Phase II Trial of Paclitaxel by 96-Hour Continuous Infusion Plus Cisplatin

Breathnach et al Clin Cancer Res 2670, 2000
Woman with Adenocarcinoma of Lung Treated with Gefitinib

January 2002  October 2004
Impact of Genomic Changes on the Treatment of Lung Cancer

- Discovery of the Association between Response to Gefitinib and Erlotinib and Somatic Mutations of the Epidermal Growth Factor Receptor
- Identification of Mechanisms of Resistance to EGFR-TKIs
- Validation in Prospective Clinical Trials
- EML4-ALK Translocations
The Paradigm Shift

The 20th Century Paradigm
“Search and Destroy”

- Reactive
- Based on Gross Differences
- Toxic (MTD/DLT)
- Emerging Resistance
- Poor Life Quality

The New Paradigm
“Target and Control”

- Proactive
- Rational/Targeted
- No/Low Toxicity
- Resistance (Unlikely)
- Improved Life Quality

Research
- Human Genome
- Genomics
- Proteomics
- Immunology
- Mechanisms
- Rational Design
NCI’s Cooperative Group Program

- Established in 1955; approved by Congress
  - Main focus was to test new anticancer agents from NCI’s drug development program
  - Emphasis on single agent chemotherapy gradually shifted to studies of combined therapy
NCI’s Cooperative Group Program

Clinical Trials Research

• Cooperative Groups
  – 10 groups
  – 10 biostatistics centers
• CCOPs
• Minority CCOPs
• CTSU (Clinical Trials Support Unit)
NCI’s Cooperative Group Program

- ~22,000 new patients accrued to cancer treatment studies each year in >1,700 institutions
- >12,000 patients evaluated annually in ancillary laboratory correlative studies
NCI’s Cooperative Group Program

- Annual funding for the Cooperative Group Program is now >$145M
- Administered by the Cancer Therapy Evaluation Program (CTEP) of the Division of Cancer Treatment and Diagnosis
NCI Clinical Trials System: Current Status

• System is inefficient, time consuming, and under-funded

• In an era of targeted therapy, the system is geared toward the testing of non-specific regimens
  – Lacks the capacity to highly characterize each patient and carefully match that patient profile to targeted therapeutic combinations
### Replication Studies in CGEMS Prostate Cancer GWAS

#### rs6983267

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Cases</th>
<th>Cont.</th>
<th>P-value</th>
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#### rs1447295

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<td>ALL</td>
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<td>1.5x10^{-14}</td>
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</table>

#### Estimated Odds Ratios Overall

- **Heterozygotes**: 1.26 (rs6983267) vs. 1.43 (rs1447295)
- **Homozygotes**: 1.58 (rs6983267) vs. 2.23 (rs1447295)
The Cancer Genome Atlas

- **Pilot Project of NCI-NHGRI**
  - Cancers: Brain, Lung and Ovarian

- **Components**
  - Human Cancer Biospecimen Core Resource
  - Genome Sequencing Centers
    - Targeting sequence in phase 1
  - Cancer Genome Characterization Centers
  - Data Management, Bioinformatics and Computational Analysis

- **Data Access-Registered**
Functional Genomics

- Alterations in cellular function
  - Cell biology and protein carbohydrate chemistry
    - Regulation of gene expression
      - Whole genome sequencing
        - Genome-wide association studies

- Therapy Prevention
- Behavioral science
- Populations w/disease (environmental risk exposure)
- Large populations
- Longitudinal history

- Normal vs. abnormal phenotype
- Genes and environment
- Somatic mutations
- Germline markers of risk
NCI Targeted Drug Development Platform

GWAS
TCGA

NIH Chemical Genomics Center
Chemical Biology Consortium
RAID Program
Clinical Research Center
From Molecules to Man

100 mm Hg
Bridging the imaging gap

Dynamic multiprotein complexes

~50 nm

Signaling assemblies in intact cells

~2000 nm

HIV structure and cell entry mechanisms

~150 nm

Subcellular architecture of melanoma cells

~30,000 nm

Sriram Subramaniam, Ph.D.
Report of the Clinical Trials Working Group of the National Cancer Advisory Board

Restructuring the National Cancer Clinical Trials Enterprise

June 2005
NCI Clinical Trials System: Challenges

Not Drug Development but Therapeutic Solutions

• Design a trials structure that:
  – can obtain drug approval and demonstrate safety and benefit
  – has the ability to incorporate multiple, specifically targeted agents optimally matched to the patient

• Must seek short term, long term, and regulatory solutions
A Need to Think Creatively for Future of Translational Research

<table>
<thead>
<tr>
<th>Clinical Trials Research</th>
<th>Translational Model</th>
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<tbody>
<tr>
<td>• Cooperative Groups</td>
<td>• 2 patient tissue characterization centers</td>
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<tr>
<td>– 10 groups</td>
<td>• Biostatistics center</td>
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<tr>
<td>– 10 biostatistics centers</td>
<td>• Central IRB for all approvals</td>
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<td>• CCOPs</td>
<td>• CRC and CTSU</td>
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<td>• Minority CCOPs</td>
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</tr>
<tr>
<td>• CTSU</td>
<td></td>
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</tbody>
</table>
Disease with Genetic Component

Identify Genetic Defect(s)

Diagnostics

Pharmacogenomics

Therapeutic Developments
- Gene Therapy
- Drug Therapy

Accelerated by Human Genome Project and HapMap

Preventive Medicine

Time

Courtesy Francis Collins, NHGRI
Cooperative Group Processes

- Concept development: 193 days
- Concept review: 126 days
- Concept voting: 2 days
- Concept approval: 7 days
- Study learn teleconference: 16 days
- Protocol development: 477 days
- Protocol review: 277 days
- FDA review: 100 days
- CIRB review: 111 days
- CDE compliance review: 240 days
- Grant development: 222 days
- Regulatory affairs development: 350 days
- Activation: 7 days

Dilts et al. Journal of Clinical Oncology 2006
Impact of Genomic Changes on the Treatment of Lung Cancer

A Case in Point

Bruce Johnson, M.D.
Dana Farber Cancer Institute
NCI’s Cooperative Group Program

- Program currently includes researchers, cancer centers, and community physicians throughout the United States, Canada, and Europe

- Currently 10 NCI funded clinical trials cooperative groups, with various emphases related to modality, physician specialty, disease site, and technology
– The discovery process is too long and too costly
– No longer test one drug at a time
– Regimens rather than single agents
Cancer is a Disease of the Genome

It arises from changes within the DNA of our cells during their lifespan

- Deletions
- Amplifications
- Mutations
- Translocations
- Epigenetic changes
SNPs travel in neighborhoods

- linkage disequilibrium
- therefore, small number of SNPs serve as proxies for all the rest
Phase II Trial of Paclitaxel by 96-Hour Continuous Infusion Plus Cisplatin

- Untreated Non-Small Cell Lung Cancer
- Stage IIIB and IV
- PS 0-2
- Adequate Hematologic, Hepatic and Renal Function

**Paclitaxel**
- 30 mg daily for 4 days every 3 weeks

**Cisplatin**
- 80 mg per week on Day 5

Continue until disease progression or development of toxicity

Breathnach et al Clin Cancer Res 2670, 2000
Phase II Trial of Paclitaxel by 96-Hour Continuous Infusion Plus Cisplatin

- **Gender**
  - Men 34
  - Women 24

- **Age**
  - Median 60 (34-75)

- **Histology**
  - Adenocarcinoma 34
  - Bronchioloalveolar 10
  - Squamous 4
  - Non-Small Cell NOS 9

Breathnach et al Clin Cancer Res 2670, 2000
## Sensitivity of NSCLC Cell Lines from Pts Treated with Prolonged Infusions of Paclitaxel

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>IC50 Paclitaxel @ 120 Hrs</th>
</tr>
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<tbody>
<tr>
<td>NCI-H2882</td>
<td>0.020 µmol</td>
</tr>
<tr>
<td>NCI-H2887</td>
<td>&gt;10 µmol</td>
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<tr>
<td>NCI-H2973</td>
<td>6.74 µmol</td>
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<tr>
<td>NCI-H3122</td>
<td>0.020 µmol</td>
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<tr>
<td>NCI-H3255</td>
<td>&gt;10 µmol</td>
</tr>
</tbody>
</table>

Plasma concentration in Phase II trial was 0.075 µmol (range, 0.021–0.166 µmol)

Fujishita et al.  Oncology 2003;64:399
Non-Small Cell Lung Cancer Cell Lines and Their Sensitivity to Pemetrexed

- **Bronchioloalveolar**, N=4

- **Adenocarcinoma**, N=6
Non-Small Cell Lung Cancer Cell Lines and Their Sensitivity to Gefitinib
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• EML4-ALK Translocations
Discovery of the Association Between Response to Gefitinib and Erlotinib and Mutations of the EGFR

Paez et al. 2004
EGFR Mutant NSCLC Cell Lines are Dependent on EGFR for their Survival

Tracy et al., Cancer Research 2004;64:7241
Epidermal Growth Factor Receptor Mutations

Paez et al. 2004
Impact of Genomic Changes on the Treatment of Lung Cancer

• Discovery of the Association between Response to Gefitinib and Erlotinib and Somatic Mutations of the Epidermal Growth Factor Receptor
• Identification of Mechanisms of Resistance to EGFR-TKIs
• Validation in Prospective Clinical Trials
• EML4-ALK Translocation in NSCLC
Mutations in EGFR are in Exons 18-21 of the TK Domain

EGF Ligand Binding

TM

Tyrosine Kinase

G719A/C (5%)

S768I (2%)

R776C (2%)

L858R (24%)

L861Q (4%)

Deletions (61%)

E746-A750

766-768

Insertions (3%)

18 19 20 21 22 23 24
Exon 20 Insertion (D770_N771insSVD) is Resistant to Erlotinib Treatment
D770_N771insNPG EGFR Is Resistant to Inhibition by Erlotinib

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<th>µM</th>
<th>0</th>
<th>0.001</th>
<th>0.01</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>100</th>
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</table>

Greulich et al., PLOS Medicine, 2005
A
July 2002

B
747-752 Deletion

May 2004

747-752 Deletion

Sep 2004

T790M
T790M Point Mutations in \textit{EGFR}

- Threonine 790 is a critical amino acid in the TK binding pocket of \textit{EGFR} making a water-mediated hydrogen bond with erlotinib.
- It is analogous to T315 of the ABL kinase.
- It has been engineered into WT-EGFR and demonstrated high-level resistance (JBC in 2002).

\textit{The NEW ENGLAND JOURNAL of MEDICINE}
Kobayashi et al, 352:786, 2005
T790M Point Mutations in \textit{EGFR}

Wild Type

EGFR T790M found in 50\% of patients who become resistant to gefitinib/erlotinib

Mechanism of resistance increased ATP affinity not steric hindrance (Yun et al. PNAS 2008)
Patient with EGFR Deletion Mutation
Treated with High Doses of Gefitinib

September 2004
Del E746_A750 is Sensitive to Erlotinib Treatment

Mar 2007

May 2007
# Gefitinib Dose, Plasma Levels, and CSF Levels

<table>
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<th>Dose</th>
<th>Plasma Level</th>
<th>CSF Level</th>
<th>CSF Cytology</th>
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<tr>
<td>500 mg (09/04)</td>
<td>6.2 nM</td>
<td>Positive</td>
<td></td>
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<tr>
<td>500 mg (09/04)</td>
<td>18 nM</td>
<td>Positive</td>
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<tr>
<td>750 mg (10/04)</td>
<td>32 nM</td>
<td>Positive</td>
<td></td>
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<tr>
<td>1000 mg (01/05)</td>
<td>4200 nM</td>
<td>42 nM</td>
<td>Negative</td>
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<tr>
<td>1250 mg (02/05)</td>
<td>3800 nM</td>
<td>40 nM</td>
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</table>

DFCI-LU011 had an IC50 of 10-50 nM
Patient with EGFR Deletion Mutation
Treated with High Doses of Gefitinib

September 2004  March 2005
Patient with EGFR Deletion Mutation
Treated with High Doses of Gefitinib

September 2004
March 2005
Impact of Genomic Changes on the Treatment of Lung Cancer

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• EML4-ALK Translocations
Generation of Gefitinib *in vitro* Resistant HCC827

IC$_{50}$ = 10 nM

Increasing gefitinib dose

EGFR amplification ~20 fold

EGFR exon 19 deletion

IC$_{50}$ > 10 mM

DANA-FARBER CANCER INSTITUTE

DANA-FARBER/BRIGHAM AND WOMEN'S CANCER CENTER
HCC827 – a Model of Non-T790M Mediated Resistance

Engelman et al, 2007
Phospho-RTK Array Identifies Persistent EGFR, MET and ERBB3 Phosphorylation in HCC827 GR Cells
MET Amplification in Gefitinib Resistant EGFR Mutant NSCLC

Chromosome 7

Confirmed by QPCR; no mutations detected in MET
Inhibition of *Both* EGFR and MET is Necessary for Growth Inhibition of HCC827 GR Cells

- Irreversible EGFR inhibitors have no effect on HCC827 GR
- MET shRNA restores sensitivity to gefitinib
# MET Amplification Detected in Resistant NSCLC

<table>
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<tr>
<th>#</th>
<th>Specimen</th>
<th>EGFR mutation</th>
<th>T790M</th>
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<td>QPCR</td>
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<td>Del E746_A750</td>
<td>No</td>
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<td>26%*</td>
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EGFR T790M and MET Amplification can Occur in the Same Patient

<table>
<thead>
<tr>
<th>#</th>
<th>Specimen</th>
<th>EGFR mutation</th>
<th>T790M</th>
<th>Method</th>
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<td>QPCR</td>
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</table>
Phase II Trial of Women with Adenocarcinoma with Minimal Smoking History

- Women
- Adenocarcinoma Histology
- Adequate Tissue for Analysis
- Stopped Smoking for More than 1 Year

Erlotinib

150 mg daily

Continuous

Continue until disease progression or development of toxicity
Waterfall Plot: Mutation Status

% change in tumor size

-100
-50
0
50
100
150

KRAS mutation
EGFR exon 20 insertion
Wild-type for KRAS and EGFR
EGFR mutation

n = 43

DANA-FARBER
CANCER INSTITUTE

DANA-FARBER/BRIGHAM AND WOMEN’S CANCER CENTER
Median OS by *EGFR* status

<table>
<thead>
<tr>
<th></th>
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<th>Median OS</th>
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<tbody>
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<td>Not reached</td>
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<tr>
<td>EGFR wild-type</td>
<td>25</td>
<td>15.8 mo</td>
</tr>
</tbody>
</table>

Logrank p = 0.001
DFCILU026 – EGFR Del E746_A750

Mar 2007

May 2007
Exon 20 Insertion (D770_N771insSVD) is Resistant to Erlotinib Treatment

October 2005

November 2005
EGFR Inhibitors Directed Against Ba/F3 Cell with EGFR Mutations

<table>
<thead>
<tr>
<th>EGFR Mutation</th>
<th>(IC_{50}) Gefitinib</th>
<th>(IC_{50}) PF299804</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del E746_A750</td>
<td>4.8 nmol/L</td>
<td>&lt;1 nmol/L</td>
</tr>
<tr>
<td>Del E746_A750 /T790M</td>
<td>8,300 nmol/L</td>
<td>140 nmol/L</td>
</tr>
<tr>
<td>A767_V769dusp ASV</td>
<td>3,100 nmol/L</td>
<td>230 nmol/L</td>
</tr>
</tbody>
</table>

PF-299804 Directed Against EGFR Mutant NSCLC Cell Lines Transfected with Resistance Mutation
Exon 20 Insertion (D770_N771insSVD) is Resistant to Erlotinib Treatment

• Non-Smoking Woman Diagnosed with Stage IV NSCLC in July of 2004
• Treated with Gemcitabine Carboplatin, Erlotinib, Docetaxel
• Progressed on Erlotinib Therapy
Exon 20 Insertion (D770_N771insSVD) Treated with PF-299804
Exon 20 Insertion (D770_N771insSVD) Treated with PF-299804 for 13 Months

April 2007

May 2008
Sensitivity of NSCLC Cell Lines from Pts Treated with Prolonged Infusions of Paclitaxel

- **Cell Line**
  - NCI-H2882
  - NCI-H2887
  - NCI-H2973
  - NCI-H3122
  - NCI-H3255

- **IC50 Paclitaxel @ 120 Hrs**
  - 0.020 µmol
  - >10 µmol
  - 6.74 µmol
  - 0.020 µmol
  - >10 µmol

Plasma concentration in Phase II trial was 0.075 µmol (range, 0.021–0.166 µmol)

Fujishita et al. Oncology 2003;64:399
EML4-ALK Variants in NSCLC

Variant 1
1059aa
117kDa

Variant 2
1310aa
146kDa

Variant 3a/b
786/796aa
86/87kDa

codon 569 (exon 15)

codon1078 (exon 20)

Variant 4
1108aa
122kDa

DFCI032 NSCLC Cell Line

36 yo female
Caucasian
Never smoker
FISH Assay for EML4-ALK
ALK Kinase Inhibitors

MET/ALK inhibitor
Currently in Phase I trials
TAE684 Affects Growth of EML4-ALK in NCI-H3122 in vivo
Impact of Genomic Changes on the Treatment of Lung Cancer

- Discovery of the Association between Response to Gefitinib and Erlotinib and Somatic Mutations of the Epidermal Growth Factor Receptor
- Identification of Mechanisms of Resistance to EGFR-TKIs
- Validation in Prospective Clinical Trials
- EML4-ALK Translocations
Total Processes to Open a Cooperative Group Study

Cooperative Group Processes

- Protocol development: 477 days
- Draft protocol review: 277 days
- Regulatory affairs development: 350 days
- Grant development: 222 days
- Study team teleconference: 16 days
- Activation: 7 days

Median: 784 - 808 days
Range: 435 - 1604 days

Comprehensive Cancer Center Processes

- Preliminary Budget Assessment
- LCI and protocol development (including industry sponsored review)
- IRB Review
- Final Contract Signing
- Study Activation

Median: 116 - 252 days
Range: 21 - 836 days
By Year


Time From Concept Receipt to Activation

Total Days

Total Days
Accrual to 150 Cooperative Group Phase III Trials
Active 2000-2005

<table>
<thead>
<tr>
<th>Number of Patients Accrued to Trials, by Institution</th>
<th>Percentage of Institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5 patients</td>
<td>29%</td>
</tr>
<tr>
<td>6-10 patients</td>
<td>12%</td>
</tr>
<tr>
<td>11 to 25 patients</td>
<td>16%</td>
</tr>
<tr>
<td>26 to 50 patients</td>
<td>14%</td>
</tr>
<tr>
<td>51 to 100 patients</td>
<td>13%</td>
</tr>
<tr>
<td>101 to 300 patients</td>
<td>13%</td>
</tr>
<tr>
<td>301 to 500 patients</td>
<td>2%</td>
</tr>
<tr>
<td>500+ patients</td>
<td>1%</td>
</tr>
</tbody>
</table>

CTWG Operational Efficiency Initiatives
Efficiency of Phase III Trial Accrual
Operational Efficiency Timeline

- **Initiate analysis of bottlenecks in clinical trials**
- **Completed evaluation of Cancer Centers, Coop Groups, and CTEP**
- **Recommendations for operational improvement**
- **Operational Efficiency Working Group**
- **Implementation**
- **'06**
- **'07**
- **'08**
- **'09**
- **'10**
- **50% Reduction In Clinical Trial Activation Time**
Intestine

Brain
High Dose Gefitinib for Carcinomatous Meningitis in Non-Small Cell Lung Cancer

• PR to Gefitinib or Erlotinib or EGFR Mutation
• + CSF Cytology
• PS 0-3
• No Uncontrolled Brain Mets

Gefitinib
750-1250 mg daily for 2 weeks, 500 mg daily 2 weeks

Continue until disease progression or development of toxicity

EGFR Sequencing plus Serum and CSF levels of Gefitinib