoint: Recurrences
Biologic Endpoint: Detection of molecular drivers

Kadara and Wistuba et al; Kim and Hong et al
PI3K Gene Expression in Adjacent Fields are Associated with Recurrence

Paired t-test analysis of expression in adjacent compared to non-adjacent airways

Top activated network and potential target for adjuvant therapy: PI3K

Clustering of PATIENTS by adjacent vs non-adjacent gene expression
Hypothetical Proposal of BATTLE Adjuvant Trial

All patients with NSCLC Stages I–III undergoing resection

Enrollment into Umbrella Protocol

Resected Tumor and Adjacent Field

Molecular Profiling and Randomization

EGFR vs EGFR Inhibitor vs Adjuvant CT

RAS vs CT + Ras Inhibitor vs CT

PI3K vs CT + PI3K Inhibitors vs CT

COX-2 vs CT + Celecoxib Vs CT

EML-ALK vs ALK Inhibitor Vs Adjuvant CT
Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST)

- N=6000-8000
- Resectable lung adenocarcinoma (stage IB>4cm – IIIA)
- Biomarker and genomic analysis, clinical follow-up for all patients
- Adjuvant clinical trials for selected populations (EGFR, ALK, others)
- Biopsy at time of progression
Challenges

- Linking markers to targeted therapy
  Prognostic markers
  Predictive markers
    - Sensitivity
    - Resistance
- Genomic Heterogeneity
- Functional genomics:
  - Drivers and passengers
- Cost and Insurance reimbursement
- Need to train more translational investigators
Opportunities

1. Matched targeted therapy is better than standard non-targeted therapy?

2. Combined targeted therapy?

3. Combined targeted and cytotoxic therapy?

4. Combined targeted and immunotherapy?
Summary of my Talk

Concepts and Completion of BATTLE-1 trial

Progress of BATTLE-2 trial

Ongoing BATTLE-Like trials in MDACC

Ongoing BATTLE-Like trials (Umbrella, Basket)

BATTLE Adjuvant Trial

Challenges and Opportunities for personalized targeted therapy
Acknowledgements

George Blumenschein, MD
Kathryn Gold, MD
Roy S. Herbst, MD, PhD
Edward S. Kim, MD
Scott Kopetz, MD
J. Jack Lee, PhD

Scott M. Lippman, MD
Vali Papadimitrioupolou, MD
Lia Tsimberidou, MD
Anne Tsao, MD
Ignacio I. Wistuba, MD
Lung Cancer Moonshot Program at MDACC

- **BATTLE-XRT**
- **BATTLE-FL**
- **BATTLE-Adjuvant**
- **BATTLE-P**
- **Bioinformatics**

**Genomic Profiling**
DOD Lung Cancer Research Program (1997-2012)

**BATTLE**
- Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination

**PROSPECT**
- Profiling of Resistance Patterns & Oncogenic Signaling Pathways in Evaluation of Cancers of the Thorax and Therapeutic Targets

**BESCT**
- Biology, Education, Screening, Chemoprevention & Treatment

**IMPACT**
- Imaging and Molecular Markers for Patients with Lung Cancer: Approaches with Molecular Targets, Complementary, Innovative and Therapeutic Modalities

**VITAL**
- Vanguard Investigations of Therapeutic Approaches to Lung Cancer

**Basic, Clinical, and Translational Research ... Towards a Personalized Medicine Approach in Lung Cancer**
Order of my presentation

BATTLE-1

BATTLE-2

BATTLE Like Trials

BATTLE Adjuvant

Challenges and Opportunities
Order of my Presentation

BATTLE-1

BATTLE-2

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Challenges and Opportunities
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BATTLE-1

BATTLE-2

BATTLE Like Trials

BATTLE Adjuvant

Challenges and Opportunities
Reverse Migration BATTLE Strategy

- BATTLE Therapeutic Approach
- BATTLE Adjuvant Approach
- BATTLE Prevention Approach

Levels of Disease:

- Pre-Cancer
- Resectable Disease
- Local-Regional Disease
- Advanced Disease
Significance of BATTLE-1 Trial

• First prospectively conducted biopsy-driven, biomarker-integrated study in lung cancer in history

• Epitomizes as Team Science Research

• BATTLE concept paves the way for novel adjuvant and screening / early detection / prevention strategies

• Galvanize biopsy driven biomarker integrated trials worldwide
Study Accrual and Randomization

Patients Enrolled

Time (months)

Est. reg
Cum. reg
Est. rand
Cum. rand

341
255
### BATTLE-2: Stage 1. Results

<table>
<thead>
<tr>
<th>Randomized Arm</th>
<th>8-wk disease-control rate, % (Evaluable, n=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Eval.</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>20</td>
</tr>
<tr>
<td>Erlotinib+AKT inhibitor</td>
<td>51</td>
</tr>
<tr>
<td>AKT+MEK inhibitors</td>
<td>53</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>43</td>
</tr>
</tbody>
</table>

*Papadimitrakopoulou et al, ASCO 2014, Abstr. 8042*
Bayesian Adaptive Randomization: The Basics

- More patients are assigned to more effective therapies
- Based on accumulating patient data

Prior Probability:
- Estimated efficacy of markers to predict benefit from RX
  - Used for randomizing patient to a treatment

Posterior Probability
- Updating Prior Prob by observed outcomes: How did markers do at predicting benefit?

Pt adaptively randomized to treatment

We learn as we go!

Success is dependent on good biomarkers guiding assignments to good treatment options
Reverse Migration BATTLE Strategy

- Pre-Cancer
- Resectable Disease
- Local-Regional Disease
- Advanced Disease
- BATTLE Therapeutic Approach
- BATTLE Adjuvant Approach
- BATTLE Prevention Approach
Biomarker-Integrated BATTLE-like Trials in USA

MSKCC’s “Genotyping” and “BASKET” Trials

SWOG MASTER Protocol
(Biomarker-Driven Squamous Cell Lung Cancer)

NCI’s MATCH
(Molecular Analysis for Therapy Choice)

NCI’s M-PACT Clinical Trial

I-SPY2 Trial
(Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis)
BATTLE Discovery Platform

Gene expression profiling
- Affymetrix array
- RT-PCR

Tumor genetic profiling
- Mutation profiling (Sequenom, Inc)
- Copy number changes (FISH, etc)

Proteins
- Immunohistochemistry
- Proteomic arrays

Blood-based markers
- Profiling of cytokines and angiogenic factors (multiplex bead assays)

Germline genetic profiling
- SNP arrays

Personalized Medicine

TUMOR SUBTYPE is SCLC: 17/17 (all: 17/62, PValue: 0.0000)
BATTLE Team Members in MDACC
Results of Empirical Targeted Therapies in Lung Cancer

Positive Studies (OS)
- BR.21 (erlotinib)
- ECOG 4599 (bevacizumab)
- INTEREST (gefitinib)
- FLEX (cetuximab)

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- Farnesyltransferase inhibitors
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  - Glutathione (NOV-002)
  - ZEAL (vandetanib)
  - ZEST (vandetanib)
  - ZEPHIR (vandetanib)
  - Affinitak (LY900003) antisense
  - IGFR (Figitumumab)

Clearly we do not know how to choose the right therapy for patients with lung cancer
## BATTLE Results: Disease Control in % (n)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>EGFR</th>
<th>KRAS</th>
<th>VEGF</th>
<th>RXR/CycD1</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>35% (17)</td>
<td>14% (7)</td>
<td>40% (25)</td>
<td>0% (1)</td>
<td>38% (8)</td>
<td>34% (58)</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>41% (27)</td>
<td>0% (3)</td>
<td>38% (16)</td>
<td>NA (0)</td>
<td>0% (6)</td>
<td>33% (52)</td>
</tr>
<tr>
<td>Erlotinib + Bexarotene</td>
<td>55% (20)</td>
<td>33% (3)</td>
<td>0% (3)</td>
<td>100% (1)</td>
<td>56% (9)</td>
<td>50% (36)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>39% (23)</td>
<td>79% (14)</td>
<td>64% (39)</td>
<td>25% (4)</td>
<td>61% (18)</td>
<td>58% (98)</td>
</tr>
<tr>
<td>Total</td>
<td>43% (87)</td>
<td>48% (27)</td>
<td>49% (83)</td>
<td>33% (6)</td>
<td>46% (41)</td>
<td>46% (244)</td>
</tr>
</tbody>
</table>

**Marker Groups**
- **EGFR**
- **KRAS**
- **VEGF**
- **RXR/CycD1**
- **None**
Rationale for Adjuvant BATTLE Trial

1. Marginal benefit from adjuvant chemotherapy

2. Toxicity and cost of adjuvant chemotherapy

3. Conflicting data from empirically selected targeted agent trials

4. Persistent Molecular defects in Bronchial Airway after surgery
BATTLE Program Project (2004 - 2011)
PI: Waun Ki Hong

Project 1: BATTLE-1 Trial
WK Hong, ES Kim, R Herbst, G Blumenschein, A Tsao

Project 2: Molecular Mechanisms of Response or Resistance
B Johnson, H Lee, J Heymach, R Lotan

Project 3: Identify Biomarkers as Novel Predictors and Potential Targets
L Mao

Project 4: Explore New Combinations with mTOR (Preclinical → Clinical)
F Khuri, S Sun

Personalized Targeted Therapy and Prevention

Biostatistics Core
JJ Lee

Pathology Core
I Wistuba
### Characteristics of Randomized Patients (N=255)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Range)</td>
<td>62 yrs (26-84)</td>
</tr>
<tr>
<td>Male / Female</td>
<td>54% / 46%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>82%</td>
</tr>
<tr>
<td>Never / Current Smokers</td>
<td>22% / 9%</td>
</tr>
<tr>
<td>ECOG PS 0 / 1</td>
<td>9% / 77%</td>
</tr>
<tr>
<td>Adenocarcinoma / Squamous</td>
<td>63% / 18%</td>
</tr>
<tr>
<td>Prior Brain Metastases</td>
<td>33%</td>
</tr>
<tr>
<td>Prior EGFR-TKI</td>
<td>45%</td>
</tr>
<tr>
<td>Prior Docetaxel / Pemetrexed</td>
<td>40% / 40%</td>
</tr>
<tr>
<td>Prior Systemic Therapy</td>
<td>2 (1-6)</td>
</tr>
</tbody>
</table>
8-week Disease Control Predicts Overall Survival

- Median Overall Survival: 9 months
- 1-year survival: 38%

P = 0.002
**Individual Biomarkers for Response and Resistance to Targeted Treatment:**

<table>
<thead>
<tr>
<th>Drug Treatment</th>
<th>Biomarker</th>
<th>P–value</th>
<th>DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td><em>EGFR</em> mutation</td>
<td>0.04</td>
<td>Improved</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>High VEGFR-2 expression</td>
<td>0.05</td>
<td>Improved</td>
</tr>
<tr>
<td>Erlotinib + Bexarotene</td>
<td>High Cyclin D1 expression</td>
<td>0.001</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td><em>EGFR</em> FISH Amp</td>
<td>0.006</td>
<td>Improved</td>
</tr>
<tr>
<td>Sorafenib</td>
<td><em>EGFR</em> mutation</td>
<td>0.012</td>
<td>Worse</td>
</tr>
<tr>
<td></td>
<td><em>EGFR</em> high polysomy</td>
<td>0.048</td>
<td>Worse</td>
</tr>
</tbody>
</table>
BATTLE Team Members in MDACC
BATTLE Hypothesis in 2004:
Can we develop *personalized* therapy for lung cancer patients?

- Erlotinib
- Vandetanib
- Erlotinib + Bexarotene
- Sorafenib

ES Kim et al. Cancer Discovery 2011
BATTLE Implications

- A step towards personalizing medicine
- New research paradigm
  - Real-time tumor profiling of “current” disease status
  - Novel adaptive clinical trial design
- Discovery of new biomarkers
- BATTLE paves the way forward for our next study
Traditional Characterization of NSCLC by Histology

- Squamous
- Adenocarcinoma
- Large Cell

Molecular characterization

Adenocarcinoma
Pao and Hutchinson, Nat Med 2012

Squamous Cell Ca

Wistuba, 2011
NCI RO1 BATTLE-2 Trial

Co-PIs

Roy Herbst

Vali Papadimitrakopoulou
Most Frequent Genomic Events by Targeted NGS (181 genes FMI)

Papadimitrakopoulou
Targeted therapy*

If:
- Progressive disease
- Toxicity

Treatment not selected based on molecular analysis

Crossover

* Expansion phase of phase I studies or phase II studies